İLAÇLARDA
TEST VE DENEY VERİLERİNİN
KORUNMASI:
AVRUPA BİRLİĞİ'NDE YENİ SİSTEM

İKTİSADİ SEKTÖRLER VE KOORDİNASYON GENEL MÜDÜRLÜĞÜ

ANKARA 2005

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HASİBE IŞIKLI

İKTİSADİ SEKTÖRLER VE KOORDİNASYON GENEL MÜDÜRLÜĞÜ
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İÇİNDEKİLER

Sayfa

Sayfa

ÖNSÖZ

İlaç sanayii, ürünleri itibariyle diğer sanayii dallarından ayrı ve özel bir önem taşıyan; sadece üretim boyutuyla değil, sağlık ve sosyal güvenlik boyutuyla da toplumsal düzeyde önemli etkilere sahip bulunan bir sanayiidir. Ürünlerinin doğrudan insan sağlığı için kullanılıyor olması, bu sektörde yer alan tüm faaliyetlerin resmi makamlarca sürekli biçimde kontrole, denetime ve incelemeye tabii tutulmasını gerektiren en önemli faktör olmaktadır. İlaç sanayiinde diğer sanayiilerde olduğu gibi ürün kalitesi sıralaması yoktur, ikinci ya da üçüncü kalite bir ilaç üretilmesi mümkün değildir, ilaç her zaman birinci kalite ürün olmalıdır. Üretim standartları hassasiyetle oluşturulmuş, ilaç üretimi belli koşullara bağlanmıştır. Ürün pazarlaması, reklamı, satışı serbest değildir; devletin bu faaliyetlere ilişkin olarak çeşitli denetim mekanizmaları vardır.

İlaç sanayiinde mevcut olan bu özel durum, bu alana yapılacak yatırımların ve araştırma-geliştirme (Ar-Ge) çalışmalarının değerlendirilmesinde de ortaya çıkmaktadır. Yüksek standartlarda üretim teknikleri, ileri teknoloji araştırma yöntemleri gibi maliyet artırıcı faktörler, bu alana yönelik yatırım faaliyetlerinde karar vermeyi zorlaştırıcı olarak değerlendirilmektedir.

İlaç sanayiinde Ar-Ge özel bir önem ve ayrıcalık taşımaktadır. Bu alandaki Ar-Ge faaliyetleri doğrudan insan sağlığını iyileştirmeye, hastalıkları tedavi etmeye ve yeni tedavi yöntemlerini geliştirmeye yönelik olduğundan ülkelerin hükümetlerince desteklenmekte ve yakından takip edilmektedir. Bu alana yapılan harcamalar ve Ar-Ge maliyetleri de dönemsel olarak artış göstermektedir. Herhangi bir molekülün ilaç etkin maddesi olarak bulunması ve ilaç biçiminde piyasaya sunulması için gerekli harcama 1970'lerde 57 milyon $ iken günümüzde 500 milyon $ düzeyine ulaşmıştır. Yeni ilaçların ve yeni tedavi yöntemlerinin kullanılmasıyla; hastalar daha uzun yaşamakta, hastanelerde kalma süresi ve doktor meşguliyetinin azalmasıyla birlikte hasta bakım masrafları da azalmakta, toplamda ülkelerin sağlık harcamalarında önemli düşüşler kaydedilmektedir. Yeni ilaçların ülke ekonomilerine

sağladığı çok yönlü katkılar, bu alana yapılan harcamaların desteklenmesi için çeşitli araçlar geliştirilmesine de yol açmıştır. Bu araçlar arasında "fikri haklar sistemi" oldukça önemli bir yer tutmaktadır.

Fikri haklar sistemi içerisinde "patent koruması" ve "veri koruması/veri münhasiriyeti" ilaç sanayiinde Ar-Ge maliyetlerinin karşılanması için alternatif yöntemler sunmaktadır. Uzun süren araştırmalar ve yüksek harcamalar sonucu bulunan kimyasal maddeye sağlanan patent koruması ile, bu araştırmaları yapanlar ortalama 20-25 yıllık bir süre için rakiplerinden korunarak ödüllendirilmektedir. Benzer şekilde, ilaç haline gelen molekülün etkinlik, kalite ve etkililik test ve deneylerine yapılan harcamalar da, bu verilerin 5-10 yıllık bir süre için veriyi üreten dışında başka firmalara kullandırılmamasıyla desteklenmektedir. Böylelikle, bir taraftan yeni araştırmaların yapılması ve toplumun yeni ilaçlardan yararlanması sağlanmakta, diğer taraftan da yüksek maliyetleri göze alarak bu araştırmaları yapanlar teşvik edilmiş olmaktadır.

Bu çalışmada, "veri koruması" olarak tanımlanan, ilaçların piyasaya sunulmasından önce yapılması gerekli test ve deneylerin sonucunda elde edilen ve ilacın ruhsatlandırılması için resmi makamlara sunulması gereken verilerin korunması konusu ele alınmaktadır. Çalışmanın kapsamı Avrupa Birliği'nde veri koruma düzenlemeleri ile sınırlandırılmıştır. Avrupa Birliği'nde yirmi yıldan fazla bir süredir var olan veri koruması uygulaması özellikle son yıllarda yoğun tartışmalara yol açmış; bir taraftan halk sağlığının daha da iyileştirilmesi amaçlanırken diğer taraftan da Avrupalı ilaç üreticilerinin dünya ölçeğinde rekabet edebilirliklerinin artırılması hedeflenerek yeni bir sistem yaratılmıştır. Yeni sistem 2005 yılı sonlarında uygulamaya geçecek olup Avrupa Birliği'ne yeni katılan ve aday statüsünde olan ülkeler açısından da önemli değişiklikler getirmektedir.

Çalışma üç ana bölümde yapılandırılmıştır. İlk bölümde ilaç sanayiinde Ar-Ge süreci ve veri korumasına ilişkin genel bir bilgi verilmekte, veri korumasının ilkelerine ve bu koruma biçiminin patent koruması ile bağlantısına değinilmektedir. İkinci bölümde, Avrupa

Birliği bünyesinde ilaç sanayiinin durumu, mevcut olan ve getirilen yeni sistemin temel ilkeleri, veri korumasına ilişkin son yasal değişiklikler ve yeni üye olan ülkeler ile aday ülkelerdeki veri koruma düzenlemeleri incelenmektedir. Son bölümde ise, Türkiye'nin AB ile ilişkiler bağlamında veri korumasına ilişkin yükümlülükleri ve bu kapsamdaki yasal düzenlemeler değerlendirilmektedir.

Bu çalışmanın gerçekleştirilmesinde sırasında, başlangıç aşamasından itibaren yönlendirici ve destekleyici yorumlarıyla son derece değerli katkılar sunan ve raporun şekillenmesinde büyük emeği olan Sayın Hülya ÇAYLI'ya; raporu okuyarak üzerinde gerekli düzeltmelerin yapılmasına yardımcı olan Sayın Osman YILMAZ ve Sayın Derya FIRATOĞLU'na; metnin biçimsel düzenlemesinde yardımlarını esirgemeyen Sayın Uğur EMEK'e teşekkür ederim. Bu faydalı katkı ve yardımlara rağmen, çalışmada olabilecek hata ve eksikliklerin sorumluluğu hiç kuşkusuz ki tamamiyle şahsıma aittir.

BÖLÜM I. İLAÇLARDA TEST VE DENEY VERİLERİNİN KORUNMASI

1. GİRİŞ[1]

Yeni bir ilaç bileşiminin ya da aşının keşfedilmiş olması, onun hastalar tarafından kullanılabilecek düzeyde etkili ve güvenli bir ürün olduğunu göstermemekte; tam tersine, bu yeni ürünün toplum tarafından kullanılabilir bir ilaç ya da aşı haline gelmesi için, yetkili kurumlara ilacın güvenliğini, kalitesini ve etkinliğini gösteren ve yoğun çaba gerektiren bir dizi klinik deneylerin yapılması gerekmektedir.

Yeni bir ilacın maliyeti, klinik öncesi ve klinik deneme fazlarıyla birlikte değerlendirildiğinde ortalama 500 milyon $ gerektirmekte ve 15 yıla kadar uzayan bir zamana yayılmaktadır. ABD'de araştırma üzerine kurulmuş ilaç şirketleri, Ar-Ge'ye 1998 yılında 21,8 milyar $ yatırım yapmışlardır. Bu Ar-Ge harcamalarının % 70'i yasal ruhsat alma prosedürü için (% 40 oranında klinik öncesi işlemler, % 30 oranında Faz I, II ve III'ün yer aldığı klinik deneyler) harcanmıştır. Tek bir tedavi için, klinik deneme evresindeki ilaca ilişkin tüm testler 150 milyon $ ya da daha fazla maliyete neden olmaktadır. Diğer taraftan, bu tür yüksek oranda harcamaların yapıldığı ilacı piyasaya sunmak isteyen bir jenerik üreticinin, eğer kendisinden ruhsat için kendi verisini üretmesi istenmiyorsa, biyoeşdeğerliğini göstermesi şartıyla sadece 1 milyon $ yatırım yapması yeterli olmaktadır. Bu durumda jenerik üretici, gerekli tüm test ve deneyler için herhangi bir yatırım yapmadan orijinal ilaç sahibinin verilerini kullanarak kendisine önemli ölçüde ticari avantaj yaratmaktadır. Böyle bir durum, ilacın orijinal sahibinin sonuçlarını rakiplerine sıfır maliyetle anında erişilebilir kıldığından, güçlü ve etkili bir patent korumasına sahip ülkelerde bile varolan yatırım potansiyelini azaltmaktadır.

[1] Bu bölümde "Encouragement of New Clinical Drug Development: The Role of Data Exclusivity", International Federation of Pharmaceutical Manufacturers Associations, s:1, 2000, Switzerland, dokumanından yararlanılmıştır.

İlaç sanayiinde deney verilerinin korunması, fikri haklar sisteminin hukuki ve ekonomik anlamda önemli bir bileşenidir. İlacın ruhsatının alınabilmesi için gerekli verinin üretilmesi hiç şüphesiz ki önemli ölçüde zaman, uzmanlık, kaynak ve paraya yatırımı gerektirmektedir. Fikri haklar sistemindeki diğer uygulamalara benzer şekilde, ilacı ortaya çıkaran kişiye bir teşvik unsuru olarak bu maliyetleri geri alabileceği bir ortam yaratılması gerekli olmakta, bu da rakiplerinin bu veriyi kullanarak jenerik alternatiflerinin ruhsatını almalarından önce piyasada belli bir süre tek başına yer almalarıyla sağlanmaktadır.

Bu özel koruma biçimi uluslararası platformda yoğun tartışmalara konu olmuştur. Tartışmalar halen günümüzde de çeşitli boyutlarda devam etmekte, bu alanda ülkeler kendi koşullarına uygun koruma sistemini oluşturmaktadır. ABD'de genellikle "data exclusivity", AB'de ise "data protection" ya da "regulatory data protection" olarak tanımlanan ve bu çalışmada "veri koruması" olarak adlandırılan bu hak türü bağımsız bir fikri mülkiyet hakkıdır ve diğer haklarla, özellikle patentle sağlanan koruma ile karıştırılmamalıdır. Bu hak, sahibi tarafından üretilen verinin bir başka kişi ya da şirket tarafından belirli bir süre için kullanılamayacağını ya da referans olarak gösterilemeyeceğini ifade eder. Ancak, bir başka şirketin aynı veriyi üretmesine de engel olmaz. Dolayısıyla ilk bakışta çok sınırlı bir hak olarak gözükmekteyse de, ülkeler buna büyük önem vermekte ve ihtiyaç duyulan verinin üretilmesini tıbbi ürünlerin ruhsat (pazarlama izni) sürecine dahil ederek şirketlere gereken teşvikleri sağlamaktadır.

2. İLAÇ SANAYİİNDE AR-GE SÜRECİ[2]

İlaç sanayiinde Ar-Ge süreci klinik deneyler öncesi çalışmalar ve klinik deneyler olarak iki ana bölüme ayrılmakta; her bölümün de alt fazları bulunmaktadır.

[2] 8.Beş Yıllık Kalkınma Planı İlaç Sanayi ÖİK Raporu için Hülya Çaylı ve Hasibe Işıklı tarafından hazırlanan rapordan alınmıştır.

2.1. Klinik öncesi deneyler

- Kimyasal (aktif maddenin araştırması),
- Farmakolojik (toksikoloji, çeşitli hayvan türleri üzerindeki etkilerin incelenmesi),
- Yeni İlacın Denenmesi (yeni ilacın insanlar üzerinde denenmesi süreci için resmi makamlardan izin alınması),

aşamalarını kapsamaktadır. Bu dönem içerisinde kimyasal ve farmakolojik araştırmalar 2-4 yıl arasında, ilacın denenmesi için izin alınması süreci ise 2-6 ay arasında değişmektedir.

2.2. Klinik deneyler

- Faz I, sağlıklı insanlar üzerindeki etkinin değerlendirilmesi(50-100 kişi)
- Faz II, sınırlı sayıda hasta üzerinde klinik çalışmalar (100-200 kişi)
- Faz III, çok sayıda hasta üzerinde karşılaştırmalı çalışmalar (500-5000 kişi)
- Yeni İlacın Uygulanması (yeni ilacın pazarlanması için resmi makamlardan izin süreci)
- Faz IV, karşılaştırmalı çalışmaların sürdürülmesi, ruhsatlandırma, piyasaya sunma,

aşamalarını kapsamaktadır. Bu dönemde süre, ilk üç faz 3-6 yıl arasında, pazarlama izni süreci 1-3 yıl arasında ve son fazda ise belli bir zaman kısıtı olmaksızın toplam 6-10 yıl arasında değişmektedir.

Yukarıda belirtildiği üzere, bir kimyasal maddenin buluş aşamasından piyasaya sunulacak bir ilaç haline gelmesi için minimum 10-15 yıl arasında değişen uzun ve maliyetli bir "Araştırma Prosesi" gerekmektedir. 1970'li yıllarda bir ilacın Ar-Ge maliyeti 57 milyon $ iken, bu rakam 1990 başlarında 230 milyon $ ve günümüzde ise 500 milyon $ civarına yükselmiştir.

3. VERİ KORUMASI/MÜNHASIRIYETİ

Bir ilacın amaçlanan tedavi yöntemi için etkin ve güvenli olduğunun gösterilmesi için, ilacın buluşçusu tarafından klinik öncesi ve klinik deneyler olmak üzere hayvanlar ve insanlar üzerinde yoğun testlerin ve aynı zamanda ilacın toksikolojisi, üretim fizibilitesi ve diğer bilimsel çalışmalarının yapılması gerekmektedir[3]. Bu testlerin ve çalışmaların sonuçları, ilacın piyasaya sunulması için hükümet otoritelerine verilecek olan ruhsatlandırma dosyasının içinde yer alır.

Üretilen veri, yetkili makamlara güvenilerek verilir ve üçüncü kişilerin referans olarak kullanmaları istenmez. Eğer bu veri, üçüncü kişiler için anında ulaşılabilir olursa, o zaman firma açısından bu verinin ilk önce kendisi tarafından üretilmesinin anlamı kalmaz. Genel olarak ilaç ürünleri patent korumasından yararlanmaktadır, ancak herhangi bir nedenle patent korumasından yararlanmayan birçok bileşik de geliştirilmekte ve bu durumda sadece veri koruması uygulanabilir bir fikri hak olarak gözükmektedir. Bu verinin gizliliğinin haksız kullanımlara ya da açıklamalara karşı korunması, daha ileri ilaç Ar-Ge çalışmaları için ekonomik bir destek sağlaması ve bilim adamlarının çabalarının korunması açısından çok önemli olmaktadır.

Diğer taraftan, hayvanlar ve insanlar üzerinde yapılan test ve deneylerin tekrarından kaçınmak üzere, buluşçunun mülkiyet hakkına belli bir sınır getirilmiştir. Bu sınırlı süre sona erdiği zaman verinin jenerik firmalarca referans olarak kullanımı mümkün hale gelmekte; böylece, buluşu yapanın yatırımı korunurken aynı zamanda test ve deneylerin gereksiz tekrarı da önlenmiş olmaktadır.

[3] "Encouragement of New Clinical Drug Development: The Role of Data Exclusivity", International Federation of Pharmaceutical Manufacturers Associations, s:2, 2000, Switzerland.

3.1.Tanım[4]

Veri koruması, bir kuruluşun bir ürünü için ruhsat almak amacıyla devletin ruhsat otoritesine sunduğu test ve klinik verilerine atıfta bulunarak veya kullanarak, bir başka kuruluşun ruhsat almak için başvuramadığı bir süreyi ifade eder. Diğer bir anlatımla, ilaçta veri koruması bir devletin ilaçlara ilişkin ruhsat verileri için sağlaması gereken "ifşa edilemezlik" ve "isnat edilemezlik" süresidir.

Veri koruması, ruhsatlandırma için başvuruda bulunulan bir ürün hakkındaki bilimsel bilgilerin, ürün pazarlama izni aldıktan sonra ilgili otorite tarafından belli bir süre ile orijinal firma lehine münhasıran korunmasını ifade etmektedir. İdari otoritenin bu konudaki sorumluluğu, orijinal ürün verilerini referans gösteren herhangi bir jenerik ürün başvurusunu, belirlenen süre içerisinde kabul etmemek/değerlendirmemektir. Farklı bir klinik araştırma dosyası sunmaları durumunda veya orijinal ilaç şirketinden izin alınması yoluyla bu süre içinde de jenerik ilaçların piyasaya sürülmesi mümkündür.

Bir ilacın piyasaya sunulması; birincisi yeni bir molekülün/farmasötik bileşiğin bulunması için gösterilen çalışmalar, ikincisi ise söz konusu molekülün/farmasötik bileşiğin emniyetli, kaliteli ve etkili bir ilaç olduğunun yetkili otoritelere kanıtlanması için gerekli deney ve testlerin yapılmasını içeren iki aşamayı gerektirir. Burada birinci aşama çalışmaları genellikle patent korumasından yararlanmakta, ikinci aşama çalışmaları ise veri koruması kapsamına girmektedir.

Veri korumasının konusu ilacın bileşiminde yer alan "yeni kimyasal" dır. ABD Gıda ve Sağlık Kurumu (FDA-Food and Drug Administration) ile Avrupa ruhsat otoriteleri "yeni kimyasal" kavramını, "daha önceden ilaç olarak ruhsat almamış, tüm geliştirme aşama ve

[4] Bu bölüm "İlaçta Veri Korumasının Mali Yansımaları" Baykara T. Prof.Dr., Çaylı H., Çelik H. Uz., Tokat M. Prof Dr., Ünalan T. Doç.Dr., Bilimsel Çalışma Grubu, Haziran 2003, Ankara, dokumanından alınmıştır.

testlerinden geçmiş, etkili ve emniyetli olduğu kanıtlanmış yeni bir bileşiktir" şeklinde açıklamaktadır (65/65 EEC, 87/21/EEC).

AB konuya ilişkin yasal düzenlemelerinde, veri korumasına konu yeni kimyasal terimi için "Yeni Etkin Madde (New Active Substance)" terimini kullanmış ve kapsamını aşağıdaki gibi belirlemiştir5.

"Yeni bir kimyasal, biyolojik veya radyofarmasötik etken madde;

- *AB'de daha önce tıbbi ürün olarak izin almamış bir kimyasal, biyolojik veya radyofarmasötik maddeyi içerir.*
- *AB'de daha önce tıbbi ürün olarak izin almış bir kimyasal maddenin izomeri, izomerler karışımı, kompleksi veya derivesi veya tuzunu içerir; ancak bu maddenin emniyet ve etkinlik özellikleri bir önce izin almış olan kimyasal maddeninkinden farklı olmalıdır.*
- *AB'de daha önce tıbbi ürün olarak izin almış olan bir biyolojik maddeyi içerir; ancak molekül yapısı, kaynak materyalin cinsi ve üretim prosesi farklı olmalıdır.*

AB'de daha önce tıbbi ürün olarak izin almamış radyonükloid veya ligand olan bir radyofarmasötik maddeyi içerir; veya molekül ve radyonükloidi bir arada tutan bağlanma mekanizması daha önce AB'de onay almamış olmalıdır."

4. PATENT VE VERİ KORUMASI

Patent ile veri koruması fikri haklar sistemi içerisinde yer alan, birbirine benzemeyen ancak çeşitli durumlarda birbirine karıştırılan iki ayrı hak türüdür. Bu hakların tek temel benzerliği, uygulamada hak sahibine bazı münhasır yetkiler vermesidir.

[5] "Notice to Applicants, Volume 2A Procedures for Marketing Authorisation, Chapter 1 Marketing Authorisation" , Final-Revision 1, European Commission, Enterprise Directorate-General, ENTR/F2/BL D(2002), Brussels, November 2002.

Yeni bir molekülün ya da ilaç bileşiminin bulunması, buluşla ilgili patent başvurusunun yapılmasına yol açmaktadır. Buluşların patent konusu olabilmeleri için üç temel kriter vardır: *yenilik, tekniğin bilinen durumunun aşılması ve sanayiye uygulanabilirlik*. Burada yenilikten kastedilen tüm dünyada yeniliktir, yani bulunan molekül o ana kadar dünyanın hiç bir yerinde açıklanmamış ve kamunun bilgisine sunulmamış olmalıdır. Tekniğin bilinen durumunun aşılması kriteri ise, bulunan yeni molekülün alanın uzmanları tarafından mevcut teknik yöntemlerin kullanılmasıyla açıkça ve kolayca bulunamaması anlamına gelmektedir. Son olarak ise, buluşun sanayii üretimine konu olması gerekmektedir; üretim imkanı bulunmayan bir buluşun patentlenebilmesi mümkün değildir. Dolayısıyla yeni bir molekülün patent konusu olabilmesi için tüm bu koşulları sağlaması ve patentlendirme sürecini tamamlaması gerekmektedir.

Veri korumasından yararlanacak ürünler ise sadece "yeni bir kimyasal madde" olmalıdır. Buradaki yenilik, patentlenebilirlik kriterlerindeki yenilik ile aynı değildir. Yukarıdaki bölümde de bahsedildiği gibi; bir ülkede ruhsatlandırma için daha önce başvuruda bulunulmamış, ilaç olarak geliştirilmesine yönelik gereken tüm testleri yapılmış, güvenli ve emniyetli olduğu deneylerle kanıtlanmış yeni bir molekül anlamına gelmektedir. Dolayısıyla bir başka ülkede piyasaya sunulmuş olsa bile, korumanın sağlandığı ülke sınırları içerisinde ruhsat başvuru yapılmamış bir ürün "yeni" olarak değerlendirilmektedir.

Patent ile veri koruması arasında "hakkın kapsamı" yönünden de fark vardır. Patent hakkı, buluşu yapana buluşla ilgili ürününü üretme, satma, satış için teklifte bulunma ve ithal etme için 20 yıllık bir tekel hakkı verir. Bir başkası patent sahibinin izni olmadan buluşla ilgili hiçbir tasarrufta bulunamaz. Veri koruması ise, veriyi üretenin ruhsat otoritelerine sunduğu test verilerini kullanarak bir başkasının ruhsat başvurusunda bulunmasını 5-10 yıllık bir süre ile engeller ve böylece hak sahibine pazarda tek başına bulunma hakkı verir; ancak, herhangi bir jenerik ilaç üreticisinin kendi test verilerini üreterek başka bir başvuruda bulunmasına da engel olmaz.

Patent ve veri koruması birbirine bağlı koruma biçimleri değildir, nitekim ilacı oluşturacak yeni bir molekül patent konusu olmasa dahi veri koruma konusu olabilmektedir. Ayrıca, patentten doğan hakkın kullanılması doğrudan hak sahibinin talebine bağlıdır, talep yapıldığı zaman hak tesis edilmektedir. Veri korumasında ise, bu hakkın tesisi ve korunması görevi tamamiyle devletin yükümlülüğündedir, hak sahibinin talebine bağlı olarak ortaya çıkan bir hak değildir. Devlet hukuken hakkın korunmasını düzenler, hak sahibi de bu düzenlemeden yararlanır.

Her iki hak türü arasında sahip olunan bilginin açıklanması yönünden de önemli bir fark bulunmaktadır. Patent başvuruları patent ile sonuçlandığı zaman, buluşa yönelik bilgi kamunun istifadesine sunulur. Böylece geliştirilmiş olan teknik bilgi, diğer bilimsel çalışmalara baz teşkil eder. Veri korumasında ise, ruhsatlandırma sürecinin sonunda ilaç piyasaya çıktığı zaman, bu ilacın geliştirilmesine yönelik bilgi saklı tutulur, ancak koruma süresi sonunda başkaları tarafından kullanılır hale gelir.

BÖLÜM II. AVRUPA BİRLİĞİ'NDE OLUŞTURULAN YENİ SİSTEM

Avrupa Birliği'nde (AB) ilaçlara yönelik ilk düzenleme 1960'ların başlarında yaşanan "thalidomide felaketi"ne bir tepki olan 65/65/EEC sayılı Direktif'tir. Bu direktifin amacı, kamu sağlığının yüksek düzeyde korunmasını sağlamak ve sürdürmek olarak belirlenmiştir. Bundan on yıl sonra getirilen iki direktif (75/318/EEC ve 75/319/EEC) ise bu sektörde bir dönüm noktası olmuş; üye ülkelerin ruhsatlandırmaya ilişkin yetkili makamlarının karşılıklı tanınmasını sağlamıştır. 1985 yılından itibaren ise, ilaçlarda Avrupa çapında tek pazarın oluşturulmasına yönelik bir dizi düzenleme kabul edilmiştir.

1992 yılında yine bir dizi mevzuat oluşturulmuş, ilaç ürünlerinde toptan dağıtım, sınıflandırma, etiketleme ve paketleme ile reklama ilişkin direktifler Konsey tarafından kabul edilmiştir. Bu dönemde ayrıca, ilaçların zararlı etkilerine ilişkin bilginin toplanması ve değerlendirilmesi için ulusal sistemlerin kurulmasını gerekli kılan farmakovijilans (ilacın yaşam süresi boyunca güvenliğinin izlenmesi) ilkesi de getirilmiştir.

İlaçların ruhsatlandırılması için yeni bir sistem yaratan düzenleme seti de (2309/906 sayılı Tüzük, 93/41/EEC sayılı Direktif) 1 Ocak 1995 tarihinde yürürlüğe girmiş; iki farklı ruhsatlandırma prosedürü getirmiştir. Bunlardan birisi Avrupa İlaç Değerlendirme Ajansı (European Medicines Evaluation Agency-EMEA) tarafından yürütülen "merkezi ruhsatlandırma prosedürü (centralised procedure)", diğeri ise başvuran tarafından seçilen ülkelerde karşılıklı olarak birbirini tanıyan yetkili makamlar aracılığıyla gerçekleştirilen "karşılıklı tanıma prosedürü (mutual recognition or decentralised procedure)"dür.

Bu düzenlemelerin ardından 2000 yılında yapılan çeşitli değerlendirmelerin sonucunda mevzuatın yeniden gözden geçirilmesine (Review 2001) karar verilmiş ve dört yıl kadar süren bir hazırlık, danışma ve yasama sürecinden sonra 2004 yılında AB'de ilaçlara yönelik yeni bir sistem getirilmiştir. Bu sistem, her yönüyle çeşitli değişiklikler getirirken,

ilaçlarda test verilerinin korunmasına yönelik olarak da tam anlamıyla "yeni" bir sistem yaratmıştır.

1. AB'DE İLAÇLARA YÖNELİK MEVZUATIN GÖZDEN GEÇİRİLMESİ SÜRECİ (REVIEW 2001)

Avrupa Birliği'nde ilaçlara yönelik mevzuatın yenilenmesi süreci ("Review 2001" adı verilir) 2001 yılının Temmuz ayında Komisyonca hazırlanan bir dizi yasa önerisi ile başlamış ve 2004 Mart ayında söz konusu düzenlemelerin yasalaşması ile sona ermiştir. Kamu sağlığının ileri düzeyde korunması ve iç pazarın tamamlanması, bu reform çalışmalarında ele alınan iki temel amaç olmuş ve düzenlemeler bu temel amaçlar çerçevesinde oluşturulmuş ve yönlendirilmiştir. Reform ya da gözden geçirme süreci, ruhsatlandırma prosedürleri, hastaların bilgilendirilmesi, test verilerinin korunması ve farmakovijilans gibi oldukça tartışmalı konuları ele almış ve AB'de bu alanda yeni bir sistem yaratmıştır.

Bu gözden geçirme sürecindeki çalışmalar, Komisyon tarafından aynı süre içinde oluşturulan ve "G10 Medicines"[6] adı verilen ve ulusal hükümetlerin yetkilileri, sanayiciler, hastalar ve sağlık sigorta kuruluşlarının (mutualities) üst düzey temsilcilerinden oluşturulmuş bir grup tarafından da desteklenmiştir. Grubun amacı, bir taraftan halk sağlığının yüksek düzeyde korunmasının temin edilmesi, diğer taraftan da sanayinin rekabet gücünün artırılması için Avrupa çapında bir girişim başlatmak olmuştur. Gözden geçirme süreciyle aynı amaçlara sahip olan bu grubun oluşturulmasındaki temel neden, endüstrinin karşılaştığı sorunların tek başına mevzuat ile çözülemeyeceğinin anlaşılması ve bunun ulusal eylemlerle de desteklenmesi ihtiyacıdır. Grubun hem ulusal düzeyde hem de Avrupa düzeyinde, yetkili tüm taraflar arasında bir köprü görevini üstlenmesi hedeflenmiştir.

[6] "A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient (G10 Medicines), Speech for Mr. Erkki Liikanen (Commissioner for Enterprise and Information Society), 25 February 2004, Alliance UniChem Seminar.

1.1. Reform İhtiyacının Nedenleri

Avrupa ilaç sanayi, Avrupa'nın en iyi performansa sahip yüksek teknoloji sektörlerinden biridir. Üretim, katma değer, yüksek nitelikli istihdam, Ar-Ge ve ticaret fazlası gibi standart göstergelerde oldukça başarılı olan bir sanayi dalıdır. AB ticaret dengesine önemli bir pozitif katkı sağlamakta, mevcut yüksek nitelikli işgücü ise Avrupa bilimsel tabanının sürekliliğini sağlayan önemli bir kaynak olarak görülmektedir[7]. Ayrıca, sanayinin ürettiği etkili ve güvenli ilaçlar ile hastalara sağladığı büyük faydanın da hepsinden daha önemli bir unsur olduğu ifade edilmektedir.

Avrupa kökenli ilaç sanayi 1990'lı yıllara kadar dünyada en güçlü sanayi dalı olmuş, ilaçlarda Ar-Ge ve yenilikte dünya lideri konuma gelmiştir. Ancak, sanayiinin bu öncü pozisyonu özellikle 1990'ların ikinci yarısından sonra gerilemeye başlamış ve 1997 yılında ABD ilaç sanayi ilk kez, Avrupalı rakiplerinin yerini almıştır. Günümüzde yeni kimyasallar ve biyolojik maddelerin keşfinde ABD önde gitmektedir. 1999-2003 döneminde geliştirilen 171 yeni kimyasal ve biyolojik maddenin 73 adedi ABD (% 43), 62 adedi Avrupa (% 36) kökenlidir[8]. Bu durum, 1990 yılından itibaren ABD'de ilaç araştırmalarına yapılan harcamanın, Avrupa'da yapılan harcamanın iki katına ulaşmasının bir sonucu olarak görülmektedir. 1990-2003 döneminde Ar-Ge yatırımları Avrupa'da 2,6 kat artarken ABD'de 4 kat artış göstermiştir.

Avrupa ilaç sanayiinde Ar-Ge alanında görülen bu gerileme, geliştirilen yeni ilaçların dünya pazarlarındaki payları açısından daha çarpıcı sonuçlar vermektedir. Bu alandaki gerileme daha fazla olmuş, ABD kökenli firmalar dünyada en çok satılan yeni ilaçlardaki paylarını önemli ölçüde artırmışlardır. 1998-2002 döneminde dünya piyasalarında satılan yeni ilaçların % 70'i ABD'de, % 18'i de Avrupa'da üretilmiştir.

[7] A.g.e., p:4.
[8] "The Pharmaceutical Industry in Figures 2004", EFPIA, Brussels.

2002 yılındaki Ar-Ge harcamaları açısından en büyük 40 firma arasında ABD ile başabaş giden Avrupa'nın (14 ABD, 14 Avrupa, 12 Japon firması) hem yeni kimyasalların keşfinde hem de dünya pazarlarındaki payının bu şekilde gerilemesindeki nedenlerin araştırılması ve sanayiinin rekabet gücünün yeniden artırılmasına yönelik yeni girişim gerekliliği böylece ortaya çıkmıştır.

1.2. Reform Süreci

Avrupa ilaç sanayinin ABD'li firmalar karşısında rekabet gücünü kaybetmesinin nedenleri araştırılırken mevcut sistem yeniden ele alınmıştır. Mevcut sistem, ilaç sanayiinde ortaya çıkan bu sorunları gidermeyi amaçlayan ve 1995 yılında yürürlüğe giren yeni ruhsatlandırma (merkezi ruhsatlandırma ve karşılıklı tanıma) ve izleme prosedürlerini[9] içermektedir. Bu sistemin ana düzenlemesi 2309/93 sayılı Tüzük'tür ve Tüzük kapsamında Komisyona bir görev yüklenmiştir. Buna göre Komisyon, uygulamanın başlamasından itibaren altı yıl içerisinde, sistemi izleyecek ve amaçlara ne kadar ulaşıldığını gösteren bir raporu hazırlayacaktır. Bunun yanısıra, bilimsel ilerlemenin son derece hızlı olması ve sürekli biçimde yeni tedavilerin geliştirilmesi de Komisyonca ortaya konmuş olan; ilaçların serbest dolaşımının sağlanması, kamu sağlığının yüksek seviyede korunması ve yeni jenerasyon ilaçların üretilmesi hedeflerinin halen geçerliliğini korumakta olduğunu göstermiştir[10]. Dolayısıyla zaten Tüzük'ten kaynaklanan yasal bir gereklilik olan sistemin gözden geçirilmesi, sorunların devam etmesi nedeniyle daha sistematik bir şekilde ele alınmıştır. Mevcut yasal düzenlemelerin AB ülkelerinde uyumlaştırılması ve geleceğin pazarlarında yer alacak ilaçların ruhsatlandırılması için daha basit bir yöntem geliştirilmesi gibi düşünceler daha sık ifade edilir olmuş ve Komisyonun başlattığı girişimi güçlendirmiştir.

Komisyon bu amaçlarla, ilk olarak bu alanda sektörün tüm yönleriyle analizini öngören bir çalışma başlatmıştır. Çalışmanın ilk sonucu 2000 yılında Cameron McKenna ve

[9] 93/39/EEC, 93/40/EEC, 93/41/EEC Direktifleri ve 2309/93 sayılı Tüzük.
[10] "Review of Pharmaceutical Legislation", Discussion Document (Final Version), European Commission, Enterprise Directorate-General, 22 January 2001, Brussels.

Andersen Danışmanlık Şirketi'nin raporunun[11] yayınlanması olmuştur. Rapordan da esinlenerek Komisyon, ilaçlara ilişkin yasal düzenlemelerin gözden geçirilmesinde 7 temel hedef belirlemiştir[12]:

1. Avrupa vatandaşlarına olabildiğince güvenli ve yeni ürünler aracılığıyla yüksek sağlık koruması garantisini vermek,
2. Farmakovijilans sürecinin güçlendirilmesiyle piyasanın daha sıkı izlenmesini sağlamak,
3. Veteriner ilaçlarında ilaç sayısının artırılmasıyla hayvan sağlığının daha iyi korunmasını sağlamak,
4. Küreselleşmenin de dikkate alınmasıyla ilaçlarda tek pazarın tamamlanmasını sağlamak,
5. Avrupa ilaç sanayiinin rekabet edebilirliğini teşvik edici yasal bir çerçeve oluşturmak,
6. AB genişlemesinin yaratacağı zorlukların üstesinden gelmek,
7. Sistemi modernleştirme ve mümkünse basitleştirme ("daha iyi düzenleme") fırsatını değerlendirmek; böylelikle sistemin tutarlılığını, profilini ve karar alma sürecinin şeffaflığını geliştirmek.

Belirlenen bu hedefler çerçevesinde Komisyon bir düzenleme seti tasarısı hazırlamış ve bu düzenleme seti 8 Temmuz 2001 tarihinde görüşülerek kabul edilmiştir[13]. Komisyonun teklifi 3 temel düzenlemeyi içermiştir: *ruhsatlandırmaya ve Avrupa İlaç Değerlendirme Ajansı'nın (European Medicines Evaluation Agency-EMEA) fonksiyonlarına ilişkin bir taslak tüzük, beşeri ilaçlar için bir taslak direktif ve veteriner ilaçları için bir taslak direktif.*

[11] "Evaluation of the Operation of Community Procedures for the Authorization of Medicinal Products", CMC Cameron McKenna and Andersen Consulting, carried out on behalf of the European Commission Directorate-General Enterprise Pharmaceuticals and Cosmetics, 17 November 2000.

[12] Bu hedefler Komisyon çalışmaları sonuçlanıncaya kadar değişmemiş ancak, ilk 3 hedefin tek bir başlıkta toplanması ve 4 ile 5 inci hedeflerin de birleştirilmesiyle sonraki Komisyon yayınlarında 4 temel hedefe indirgenmiştir.

[13] "Commission Proposes Comprehensive Reform of EU Pharmaceutical Legislation", IP/01/1027, European Commission, Brussels, 18 July 2001.

Mevcut sistemi uyumlaştıran, modernleştiren ve basitleştiren önemli bir girişim olan bu düzenlemeler, karar alma yöntemi ve sürecinde daha çok şeffaflığı getirirken, mevcut ruhsatlandırma prosedürlerinin temel ilkelerinde herhangi bir değişiklik yaratmamıştır.

Bu düzenlemelerin temel hedeflerinden biri, 1995 yılında merkezi ruhsatlandırma prosedürünün uygulanmasıyla ilaçların tüm üye ülkelerde aynı anda piyasaya sunulmaları amacıyla kurulmuş olan EMEA'nın sadece biyoteknoloji ürünü ilaçlarda değil, daha geniş bir yelpazede yer alan yeni ilaçlara uygulanabilmesi ve yeni uzmanlar ve çalışma gruplarının eklenmesiyle EMEA'nın bilim komitelerininin güçlendirilmesidir. Ayrıca, EMEA'nın ilaçları ilgilendiren tüm bilimsel konularda; uluslararası faaliyetlerdeki etkinliği artırılmış ve ruhsatlandırma için gerekli tüm deney ve testlere başlamadan önce şirketlere bilimsel öneriler sunma alanındaki rolü de güçlendirilmiştir.

Taslak düzenlemelerle, kaliteli, etkili ve güvenli yeni ilaçların Avrupa pazarına bir an önce girmeleri ve her an bulunabilir olmalarını artırmak hedeflenmiştir. Belirli tedavi gruplarındaki ilaçlar için "hızlı (fast-track)" ruhsatlandırma süreci getirilmiş; böylelikle bu ürünlerin ABD'de uygulanan ruhsat verme süreciyle eş anlı olarak Avrupa'da da hızlı bir şekilde incelenip ruhsatlandırılmaları öngörülmüştür. Bu süreç ile inceleme süresi iki ay kısaltılmış, böylelikle ABD'de de öncelikli inceleme sistemine göre 30 gün daha erken sonuç alınması öngörülmüştür[14]. Buna ek olarak, bir yıllık bir süre için "*şartlı ruhsatlandırılma (conditional marketing authurisation*)" yöntemi getirilmiştir. Bu yöntem, "*şefkatli (compassionate) kullanım*" durumunda önem kazanan bir uygulama olacaktır. "Şefkatli kullanım" hükmü de yeni bir uygulama biçimi olup, kronik ya da ciddi bir şekilde kuvvetten düşüren hastalığı olan ya da yaşamı tehdit edici hastalığı bulunan ve ruhsatlı bir ilaçla iyi bir şekilde tedavi edilemeyen hastalarda, geliştirilen yeni ilacın ruhsatlandırma öncesi kullanımına izin veren bir hükümdür. Böylelikle, hasta sağlığı için önemli yarar sağlayacağı düşünülen ilaçlarda, şirketin de ek klinik çalışmalar ve izleme yapmayı kabul etmesi halinde, şartlı ruhsat verilecek ve 1 yıl sonunda bu ruhsat gözden geçirilerek ya normal ruhsat

[14] "EU Surprises Itself by Agreeing to Pharma Rules" O'Donnell, P., Applied Clinical Trials, Feb 1, 2004.

başvurusuna konu olacak ya da klinik deneylerin sürdürülmesi mecbur tutulacaktır. Bu yöntemin hastaların sağlığına önemli derecede yarar sağlayacağı ve şirketlerin süre sonunda yeniden gözden geçirilecek olan ek bir izleme ve klinik çalışma yapmayı üstlenecekleri düşünülmüştür. Bunların yanısıra getirilen bu yeni tedbir ile, "şefkatli kullanım" için "ruhsatlandırma öncesinde" ilaçların Avrupa çapında bulunabilir olması da sağlanmaktadır. Liikanen'e[15] göre bu uygulama ile; belli bir şirket tarafından belli bir hasta grubunda sürdürülen klinik deneylerin, yer farkı gözetilmeksizin diğer hastaların da kullanımına açılması sağlanacaktır. Ayrıca bu uygulama, ruhsatlandırmanın incelenmesi esnasında tedavinin de sürdürülmesini gerektirdiğinden, klinik deneylerde hastaların daha güvenli ve başarılı bir şekilde tedavi edilmelerini sağlayacaktır.

Komisyon teklifi ayrıca, hem yenilikçi hem de jenerik ilaç sanayiin rekabet edebilirliğini geliştirecek mekanizmaları da ortaya koymuştur. İlaçların ruhsatlandırılmasında sunulan verinin korunmasını içeren ulusal idari koruma süreleri 10 yıl olarak uyumlaştırılmakta; böylece yenilikçi ilaç sanayiine, jenerik ürünlerin ruhsatlandırılmalarından önce kendi yatırımlarını telafi etmek için daha uzun zaman tanınmaktadır. Jenerik ilaç sanayi için ise, Avrupa'da uygulanacak jenerik ilaç ruhsatları için gereken testlerin fikri hak koruma süresi bitmeden önce başlatılabileceği hükmü getirilmektedir.

1.3. Mevcut Sistemin ve Komisyon Önerilerinin Değerlendirilmesi[16]

AB Komisyonu'nun 2001 yılında hazırladığı yasa teklifi yasama süreci dahilinde çeşitli aşamalardan geçerek 2 Haziran 2003 tarihinde Sağlık Bakanları Konseyi'nde görüşülmüştür. Burada bazı değişikliklere uğramış, son olarak da 18 Aralık 2003 tarihinde Avrupa Parlamentosu'nda görüşülerek nihai metne dönüşmüştür. Avrupa Parlamentosu'nun

[15] A.g.e.
[16] "Reform of EU Pharmaceutical Legislation", MEMO/01/267, European Commission, Brussels, 18 July 2001 ve "Reform of EU Pharmaceutical Legislation", MEMO/03/262, European Commission, Brussels, 18 December 2003 dokumanlarından yararlanılmıştır.

önerdiği değişiklikler Konsey tarafından da kabul edilmiş ve düzenleme seti 30 Nisan 2004 tarihinde Topluluk Resmi Gazetesi'nde yayımlanarak yürürlüğe girmiştir. Sistemde getirilen değişiklikler bu bölümde daha detaylı ele alınacaktır.

1.3.1. Merkezi Ruhsatlandırma Prosedürü

Avrupa Birliği'nde merkezi ruhsatlandırma prosedürü, yüksek teknoloji gerektiren yenilikçi ilaç ürünlerinde ve özellikle biyoteknolojik ürünlerde zorunlu olarak kullanılmaktadır. Bunun yanısıra, yeni geliştirilen ilaçların üye ülkelerin tümünde ruhsatlandırılması istendiğinde de kullanılan bir yöntemdir. Merkezi ruhsatlandırma prosedürü EMEA tarafından uygulanır. Yeni düzenleme ile bu sistem daha geniş bir ürün yelpazesine yayılmış, son dönemde piyasanın gereklerini ve özellikle belli hastalık alanlarında tek, yani tüm üye ülkelerde geçerli bir bilimsel değerlendirmeye duyulan ihtiyacı karşılamayı da amaçlamıştır. Bu sistemde getirilen değişikler aşağıda verilmektedir:

1. Komisyon, merkezi ruhsatlandırma prosedürünün zorunlu olarak uygulanacağı ilaç ürünlerinin bütün yeni aktif maddelere genişletilmesini, yani herhangi bir üye ülkede ilaç olarak onay almamış tüm maddelerin bu prosedüre dahil edilmesini teklif etmiştir. Ancak, görüşmeler sonunda bu hüküm daraltılmış ve sadece "herhangi bir ülkede onaylanmış bir ilacın parçası olmayan, AIDS, kanser, şeker ve sinir bozukluğu hastalıklarının tedavisinde etki gösteren tüm maddeler" olarak kapsam belirlenmiştir. Nadir hastalıklara tahsis edilen ilaçlar da zorunlu olarak merkezi ruhsatlandırma prosedürüne tabi tutulacaktır. Bu prosedür yeni mevzuatın yürürlüğe girmesinden 4 yıl sonra, antiviral ve bağışıklık sistemi hastalıklarının tedavisinde etkili iki yeni ilaç kategorisine genişletilecektir. Sistemde ayrıca bir "gözden geçirme hükmü" de öngörülmektedir.
2. Merkezi ruhsatlandırma prosedürü,
   - Başvuruyu yapan tarafından önemli bir yenilik getirdiği ortaya konan ya da hastalar ya da hayvanlar için bir Topluluk kararı olan herhangi bir ürüne,

- Topluluğun hastalıklardan koruyucu ilkelerine tabi imunolojik veteriner ilaçlarına,
- Merkezi ruhsat almış ilaçların jeneriklerine,

istenildiği zaman uygulanabilir olacaktır.

3. Ruhsatlandırma prosedürünün uygulama basamakları, hem insan hem de veteriner ilaçları için temelde aynı kalmıştır.
4. Ruhsatlandırma prosedürü, farklı aşamalardaki nihai tarihlerin bazılarının kısaltılması aracılığıyla hızlandırılmıştır.
5. Kamu sağlığı ve teropatik yenilik açısından büyük ölçüde yarar görülen ilaçlarda hızlandırılmış değerlendirme prosedürleri (fast-track procedures) öngörülmüştür.
6. Olağanüstü durumlarda şartlı ruhsat (conditional marketing authorisation) alma imkanı getirilmiştir.
7. İnsanlarda ilaçların "şefkatli kulanımı (compassionate use)" yönünden EMEA, bunun başvurulacağı ülkelerde uygulama koşullarını belirleyerek tavsiyelerde bulunabilecektir.
8. Ruhsatların geçerliliğine yönelik süre limitinin kaldırılması ve ruhsatlara sınırsız geçerlilik sağlanması Komisyonca önerilmiş; ancak bu hüküm daha sonra "ruhsatın verilmesinden sonraki ilk beş yıllık yenilemeden sonra, farmakovijilans nedenlerine bağlı küçük değişiklikler getirilmediği sürece ruhsatlar sınırsız geçerli olacaklardır" şeklinde düzeltilmiştir.
9. Ruhsat sahibi ürününü gerçek anlamda belirli bir süre piyasada bulunduracak, aksi halde olağanüstü durumlar ve kamu sağlığı nedenleri dışında ruhsatların geçerliliği sona erecektir. Ayrıca, ilacın üye ülke piyasalarında gerçekten var olduğu sürelerin ya da ürünün piyasada satılmasına son verilmesi halinde bu durumun EMEA'ya bildirilmesi zorunluluğu bulunmaktadır.
10. Farmakovijilansın da yer aldığı güvenlik raporları düzenli olarak hazırlanacak ve mevcut sistemde olduğundan daha sık bir şekilde gözden geçirilecektir.

1.3.2. EMEA-Avrupa İlaç Değerlendirme Ajansı

Komisyon, EMEA'nın bilimsel komitelerinin ve Yönetim Kurulunun oluşumu ve yapısının AB'nin geleceğe yönelik genişlemesi dikkate alınarak gözden geçirilmesini teklif etmiştir. Buna gerekçe olarak, EMEA'nın faaliyet alanının sadece ilaçlara ruhsat verme sürecindeki değerlendirme ile sınırlı kalmadığını, bilimsel danışmanlık rolünün giderek arttığını; EMEA'nın şirketlere özellikle küçük ve orta büyüklükteki işletmelere biyoteknolojik ya da yenilikçi ürünleri geliştirmeleri için bilimsel tavsiyeler vermeye yetkili kılındığını; dünyada bazı ülkelerde piyasaya sunulması istenen belli ilaçların değerlendirilmesi için Dünya Sağlık Örgütü (World Health Organisation-WHO) ile yakın işbirliğinin vazgeçilmez olduğunu göstermektedir.

Komisyon ayrıca, ruhsat sahiplerinin sahip oldukları ruhsatlarla bağlantılı belirli zorunlulukları gözlemlemeleri hususunda başarısız olmaları durumunda, ruhsat sahiplerine doğrudan mali müeyyideler yükleme imkanının verilerek EMEA'nın gözetici fonksiyonunun kuvvetlendirilmesi gerektiğini de savunmaktadır.

Bu kapsamda getirilen yeni sistem aşağıdaki gibidir:

1. EMEA'nın yapısı, zaten var olan "Nadir İlaçlar Komitesi (Committee Orphan Medicinal Products)" ve yeni bir yasa ile oluşturulacak olan "Bitkisel İlaçlar Komitesi (Committee of Herbal Medicinal Products)" gibi belirli Komitelerin eklenmesiyle tamamlanmıştır.
2. Komisyon ulusal otoritelerin temsilcilerinden oluşan ve ruhsatlandırma prosedürlerinde istişari görev yapacak bir Danışma Kurulu oluşturulmasını önermiş ancak bu hüküm kabul görmemiştir.
3. Farklı alanlarda uzmanlık grupları, çalışma grupları, bilimsel komitelerin oluşturulması ve bunlara farklı görevlendirme yapılabilmesi hususlarında daha

fazla esneklik getirilmiştir. Ayrıca, gerektiği zaman AB dışından uzmanlardan yararlanma imkanı da sağlanmıştır.

4. Yönetim Kurulu'nun yapısı, AB'nin gelecekteki genişlemesi ve sivil toplum kuruluşlarının temsil edilmesi gözönünde bulundurularak yeniden gözden geçirilmiştir.
5. EMEA, uluslararası uyum arayışlarının çerçevesinin belirlenmesinde daha aktif bir şekilde katkıda bulunacaktır.
6. EMEA, merkezi ruhsatlandırma prosedürü altında izin verilen paralel dağıtım durumuna uyan ruhsatlandırma işinde ve ilaçlarla ilgili Topluluk mevzuatında yer alan şartların yerine getirilmesini sağlamak ile görevlendirilmiştir.
7. EMEA'nın komiteleri oluşturmakla görevli bölümü, EMEA'nın Yöneticisine ve talep edildiği durumda Komisyona, ilaçları ilgilendiren bilimsel konularda görüş hazırlamak için yardımcı olacaktır.
8. EMEA'ya mali müeyyide uygulama yetkisi verilmiştir.

1.3.3. Karşılıklı Tanıma Prosedürü

Karşılıklı tanıma prosedürü AB bünyesinde az sayıda ülkede uygulanmakta ve Avrupa pazarının sadece sınırlı bir bölümü için düşünülen ilaçlarda, özellikle veteriner ilaçlarında, önemli bir kolaylık/esneklik sunmaktadır. Bu prosedür ile ilgili olarak yapılan en önemli eleştiri, sürenin çok uzun olduğu ve uygulamada üye ülkelerin bir diğer ülkede alınmış ruhsatı ve bilimsel değerlendirmeyi tanımadığı şeklindedir. Sistemin işlerlik kazanması için gayri resmi olarak çalışma grupları (MRFG: Mutual Recognition Facilitation Group, VMRFG: Veterinary Mutual Recognition Facilitation Group) oluşturulmuş ve büyük başarı sağlanmış olup, bu grupların yasal bir zemine oturtulmaları yönünde de eğilim bulunmaktadır.

Komisyon ayrıca, farmakovijilans önlemlerinin izlenmesi için yasal bir çerçeve geliştirilmesi gerektiğini düşünmüştür. Mevcut kurallara göre, acil durumlarda üye ülkeler

kendi bölgelerindeki bir ruhsatı, Topluluk düzeyinde gerekli izleme sonuçları tamamlanmadan yürürlükten kaldırabilmektedir.

Bunun yanısıra Komisyon, gen tedavisi ve hücre tedavisine yönelik tıbbi tedavilerin yeni ya da gelecekteki biçimlerini kapsayacak ve yenilikçi ilaçlar ile jenerik ilaçlar arasında optimal bir denge sağlayacak yeni bir düzenleyici çerçeveye ihtiyaç olduğunu da tespit etmiştir. Komisyon ayrıca, ulusal ruhsatlı ilaçlar için sağlanan veri koruma (data protection) süreleri ve patent koruması ile bağlantılı veri koruması uygulamalarının uyumlaştırılmasına dikkati çekmiştir.

Bu çerçevede gerçekleştirilen değişiklikler şu şekildedir:

1. Ulusal ruhsatlandırma prosedüründeki sürenin 210 günden 150 güne indirilmesi önerilmiş, ancak bu hüküm kabul görmemiştir.
2. Karşılıklı tanıma prosedürü;
   - bir üye ülkede önceden ruhsat almış bir ilaç olup olmadığına bağlı olarak farklı uygulama şekillerinin getirilmesiyle,
   - kamu sağlığı riski kavramının daha kesin bir şekilde tanımlanmasıyla,
   - mevcut MRFG ve VMRFG'ya yasal ve resmi bir statü verilmesiyle,
   - kamu sağlığı için ciddi risk konusundaki itirazların düzgün bir şekilde değerlendirilmesi ve gerekli izleme tedbirlerinin alınmasını sağlamak ve ayrıca değerlendirme prosedüründeki süreleri kısaltmak amacıyla arabuluculuk evresinin iyileştirilmesi,

   gibi önlemlerle kolaylaştırılmaktadır.
3. Bir üye ülkede alınan acil bir önlem Avrupa düzeyinde değerlendirilecek ve gerekiyorsa bütün üyelerde de uygun tedbirler alınacaktır.
4. İlaçlarda başlatıcı maddeler olan aktif maddelerin üretimine ve kullanımına ilişkin rehber ilkelerin belirlenmesi için Komisyon yetkilendirilmiştir.
5. İlaç ürünlerinin tanımı, yeni tedavileri de içerecek şekilde değiştirilmiştir.

6. Veri koruma süresi, merkezi ruhsatlandırma prosedüründeki süre ile uyumlaştırılmıştır. Normal bir veri koruma süresine sahip olan ilaçla ilgili olarak, hastalara önemli bir yarar sağlayacak yeni bir tedavi endikasyonu geliştirilirse bir yıllık bir ek koruma süresine daha izin verilecektir.
7. Jenerik ilaç terimi ve biyo-benzer ilaç terimi getirilmiş ve mevzuatta tanımlanmıştır.
8. Referans ilaca verilen ek koruma sertifikasının geçerliliği esnasında jenerik bir müracaatın hazırlanması ve yapılabilmesi imkanı getirilmiştir.
9. Belirli homeopatik ilaçlar için basitleştirilmiş tescil prosedürünün oluşturulması seçeneğinin bir zorunluluk haline getirilmesi önerilmiş ancak kabul görmemiştir.
10. Veteriner ilaçlarında veri koruması süresine yönelik özel tedbirler getirilmiş, 10 yıllık veri koruma süresi, firmanın alacağı ruhsatın kaç hayvan türü için olduğuna bağlı olarak genişletilmiştir.

Böylelikle Temmuz 2001'de başlayan uzun bir gözden geçirme sürecinden sonra, Avrupa Komisyonu, Avrupa Parlamentosu ve Avrupa Konseyi, Aralık 2003 tarihinde Parlamento tarafından kabul edilen ve Mart 2004 tarihinde de Konsey tarafından resmi olarak uzlaşılan ortak tutum üzerinde fikir birliğine varmıştır. Düzenlemelerin 10 yeni üye ülkenin AB'ne katılım tarihi olan 1 Mayıs 2004 tarihinden önce yasalaşması AB yönetimi için bir tür zorunluluk olarak görülmüş ve çalışmalar bu takvime göre sonuçlandırılmıştır. Ek.1'de yer alan tabloda AB'nde yasama sürecinin aşamaları özetlenmektedir. Bu yasama sürecinde Ortak Karar usulü (Co-decision procedure) uygulanmıştır.

2. VERİ KORUMASI DÜZENLEMELERİ

AB Komisyonu tarafından başlatılan 2001 gözden geçirmesine temel teşkil eden Cameron McKenna&Andersen Danışmanlık Şirketi'nin raporunda, ilaçlarda test verilerinin korunmasına ilişkin koruma sürelerinin ve Birlik içerisinde farklılık arzeden ruhsatlandırma sistemlerinin üye ülkelerde uyumlaştırılması hususunda genel bir fikir birliği olduğu ve

65/65/EEC sayılı Direktifin 4/8(a)(iii)[17] maddesinin mevcut halinden daha açık bir tanıma ihtiyaç bulunduğuna ilişkin genel bir bakış açısı bulunduğu ifade edilmektedir[18].

Benzer şekilde "G10 Medicines[19]" grubunun çalışmalarında, fikri haklar ve veri korumasının sanayinin rekabet gücünün artırılmasında ve yenilikçi ürünler ortaya çıkarılmasında önemli rolü bulunduğu, mevcut ürünlerin yeni tedaviler için geliştirilmesine imkan tanınması ve jenerik ilaçların mevcudiyetinin sağlanması için uygun bir koruma düzeyinin olması gerektiği tespiti yapılmıştır. Bu çalışmaların sonucunda ortaya çıkan 26 Şubat 2002[20] tarihli raporda da öneriler arasında; yenilikçi ilaçlar için yeterli fikri hak korumasının sağlanması ile jenerik ürünlerin piyasaya girişini kolaylaştıran Bolar ilkesinin getirilmesi arasında uygun bir denge oluşturulmasına yönelik bir yöntem geliştirilmesi yer almaktadır.

Avrupa Birliği'nde veri koruması ilk olarak 65/65/EEC sayılı Direktifin 4/8(a)(iii) maddesi ile düzenlenmiş ve daha sonra 1987 yılında 87/21/EEC sayılı Direktif ile değiştirilmiştir. Değişiklik ile amaçlanan, insanlar ve hayvanlar üzerinde yapılan testlerin gereksiz yere tekrarının önüne geçmek ve yenilikçi ilaç endüstrisini de koruyucu önlem getirmek olmuştur[21]. Bu nedenle jenerik ilaç üreticileri için, yeniden kendi çalışmalarını yapmak/tekrar etmek yerine yenilikçi firma tarafından yapılan önceki çalışmalara (yenilikçinin başvuru dosyasında yer alan) atıf yapılması imkanı getirilmiştir. Bu kısaltılmış prosedürü kullanmak için aşağıdaki şartlar gerekmektedir:

[17] Bu madde 2001 yılında yapılan düzenleme ile 2001/83/EC Direktif'te Madde 10/1/(a)(iii) olmuştur.
[18] "Evaluation of the Operation of Community Procedures for the Authorization of Medicinal Products", CMC Cameron McKenna and Andersen Consulting, carried out on behalf of the European Commission Directorate-General Enterprise Pharmaceuticals and Cosmetics, 17 November 2000, p: 41-42.
[19] "G10 Medicines, High Level Group on Innovation and Provision of Medicines", Consultation Paper, European Commission, Enterprise Directorate-General, Brussels, 27 September 2001, p: 14.
[20] "G10 Medicines, High Level Group on Innovation and Provision of Medicines", Report, European Commission, Enterprise Directorate-General, Brussels, 26 February 2002, p: 8.
[21] "Data Exclusivity and the 2001 Review", EGA Discussion Paper, July 2001.

- ✓ 6 ya da 10 yıllık veri koruma süresinin sona ermesi,
- ✓ İkinci -jenerik- başvuruyu yapanın ürününün yenilikçi firmanın ürününe "önemli ölçüde benzer (essentially similar)" olması,
- ✓ Yenilikçi firmanın ürününün başvurunun yapıldığı ülkede "pazarda" olması.

Bu süreçte veri koruması açısından üzerinde durulması gereken en önemli husus, 6 ya da 10 yıllık veri koruma süresinin sonunda firmanın dosyasında bulunan bilginin kamuya açıklanır hale gelmemesi, sadece jenerik müracaatçının dosyasını değerlendirirken yetkili makamlara bu bilgiyi kullanma izninin verilmiş olmasıdır.

Kamu sağlığının korunması, hastaların yeni ilaçlara anında ulaşabilmesi ve yeni tedavi yöntemlerinin geliştirilmesinin, aynı zamanda etkin bir jenerik ürün piyasasanın gelişimiyle paralel bir şekilde sağlanabileceğinin farkında olan AB yetkilileri, 2001 gözden geçirmesinde özellikle bu alanda özel bir hassasiyet göstermişler ve yenilikçi ürünlerin özendirilmesine yönelik tedbirler getirirken jenerik sanayiinin ihtiyaçlarını da gözönünde bulundurmuşlardır.

Avrupa Birliği'nde ilaçlara yönelik yeni mevzuat 31 Mart 2004 tarihinde kabul edilmiş ve 30 Nisan 2004 tarihinde Topluluk Resmi Gazetesi'nde yayımlanmıştır. Söz konusu mevzuat ile "veri koruması"na ilişkin bir takım düzenlemeler getirilmiştir. Bir Tüzük (Regulasyon) ve 3 tane Direktifi[22] içeren düzenleme seti ile oluşturulan yeni mevzuatta konuyla bağlantılı hükümler aşağıda verilmektedir.

[22] *Regulation (EC) No **726/2004** of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
*Directive **2004/27/EC** of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.
*Directive **2004/28/EC** of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products.
*Directive **2004/24/EC** of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

2.1. Veri Korumasında Temel İlkeler [23]

1. *8+2+1 (8 yıl veri koruma+ 2 yıl pazar koruması+ 1 yıl yeni tedavi yöntemleri) bütün prosedürler için:*

➢ **726/2004** sayılı Tüzük;

***"Madde 14(11)**: Sınai ve ticari mülkiyet haklarının korunmasını sağlayan mevzuat hükümlerine bir zarara vermemek kaydıyla, bu Tüzük hükümlerine göre ruhsatlandırılmış bir ilaç ürünü için 8 yıllık veri koruması ve 10 yıllık pazar koruması sağlanacak; bu 10 yıllık sürenin ilk 8 yılı içerisinde ruhsat sahibi tarafından, ilacın mevcut tedavi yöntemleri dışında önemli bir klinik fayda sağlayacak yeni bir ya da birden çok tedavi biçimi için (new therapeutic indications) ruhsat alınması durumunda ki bu durum ruhsat verilmeden önceki bilimsel değerlendirme aşamasında ortaya çıkarsa, pazar koruma süresi 11 yıla uzatılabilecektir."*

Bu madde ile AB'de yenilikçi ilaç endüstrisinin ruhsatlandırma sürecinin gereği olarak sundukları test verileri koruması 6 yıldan 10 yıla çıkarılmıştır. Ayrıca, bu 10 yıllık sürenin ilk 8 yılı içerisinde aynı ilacın başka bir tedavi yöntemi için de kullanılabilirliği anlaşıldığında bu 10 yıllık süre ek 1 yıl ile 11 yıla uzatılmaktadır. Burada, yeni ilaçların 10 yıl süre ile piyasada jenerik rekabetinden korunmaları sağlanmakta ancak, bu sürenin ilk 8 yılında pazar korumasına eş anlı veri koruması getirilmektedir. Son 2 yıl içerisinde jenerik firmaların başvuru yapabilmelerine imkan sağlamak için (bkz. Direktif Madde 10(1)) bu verilerin kullanılma imkanı getirilmiştir.

[23] "Main Outcomes of the Pharma Review-after the Compromise between the Council and the European Parliament", The European Generic Medicines Association, December 2003 dokumanından yararlanılmıştır.

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(1): *Madde 8(3)(i)'de yapılan değişiklikle ve sınai ve ticari mülkiyet haklarının korunmasını sağlayan mevzuat hükümlerine bir zarar vermemek kaydıyla, Madde 6 hükümlerine göre bir üye ülkede ya da Toplulukta 8 yıldan daha az olmamak üzere ruhsatlı bir referans ilacın jeneriği olan ilaç başvurularında klinik öncesi ve klinik test sonuçlarının verilmesi istenmeyecektir."*

Bu hüküm ile AB ilaç sanayiinde jenerik üreticiler lehine bir uygulama başlatılmaktadır. Orijinal ilacın 10 yıllık veri koruma süresinin bitmesinden 2 yıl önce jenerik ürün ruhsat başvurusu yapılabilmesine imkan tanınmıştır. Bu nedenle, 10 yıllık koruma süresinin ilk 8 yılı için "veri koruması", son 2 yılı için ise "pazar koruması" terimleri kullanılmaktadır. Böylelikle, Tüzük Madde 14(11) ile birlikte değerlendirildiğinde AB ilaç pazarında orijinal-jenerik dengesinin gözetilmesine çalışıldığı ortaya çıkmaktadır.

2. *+2 yıllık Pazar koruması esnasında üretim kısıtlamasının olmaması:*

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(1): *Bu hükme göre ruhsatlandırılmış bir jenerik ilaç ürünü, referans ilaç için mevcut ruhsatın başlangıcından 10 yıl geçmeden piyasaya sunulamayacaktır."*

Yukarıdaki hüküm ile birlikte düşünüldüğünde, bu düzenleme hem yenilikçi firmaların piyasa hakimiyetini korumakta, hem de orijinal ilacın veri koruma süresi bitmeden jenerik ilacın üretiminin yapılabilmesine ve süre biter bitmez anında piyasaya çıkarılmasına fırsat yaratmaktadır.

3. *Yeni endikasyonlar için sadece bir kez +1 yıllık veri koruması:*

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(1): *Bu paragrafta geçen 10 yıllık veri koruma süresi; bu 10 yılın ilk 8 yılı içerisinde ruhsat sahibi tarafından, ilacın mevcut tedavi yöntemleri dışında önemli bir klinik fayda sağlayacak yeni bir ya da birden çok tedavi biçimi için (new therapeutic indications)ruhsat alınması durumunda ki bu durum ruhsat verilmeden önceki bilimsel değerlendirme aşamasında ortaya çıkarsa, maksimum 11 yıla uzatılacaktır."*

Tüzük Madde 14(11)'de de yer alan bu hüküm ile AB ilaç sanayiinde yenilikçi firmalar lehine önemli bir avantaj sağlanmıştır. ABD yasalarıyla karşılaştırıldığında, yeni endikasyonlara sağlanan ek 1 yıllık korumanın orijinal ürünün koruma süresine eklenmesi önemli bir farklılık olarak ortaya çıkmaktadır. ABD'de yenilikçi firma veri korumasını orijinal üründen bağımsız olarak sadece yeni endikasyon için alabilmektedir[24]. Böylelikle, AB ilaç sanayiinin ABD ilaç sanayii karşısında avantajlı duruma getirilmesi amaçlanmıştır.

4. *Geleceğe yönelik uygulama:*

- **726/2004** sayılı Tüzük;
  "Madde 89: *Madde 90(2)'de bahsi geçen tarihlerden (veri koruma süreleri için 20 Kasım 2005 ve bağışıklık sistemi hastalıkları ile viral enfeksiyonlar için 20 Mayıs 2008) önce ruhsat başvurusu yapılan referans ilaç ürünlerine, Madde 14(11)(beşeri ilaçlar için veri koruma) ve 39(10)(veteriner ilaçları için veri koruma) da öngörülen koruma süreleri uygulanmayacaktır."*

Tüzük, yayım tarihinden 20 gün sonra yani 20 Mayıs 2004 tarihinde yürürlüğe girmiştir. Direktifler de aynı tarihte yayımlanmış ancak, üye ülkelerdeki

[24] "European revisions offer new freedoms for generics", Generics Bulletin, 16 January 2004, p:20.

uyumlaştırmanın bitiminden sonra (30 Ekim 2005) yürürlüğe gireceklerdir. Bu madde ile bu düzenlemelerin tamamlanması sürecinde bir derogasyon tanınmakta, piyasada mevcut ürünlerin etkilenmemesi sağlanmaktadır. 20 Kasım 2005 tarihinden itibaren biyoteknolojik ürünler ile AIDS, kanser, şeker, sinir bozukluğu hastalıkları için olan yeni kimyasallar; 20 Mayıs 2008 tarihinden itibaren ise viral enfeksiyonlar ile bağışıklık sistemi hastalıkları için olan yeni kimyasallar merkezi ruhsatlandırma prosedürüne tabi olacaklardır.

2.2. Global Ruhsat ("line extention"[25] için veri korumasının olmaması)

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 6(1)*: Bir ilaç ürünü ilk kez ruhsatlandırıldıktan sonra; aynı ilacın değişik varyasyonları veya formlarında da olduğu gibi, ilacın bünyesindeki maddenin daha sonraki değişik kombinasyonları (any additional strengths[26]), farmasötik formları (pharmaceutical forms[27]), ilacın veriliş yolları (administration routes[28]), sunum biçimleri de (presantations) ayrıca ruhsat alabilir ya da bu ilk ruhsat bünyesine dahil edilir. Tüm bu ruhsatların Madde 10(1)'in uygulaması anlamında aynı global ruhsata ait olduğu kabul edilir."*

Bu hükmün, genel olarak "line extension" adı verilen ve orijinal bir ilacın başka bir hastalığın tedavisindeki kullanımı, kullanım yolunun değiştirilmesi, kullanım dozunun değişimi, bünyesindeki etken madde miktarının değişimi, farmasötik formunun değişimi gibi

[25] "line extension"; orijinal bir ilacın, başka bir hastalık tedavisi için kullanımı, insanlardaki kullanım yolunda değişim (ağızdan, enjeksiyon şeklinde vb.), dozundaki değişim (4 saatte 1, 12 saatte 1 gibi günlük kullanım dozları,), etkinliğinde (birim hacimde ya da ağırlıktaki etken madde oranının değişimi), ya da farmasotik formundaki değişim (tablet, kapsül, serum, vb.) sonucunda ortaya çıkan yeni ilaç ürünü anlamına gelir.
[26] "any additional strength"; ilacın bünyesindeki maddenin konsantrasyonunu (örneğin, ağırlık/ağırlık, ağırlık/hacim ya da birim doz/hacim) ve/veya etkisini yani, ilacın uygun laboratuvar testleriyle ya da kontrollü klinik deneylerle kanıtlanan tedaviye yönelik etkinliğini ifade eder.
[27] "pharmaceutical forms"; ilacın tablet, kapsül, şurup, enjeksiyon, serum, krem, vb. biçimlerini ifade eder.
[28] "administration routes"; ilacın ağızdan, enjeksiyonla, yüzeye tatbik edilerek, vb. kullanım yollarını ifade eder.

yeni kullanım biçimleriyle veri koruması talep eden ve böylelikle jenerik rekabeti ile mücadele etmeye çalışan orijinator firmaları durduracağı yorumu yapılmaktadır[29].

2.3. Bilinen/Tanınmış (well-established) İlaçların Yeni Endikasyonlarına Veri Koruması

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(5): *Madde 10(1)'de yer alan hükümlere ek olarak, iyi bilinen bir maddenin yeni bir tedavi biçimi için yapılan bir müracaat olduğu durumda, bu yeni endikasyona ait klinik ve klinik öncesi testlerin yapılmış olması halinde, sadece 1 yıllık bir veri (toplama ait olmayan) koruması sağlanacaktır."*

Bu madde ile mevcut veri koruma süresi uzatılmamakta, bütün ürüne değil sadece yeni endikasyona uygulanmakta ve bunun için ayrı bir yıllık bir koruma getirilmektedir. Bilinen bir ilaç hammaddesinin yapılan araştırmalar sonucu bir başka hastalığın tedavisinde kullanılabilirliğinin ortaya çıkması durumunda uygulanacak olup, bu tür çalışmaların teşvik edilmesini amaçlamaktadır. Bu koruma tüm firmalar tarafından kullanılabilecek bir koruma biçimidir. Sadece ilk ruhsatlı ürüne değil, jenerikler de dahil olmak üzere bilinen herhangi bir ilaca uygulanabilecektir[30].

2.4. Reçetesiz İlaç (OTC) Sınıfına Değiştirme Durumunda Veri Koruması

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 74a: *Klinik ve klinik öncesi testleri temel alınarak ruhsatlandırılmış bir ilacın kategorisinin değişimi durumunda; yetkili makamlar, ilk değişikliğin onaylanmasından sonra 1 yıl süresince aynı maddenin sınıfının*

[29] "European revisions offer new freedoms for generics", Generics Bulletin, 16 January 2004, p:20.
[30] A.g.e., p:21.

değiştirilmesi için ruhsat sahibinin ya da bir başkasının başvurusunu incelerken bu testlerin ya da deneylerin sonuçlarını referans olarak kullanamayacaklardır ."

Yeni sistem ile, reçetesiz ilaçlar iki durumda ruhsat alabilecektir[31]; birincisi "Topluluk düzeyinde hastaların tedavisi" için reçetesiz ilaç ruhsatının alınması, ikincisi, merkezi ruhsat almış bir ilacın ruhsatının reçetesiz ilaç sınıfına değiştirilmesi durumunda olacaktır. Bu durumda, ilacın kategorisinin reçetesiz ilaç kategorisine alınması amacıyla sunulan gerekli klinik öncesi test ve klinik deney sonuçları için de 1 yıllık bir veri koruması öngörülmektedir.

2.5. Bolar İlkesi Uygulaması

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(6): *Bu maddenin veri korumasına ilişkin 1, 2, 3, ve 4 nolu paragraflarının uygulanması ve sonrasındaki pratik talepler nedeniyle ihtiyaç duyulan çalışmaların ve denemelerin yapılması, ilaçlarda patent hakkının ya da ek koruma belgesinin ihlali anlamına gelmeyecektir."*

AB'de daha önce mevcut olmayan ve "Bolar ilkesi" adı verilen bu yeni düzenleme ile jenerik ilaç üretiminde önemli bir yenilik getirilmiştir. Bolar ilkesinin bulunmaması nedeniyle, AB'de patent konusu ilaçların jeneriklerinin üretimi ve satışa sunulabilir hale gelmesi, ancak patent süresi sonunda mümkün olabilmekte, bu ise en az 2 yıllık bir süreyi gerektirmektedir. AB'de jenerik ilaç için yapılamayan bu tür geliştirme çalışmaları ve ilaçların ilk üretimleri, Bolar ilkesinin mevcut olduğu AB dışı ülkelerde yapılmakta ve patent süresi sonunda da hemen AB'ne ithal edilmektedir. Avrupa Jenerik İlaçlar Birliği (European Generic Medicines Association-EGA) tarafından, AB jenerik ilaç sanayiinin dünya jenerik sanayiiyle rekabet avantajını bu yüzden kaybettiği ve AB'nin yıllık 1 milyar EURO civarında

[31] "The Right Treatment?", Britton I., Gavey M., Linklaters 2004.

ekonomik kaybı olduğu ifade edilmektedir[32]. Getirilen bu yeni düzenleme ile AB'nde jenerik ilaç ruhsatlandırmasında ortaya çıkan bu tür kayıpların giderilmesi amaçlanmaktadır.

2.6. Referans İlaç Tanımı

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(2)(a): *Referans ilaç, Madde 8'de yer alan hükümlere bağlı olarak Madde 6 hükümlerine göre ruhsatlandırılmış ilaçtır."*

Yeni düzenleme ile "referans ilaç" tanımı yapılmıştır. Direktifte Madde 8'de ruhsat başvurusunun yapılma biçimi ile içereceği bilgi ve dokumanlar sıralanmakta; madde 6'da ise ruhsatın kapsamı belirlenmektedir.

2.7. Jenerik İlaç Tanımı

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)
  "Madde 10(2)(b): *Jenerik ilaç, referans ilaç ile aynı farmasötik formda ve aktif maddeleri nitelik ve nicelik olarak aynı bileşimde olan ve referans ilaç ile biyoeşdeğerliliği uygun biyoeşdeğerlik çalışmalarıyla ispatlanmış ilaçtır. Aktif maddenin farklı tuzları, esterleri, eterleri, izomerleri, izomerlerinin karışımı, kompleksleri ve türevleri; güvenlik ve/veya etkililik açısından özellikleri önemli ölçüde farklılık göstermediği sürece aynı aktif madde olarak kabul edilecektir. Eğer bu özelliklerde farklılık varsa o zaman, ruhsatlı aktif maddenin muhtelif tuzları, esterleri veya türevlerinin güvenlik ve/veya etkililiğinin ispatını gösteren ek bilginin başvuran tarafından sunulması zorunlu olacaktır. Oral farmasötik formdaki ilaçların vücutta farklı salıverilme biçimleri, tek ve aynı farmasötik form olarak kabul edilecektir.*

[32] EurActive.com Portal-Links Dossier- Generic Medicines, 26 March 2004, http://www.euractive.com

Başvuruyu yapan, jenerik ilaç ürününün ayrıntılı rehber ilkelerde tanımlanan ilgili kriterlere sahip olduğunu gösterebiliyorsa o zaman biyoeşdeğerlilik çalışmaları istenmeyecektir."

Görüldüğü gibi, "jenerik ilaç" tanımı oldukça detaylı ve kapsamlı bir şekilde yapılarak Direktife yerleştirilmiş ve uygulamalar yasal bir netliğe kavuşturulmuştur.

2.8. Biyo-benzerlik İçin Kısaltılmış Prosedürün Uygulanması

- **2004/27/EC**

  "Giriş 14: *Referans ilaca benzer olan biyolojik ilaç ürünü, daha çok üretim prosesi özellikleri, kullanılan hammaddeler, moleküler özellikler ve etki gösterdiği tedavi biçimi açısından jenerik ilaç olarak kabul edilebilecek bütün şartları genelde karşılamaz. Biyolojik ilaç ürünü jenerik ilaç olarak kabul edilebilecek bütün şartları karşılamadığı zaman, bu durumda güvenliği (klinik öncesi testler) ya da etkililiği (klinik testler) ya da her ikisini ilgilendiren gerekli testlerin sonuçları verilecektir."*

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)

  "Madde 10(4): *Referans biyolojik ürüne benzer olan biyolojik ilaç; özellikle, biyolojik ilacın ve referans biyolojik ilacın hammaddeleri ya da üretim proseslerindeki farklılıklar nedeniyle jenerik ilaç tanımındaki şartları karşılamıyorsa, bu şartların gerektirdiği klinik öncesi testler ya da klinik deneylerin sonuçları verilmek zorundadır. Bu ek verinin niceliği ve çeşidi, EK 1'de ve ayrıntılı rehber ilkelerde yer alan kriterlere uygun olmak zorundadır. Referans ilaç ürününün dosyasındaki diğer test ve deney sonuçlarının verilmesine gerek yoktur."*

2.9. Avrupa Referans İlaç Ürünü

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)

  "Madde 10(1): *(Bu maddenin 3. paragrafı)*

  Referans ilaç ürünü, jenerik ilaç başvurusunun yapıldığı üye ülkede ruhsatlanmamışsa da bu maddenin 1. paragrafı uygulanır. Bu durumda, başvuru sahibi, başvuru formunda referans ilaç ürününün ruhsatlı olduğu ülkenin adını belirtir. Başvurunun yapıldığı ülkenin yetkili makamının talebi üzerine, diğer ülkenin yetkili makamı bir aylık bir süre içinde, referans ilaç ürününün tüm kompozisyonuyla ve gerekiyorsa diğer ilgili dökumanlarıyla birlikte ruhsatlı olup olmadığının teyitini iletir."

Bu düzenleme jenerik ilaçlara yönelik bir hükümdür. Eğer orijinal ilacın sahibi bir ülkede, ticari nedenlerle kendi ilacını piyasaya sürmemişse ya da piyasadan çekmişse, bu ilacın jenerikleri "Avrupa Referans İlacı" ve buna bağlı tek bir "Avrupa Ruhsatı" uygulamasının sonucu olarak o ülkede satışa sunulabilecektir[33].

2.10. Ürün Özelliklerinin Özeti (SmPC) ve Patentin Kullanımı

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)

  "Madde 30(2): *Toplulukta ruhsatlı ilaç ürünlerinin ruhsatlandırılmasının uyumlaştırılması için, üye ülkeler, her yıl, koordinasyon grubuna, ürün özelliklerinin uyumlaştırılmış özetinin yer aldığı ilaç listelerini göndereceklerdir."*

[33] "MEPs Recommended to Accept EU Pharmaceutical Compromise", EGA Press Release, 16 December 2003, http://www.egagenerics.com/pr-2003-12-16.htm

- **726/2004** sayılı Tüzük;

  "Madde 3(3)(b): *Ürün karakteristiklerinin özeti, jenerik ilaç piyasaya sunulduğu anda hala patent hukukuyla korunan endikasyon ve dozaj formlarına atıf yapan ürün karakteristiklerinin özet bölümleri hariç olmak üzere, Toplulukça ruhsatlandırılmış bir ilaçla her yönden tutarlılık arzeder."*

Bu düzenleme ile, tüm ülkelerde ilaçların özelliklerinin yer aldığı ürün bilgisinin uyumlaştırılması amaçlanmaktadır. Bu madde kapsamında, jenerik ilaç üreticilerinin patentli tedavi biçimleri ve dozaj formları ile ilgili bilgiyi, patent yasalarının ihlaline meydan vermemek amacıyla, ürün özelliklerinin kapsamından çıkarmaları imkanı sunulmaktadır[34].

2.11. Merkezi Ruhsatlandırma Prosedürünce Onaylanmış Referans İlaçların Jeneriklerinin Ruhsatlandırılması

- **726/2004** sayılı Tüzük;

  "Madde 3(3): *Toplulukta ruhsat almış bir referans ilacın jeneriğine, üye ülkelerin yetkili makamlarınca 2001/83/EC ve 2001/82/EC sayılı Direktifler kapsamında aşağıdaki şartlar altında ruhsat verilebilir:*

  (a) ruhsatlandırma başvurusu, 2001/83/EC sayılı Direktifin 10. maddesi ve 2001/82/EC sayılı Direktifin 13. maddesi gereğince yapılır;

  (b) ürün karakteristiklerinin özeti, jenerik ilaç piyasaya sunulduğu anda hala patent hukukuyla korunan endikasyon ve dozaj formlarına atıf yapan ürün karakteristiklerinin özet bölümleri hariç olmak üzere, Toplulukça ruhsatlandırılmış bir ilaçla her yönden tutarlılık arzeder; ve

  (c) *jenerik ilaç ürünü başvurunun yapıldığı bütün üye ülkelerde aynı isim altında ruhsatlandırılır. Bu amaçla, INN'in (international non-proprietary name) tüm dillerdeki karşılığının aynı isim olduğu kabul edilir."*

[34] A.g.e.

2.12. Merkezi Ruhsatlandırma Prosedürünün Zorunluluk Kapsamı

- **726/2004** sayılı Tüzük;

  "Ek:*-biyoteknolojik ürünler;*

  -AIDS, kanser, şeker, sinir bozukluğu hastalıkları, bağışıklık sistemi hastalıkları ve bozuklukları, viral hastalıklar için olan yeni kimyasallar;

  -nadir (orphan) bulunan ilaçlar."

Merkezi ruhsatlandırma prosedürü bütün "yeni kimyasal madde"ler için zorunlu değildir. Sadece yukarıda belirtilen gruplardaki ilaçlara uygulanacaktır. Bu gruplardan bağışıklık sistemi ve viral enfeksiyonlar için geliştirilen ilaçlar bu kapsama 20 Mayıs 2008 tarihinden itibaren dahil olacaktır.

2.13. Ruhsatların Sona Erme Durumu

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)

  "Madde 24(4): *Ruhsatın alınmasından sonraki 3 yıl içerisinde ruhsatlı ürünün ruhsatı veren üye ülke piyasasında gerçek anlamda yer almaması halinde ruhsat geçerliliğini kaybeder."*

  "Madde 24(5): *Ruhsatın verildiği üye ülke piyasasında önceden yer aldığı halde, birbirini izleyen 3 yıl piyasada gerçek anlamda bulunmamışsa, o ürüne ait ruhsat geçerliliğini kaybeder."*

2.14. Ruhsatların Yenilenmesi

- **2001/83/EC** sayılı Direktif (**2004/27/EC** ile değiştirilmiş)

  "Madde 24(1): *Bu maddenin 4 ve 5 nolu paragraf hükümlerine zarar vermeksizin bir ruhsatın geçerliliği 5 yıldır."*

> ***"Madde 24(2):*** *Ruhsatlar, üye ülkenin yetkili makamlarınca kar-zarar dengesinin gözden geçirilmesiyle 5 yıl sonra yenilenebilir.*
> *Bu durumda ruhsat sahibi, yetkili makamlara, kalite, güvenlik ve etkililik açısından ruhsatın verildiği tarihten itibaren getirilen bütün değişiklikleri de içeren birleştirilmiş dosyayı, ruhsatın paragraf 1'e göre bitiş tarihinden en az 6 ay önce verecektir."*
> ***"Madde 24(3):*** *Yetkili makamların farmakovijilansa dayalı haklı gerekçelerle Paragraf 2'deki ek 5 yıl yenilemeye karar vermemeleri haricinde, ruhsatlar bir defa yenilendikten sonra sınırsız geçerli olacaktır."*

Bu bölümde, AB'nde 1 Kasım 2005 tarihinden itibaren geçerli olacak yeni sistemi getiren düzenlemelerin veri korumasına doğrudan ya da dolaylı olarak etki eden hükümleri kısaca incelenmiştir. Komisyon tarafından önerilen bu düzenlemelerin bir amacının da Avrupa ilaç sanayiinin dünya ölçeğinde yitirdiği rekabet avantajına yeniden kavuşması olduğu bir çok ortamda ifade edilmiştir. Yeni düzenleme ile getirilen bazı hükümlerle, AB ilaç sanayii dünyadaki bir çok ülkedeki rakiplerinden daha avantajlı bir duruma gelmektedir.

3. AB'NE YENİ KATILAN ÜLKELERDE VERİ KORUMASINA İLİŞKİN DÜZENLEMELER

AB'nin üye sayısı 1 Mayıs 2004 tarihinden itibaren katılan 10 yeni ülke ile beraber 25 üyeye ulaşmıştır. Yeni katılan bu ülkeler; Çek Cumhuriyeti, Estonya, Macaristan, Letonya, Slovak Cumhuriyeti, Kıbrıs Rum Kesimi, Litvanya, Malta, Polonya ve Slovenya'dır. Bulgaristan ve Romanya 2007'de üye olacak olup, Türkiye ise aday ülke konumundadır.

Veri korumasına ilişkin olarak, yeni üye olan tüm ülkelerde 2001/83/EC sayılı direktifte yapılan son değişiklikler öncesinde öngörülen koruma süreleri uygulanmaktadır. Yeni mevzuata uyum için ise bir geçiş süresi olabileceği yönünde yaklaşımlar bulunmaktadır. Yeni üye ülkeler, halihazırda 6 yıl olan veri koruma süresinin 4 yıl daha uzatılmasının ulusal

sağlık bütçelerine zarar vereceği yönünde fikir birliğine varmıştır. Nitekim, 5 Eylül 2003 tarihinde 10 yeni üye ülkenin yayınladıkları bildiri[35] (Milan Declaration) ve 26 Kasım 2003 tarihinde bu ülkelerden 94 gözlemci tarafından Avrupa Parlamentosuna gönderilen dilekçede[36]; yeni düzenlemenin taslak çalışmaları esnasında henüz üye olmadıkları için aktif bir katılım sağlayamadıklarından, özellikle veri korumasına getirilen ek koruma sürelerinin zaten hassas olan ilaç sanayilerini olumsuz etkileyeceği, ulusal sağlık sigorta sistemlerine daha fazla yük getireceği, toplumun ilacı temin etme ve bedelini ödemede sorunlarla karşılaşacağından bahisle veri koruma süresinin yeni üyeler için 6 yıl olarak muhafaza edilmesi talep edilmektedir. Bu belgelerde ayrıca, bu ülkelerde jenerik ilaçların tüm reçeteli ilaçlar içerisindeki oranının hacimsel olarak % 70 olduğu ancak, ilaç harcamalarının ise sadece % 30'una karşı geldiği belirtilmektedir. Güçlü bir jenerik sektörün yeniliği uyarıcı olduğu, yeni geliştirilen ilaçların satın alınması için bütçelerde imkan yarattığı, jenerik ilaçların sağlık harcamalarını azaltıcı politikalarda hayati önem taşıdığı ve ulusal geri ödeme sistemlerinin temelini oluşturduğu ifade edilmektedir.

AB Komisyonu, yeni üye ülkelere Katılım Antlaşmaları'nda yer alan hükümler çerçevesinde, yeni düzenlemelere uyum için bir geçiş süresi talebi yapma imkanı vermiş bulunmaktadır. Bu kapsamda ilk olarak Nisan 2004'te Polonya hükümeti[37], AB'nin ilaçlara ilişkin yeni düzenlemesinde yer alan veri korumasına ilişkin hükümlerinin uygulanması için 15 yıllık bir geçiş süresi talebinde bulunmuştur. Diğer ülkelerden Malta 15 yıl, Macaristan 10 yıl, Slovenya ve Slovakya ise 4 yıl olmak üzere geçiş süreleri talep etmiştir[38].

AB ülkelerinden Avusturya, Danimarka, Finlandiya, Yunanistan, İrlanda, Portekiz ve İspanya'da 6 yıl; Belçika, Almanya, Fransa, İtalya, Lüksemburg, Hollanda, İsveç ve

[35] "The Acceding Countries Declaration", 5 September 2003.
[36] "Petition to the European Parliament", 26 November 2003.
[37] "Pharmaceuticals; Poland is the first to request transition period on data protection", Health & Pharma, Euractiv.com Portal-news nr 1507517, 8 April 2004, http://www.euractiv.com
"Government seeks 15-year transition period on EU pharmaceutical law", Warsaw Business Journal, 7 April 2004, http://www.wbj.pl/?command=article&id=22008&
[38] "What the EU Pharmaceutical Review Legislation Means for the New Member States", Hogan&Hartson, http://www.hhlaw.com/articles/1815_EU%20Accession%20Guide%20-%20EU%20Pharmaceutical%20Review%20Legislation%20April%202005.pdf

İngiltere'de 10 yıl olarak veri koruma süreleri mevcuttur[39]. Yunanistan, Portekiz ve İspanya'daki veri koruması patent koruma süresinin sonuna kadar uygulanmaktadır[40]. Yeni düzenleme ile bütün ülkeler mevzuatlarını uygulamanın başlayacağı tarih olan 1 Kasım 2005'e kadar değiştirmek durumundadır. Sadece yeni katılan 10 ülkenin durumu netlik kazanmamıştır. Yukarıda anlatılanlar çerçevesinde bu ülkelere son düzenlemedeki veri koruma süreleri için bir geçiş süresi tanınıp tanınmayacağı hususunda belirsizlik bulunmaktadır. AB Komisyonunca yapılacak değerlendirmenin Eylül 2005'ten önce sonuçlanması beklenmemektedir.

Yeni katılan 10 ülkede veri korumasına ilişkin düzenlemeler katılım öncesi süreçte gerçekleştirilmiştir. Üyelik öncesinde tüm ülkelerde 6 ile 10 yıllık koruma süreleri getirilmiş, sadece Polonya bu süreyi 3 yıl olarak devam ettirmiştir. Macaristan, Litvanya, Polonya, Slovenya'da patentle bağlantılı veri koruması vardır. Yapılan düzenlemeler ülke bazında aşağıda verilmektedir.

Çek Cumhuriyeti'nde, 1997 tarihli İlaç Yasası (Article 32 of Law No. 79/1997 Col. on Pharmaceuticals[41]) ile, 1 Ocak 1998 tarihinden itibaren 6 yıllık veri koruması getirilmiştir. Çek Cumhuriyeti'nin bu alanda AB'ne yükümlülüğü 65/65/EEC sayılı Direktifle uyumlu veri korumasını 1 Ocak 1997 tarihinden itibaren sağlamaktır. Yapılan düzenleme ile, AB'ndeki sisteme göre merkezi ruhsatlandırmaya tabi yüksek teknoloji ürünü ilaçlara 10 yıl, diğer ürünlere ise 6 yıllık bir veri koruma süresi uygulaması başlatılmıştır[42].

Macaristan'da veri korumasına ilişkin düzenleme AB mevzuatı (65/65/EEC sayılı Direktif) ile uyumlu bir şekilde, 12/2001 sayılı Sağlık Bakanlığı Kararı'nda yer almıştır[43]. 12

[39] Data Exclusivity and Market Protection, http://www.egagenerics.com/gen-dataex.htm
[40] "The Impact of the EU-Enlargement on the Pharmaceutical Industry", Alexa von Uexküll, Vossius and Partner, 4 May 2004, http://www.voissiusandpartner.com/eng/publication/impact_eu-enlargement.html
[41] Review of Legislation, Czech Republic, TRIPS Council, IP/Q3/CZE/1, 17 December 1997.
[42] http://www.cptech.org/ip/health/phrma/nte-99/czech.html
[43] "Striking New Balances: The Protection of Pharmaceuticals and the Future of the Industrial Property System in Europe, A Central and Eastern European Perspective", Fiscor, M.Z., Vice-President, Hungarian Patent

Nisan 2001 tarihinde yayımlanan ve 12 Haziran 2001 tarihinde yürürlüğe giren bu Karar'a göre veri koruması fiili olarak 1 Ocak 2003 tarihinde başlayacak ve bu tarihten sonra başlatılan ruhsatlandırma prosedürlerine uygulanacaktır. Ancak, geriye dönük bir uygulama olarak Karar'ın yayımlandığı 12 Nisan 2001 tarihinden sonra ruhsat başvurusu yapılan tüm ürünlere uygulanması hükmü getirilmiş, ancak bu uygulama başarılı olamamıştır. AB'nde olduğu gibi merkezi ruhsatlandırma prosedürünün uygulanacağı yüksek teknoloji ürünlerinde 10 yıl olan veri koruması, diğer ürünlerde 6 yıl olarak belirlenmiş ve patent süresi ile sınırlı tutulmuştur.

Polonya'da 15 Aralık 1993 tarihli düzenlemeyle ilaçlarda 3 yıllık bir veri koruma süresi uygulanmaktadır[44]. AB mevzuatına uyum kapsamında tüm ilaç mevzuatı 6 Eylül 2001 tarihli yasa (Art.3 of the Act of 6th September 2001 introducing the Pharmaceutical Law, Act on Medical Devices and Act on the Office for Registration of Medicinal Products, Medical Devices and Biocides[45]) ile değiştirilmiştir. Söz konusu yasa 1 Nisan 2002 tarihinde yürürlüğe girmiş ve veri koruması alanında Polonya tam üye oluncaya kadar 3 yıllık koruma süresinde herhangi bir değişiklik getirmemiştir. Veri koruma süresi, ilacın dünyanın herhangi bir ülkesinde ilk ruhsat aldığı tarihten başlatılmaktadır ve bunun gerçekte 3 yıldan daha az bir koruma süresine karşı geldiği şeklinde yorumlanmaktadır[46]. Tam üyelik ile AB mevzuatındaki 6-10 yıllık koruma süreleri AB'de ilk ruhsatlandığı tarih itibariyle ürünün patent süresiyle bağlantılı olarak uygulanmaya başlamıştır.

Slovenya'da yeni Tıbbi Ürünler Yasası'nda (Slovenian Medicinal Law) veri korumasına ilişkin hükümler getirilmiştir. Gizli verilerin korunması 6 yıl ile ve patent koruma

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Office, International Conference on Intellectual Property, The Internet, Electronic Commerce and Traditional Knowledge, WIPO/ECTK/SOF/01/2.2, May 2001.

[44] "Preparing for Enlargement by Revising the Rules: An Opportunity for Self-Medication", AESGP Members' Meeting, Warsaw, 30-31 January 2002, http://www.aesgp.be/Warsaw2002/WarsawJan2002.pdf

[45] "Parliamentary Legislative Procedures", Request No 084 "Pharmaceutical Law-Treaty of Accession", August 2003, http://www1.ukie.gov.pl/HLP/files.nsf/ 0/e16a25fd53e9f64ac1256e840036da42?OpenDocument

[46] http://www.ustr.gov/assets/World_Regions/Europe_Mediterranean/European_Union/asset_upload-file21_4196.pdf

süresiyle sınırlandırılmıştır[47]. Veri korumasına ilişkin düzenleme 2000 yılında yapılmış olmasına rağmen, fiili olarak Mart 2002 tarihinde uygulamaya geçilmiştir. Veri korumasının başlangıcı olarak, Slovenya'da ya da AB ülkelerinden herhangi birindeki (hangisi daha erkense) ruhsatlandırma tarihi esas alınmıştır[48].

Estonya'da veri korumasına ilişkin düzenleme, 1996 tarihli ruhsatlandırmaya ilişkin yönetmeliği değiştiren 26 Şubat 2001 tarih ve 25 sayılı Yönetmelik ile yapılmış ve AB mevzuatına uyumlu 6 ve 10 yıllık veri koruma süreleri getirilmiştir49 (Regulation No. 25 of the Minister of Social Affairs of 26 February 2001, amending the Regulation No. 13 of the Minister of Social Affairs of 29 March 1996 on the Procedure for Registration of Medicinal Products and Approval of Variations to the Terms of Registered Medicinal Products).

Slovak Cumhuriyeti'nde, 1998 tarihli İlaçlar ve Tıbbi Cihazlar Yasası'nda (Act No. 140/1998 Coll. on Medicines and Medical Devices) 2000 yılında yapılan değişiklikle (Act No. 119/2000 Coll.) 6 yıl süreli veri koruması getirilmiştir[50]. Aynı yasada daha sonra yeniden yapılan değişiklik Aralık 2001'de yürürlüğe girmiş ve yüksek teknoloji ürünü ilaçlar için 10 yıl veri koruması getirmiştir[51]. Bu yasadaki son değişiklik 1 Ağustos 2003 tarihinde yapılmış ve AB mevzuatına tam uyum sağlanmıştır[52].

Litvanya-AB Ortaklık Anlaşması (Association Agreement) 65/65/EEC Direktifin uygulamasını da içermekte olup 10 yıllık veri koruması 1 Ocak 2000 tarihine kadar yürürlüğe

[47] http://www.cptech.org/ip/health/phrma/nte-99/slovenia.html
[48] PhRMA "Special 301" Submission, 2004, p:127.
[49] Review of Legislation, Estonia, TRIPS Council, IP/Q/EST/1, IP/Q2/EST/1, IP/Q3/EST/1, IP/Q4/EST/1, 29 March 2001.
[50] http://www.foreign.gov.sk/En/files/add.php3?text=Slovakia%20and%20EU&file=eu_poz1e.html
[51] "2002 Regular Report on Slovakia's Progress towards Accession- Chapter 1:Free Movement of Goods", http://www.fifoost.org/slowakei/EU_Slovakia_2002/node36.php
[52] http://www.safs.sk/En/presscenter_06.html

girecektir[53]. Ancak bu tarih realize edilememiştir. 22 Aralık 2001 tarih ve 669 sayılı Karar ile AB mevzuatına uyumlu veri koruma uygulaması 1 Mart 2003 tarihi itibariyle başlatılmıştır[54].

Letonya'da 20 Ocak 1998 tarih ve 24 sayılı İlaç ve Tıbbi Ürünler Tesciline İlişkin Genel İlkeler'inde yer alan veri korumasına 2000 yılında yapılan düzenleme ile açıklık getirilmiş ve AB mevzuatına uyumlu 6-10 yıl süreli veri koruması sağlanmıştır[55].

4. AB'NE ADAY ÜLKELERDE VERİ KORUMASI

Romanya'da ilaçlara ilişkin olarak AB üyeliği gözetilerek 1999 yılında başlatılan yeni düzenlemeler, ruhsatlandırma işlemlerinden ilaçların gözetimine, kalite değerlendirme ve veri korumasına yönelik bir dizi tedbiri içermektedir (Government Emergency Ordinance No 152/1999) [56]. Veri korumasına ilişkin düzenleme ise ilk olarak 2.3.2001 tarihli ve 3 sayılı Karar ile, daha sonra da bu Kararı değiştiren 17.5.2002 tarih ve 12 sayılı Karar ile yapılmış ve AB mevzuatına uyumlu veri koruması getirilmiştir (Decision No. 3/02.03.2001 regarding the approval of Regulations on data exclusivity for medicinal products for human use-Modified by Decision No. 12/17.05.2002). Ancak, veri koruması uygulamasına 14 Nisan 2004 tarihinde, 152 sayılı Karar'ın yeni 23.1 maddesiyle beraber (Ordinance No 152 of October, 1999) başlanılmıştır[57]. Bu kapsamda, 6 yıllık veri koruması (yüksek teknoloji ürünler için 10 yıl), orijinal ilaç ürününün AB'de ya da üretildiği ülkede alınan ruhsat tarihinden itibaren başlamaktadır.

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[53] http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr-84232e.html
[54] Medford-Rosow T., Williams C.A., "A Review of Existing Data Exclusivity Legislation in Selected Countries", Third Revised Version, January 2004, Intellectual Property Institute, London.
[55] Review of Legislation, Latvia, TRIPS Council, IP/Q/LVA/1/Add.1, IP/Q2/LVA/1/Add.1, IP/Q3/LVA/1/Add.1, IP/Q4/LVA/1/Add.1, 26 May 2000.
[56] "Romania's Position Paper", Conference on Accession to the European Union, CONF-RO 52/01, Brussels, 14 December 2001, p:16-21, http://www.mie.ro/Negocieri/English/position_doc/CAP01-DP%20eng.doc
[57] "A Guide to Patent Infringement Legislation", Oproiu M., Vasilescu R., Managing Intellectual Property, Supplement-IP at the border 2005. http://www.managingip.com/includes/supplements/PRINT.asp?SID=495086&ISS=14231&PUBID=199

Bulgaristan'da veri korumasına ilişkin düzenleme 2002 yılında yapılmış ve 1 Ocak 2003 tarihinden itibaren de yürürlüğe girmiştir[58]. 1995 tarihli Bulgaristan İlaç ve Eczaneler Yasası[59], Şubat 2000 ve Aralık 2002 tarihlerinde değişikliğe uğramış ve son değişiklikte, geçerli bir patentle bağlantılı 6 yıllık veri koruması ile patent süresinin bitiminden 2 yıl once yapılan klinik deney ve uygulamaları kapsayan Bolar hükmü getirilmiştir[60].

Hırvatistan'da AB mevzuatına uyumlu bir veri koruma uygulaması bulunmamaktadır.

[58] Bulgaria Country Commercial Guide FY 2004: Invest Climate http://strategis.ic.gc.ca/epic/internet/inimr-ri.nsf/en/gr121087e.html
[59] Bulgarian Law of Medicines and Pharmacies in Human Medicine, generally referred to as Drug Act, State Gazette No. 36/1995.
[60] "Economic and Legal Framework for Non-Prescription Medicines", Country Profiles, Bulgaria, The Association of the European Self-Medication Industry, June 2004, http://www.aesgp.be/CountryProfiles/Bulgaria2004.pdf

BÖLÜM III. TÜRKİYE'DE VERİ KORUMASI

1. AB İLE İLİŞKİLER KAPSAMINDA YÜKÜMLÜLÜKLER

1. Türkiye-AB Gümrük Birliği Anlaşması

Türkiye ile Avrupa Birliği (AB) arasında Gümrük Birliği kurulmasını düzenleyen 22 Aralık 1995 tarih ve 1/95 sayılı Ortaklık Konseyi Kararı, 1 Ocak 1996 tarihinde yürürlüğe girmiştir. 1/95 sayılı Kararın KISIM I, BÖLÜM II'si miktar kısıtlamalarının ve eş etkili tedbirlerin kaldırılması ile ilgili hükümleri kapsamaktadır. Bu bölümde Madde 8 paragraf 1 ile, Kararın yürürlüğe girmesinden itibaren beş yıl içerisinde Türkiye'nin, ticarette teknik engellerin kaldırılması konusundaki Topluluk araçlarını kendi iç yasal düzenlemelerine dahil edeceği; paragraf 2 ile de, bu araçların listesi ve bunların Türkiye tarafından uygulanma koşul ve kurallarının Kararın yürürlüğe girmesinden itibaren bir yıl içerisinde Ortaklık Konseyi Kararı ile belirleneceği ifade edilmektedir.

Bu çerçevede Türkiye tarafından uyumlaştırılacak söz konusu teknik mevzuatı uyumlaştıracak kamu kurum ve kuruluşlarını belirleyen 97/9196 sayılı Bakanlar Kurulu Kararı 29 Nisan 1997 tarihli Resmi gazetede yayımlanmıştır. Bu kararın eki listede 13. maddede Tıbbi Ürünler altında "a)Beşeri İlaçlar" alanındaki teknik mevzuatın Sağlık Bakanlığı tarafından uyumlaştıracağı belirtilmektedir. Diğer taraftan mevzuatın ayrıntılı listesi ise, 21 Mayıs 1997 tarih ve 2/97 sayılı Ortaklık Konseyi Kararı (EK II) ile belirlenmiştir. Buna göre, test verilerinin korunmasına ilişkin mevzuatı belirleyen 65/65 sayılı Direktif listenin ilk sırasında yer almaktadır.

Böylelikle, veri korumasına ilişkin AB'ndeki sisteme uyumlu düzenleme yapma yükümlülüğümüz teknik mevzuat uyumu kapsamında 1 Ocak 2001 tarihi itibariyle başlamış bulunmaktadır.

2. 2003 Türkiye Ulusal Programı

2003 yılında gözden geçirilerek yeniden oluşturulan Türkiye Ulusal Programı'nda test verilerinin korunmasına yönelik olarak yer alan hüküm şu şekildedir:

ÖNCELİK 5.3 Sınai Mülkiyet Hakları

"İlaveten, ilaçlardaki test verilerinin korunması (veri imtiyazı) konusunda Mart 2003 tarihinde Avrupa Komisyonuna bir eylem planı verilmiştir. Buna göre, ülkemizin yol haritasının belirlenmesinde ilk adımı teşkil edecek olan ve bu yükümlüğünün getireceği mali yükün boyutlarını ortaya koymayı hedefleyen sektör raporu tamamlanmıştır. Sektör raporu, Avrupa Komisyonu uzmanları ile değerlendirilecek ve bu çerçevede mevzuat yönünden ihtiyaç duyulan değişiklik çalışmaları başlatılacaktır. Bu çalışmaların 2003-2004 yasama döneminde tamamlanması öngörülmektedir."

3. 2003 Katılım Ortaklığı Belgesi

Katılım Ortaklığı Belgesi'nde kısa vadede veri korumasına ilişkin aşağıdaki hüküm yer almaktadır:

KISA VADE:

"Eczacılık ürünleri konusundaki fikri mülkiyet hakları mevzuatı dahil olmak üzere, fikri ve sınai mülkiyet hakları alanındaki müktesabata uyumun tamamlanması ve korsanlık ve sahtecilik ile mücadelenin güçlendirilmesi."

2. YASAL DÜZENLEMELER

2.1. Patent Haklarının Korunması Hakkında 551 sayılı Kanun Hükmünde Kararname

Türkiye'de 1 Ocak 2005 tarihinden önce, veri koruması ile ilgili tek özel düzenleme 1995 tarihli Patent Haklarının Korunması Hakkında 551 sayılı Kanun Hükmünde Kararname (KHK) olmuştur. KHK'nın "Patent Başvurusu veya Patentten Doğan Koruma Kapsamı ve İstem veya İstemlerin Yorumlanması" başlıklı 83. Maddesinin 3. paragrafında yer alan hüküm aşağıdaki şekildedir:

> "*Patent başvurusu yapılmış olan beşeri, veteriner ve zirai ilaçların imalat ve satış ruhsatlarının tasdiki için ilgili makamlarca talep edilen ve yaratılmaları ve birikimleri önemli bir gayret ve masraf gerektiren ve sahipleri tarafından umuma açıklanmamış olan bilgi ve test sonuçları talep sahibi makam tarafından gizli tutulur. Bilgi ve test sonuçlarını talep eden makam bunların haksız kullanımının önlenmesi için gerekli önlemleri alır.*".

Görüleceği üzere mevzuatımızda veri korumasına ilişkin hüküm AB'nde olduğu gibi ruhsatlandırma sürecinde değil, patentlendirme sürecinde ele alınmış ve sedece patent koruması ile bağlantılı ilaç ürünleri için düzenlenmiştir. Veri koruma sisteminde uygulayıcı kurum Türk Patent Enstitüsü (TPE) değil Sağlık Bakanlığı olduğundan ve bu maddeye aykırılık halinde herhangi bir yaptırım getirilmediğinden, bir yasa maddesi olmanın ötesine geçememiştir. Ayrıca, bu düzenleme ile herhangi bir süre tespiti de yapılmamış olduğundan uygulanabilirliği mümkün olmamış; diğer taraftan patent başvurusu bulunmayan ilaçlar için açıklayıcı bir hüküm içermediğinden sistemin bütünlüğünü sağlayamamıştır.

2.2. Tıbbi Farmasötik Ürünler Ruhsatlandırma Yönetmeliği (2 Mart 1995)

Sağlık Bakanlığı tarafından yürütülen "Tıbbi Farmasötik Ürünler Ruhsatlandırma Yönetmeliği" 2 Mart 1995 tarihli ve 22218 sayılı Resmi Gazete'de yayımlanmış ve 19 Ocak 2005 tarihli "Beşeri Tıbbi Ürünler Ruhsatlandırma Yönetmeliği" nin yayımlanmasıyla 1 Ocak 2005 tarihinden itibaren yürürlükten kalkmıştır. İlaçların ruhsatlandırılması sürecine yönelik bir düzenleme olan bu Yönetmelikte, veri korumasına ilişkin özel bir hüküm bulunmamakla birlikte "kısaltılmış başvurular" başlıklı 9. maddede, ilaçların ruhsat başvuruları ekinde istenmeyecek durumlar sayılmakta ve böylelikle test verilerine atıfta bulunulmaktadır. Madde hükmü şu şekildedir:

"Kısaltılmış Başvurular
Madde 9- Aşağıda belirtilen durumların yeterince belgelenmesi ve desteklenmesi halinde, tıbbi farmasötik ürüne ait farmakolojik ve toksikolojik test sonuçlarının veya klinik çalışmaların başvuru ekinde sunulması gerekmeyebilir.
a) Ürünün, Bakanlıkça daha önce ruhsatlandırılmış bir diğer ürünle tamamen aynı (etkin maddeler açısından aynı kalitatif ve kantitatif terkibe sahip, aynı farmasötik formda, aynı yoldan kullanılan ve gerektiğinde ilgili yönetmeliğe göre biyoeşdeğerliği kanıtlanmış) olması,
b) Yayınlanmış literatüre referans yapılmak suretiyle etkin madde/maddelerin bilinen bir etkinliğe, kabul edilebilir bir emniyete ve yerleşmiş bir tıbbi kullanıma sahip olduğunun ispatlanması,
Bu durumlarda, başvuru sahibi, ürünün etkinlik emniyetine ilişkin yayınlanmış literatür bilgilerini başvuru ekinde sunmak zorundadır."

Söz konusu hüküm, uygulamada orijinal ilaç geliştirenlerin test verilerinin jenerik üreticilerce kullanılmasına, belirlenen koşullar dahilinde herhangi bir engel getirmemekte, söz konusu verilerin AB'nde mevcut sistemde olduğu gibi korunmasını sağlamamaktadır.

2.3. Beşeri Tıbbi Ürünler Ruhsatlandırma Yönetmeliği (19 Ocak 2005)

2 Mart 1995 tarihli Tıbbi Farmasötik Ürünler Ruhsatlandırma Yönetmeliği, 19 Ocak 2005 tarihli ve 25705 sayılı Resmi Gazete'de yayımlanan "Beşeri Tıbbi Ürünler Ruhsatlandırma Yönetmeliği" ile yürürlükten kaldırılmıştır. Yönetmeliğin veri koruması hükümlerini içeren 9. maddesi 1 Ocak 2005 tarihi itibariyle, diğer maddeleri ise 30 Haziran 2005 tarihi itibariyle yürürlüğe girmiştir. Söz konusu madde "Kısaltılmış Başvuru" başlığıyla aşağıda verilmektedir.

"Kısaltılmış Başvuru

Madde 9- 24/6/1995 tarihli ve 551 sayılı Patent Haklarının Korunması Hakkında Kanun Hükmünde Kararname hükümleri saklı kalmak kaydıyla;

a) Yapılacak kısaltılmış başvurularda başvuru sahibi, aşağıdaki hususlardan birinin kanıtlanması şartıyla, toksikolojik ve farmakolojik testlerin ve klinik araştırmaların sonuçlarını sunmak zorunda değildir:

1) Tıbbi ürünün esas itibarıyla Türkiye'de daha önce ruhsatlandırılmış bir tıbbi ürüne büyük ölçüde benzer olması ve orijinal tıbbi ürüne ilişkin pazarlama ruhsatı sahibinin, söz konusu başvurunun incelenmesi amacıyla orijinal tıbbi ürün dosyasında bulunan toksikolojik, farmakolojik ve/veya klinik referansların kullanılmasına rıza göstermesi,

2) Tıbbi ürünün bileşen veya bileşenlerinin, detaylı bilimsel bibliyografi yoluyla tespit edilen, makul düzeyde etkinlik ve kabul edilebilir güvenilirlikle yerleşmiş bir tıbbi kullanımının olması,

3) Tıbbi ürünün, yürürlükteki mevzuat hükümleri uyarınca ruhsatlandırılmış ve veri imtiyazı süresini doldurmuş bir tıbbi ürüne temelde benzer olması. Bu alt bent ile hükme bağlanan veri imtiyazı süresi, Gümrük Birliği Alanında yer alan ülkelerden birinde 1/1/2001 tarihinden sonra ilk defa ruhsatlandırılmış orijinal ürünlerden 1/1/2005 tarihine kadar Türkiye'de herhangi bir jenerik ruhsat başvurusu yapılmamış olanlar ile Gümrük Birliği Alanında yer alan

ülkelerden birinde 1/1/2005 tarihinden sonra ilk defa ruhsatlandırılacak orijinal ürünler açısından geçerli olup, Gümrük Birliği Alanında ilk defa ruhsatlandırıldığı tarihten başlayarak molekülün Türkiye'deki patent süresi ile sınırlı olmak üzere 6 (altı) yıldır.

Bununla birlikte, piyasaya sürülmüş tıbbi ürünlerden farklı terapötik endikasyon, farklı kullanım yolu, farklı doz uygulanmasının öngörülmesi halinde, buna yönelik yapılmış klinik araştırmaların sonuçları ve eğer gerekli ise toksikolojik, farmakolojik çalışmaların sonuçlarının sağlanması zorunludur.

b) Bilinen bileşenleri içeren, ancak henüz terapötik amaçlarla, kombine olarak kullanılmamış, yeni tıbbi ürünlerin, bu kombinasyonla ilgili toksikolojik ve farmakolojik testler ve klinik araştırmalarının sonuçlarının sağlanması zorunludur. Ancak her bir bileşene ilişkin referansların sağlanması gerekli değildir.

Bu maddenin birinci fıkrasının (a) bendinin (2) numaralı alt bendine uygun olarak, yayımlanmış verilere dayanan bibliyografik referansların sunulması durumunda, başvurular Ek-1'e uygun şekilde yapılır.

Bakanlık, kamu sağlığını ciddi olarak tehdit eden istisnai durumlarda bu maddedeki hükümlerden bağımsız olarak literatürde yayımlanan toksikolojik, farmakolojik ve klinik verilere dair bilgilere dayanarak yapılan jenerik ürün ruhsat başvurularını, bilimsel veriler ve uygulamalar doğrultusunda dikkate alabilir. "

Maddenin incelenmesinden görüleceği üzere, Türkiye'de 1 Ocak 2005 tarihinden itibaren başlayan veri koruması uygulaması yeni bir takım düzenlemeler getirmektedir. Yönetmeliğin "Dayanak" başlıklı 3. maddesinde, AB'nin beşeri tıbbi ürünler ile ilgili mevzuatına uyum sağlanması amacıyla, 2001/83 sayılı Direktifine paralel olarak hazırlandığı belirtilmektedir. Dolayısıyla, veri koruması yönünden bakıldığında, söz konusu Direktif'in 10. maddesinde yer alan düzenlemelere esas itibariyle uyumlu bir değişiklik yapılmış ve

ayrıca yeni bazı hükümler getirilmiştir. Yeni sistemde veri korumasının ilkeleri (başlangıcı, kapsamı, yöntemi ve süresi) şu şekilde belirlenmiştir:

- Veri koruma süresi 6 yıldır.
- Veri koruma süresi, Gümrük Birliği alanında yer alan ülkelerden birinde 1 Ocak 2005 tarihinden sonra ilk defa ruhsatlandırılacak orijinal ürünler için geçerli olacaktır.
- Veri koruma süresi, orijinal ürünün Gümrük Birliği alanında ilk defa ruhsatlandırıldığı tarihten başlayacaktır.
- Veri koruması, orijinal tıbbi ürünün (molekülün) Türkiye'deki patent süresi ile sınırlı olacaktır.

Getirilen bu yeni sistem ile Türkiye'de veri koruması, geriye dönük olarak 1 Ocak 2001 tarihinden itibaren başlatılmış; ancak, Gümrük Birliği Alanında yer alan ülkelerden birinde 1 Ocak 2001 tarihinden sonra ilk defa ruhsatlandırılmış orijinal ürünlerden 1 Ocak 2005 tarihine kadar Türkiye'de herhangi bir jenerik ruhsat başvurusu yapılmamış olanlar kapsam dahiline alınmıştır.

GENEL DEĞERLENDİRME VE SONUÇ

Bu çalışmada ilaç sanayiinde, kapsamı ve uygulama yöntemi yönünden oldukça tartışmalı bir konu olan test ve deney verilerinin korunması konusu değerlendirilmeye alınmıştır. Dünyada halen bir çok ülkede tartışmalar devam etmekte, ülkeler kendi yapılarına en uygun koruma sistemini getirmeye çalışmaktadır. Ülkemizin Avrupa Birliği ile ilişkileri çerçevesinde son dönemde ortaya çıkan gelişmeler gözönüne alınarak, bu çalışmada konuya sadece Avrupa Birliği bakış açısıyla yaklaşılmış, AB'nde ortaya çıkan değişim ve yakın gelecekte oluşturulacak sistem incelenmeye çalışılmıştır.

AB'nde ilaç sanayiinde yeniden yapılanmaya ve özelde veri korumasına yönelik olarak gerçekleştirilen düzenlemelerin etkilerinin ne olacağı fiili olarak 2005 yılı sonundan itibaren uygulama ile birlikte ortaya çıkacaktır. Sanayiinin rekabet gücünün artırılması, Ar-Ge faaliyetlerinin daha ileri düzeye getirilmesi ve ileri düzey sağlık hizmetlerinin sağlanması hedeflerine ne ölçüde ulaşılacağı Avrupa yetkililerinin yakından izleyecekleri temel faktörlerdir. Veri koruma sisteminde yeni yaklaşım ile orijinal ve jenerik ilaçlar arasında "kazan-kazan" ilkesi ile yaratılmaya çalışılan dengenin olumlu sonuçlar vermesi beklenmekte, ancak yasal düzenlemelerin tek başına yeterli olmadığı, sahip olunan anlayış ve uygulama yöntemlerinin daha etkili olduğu üzerinde önemle durulmaktadır.

AB'nde yaşanan bu değişimin yanısıra, ülkemizde de veri koruması alanında yeni bir sistem oluşturulmuş bulunmaktadır. Bu yeni düzenleme ile, test ve deney verilerinin korunabilirliği sağlanmış, AB ile uyum sürecinde önemli bir adım atılmış olmaktadır. İlaçlara yönelik mevzuatımızın AB ile üyelik müzakereleri çerçevesinde yeniden gözden geçirileceği ve bazı değişikliklere uğrayacağı bilinmektedir. Bu kapsamda; AB'nde olduğu gibi ülkemizde de, ilaç sanayiinde bir gözden geçirme sürecinin başlatılması ve sistemi etkileyen unsurların (sanayii, sağlık ve fiyatlandırma politikaları, ödeme sistemleri, vb.) bir bütünlük içerisinde ele alınmasında sonsuz yarar vardır. Böylelikle ülkemiz, insan sağlığının iyileştirilmesi temel hedefini benimseyen, Ar-Ge faaliyetlerine önem veren, fikri haklar

sistemininin tüm imkanlarından yararlanan güçlü bir ilaç sanayii sayesinde sahip olduğu potansiyeli daha fazla değerlendirebilecektir.

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EK:1. AB'DE İLAÇ MEVZUATININ YASALAŞMA SÜRECİ

TARİH	YASAMA SÜRECİ
8 Temmuz 2001	Avrupa Komisyonu gözden geçirme tekliflerini iletmiştir.
26 Kasım 2001	Komisyon teklifleri kabul etmiştir.
23 Ekim 2002	Arupa Parlamentosunda İlk Görüşme(First Reading) tamamlanmıştır.
10 Aralık 2002	Komisyon Tüzük taslağındaki değişiklik önerilerini kabul etmiştir.
3 Nisan 2003	Komisyon Direktif taslaklarındaki değişiklik önerilerini kabul etmiştir.
29 Eylül 2003	Konsey ortak bir tutum (Common Position) belirlemiştir.
27 Kasım 2003	Parlamento Komitesi İkinci Görüşmedeki (Second Reading) değişiklik önerilerini kabul etmiştir.
11 Aralık 2003	Bütün ikinci görüşme değişiklik önerilerinin son tarihidir. Konsey ve Parlamento arasında fikir birliğine varılan değişiklik paketi üzerinde uzlaşma sağlanmıştır.
17 Aralık 2003	Parlamento oylama oturumunda ikinci görüşmedeki uzlaşma paketine destek vermiştir.
31 Mart 2004 1 Kasım 2005	Tüzük ve Direktifler yasalaşmıştır. Direktifler ulusal yasalara aktarılacaktır.

Kaynak: "European revisions offer new freedoms for generics", Generics Bulletin, 16 January 2004.

EK:2. AB ÜLKELERİ VE ADAY ÜLKELERDE VERİ KORUMASINA İLİŞKİN MEVZUAT

ÜLKE	SÜRE	YASAL DAYANAK
BELÇİKA	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
DANİMARKA	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
FİNLANDİYA	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
FRANSA	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
ALMANYA	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
YUNANİSTAN	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
İRLANDA	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
İTALYA	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
LÜKSEMBURG	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
HOLLANDA	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
PORTEKİZ	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
İSPANYA	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III) 1993 TARİHLİ YASA
İSVEÇ	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
İNGİLTERE	10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III)
ÇEK CUMHURİYETİ	6-10 YIL	79/1997 SAYILI İLAÇ YASASI, MD.(32) (1998'de başladı) 147/1996 SAYILI BİTKİSEL TIBBİ TEDAVİ YASASI, MD.20
ESTONYA	6-10 YIL	RUHSATLANDIRMA YÖNETMELİĞİ, MD.2
MACARİSTAN	6-10 YIL	12/2001 SAYILI TIBBİ ÜRÜNLERİN TESCİLİ VE RUHSATLANDIRILMASI KARARI (1 Ocak 2003'te başladı)
LETONYA	6-10 YIL	20 OCAK 1998 TARİH ve 24 SAYILI İLAÇ ve TIBBİ ÜRÜNLERİN TESCİLİNE İLİŞKİN GENEL İLKELER, MD.17
POLONYA	6-10 YIL	DİREKTİF 2001/83, MD.10(1)(a)(III) ve 2001 TARİHLİ İLAÇ YASASI (Üye oluncaya kadar veri koruması 3 yıl olarak uygulanmıştır)
SLOVAK CUMHURİYETİ	6-10 YIL	140/1998 SAYILI İLAÇ KARARNAMESİ
SLOVENYA	6-10 YIL	TIBBİ ÜRÜNLER YASASI, MD.15
LİTVANYA	6-10 YIL	22/12/2001 TARİH VE 669 SAYILI KARAR (1 Mart 2003'te başladı)
HIRVATİSTAN	Süre belirtilmemiş	İLAÇ VE TIBBİ ÜRÜNLER YASASI, MD.15
ROMANYA	6-10 YIL	2/3/2001 TARİH VE 3 SAYILI KARAR (14 Nisan 2004'te başladı)
BULGARİSTAN	6-10 YIL	İLAÇ VE ECZANELER YASASI, MD.18 (1 Ocak 2003'te başladı)

Kaynak: -Medford-Rosow T., Williams C.A., "A Review of Existing Data Exclusivity Legislation in Selected Countries", Third Revised Version, January 2004, Intellectual Property Institute, London.
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EK:3. BEŞERİ TIBBİ ÜRÜNLER RUHSATLANDIRMA YÖNETMELİĞİ

Resmi Gazete
Tarih: 19.1.2005; Sayı: 25705

BİRİNCİ BÖLÜM
Amaç, Kapsam, Dayanak ve Tanımlar

Amaç

Madde 1- Bu Yönetmeliğin amacı; beşeri tıbbi ürünlerin istenen etkinlik ve güvenilirliğe, gereken kaliteye sahip olmalarını sağlamak üzere, ruhsatlandırma işlemlerinde uygulanacak usul ve esaslar ile ruhsatlandırılmış beşeri tıbbi ürünlere ilişkin uygulamaları belirlemektir.

Kapsam

Madde 2- Bu Yönetmelik, beşeri kullanım için endüstriyel olarak üretilen veya ithal edilen beşeri tıbbi ürünler ile bunlar için ruhsat başvurusunda bulunan ve/veya ruhsat verilmiş olan gerçek ve tüzel kişileri kapsar.

Ancak;

a) Sadece bir hasta için reçeteye göre eczanede hazırlanan ve yaygın olarak majistral formül ismiyle anılan her türlü ürün,

b) Bir farmakopenin formüllerine uygun olarak eczane tarafından doğrudan sunulmak amacıyla hazırlanan ve yaygın olarak ofisinal formül adıyla anılan her türlü ürün,

c) 29/1/1993 tarihli ve 21480 sayılı Resmi Gazete'de yayımlanan İlaç Araştırmaları Hakkında Yönetmelik hükümleri saklı kalmak kaydıyla araştırma ve geliştirme çalışmalarında kullanılması amaçlanan tıbbi ürünler,

d) Yetkili üretici tarafından ileri işlemlerde kullanılması amaçlanan yarı mamul ürünler,

e) Kapalı kaynak halinde hazırlanan her türlü radyonüklidler,

f) İnsan kaynaklı tam kan, plazma veya kan fraksiyonları,

bu Yönetmeliğin kapsamı dışındadır.

Dayanak

Madde 3- Bu Yönetmelik; 14/5/1928 tarihli ve 1262 sayılı İspençiyari ve Tıbbi Müstahzarlar Kanununa, 7/5/1987 tarihli ve 3359 sayılı Sağlık Hizmetleri Temel Kanunun 3/k maddesine, 23/6/1983 tarihli ve 2857 sayılı Kan ve Kan Ürünleri Kanununun 8 inci maddesine ve 13/12/1983 tarihli ve 181 sayılı Sağlık Bakanlığının Teşkilat ve Görevleri Hakkında Kanun Hükmünde Kararnamenin 43 üncü maddesine dayanılarak;

Avrupa Birliği'nin beşeri tıbbi ürünler ile ilgili mevzuatına uyum sağlanması amacıyla, 2001/83/EC sayılı beşeri tıbbi ürünler hakkındaki direktifine paralel olarak hazırlanmıştır.

Tanımlar

Madde 4- Bu Yönetmelikte geçen;

a) Bakanlık: Sağlık Bakanlığını,

b) Kanun: 1262 sayılı İspençiyari ve Tıbbi Müstahzarlar Kanununu,

c) Beşeri Tıbbi Ürün/Ürün : Hastalığı tedavi etmek ve/veya önlemek, bir teşhis yapmak veya bir fizyolojik fonksiyonu düzeltmek, düzenlemek veya değiştirmek amacıyla, insana uygulanan doğal ve/veya sentetik kaynaklı etkin madde veya maddeler kombinasyonunu,

d) Ruhsatlı Beşeri Tıbbi Ürün: Bakanlıkça onaylanmış, kullanıma hazır şekilde, özel bir ambalajda ve belirli bir isim ile pazara sunulan beşeri tıbbi ürünü,

e) Madde: Kaynağı insan (insan kanı ve insan kanından elde edilen ürünler), hayvan (mikroorganizmalar, bütün hayvanlar, organ parçaları, hayvan salgıları, toksinler, özler, kan ürünleri), bitki (mikroorganizmalar, bitkiler, bitkilerin bölümleri, bitki salgıları, bitki özleri), kimyasal (elementler, doğal olarak oluşan kimyasal materyaller, kimyasal değişiklik ya da sentez yoluyla elde edilen kimyasal ürünler) olabilen her türlü maddeyi,

f) İmmünolojik Ürün: Kolera, BCG, polio ve çiçek aşıları gibi aktif bağışıklık sağlayan ajanlar; tüberkülin ve tüberkülin PPD, brusella, Schick ve Dick testleri dahil bağışıklık durumunu teşhis etmek için kullanılan ajanlar ve difteri antitoksini, anti-çiçek globulini, antilenfotik globulin gibi pasif bağışıklık sağlamak için kullanılan ajanları içeren tüm aşılar, toksinler ve serumlar ile allerjen bir ajana karşı kazanılan spesifik immünolojik cevabı değiştirmek veya tanımlamak niyeti ile kullanılan allerjen ürünlerden oluşan beşeri tıbbi ürünleri,

g) Radyofarmasötik: Tıbbi amaçla kullanılmak üzere hazırlanılan ve kullanıma hazır olduğunda, yapısında bir veya birden fazla radyonüklid içeren ürünü,

h) Radyonüklid: Çekirdeği kendiliğinden bozunmaya uğrayarak, bir veya birden çok iyonlaştırıcı radyasyon yayınlayan radyoaktif nitelikli atomu,

ı) Radyoaktif Madde: Bir veya birden çok iyonlaştırıcı radyasyon yayınlayarak çekirdekleri kendiliğinden bozunmaya uğrayan alaşım, karışım, çözelti veya bileşik formunda radyonüklid içeren maddeleri,

i) Radyonüklid Jeneratör: Yavru bir radyonüklidden elüsyon yoluyla veya diğer bir yöntemle elde edilen radyofarmasötik ürünü, radyofarmasotiklerde kullanılan sabit bir ana radyonüklidle birleştiren her türlü sistemi,

j) Radyonüklid Kit: Bitmiş radyofarmasötik, genellikle kullanımdan önce radyonüklidle birleşmiş veya yeniden oluşturulmuş her türlü preparatı,

k) Radyonüklid Prekürsör: Uygulamadan önce bir başka maddenin radyoaktif işaretlenmesi için üretilen herhangi başka bir radyonüklidi,

l) Kan Ürünü: İnsan kanı veya plazmasından endüstriyel yöntemlerle kamu ya da özel kurumlar tarafından elde edilen ve özellikle albumin, immünoglobulin ve koagülasyon faktörleri gibi ürünleri içeren kan bileşenlerine dayalı tıbbi ürünleri,

m) Etkin Madde: Beşeri tıbbi ürünlerde kullanılan farmakolojik aktif maddeleri,

n) Yardımcı Madde: Bir ürünün terkibinde yer alan, etkin madde ve maddeler dışında kalan maddeleri,

o) Başlangıç Maddeleri: Bir ürünün üretiminde kullanılan, ambalaj malzemeleri dışındaki her türlü maddeleri,

ö) Bitmiş Ürün: Bütün üretim aşamalarından geçmiş, son ambalajı içinde kullanıma hazır ürünü,

p) Ruhsatlandırma: Bir ürünün, pazara sunulabilmesi için Bakanlıkça yapılan inceleme ve onay işlemlerini,

r) Ruhsat: Bir ürünün belirli bir formül ile belirli bir farmasötik form ve dozda, kabul edilen ürün bilgilerine uygun olarak üretilip pazara sunulabileceğini gösteren, Bakanlıkça düzenlenen belgeyi,

s) Plazma: Kanın hücrelerinden ayrıldığı ve içinde sadece kan proteinleri bulunan sıvı kısmını,

ş) Seri: Bir ürünün üretim sırasında tek bir üretim döngüsünde elde edilen ve homojenliğin sağlandığı miktarı,

t) TAEK : Türkiye Atom Enerjisi Kurumunu,

u) Spesifik Aktivite : Bir radyoaktif maddenin birim kütlesinin Curie veya Becquerel cinsinden ifade edilen aktivite yoğunluğunu,

ü) Gümrük Birliği Alanı: Türkiye ile Avrupa Birliği arasında Gümrük Birliğini tesis eden 1/95 sayılı Ortaklık Konseyi Kararının 3 üncü maddesinin 3 üncü bendinde tanımlanan Gümrük Birliği Gümrük Alanını,

v) Orijinal Tıbbi Ürün: Etkin madde/maddeler açısından bilimsel olarak kabul edilebilir etkinlik, kalite ve güvenliğe sahip olduğu kanıtlanarak, dünyada pazara ilk defa sunulmak üzere ruhsatlandırılmış/izin verilmiş ürünü,

y) Jenerik Tıbbi Ürün: Etkin maddeler açısından orijinal tıbbi ürün ile aynı kalitatif ve kantitatif terkibe ve aynı farmasötik forma sahip olan ve orijinal tıbbi ürün ile biyoeşdeğerliliği, uygun biyoyararlanım çalışmaları ile kanıtlanmış tıbbi ürünü,

ifade eder.

İKİNCİ BÖLÜM
Ruhsat Başvurusu

Ruhsat

Madde 5- Bu Yönetmelik hükümlerine göre Bakanlık tarafından ruhsatlandırılarak satış izni verilmeyen hiçbir beşeri tıbbi ürün pazara sunulamaz.

Ruhsatlandırma işlemi; radyonüklid jeneratörler, radyonüklid kitler, radyonüklid prekürsörler, radyofarmasötikler ve endüstriyel olarak hazırlanmış radyofarmasötikler için de geçerlidir.

Ulusal mevzuat hükümleri uyarınca, radyofarmasötik tıbbi ürünleri kullanmaya yetkili bir sağlık kuruluşunda, bu kuruluş veya yetkili kişi tarafından kullanımları sırasında üretim talimatlarına göre, özellikle ruhsatlı radyonüklid jeneratörler, radyonüklid kitler ve radyonüklid prekürsörlerden hazırlanan radyofarmasötikler için pazarlama ruhsatı aranmaz.

Başvuru

Madde 6- Türkiye sınırları dahilinde yerleşik bulunan gerçek veya tüzel kişiler, bir ürünü pazara sunmak amacıyla ruhsat alabilmek için gereken ve bu Yönetmeliğin Ek-1'inde belirtilen tıbbi ürün ruhsat başvurusunda sunulması gereken bilgi ve belgeleri, her bir farmasötik form için bu Yönetmelikte öngörüldüğü şekilde hazırlayarak Bakanlığa sunar.

Ruhsat Başvurusunda Bulunabilecek Kişiler

Madde 7- Kanunun 5 inci maddesi gereğince, ürünü pazara sunmak üzere ruhsat almak isteyen;

a) Gerçek kişilerin; eczacılık, tıp veya kimya bilim dallarında eğitim veren okullardan birisinden mezun olmaları ve Türkiye'de mesleğini icra etme yetkisine sahip olmaları,

b) Tüzel kişilerin; (a) bendinde belirtilen vasıfları taşıyan ve başvuruya konu ürün veya ürünler hakkında bilgi birikimi ve deneyimi olan birini "yetkili kişi" sıfatıyla istihdam etmeleri,

şarttır.

Diş hekimliği mesleğine mensup ve Türkiye'de mesleğini icra etme yetkisine sahip gerçek kişiler de, diş hekimliğinde kullanılan ürünler için ruhsat başvurusu yapma hakkına sahiptirler.

Başvuruda Sunulması Gereken Bilgi ve Belgeler

Madde 8- Bir ürüne ruhsat almak isteyen gerçek veya tüzel kişiler, bu Yönetmeliğin Ek-1'ine uygun olarak hazırlanmış bilgiler ve aşağıda sayılan hususların gerçekleştirildiğine dair belgeler ile birlikte Bakanlığa başvuruda bulunur:

a) Başvuru sahibinin bu Yönetmeliğin 7 nci maddesinde belirtilen mesleklerden birine mensup olduğunu gösteren diplomasının noter onaylı örneği,

b) Başvuru sahibinin başvuruyu yapmaya yetkili olduğunu gösteren onaylı belge,

c) Başvuru sahibinin tüzel kişi olması durumunda, şirketin kuruluş amaçlarını, ortaklarını ve sorumlu kişilerin görev ve unvanlarını belirten ticaret sicil gazetesinin aslı veya sureti,

d) Başvuru sahibinin adı veya firma adı, daimi adresi, elektronik posta adresi, telefon ve faks numarası,

e) Üreticinin adı, daimi adresi, telefon ve faks numarası,

f) Ürünün adı,

g) Ampirik kimyasal formülün dışında, ürünün bileşenlerinin günlük terminolojideki kantitatif ve kalitatif özellikleri, şayet varsa Dünya Sağlık Örgütü tarafından önerilen uluslararası mülkiyeti haiz olmayan ismi (INN),

h) Üretim metodunun tanımı,

ı) Terapötik endikasyonlar, kontrendikasyonlar ve advers etkileri,

i) Dozu, farmasötik formu, uygulama metodu ve yolu, raf ömrü, ambalaj miktarı,

j) Ürünün saklama koşulları, hastalara uygulanması, söz konusu ürünün çevre için yarattığı potansiyel riskler de göz önünde bulundurularak atık ürünün imha şeklinin belirtilmesi,

k) Üretici tarafından kullanılan kontrol metotlarının tanımı (bileşenlerin ve bitmiş ürünün kantitatif ve kalitatif olarak analizi, sterilite testleri, pirojen maddeler, ağır metallerin bulunup bulunmadığına dair testler gibi özel testler, stabilite testleri, biyolojik ve toksisite testleri, üretim işleminin ara aşamasında yürütülen kontroller),

l) Fiziko-kimyasal, biyolojik veya mikrobiyolojik testlerin sonuçları,

m) Toksikolojik ve farmakolojik testlerin ve klinik araştırmaların sonuçları,

n) Ürünün ithali/lisanslı üretimi durumunda orijin firma tarafından düzenlenen ve geçerlilik süresini de gösteren ürüne ait orijinal kısa ürün bilgileri (KÜB), kullanma talimatı ve ambalaj örnekleri,

o) Ürünün ithali durumunda, ithalatı yapan gerçek veya tüzel kişinin söz konusu ürünün

Türkiye'ye ithali, ruhsatlandırılması ve satışı konusunda yetkili tek temsilci olduğunu veya eğer varsa ortak pazarlama yetkisini gösteren orijin firma tarafından düzenlenmiş belge ve Türkçe tercümesi,

ö) Ürünün lisans altında üretilmesi durumunda, üretimi yapan gerçek veya tüzel kişinin, söz konusu ürünü Türkiye'de üreterek satabilecek yetkili tek temsilci olduğunu veya eğer varsa ortak pazarlama yetkisini gösteren orijin firma tarafından düzenlenmiş belge ve Türkçe tercümesi,

p) Üreticinin, Bakanlık yahut ilgili ülkenin yetkili otoritesi tarafınca onaylanmış İyi Üretim Uygulamaları çerçevesinde üretim yapabileceğini gösterir GMP belgesi,

r) Başvuru sahibinin üretici olmaması durumunda, 23/10/2003 tarihli ve 25268 sayılı Resmi Gazete'de yayımlanan Beşeri Tıbbi Ürünler İmalathaneleri Yönetmeliğinde belirtilen şartlara sahip bir üretici ile yaptığı noter onaylı fason üretim sözleşmesi,

s) Başvurusu yapılan ürün için, ruhsat başvurusu yapılmış diğer ülkelerin listesi ile birlikte ürünün pazara sunulduğu diğer ülke veya ülkelerin yetkili otoritelerince verilmiş onaylı Farmasötik Ürün Sertifikaları,

t) 24/7/1985 tarihli ve 85/9727 sayılı Bakanlar Kurulu Kararı ile yürürlüğe konulan Radyasyon Güvenliği Tüzüğü, 10/9/1997 tarihli ve 23106 sayılı Resmi Gazete'de yayımlanan Radyoaktif Maddenin Güvenli Taşınması Yönetmeliği, 24/3/2000 tarihli ve 23999 sayılı Resmi Gazete'de yayımlanan Radyasyon Güvenliği Yönetmeliği ile 2/9/2004 tarihli ve 25571 sayılı Resmi Gazete'de yayımlanan Radyoaktif Madde Kullanımında Oluşan Atıklara İlişkin Yönetmelik hükümleri de dikkate alınarak uygulanabilir halde tıbbi ürünün çevre açısından oluşturabileceği risklerin tanımı,

u) Bir radyonüklid jeneratörün ruhsatlandırma başvurusunda yukarıda belirtilenlere ek olarak, elüe edilecek nüklit preparatın kalitesini ve bileşimini etkileyebileceği için sistemin ve sistemi oluşturan bileşenlerin detaylı tanımının ve elüat veya süblimenin kantitatif ve kalitatif özelliklerinin bildirilmesi,

ü) Ambalaj ve etiketlemeye ilişkin mevzuatta belirtilen kısa ürün bilgileri ve bu doğrultuda hazırlanmış kullanma talimatı ve ürüne ait pazara sunulacak boyut ve dizaynda iç-dış ambalaj taslak örnekleri ile ithal/lisanslı üretilen ürünlerde bunların diğer ülke yetkili otoriteleri tarafından onaylanmış orijinal kısa ürün bilgileri, kullanma talimatı ve ambalaj örnekleri,

v) Başvurusu yapılan ürün diğer ülkelerin yetkili otoritesi tarafından reddedilmiş, geri çekilmiş, askıya alınmış ise veya başvuru sahibi tarafından geri çekilmiş ise, bu ülkelerin listesinin, ürünün söz konusu ülkede ruhsatlandırılmış adı, yapılan işlemlerin tarihi ve gerekçesi ile birlikte belirtilmesi.

Bu maddede yer alan bilgilerden güncellenenlerin Bakanlığa bildirilmesi zorunludur.

Kısaltılmış Başvuru

Madde 9- 24/6/1995 tarihli ve 551 sayılı Patent Haklarının Korunması Hakkında Kanun Hükmünde Kararname hükümleri saklı kalmak kaydıyla;

a) Yapılacak kısaltılmış başvurularda başvuru sahibi, aşağıdaki hususlardan birinin kanıtlanması şartıyla, toksikolojik ve farmakolojik testlerin ve klinik araştırmaların sonuçlarını sunmak zorunda değildir:

1) Tıbbi ürünün esas itibarıyla Türkiye'de daha önce ruhsatlandırılmış bir tıbbi ürüne büyük ölçüde benzer olması ve orijinal tıbbi ürüne ilişkin pazarlama ruhsatı sahibinin, söz

konusu başvurunun incelenmesi amacıyla orijinal tıbbi ürün dosyasında bulunan toksikolojik, farmakolojik ve/veya klinik referansların kullanılmasına rıza göstermesi,

2) Tıbbi ürünün bileşen veya bileşenlerinin, detaylı bilimsel bibliyografi yoluyla tespit edilen, makul düzeyde etkinlik ve kabul edilebilir güvenilirlikle yerleşmiş bir tıbbi kullanımının olması,

3) Tıbbi ürünün, yürürlükteki mevzuat hükümleri uyarınca ruhsatlandırılmış ve veri imtiyazı süresini doldurmuş bir tıbbi ürüne temelde benzer olması. Bu alt bent ile hükme bağlanan veri imtiyazı süresi, Gümrük Birliği Alanında yer alan ülkelerden birinde 1/1/2001 tarihinden sonra ilk defa ruhsatlandırılmış orijinal ürünlerden 1/1/2005 tarihine kadar Türkiye'de herhangi bir jenerik ruhsat başvurusu yapılmamış olanlar ile Gümrük Birliği Alanında yer alan ülkelerden birinde 1/1/2005 tarihinden sonra ilk defa ruhsatlandırılacak orijinal ürünler açısından geçerli olup, Gümrük Birliği Alanında ilk defa ruhsatlandırıldığı tarihten başlayarak molekülün Türkiye'deki patent süresi ile sınırlı olmak üzere 6 (altı) yıldır.

Bununla birlikte, piyasaya sürülmüş tıbbi ürünlerden farklı terapötik endikasyon, farklı kullanım yolu, farklı doz uygulanmasının öngörülmesi halinde, buna yönelik yapılmış klinik araştırmaların sonuçları ve eğer gerekli ise toksikolojik, farmakolojik çalışmaların sonuçlarının sağlanması zorunludur.

b) Bilinen bileşenleri içeren, ancak henüz terapötik amaçlarla, kombine olarak kullanılmamış, yeni tıbbi ürünlerin, bu kombinasyonla ilgili toksikolojik ve farmakolojik testler ve klinik araştırmalarının sonuçlarının sağlanması zorunludur. Ancak her bir bileşene ilişkin referansların sağlanması gerekli değildir.

Bu maddenin birinci fıkrasının (a) bendinin (2) numaralı alt bendine uygun olarak, yayımlanmış verilere dayanan bibliyografik referansların sunulması durumunda, başvurular Ek-1'e uygun şekilde yapılır.

Bakanlık, kamu sağlığını ciddi olarak tehdit eden istisnai durumlarda bu maddedeki hükümlerden bağımsız olarak literatürde yayımlanan toksikolojik, farmakolojik ve klinik verilere dair bilgilere dayanarak yapılan jenerik ürün ruhsat başvurularını, bilimsel veriler ve uygulamalar doğrultusunda dikkate alabilir.

Özel Durumlarda Ruhsatlandırma

Madde 10- Aşağıda sıralanan özel durumlarda ruhsatın verilmesini takiben daha ileri çalışmaların yürütülmesi ve tıbbi ürünle ilgili advers etkilerin bildirilmesi koşuluyla Bakanlığın kararı çerçevesinde ruhsat verilebilir:

a) Söz konusu ürünün terapötik endikasyonlarının, başvuru sahibinin ayrıntılı kanıt sağlayamayacağı kadar az olması,

b) Mevcut bilimsel verilerin ışığı altında ayrıntılı bilginin sağlanamaması,

c) Bu tür bilgileri toplamanın kabul gören etik ilkelere aykırı olması.

Özel durumlarda ruhsatlandırma halinde ürünün ambalaj ve kullanma talimatı, ürünle ilgili mevcut duruma ve ürünün belli açılardan halen yetersiz olduğuna dikkati çekecek biçimde olmalıdır.

Kısa Ürün Bilgileri

Madde 11 - Kısa Ürün Bilgileri;

a) Ürünün adını,

b)Ürünün etkin madde/maddeler ve yardımcı maddeler bakımından kantitatif ve kalitatif kompozisyonunu, uygulama yolu için gerekli bilgileri, yaygın ismini veya kimyasal tanımını,

c) Farmasötik formunu,

d) Farmakolojik özelliklerini ve terapötik amaç kapsamında faydalı olabildiği ölçüde farmakokinetik özelliklerini,

e) Klinik özellikleri;

1) Terapötik endikasyonlarını,

2) Kontrendikasyonlarını,

3) Görülme sıklığı ve ciddiyeti de belirtilecek şekilde advers etkilerini,

4) Özel kullanım önlemleri; immünolojik tıbbi ürünlerin olması durumunda, bu ürünlerle çalışan ve bunları hastalara uygulayan kişiler tarafından alınacak her türlü önlemlerle hasta tarafından alınacak her türlü önlemi,

5) Gebelik ve laktasyon döneminde kullanımını,

6) Diğer ilaçlarla etkileşme ve diğer etkileşme şekillerini,

7) Pozoloji, yetişkinler ve gerektiğinde çocuklar için uygulama yolunu,

8) Doz aşımı durumunda semptomlar, uygulanacak acil işlemler ve gerekli antidotları,

9) Özel uyarıları,

10) Araba ve diğer makine çeşitlerini kullanma yeteneği üzerindeki etkilerini,

f) Farmasötik özellikleri;

1) Başlıca geçimsizlikleri,

2) Tıbbi ürünün raf ömrü, gerektiğinde rekonstitüsyondan sonraki veya iç ambalajın ilk kez açıldığı tarih de belirtilerek raf ömrünü,

3) Saklama için özel önlemleri,

4) İç ambalajın özellikleri ve içeriğini,

5) Gerektiğinde kullanılmamış ürünlerin veya bu tür ürünlerden türetilmiş materyallerin atılması için gerekli önlemleri,

g) Ruhsat sahibinin adı, adresi, telefon ve faks numarasını,

h) Radyofarmasötikler için dahili radyasyon dozimetresinin tüm ayrıntılarını,

ı) Radyofarmasötikler için detaylı kullanım kılavuzu, hazırlama ve kalite kontrolüne yönelik bilgiler, gerekli olduğu yerlerde maksimum saklama süresi, elüat veya kullanıma hazır ürünün spesifikasyonlarına uygun maksimum saklama süresini,

içermelidir.

Uzman Raporları

Madde 12- Ruhsat sahibi, Bakanlığa başvuruda bulunurken ruhsat dosyasının kimyasal, farmakolojik, biyolojik, toksikolojik ve klinik kısımlarının her biri için ilgili uzmanlarca imzalanmış uzman raporlarını sunar.

Raporları hazırlayacak olan uzmanların niteliklerine göre görevleri şunlardır:

a) Kendi disiplinleri içindeki (analiz, farmakoloji ve benzer deneysel bilimler, klinik araştırmalar) görevleri yerine getirmek ve elde edilen kalitatif ve kantitatif sonuçları nesnel olarak tanımlamak,

b) Gözlemlerini Ek-1'e göre tanımlamak ve özellikle aşağıdaki hususları belirtmek;

1) Analiz uzmanları için, tıbbi ürünün beyan edilen kompozisyonuna uygun olup olmadığının, üretici tarafından kullanılan kontrol yöntemleriyle saptanması,

2) Tıbbi ürünün toksisitesinin ve farmakolojik özelliklerinin gözlenmesi,

3) Klinisyenler söz konusu ise, bu Yönetmeliğin hükümlerine göre başvuru sahibi tarafından Bakanlığa sunulan bilgi ve belgelerin söz konusu ürünle tedavi edilen hastalar üzerindeki etkisinden emin olunup olunmadığı, hastanın ürünü iyi tolere edip etmediği, klinisyenin pozoloji, kontrendikasyonlar ve advers etki ile ilgili tavsiyesi.

Uzmanın özgeçmişi ve başvuru sahibi ile profesyonel ilişkisinin beyanı ve gerektiğinde bibliyografik başvuru için kullanılan bilgi ve belgelerin gerekçesi belirtilmelidir.

Uzmanların ayrıntılı raporları, başvuru sahibinin Bakanlığa sunduğu başvurunun ilişiğindeki bilgi ve belgelerin bir parçasını oluşturur.

ÜÇÜNCÜ BÖLÜM
Ruhsat Başvurusunun Değerlendirilmesi ve Ruhsatlandırma

Ön İnceleme

Madde 13- Beşeri tıbbi ürün için ruhsat almak üzere Bakanlığa sunulan başvuru dosyasının, başvurunun niteliğine göre sunulması gereken bilgi ve belgeler açısından eksiksiz ve tam bir başvuru olup olmadığı hususu, Bakanlık tarafından ön incelemeye tabi tutularak değerlendirilir. Başvuru dosyasının Bakanlığa ulaşmasından itibaren 30 (otuz) gün içinde gerekli değerlendirme yapılarak durum başvuru sahibine bildirilir. Başvurunun eksik bulunması halinde başvuru sahibi eksikliklerini 30 (otuz) gün içinde tamamlar. Eksikliklerin tamamlanarak Bakanlığa sunulmasından sonra yapılacak ikinci ön inceleme de 30 (otuz) gün içinde sonuçlandırılır.

Başvurunun İadesi

Madde 14- Bakanlık tarafından bu Yönetmeliğin 13 üncü maddesi kapsamında yapılan ön incelemede, aşağıdaki durumların tesbiti halinde, başvuru usulden reddedilerek sahibine iade edilir:

a) Başvuru sahibinin Kanun ve bu Yönetmeliğin 7 nci maddesinde belirtilen niteliklere sahip olmaması,

b) İkinci ön incelemeye tabi tutulan ve eksikliği tamamlanmamış olan başvuru olması.

Ruhsatlandırma Süresi

Madde 15- Bakanlık, ön incelemesi tamamlanmış eksiksiz bir ruhsat başvurusunu, ruhsatlandırma koşullarının yerine getirilip getirilmediğini inceleyerek, bu başvurunun kabul edilmesini takiben 210 (ikiyüzon) gün içinde sonuçlandırır. Ancak, Bakanlığın başvuru sahibinden talep ettiği hususların temin edilmesi için gereken süre, olağanüstü haller ile Bakanlık dışı kuruluşların değerlendirmeleri bu süreye dahil edilmez.

Ayrıca aşağıdaki hallerde 210 (ikiyüzon) günlük süre durdurulur:

a) Üretici tarafından ürün üretiminde kullanılan ve bu Yönetmeliğin 8 inci maddesinin birinci fıkrasının (m) bendi uyarınca başvuru beraberinde sunulan bilgi ve belgelerde tanımlanan kontrol yöntemlerinin beyan edilen doğruluğunun saptanması için Bakanlık, ürünün başlangıç materyallerinin ve ihtiyaç olması halinde ara ürünlerin ve diğer bileşen maddelerinin ulusal bir laboratuvarda veya Bakanlık tarafından bu amaçla kabul edilmiş bir

laboratuvarda test edilmek üzere sunulması talep edildiği durumlarda eksiklikler tamamlanıncaya kadar,

b) Bakanlıkça ruhsatlandırma süreci sırasında gerektiği durumlarda bu Yönetmeliğin 8, 9, 10 ve 11 inci maddeleri kapsamında başvuru sahibinden ek bilgi ve belge talep edildiği durumlarda ilgili bilgi ve belgeler temin edilene kadar,

c) Bakanlığın başvuru sahibinden sözlü veya yazılı açıklamada bulunmasını talep ettiği durumlarda gerekli yazılı veya sözlü açıklama yapılana kadar.

Ruhsatlandırma Kriterleri

Madde 16- Beşeri tıbbi ürüne ruhsat verilirken, ürünle ilgili olarak Bakanlıkça dikkate alınacak kriterler şunlardır:

a) Öngörülen kullanım şartlarındaki etkinliğinin kanıtlanmış olması,

b) Güvenilirliğin kanıtlanmış olması,

c) Mevcut tedavilere katkısının olması,

d) Uygun teknik ve farmasötik özelliklere sahip olması.

Başvuruların Değerlendirilmesi

Madde 17- Başvurular değerlendirilirken asgari olarak aşağıdaki hususlar gözetilir:

a) Bir ürünün etkinlik, güvenilirlik ve kalitesini kanıtlayan bilgi ve belgelerin bilimsel ve teknolojik açıdan incelenmesi,

b) Ürüne ait formülasyonun doğruluğu ve imalatçı tarafından ürünün kontrolünde kullanılan yöntemlerin uygulanabilirliğinin tesbiti için ulusal bir laboratuvarda veya Bakanlık tarafından bu amaçla kabul edilmiş bir laboratuvarda test edilmiş olması,

c) Kan ürünlerinde viral kontaminasyon olup olmadığını belirlemek için yapılmış olan kontrol testlerinin ürünün güvenilir olduğunu kanıtlaması ve bu ürünlerin hazırlanmasında kullanılan plazmanın temin edildiği kaynağın bildirilmesi,

d) Radyofarmasötikler/kitler formülasyonlarında hayvansal kaynaklı maddeler içeriyorsa BSE virüsü olmadığına dair resmi otoriteden yazı, kan ve plazma ürünleri içeriyorsa viral kontaminasyon, AIDS, hepatit ve benzeri testlerin istenilmesi.

Ruhsat Talebinin Reddi

Madde 18- Bir ürünün ruhsatlandırılması için Bakanlığa yapılan başvurunun değerlendirilmesi sürecinde ürünün;

a) Normal kullanma şartlarında, potansiyel riskin tedavi etkisinden fazla olduğunun,

b) Terapötik etkisinin yetersiz olduğu veya bunun yeterli şekilde kanıtlanamadığının,

c) Gerekli görülen ürünlerde biyoyararlanımının yeterli olmadığının,

d) Mevcut tedavilere katkısının olmadığının,

e)Kalitatif ve kantitatif formülünün, başvuruda bildirilene uygun olmadığı veya bildirilen kontrol yöntemleri uygulandığında sonuç alınamadığı veya beyan edilen spesifikasyonlarının kabul edilebilir limitlerin dışında bulunduğu hususunda başvuru sahibi ikaz edilmesine rağmen ikinci kez yapılan kontrollerde de uygunsuzluğun devam ettiğinin,

tespit edilmesi durumlarında başvuru reddedilir.

Bildirim ve İtiraz

Madde 19- Ruhsat başvurusunun reddi halinde karar gerekçeli olarak başvuru sahibine bildirilir. Başvuru sahibinin karara 30 (otuz) gün içinde yazılı olarak itiraz etme hakkı vardır. 30 (otuz) gün içinde itiraz edilmediği takdirde, başvuru belgeleri sahibine iade edilir.

Yapılan itiraz 90 (doksan) gün içinde Bakanlık tarafından değerlendirilerek sonuç başvuru sahibine bildirilir. İtirazın değerlendirilmesi sırasında, gerekli görülür ise, başvuru sahibine sözlü açıklama ve savunma hakkı verilir. İtirazın değerlendirilmesi sonucunda çıkan karar kesindir ve bu karara itiraz edilemez.

Ruhsatın Verilmesi

Madde 20- Başvuru sahibi tarafından Bakanlığa sunulan bilgi ve belgelerin incelenmesi ve değerlendirilmesi sonucunda, bu Yönetmelikte öngörülen hususlara uygun olduğu tespit edilen ürüne ruhsat düzenlenir ve başvuru sahibi bilgilendirilir.

Bakanlıkça ruhsatlandırılan aynı formül ve farmasötik şekildeki ürün için aynı gerçek veya tüzel kişiye, farklı bir ticari isimle de olsa ikinci bir yerli veya ithal ruhsatı verilemez.

Bakanlıkça ruhsat verilen ürünlerin isimleri, ruhsat sahibinin adı soyadı ve ruhsat numarası ile birlikte Resmi Gazete'de ilan edilir.

Ruhsatın Geçerlilik Süresi

Madde 21- Ruhsatlar 5 (beş) yıl süreyle geçerlidir. Ruhsat sahibi, ruhsatın geçerlilik süresi sona ermeden en az 3 (üç) ay öncesinde, gerekli farmakovijilans verileri ile birlikte ruhsatın verildiği tarihten itibaren tüm değişiklikleri kapsayacak biçimde kalite, güvenilirlik ve etkinliğine ilişkin bilgileri ruhsatın yenilenmesi için Bakanlığa sunar.

Ruhsatın Askıya Alınması

Madde 22- Ruhsatlı bir ürün ile ilgili olarak aşağıdaki durumlardan birinin tespiti halinde, ürüne ait ruhsat Bakanlık tarafından askıya alınır:

a) Normal kullanım şartlarında zararlı etkilerinin ortaya çıkması,

b) Terapötik etkisinin olmadığının tesbiti veya yetersiz olduğunun tesbiti,

c) Ruhsata esas olan formülasyondan farklı bir formülasyon ile üretilmesi,

d) Ruhsata esas formül, doz, farmasötik form, ambalaj ve kısa ürün bilgilerinde Bakanlığın bilgisi ve/veya onayı dışında değişiklik yapılması,

e) Ruhsat sahibi tarafından üretim ve kontrol yöntemleri bakımından bilimsel ve teknik ilerlemelerin dikkate alınmaması ve tıbbi ürünün genel kabul gören bilimsel yöntemlerle üretilmesini ve kontrol edilmesini sağlamak amacıyla gerekli her türlü değişikliğin yapılmaması ve bu değişikliğin Bakanlığın onayına sunulmaması,

f) Yapılan piyasa kontrolleri sonucunda hatalı olduğu tespit edilen ürünler için yapılan uyarının dikkate alınmaması ve hatalı üretime devam edilmesi,

g) Ambalaj ve etiketleme ile ilgili mevzuat hükümlerine uyulmaması ve ruhsat sahibine yapılan uyarının etkisiz kalması,

h) Ruhsat sahibi tarafından, ürünle ilgili olarak Bakanlık talimatlarına ve uyarılarına cevap verilmemesi,

i) Bu Yönetmeliğin hükümlerine göre bir ürünün ruhsatlandırılması için sunulan bilgi ve belgelerde yanlışlık olduğunun tespit edilmesi,

j) Ruhsat verilmiş bir tıbbi ürünün ruhsatlandırıldıktan sonra 3 (üç) yıl içinde fiili olarak pazara sunulmaması,

k) Ruhsatın geçerlik süresinin dolmuş olmasına rağmen bu Yönetmeliğin 21 inci maddesi uyarınca yenileme başvurusunun yapılmamış olması,

l) Farmakovijilans uygulamaları çerçevesinde ulaşan bildirimlerin Bakanlık tarafından yapılan risk/yarar değerlendirilmesi sonucunda ruhsatın askıya alınmasına karar verilmesi.

Ruhsatı askıya alınan bir ürünün üretimi durdurulur. Dağıtımda ve satışta olan ürünler hakkındaki karar, ruhsatın askıya alınma gerekçesi dikkate alınarak, Bakanlıkça verilir.

Ruhsatın İptali

Madde 23- Aşağıda belirtilen durumlardan birinin mevcudiyeti halinde ürün için verilmiş olan ruhsat iptal edilir:

a) Bu Yönetmeliğin 22 nci maddesinde sayılan hallerden biri veya birkaçı sebebiyle ruhsatı askıya alınan ürünler hakkında ruhsat sahibi tarafından en geç 6 (altı) ay içinde askıya alınma gerekçesinin aksini ispatlayan bilgi ve belgelerin sunulmaması,

b) Ruhsat sahibinin talebi ve Bakanlığın uygun görmesi durumunda üretimden vazgeçilmesi.

Ruhsatı iptal edilen bir ürünün üretimi durdurulur. Dağıtımda ve satışta olan ürünler hakkındaki karar, ruhsatın iptal gerekçesi dikkate alınarak Bakanlıkça verilir.

Bakanlıkça ruhsatları iptal edilen ürünlerin isimleri, ruhsat sahibinin adı, soyadı ve ruhsat numaraları ile birlikte Resmi Gazete'de ilan edilir.

Ruhsat Sahibinin Sorumluluğu

Madde 24- Ruhsat sahibi, ruhsatına sahip olduğu ürünle ilgili olarak aşağıdaki hususlarda Bakanlığa karşı sorumludur:

a) Ürünün, başvuru ekinde verilen ve Bakanlıkça kabul edilen spesifikasyonlara uygun olarak üretilmesi,

b) Üretim ve kontrol yöntemleri bakımından bilimsel ve teknik ilerlemelerin dikkate alınması ve tıbbi ürünün genel kabul gören bilimsel yöntemlerle üretilmesini ve kontrol edilmesini sağlamak amacıyla gerekli her türlü değişikliği yapmak üzere Bakanlığın onayına sunulması,

c) Ürünün doğru ve güvenli kullanımını sağlamak için gerektiği durumlarda kısa ürün bilgilerinin ve kullanma talimatının güncelleştirilmesi,

d) Ürünle ilgili herhangi bir değişiklik olduğunda, ilgili kılavuz hükümleri çerçevesinde değişikliğin Bakanlığa bildirilmesi,

e) Ürün hakkında Bakanlıkça talep edilen hususlara cevap verilmesi,

f) Ürünün piyasaya verilmesini takiben farmakovijilans uygulamaları çerçevesinde gerekli yükümlülüklerin yerine getirilmesi,

g) Ürünün biyolojik bir ürün olması durumunda bulaşabilecek enfeksiyonların önlenmesi için tedbirlerin alınmasının sağlanması,

h) Ruhsatına sahip olduğu ürünün piyasada bulanabilirliğinin sağlanması,

ı) Ürünün etkinliği veya halk sağlığının korunması gerekçesiyle ruhsatının askıya alınması veya pazardan çekilmesi ile ilgili alınan her türlü tedbirin tüm gerekçeleriyle birlikte derhal

Bakanlığa bildirilmesi,

i) Ürün ile ilgili olarak mevzuatın gereklerinin yerine getirilmesi,

j) Ürünlerle ilgili belirlenmiş harçların ve ücretlerin ödenmesi.

Ruhsat Sahibi Değişikliği

Madde 25- Bakanlık tarafından ruhsatlandırılmış bir ürününün ruhsat sahibi değişikliği yapılabilir. Ruhsat sahibi değişikliği işlemleri için aşağıdaki bilgi ve belgeler Bakanlığa sunulur:

a) Mahkeme/icra dairesince ruhsat sahibi değişikliğine dair verilmiş karar veya noter huzurunda düzenlenmiş ve aşağıdaki hususları içeren sözleşme,

1) Ruhsat sahibi değişikliği işlemine konu olan ürünün ismi, ruhsat tarihi ve sayısı,

2) Ruhsat sahibi değişikliği ile ruhsatı verecek ve ruhsatı alacak olan gerçek veya tüzel kişilerin isim ve adresleri,

3) Bakanlıkça onaylanmış, tam ve güncellenmiş olan mevcut ürün dosyasının eksiksiz bir biçimde devralan kişiye teslim edildiğine dair tutanak,

b) Ruhsat sahibi değişikliği ile ruhsatı alan kişi, ruhsat sahibinden beklenen tüm sorumlulukları yerine getirme kapasitesine sahip olduğunu gösteren aşağıdaki bilgi ve belgeleri Bakanlığa sunar;

1) Bu Yönetmeliğin 7 nci maddesinde ruhsat başvurusunda bulunabilecek kişiler için belirtilen mesleklerden birine mensup olduğunu gösteren noter onaylı diploma örneği,

2) Tüzel kişi olması durumunda, şirketin kuruluş amaçlarını, ortaklarını ve sorumlu kişilerin görev ve unvanlarını belirten ticaret sicil gazetesinin aslı veya sureti,

3) Farmakovijilans uygulamaları kapsamında ürün güvenliği sorumlusunun özgeçmişi, adresi, telefon ve faks numarası ve bu kişinin görevini tanımlayan belge,

4) 23/10/2003 tarihli ve 25268 sayılı Resmi Gazete'de yayımlanan Beşeri Tıbbi Ürünlerin Tanıtım Faaliyetleri Hakkında Yönetmelik kapsamında bilim servisini tanımlayan belge ve bu servisin adresi, telefon ve faks numarası,

c) Ruhsat sahibi değişikliği ile ruhsatı alan kişinin adı, soyadı, adresi, telefon ve faks numaralarıyla birlikte, ürünün kısa ürün bilgileri, kullanma talimatı, iç ve dış ambalajın birer örneği ve noter aracılığıyla yapılan devirlerde, söz konusu ürün için evvelce verilmiş olan ruhsatın aslı.

Ürünün ithal bir ürün olması durumunda, yukarıda belirtilen bilgi ve belgelere ek olarak, orijin firmanın söz konusu ürünün Türkiye'de ruhsatlandırılması ve satışına ilişkin yetkilendirdiği gerçek veya tüzel kişiyi değiştirdiğine dair orijinal belge ve noter onaylı Türkçe tercümesi ile birlikte Bakanlığa başvuruda bulunulur.

Orijin firmanın söz konusu ürünün Türkiye'de ruhsatlandırılması ve satışına ilişkin yetkilendirdiği gerçek veya tüzel kişiyi tek taraflı değiştirmesi durumunda, orijin firmanın ürünün Türkiye'de ruhsatlandırılmasına ve satışına ilişkin verdiği yetkiyi gösterir, yeni tarihli orijinal belge, noter onaylı Türkçe tercümesi ve bu maddenin birinci fıkrasının (a) bendi hariç, Bakanlıkça onaylanmış tam ve güncellenmiş mevcut ürün dosyası ile birlikte bu maddedeki tüm gerekliliklerin yerine getirilmesi zorunludur.

Ürünlere ilişkin yapılacak olan tüm değişiklikler için ilgili kılavuz hükümlerine göre Bakanlığa ayrı bir başvuruda bulunulur. Değişikliğe ilişkin yapılmış olan başvuru, ürünün ruhsat sahibi değişiklik işlemleri tamamlandıktan sonra Bakanlık tarafından değerlendirmeye alınır.

Bakanlık, eksiksiz bilgi ve belgelerle yapılan ruhsat sahibi değişikliği başvurusunu 60 (altmış) gün içinde sonuçlandırır.

Satış İzni Alınması

Madde 26- Ruhsat sahibi, ruhsatını aldığı beşeri tıbbi bir ürünü ilk kez pazara sunmadan önce, satışa sunulacak son şekliyle iki adet numuneyi satış izni almak üzere Bakanlığa sunar. Bakanlık, satış izni vereceği ürünün numunelerini, kullanma talimatının, ambalaj ve etiket bilgilerinin doğruluğu ve fiyatının uygunluğu açısından inceler. Ürünün ruhsata esas ambalaj ve etiket bilgilerinin ve/veya özelliklerinin değişmesine yol açan işlemler için yeniden satış izni alınması zorunludur.

Ruhsatı alınan ürün, kan ürünü veya kan ürünü içeren beşeri tıbbi ürün ise, ruhsat sahibi bu ürünü piyasaya arz etmeden önce birinci fıkrada yer alan hususlara ek olarak ürünün her serisi için satış izni almak üzere Bakanlığa başvurur. Bu seriye ait ürüne göre yapılacak analizler ulusal bir laboratuvarda veya Bakanlık tarafından bu amaçla atanmış bir laboratuvarda test edilmesini müteakiben verilir.

Kan ürünleri veya kan ürünü içeren beşeri tıbbi ürünlere satış izni alınabilmesi için satışa sunulması talep edilen miktar bildirilerek aşağıda belirtilen belge ve bilgiler Bakanlığa sunulur:

a) Ürünün adı ve içeriği,

b) Her seri için akredite edilmiş ulusal veya uluslararası laboratuvar tarafından verilen Ulusal Sağlık Otoritesi tasdikli seri serbest bırakma sertifikası,

c) Her seri için üretim merkezinin teknik müdürü tarafından onaylanmış analiz sertifikası aslı,

d) Her serinin ruhsatlandırıldığı/üretildiği ülke ile hangi ülkelerde satıldığını gösteren orijin firma tarafından düzenlenmiş belge aslı (apostil onaylı),

e) Plazma bağışında esas alınan kurallar, plazmanın toplanma tarihi ve donör tipi (gönüllü, paralı) ve gerekli durumlarda donörlerin listesi,

f) Her donörün Hepatit B, Hepatit C ve HIV ½ yönünden test edildiği ve plazma havuzunda HCV RNA testinin uygulandığını ve neticelerini belirten yukarıda belirtilen laboratuvar tarafından verilen belge,

g) Her seri için donörlerin Creutzfeld-Jacob (CJ) hastalığı ile ilgili olarak hastalık veya hastalık şüphesi yönünden güvenli olduğuna ve donörler arasında CJ hastalığı tanısı olmadığına dair üretici firma tarafından verilecek orijinal belge (apostil onaylı).

Ruhsatı alınan ürün immünolojik ürün ise; ruhsat sahibi, bu ürünü piyasaya arz etmeden önce birinci fıkrada yer alan hususlara ek olarak ürünün her serisi için satış izni almak üzere Bakanlığa başvurur.

İmmünolojik ürünlere satış izni alınabilmesi için satışa sunulması talep edilen miktar bildirilerek aşağıda belirtilen belge ve bilgiler Bakanlığa sunulur:

a) Her seri için akredite edilmiş ulusal laboratuvar veya uluslararası laboratuvar tarafından verilen Ulusal Sağlık Otoritesi tasdikli Batch / Lot Release Sertifikası,

b) Her seri için üretim merkezinin teknik müdürü tarafından onaylanmış analiz sertifikasının aslı.

Ruhsata İlişkin Değişiklikler
Madde 27- Bir ruhsat verildikten sonra ürüne ilişkin tüm değişiklikler, ilgili kılavuz hükümlerine göre ruhsat sahibi tarafından Bakanlığa sunulur.

DÖRDÜNCÜ BÖLÜM
Çeşitli ve Son Hükümler

Gizlilik
Madde 28- Bir ürüne ruhsat almak üzere başvuru sahibi tarafından Bakanlığa sunulan bilgiler gizlidir. Bu gizlilik Bakanlıkça korunur.

Cezai Hükümler
Madde 29- Bu Yönetmelik hükümlerine uymayanlar hakkında 1/3/1926 tarihli ve 765 sayılı Türk Ceza Kanunu ve ilgili diğer mevzuat hükümleri uygulanır.

Yürürlükten Kaldırılan Mevzuat
Madde 30- 23/12/1993 tarihli ve 21797 sayılı Resmi Gazete'de yayımlanan Radyofarmasötik Yönetmeliği, 2/3/1995 tarihli ve 22218 sayılı Resmi Gazete'de yayımlanan Tıbbi Farmasötik Ürünler Ruhsatlandırma Yönetmeliği ile 20/5/2002 tarihli ve 24760 sayılı Resmi Gazete'de yayımlanan Kan Ürünlerinin Ruhsatlandırılmasına Dair Yönetmelik yürürlükten kaldırılmıştır.

Geçici Madde 1- Bu Yönetmelik yürürlüğe girmeden önce yapılan ruhsat/izin başvuruları, başvurunun yapıldığı tarihte yürürlükte olan mevzuat hükümlerine göre değerlendirilir.
Bu Yönetmeliğin 9 uncu maddesi haricindeki diğer hükümlerinin yürürlüğe gireceği 30/6/2005 tarihine kadar bu Yönetmeliğin 9 uncu maddesine uygun olarak yapılan kısaltılmış başvurular için, yürürlükteki Yönetmelikte yer alan başvuru formatına göre yapılan başvurular kabul edilir.

Geçici Madde 2- Tıbbi farmasötik ürün benzeri ürünlerin izinlerine ilişkin usul ve esasların belirlendiği yönetmelik ile ruhsatlandırılmış veya ruhsatlandırma başvurusu yapılmış beşeri tıbbi ürünlerdeki yapılacak değişiklik başvurularına uygulanacak esasların belirlendiği yönetmelik yürürlüğe girinceye kadar ilgili kılavuzlar mevcut şekliyle uygulanmaya devam edilir.

Geçici Madde 3- Bu Yönetmeliğin yürürlüğe girdiği tarihten önce ithalat izni ile piyasaya arz edilen aşı, antiserum ve allerjen içeren biyolojik ürünlerle ilgili gerekli değerlendirmeler yapılmak üzere ithalat izni sahibi kişiler, bu Yönetmeliğin yürürlüğe girdiği tarihten itibaren 1 (bir) yıl içerisinde Bakanlıkça istenilen belgeler ile ruhsat müracaatında bulunurlar. Bu süre zarfında ruhsat başvurusu yapılmayan ürünlerin ithalat izni geçersiz olur.

Geçici Madde 4- Bu Yönetmeliğin yürürlüğe girdiği tarihten önce 23/12/1993 tarihli ve 21797 sayılı Resmi Gazete'de yayımlanan Radyofarmasötik Yönetmeliğine göre

tescillendirilmiş ürünlerle ilgili gerekli değerlendirmeler yapılmak üzere tescil belgesine sahip ilgili kişiler, bu Yönetmeliğin yürürlüğe girdiği tarihten itibaren 1 (bir) yıl içerisinde Bakanlıkça istenilen belgeler ile ruhsat müracaatında bulunurlar. Bu süre zarfında ruhsat müracaatında bulunulmayan ürünlerin tescil belgeleri geçersiz olur.

Yürürlük

Madde 31- Bu Yönetmeliğin 9 uncu maddesi ile Geçici 1 inci maddesinin ikinci fıkrası 1/1/2005 tarihinden geçerli olmak üzere yayımı tarihinde, diğer hükümleri ise 30/6/2005 tarihinde yürürlüğe girer.

Yürütme

Madde 32- Bu Yönetmelik hükümlerini Sağlık Bakanı yürütür.

(EKLERİ ALINMAMIŞTIR)

EK :4. 2001/83/EC SAYILI DİREKTİF

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►B DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

(OJ L 311, 28.11.2001, p. 67)

Amended by:

		Official Journal		
		No	page	date
►**M1**	Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003	L 33	30	8.2.2003
►**M2**	Commission directive 2003/63/EC of 25 June 2003	L 159	46	27.6.2003
►**M3**	Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004	L 136	85	30.4.2004
►**M4**	Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004	L 136	34	30.4.2004

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DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission;

Having regard to the opinion of the Economic and Social Committee ([1]),

Acting in accordance with the procedure laid down in Article 251 of the Treaty ([2]),

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products ([3]), Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products ([4]), Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products ([5]), Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens ([6]), Council Directive 89/343/EEC of 3 May 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC and laying down additional provisions for radiopharmaceuticals ([7]), Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down special provisions for proprietary medicinal products derived from human blood or human plasma ([8]), Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use ([9]), Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use ([10]), Council Directive 92/27/EEC of 31 March 1992 on the labelling of medicinal products for human use and on package leaflets ([11]), Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use ([12]), Council Directive 92/73/EEC of 22 September 1992 widening the scope

([1]) OJ C 368, 20.12.1999, p. 3.
([2]) Opinion of the European Parliament of 3 July 2001 (not yet published in the Official Journal) and Council Decision of 27 September 2001.
([3]) OJ 22, 9.2.1965, p. 369/65. Directive as last amended by Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
([4]) OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).
([5]) OJ L 147, 9.6.1975, p. 13. Directive as last amended by Commission Directive 2000/38/EC (OJ L 139, 10.6.2000, p. 28).
([6]) OJ L 142, 25.5.1989, p. 14.
([7]) OJ L 142, 25.5.1989, p. 16.
([8]) OJ L 181, 28.6.1989, p. 44.
([9]) OJ L 113, 30.4.1992, p. 1.
([10]) OJ L 113, 30.4.1992, p. 5.
([11]) OJ L 113, 30.4.1992, p. 8.
([12]) OJ L 113, 30.4.1992, p. 13.

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of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products and laying down additional provisions on homeopathic medicinal products [1] have been frequently and substantially amended. In the interests of clarity and rationality, the said Directives should therefore be codified by assembling them in a single text.

(2) The essential aim of any rules governing the production, distribution and use of medicinal products must be to safeguard public health.

(3) However, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.

(4) Trade in medicinal products within the Community is hindered by disparities between certain national provisions, in particular between provisions relating to medicinal products (excluding substances or combinations of substances which are foods, animal feeding-stuffs or toilet preparations), and such disparities directly affect the functioning of the internal market.

(5) Such hindrances must accordingly be removed; whereas this entails approximation of the relevant provisions.

(6) In order to reduce the disparities which remain, rules should be laid down on the control of medicinal products and the duties incumbent upon the Member States' competent authorities should be specified with a view to ensuring compliance with legal requirements.

(7) The concepts of harmfulness and therapeutic efficacy can only be examined in relation to each other and have only a relative significance depending on the progress of scientific knowledge and the use for which the medicinal product is intended. The particulars and documents which must accompany an application for marketing authorization for a medicinal product demonstrate that potential risks are outweighed by the therapeutic efficacy of the product.

(8) Standards and protocols for the performance of tests and trials on medicinal products are an effective means of control of these products and hence of protecting public health and can facilitate the movement of these products by laying down uniform rules applicable to tests and trials, the compilation of dossiers and the examination of applications.

(9) Experience has shown that it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have to be provided with a view to obtaining authorization for a medicinal product which is essentially similar to an authorized product, while ensuring that innovative firms are not placed at a disadvantage.

(10) However, there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause.

(11) The adoption of the same standards and protocols by all the Member States will enable the competent authorities to arrive at their decisions on the basis of uniform tests and by reference to uniform criteria and will therefore help to avoid differences in evaluation.

(12) With the exception of those medicinal products which are subject to the centralized Community authorization procedure established by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the

[1] OJ L 297, 13.10.1992, p. 8.

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Evaluation of Medicinal Products [1] a marketing authorization for a medicinal product granted by a competent authority in one Member State ought to be recognized by the competent authorities of the other Member States unless there are serious grounds for supposing that the authorization of the medicinal product concerned may present a risk to public health. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Community standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(13) For this purpose, a Committee for Proprietary Medicinal Products should be set up attached to the European Agency for the Evaluation of Medicinal Products established in the abovementioned Regulation (EEC) No 2309/93.

(14) This Directive represents an important step towards achievement of the objective of the free movement of medicinal products. Further measures may abolish any remaining barriers to the free movement of proprietary medicinal products will be necessary in the light of experience gained, particularly in the abovementioned Committee for Proprietary Medicinal Products.

(15) In order better to protect public health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorization for medicinal products, Member States should systematically prepare assessment reports in respect of each medicinal product which is authorized by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorization to place a medicinal product on the market which is currently under active consideration in another Member State with a view to recognizing the decision reached by the latter Member State.

(16) Following the establishment of the internal market, specific controls to guarantee the quality of medicinal products imported from third countries can be waived only if appropriate arrangements have been made by the Community to ensure that the necessary controls are carried out in the exporting country.

(17) It is necessary to adopt specific provisions for immunological medicinal products, homeopathic medicinal products, radiopharmaceuticals, and medicinal products based on human blood or human plasma.

(18) Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment [2]. Account should also be taken of Council Directive 80/836/Euratom of 15 July 1980 amending the Directives laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation [3], the objective of which is to prevent the exposure of workers or patients to excessive or unnecessarily high levels of ionizing radiation, and in particular of Article 5c thereof, which requires prior authorization for the addition of radioactive

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

[2] OJ L 265, 5.10.1984, p. 1. Directive repealed with effect from 13 May 2000 by Directive 97/43/Euratom (OJ L 180, 9.7.1997, p. 22).

[3] OJ L 246, 17.9.1980, p. 1. Directive as amended by Directive 84/467/Euratom (OJ L 265, 5.10.1984, p. 4), repealed with effect from 13 May 2000 by Directive 96/29/Euratom (OJ L 314, 4.12.1996, p. 20).

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substances to medicinal products as well as for the importation of such medicinal products.

(19) The Community entirely supports the efforts of the Council of Europe to promote voluntary unpaid blood and plasma donation to attain self-sufficiency throughout the Community in the supply of blood products, and to ensure respect for ethical principles in trade in therapeutic substances of human origin.

(20) The rules designed to guarantee the quality, safety and efficacy of medicinal products derived from human blood or human plasma must be applied in the same manner to both public and private establishments, and to blood and plasma imported from third countries.

(21) Having regard to the particular characteristics of these homeopathic medicinal products, such as the very low level of active principles they contain and the difficulty of applying to them the conventional statistical methods relating to clinical trials, it is desirable to provide a special, simplified registration procedure for those homeopathic medicinal products which are placed on the market without therapeutic indications in a pharmaceutical form and dosage which do not present a risk for the patient.

(22) The anthroposophic medicinal products described in an official pharmacopoeia and prepared by a homeopathic method are to be treated, as regards registration and marketing authorization, in the same way as homeopathic medicinal products.

(23) It is desirable in the first instance to provide users of these homeopathic medicinal products with a very clear indication of their homeopathic character and with sufficient guarantees of their quality and safety.

(24) The rules relating to the manufacture, control and inspection of homeopathic medicinal products must be harmonized to permit the circulation throughout the Community of medicinal products which are safe and of good quality.

(25) The usual rules governing the authorization to market medicinal products should be applied to homeopathic medicinal products placed on the market with therapeutic indications or in a form which may present risks which must be balanced against the desired therapeutic effect. In particular, those Member States which have a homeopathic tradition should be able to apply particular rules for the evaluation of the results of tests and trials intended to establish the safety and efficacy of these medicinal products provided that they notify them to the Commission.

(26) In order to facilitate the movement of medicinal products and to prevent the controls carried out in one Member State from being repeated in another, minimum requirements should be laid down for manufacture and imports coming from third countries and for the grant of the authorization relating thereto.

(27) It should be ensured that, in the Member States, the supervision and control of the manufacture of medicinal products is carried out by a person who fulfils minimum conditions of qualification.

(28) Before an authorization to market an immunological medicinal product or derived from human blood or human plasma can be granted, the manufacturer must demonstrate his ability to attain batch-to-batch consistency. Before an authorization to market a medicinal product derived from human blood or human plasma can be granted, the manufacturer must also demonstrate the absence of specific viral contamination, to the extent that the state of technology permits.

(29) The conditions governing the supply of medicinal products to the public should be harmonized.

(30) In this connection persons moving around within the Community have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It must also

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be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for his personal use.

(31) In addition, by virtue of Regulation (EC) No 2309/93, certain medicinal products are the subject of a Community marketing authorization. In this context, the classification for the supply of medicinal products covered by a Community marketing authorization needs to be established. It is therefore important to set the criteria on the basis of which Community decisions will be taken.

(32) It is therefore appropriate, as an initial step, to harmonize the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonization completed within the framework of the United Nations, concerning narcotic and psychotropic substances.

(33) The provisions dealing with the classification of medicinal products for the purpose of supply do not infringe the national social security arrangements for reimbursement or payment for medicinal products on prescription.

(34) Many operations involving the wholesale distribution of medicinal products for human use may cover several Member States simultaneously.

(35) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Community through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements which must be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.

(36) Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorization. Pharmacists and persons authorized to supply medicinal products to the public, and who confine themselves to this activity, should be exempt from obtaining this authorization. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and persons authorized to supply medicinal products to the public keep records showing transactions in products received.

(37) Authorization must be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State must recognize authorizations granted by other Member States.

(38) Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorized to supply medicinal products to the public certain public service obligations. Those Member States must be able to continue to impose those obligations on wholesalers established within their territory. They must also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those which they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.

(39) Rules should be laid down as to how the labelling and package leaflets are to be presented.

(40) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.

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(41) The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(42) This Directive is without prejudice to the application of measures adopted pursuant to Council Directive 84/450/EEC of 10 September 1984 relating to the approximation of the laws, regulations and administrative provisions of the Member States concerning misleading advertising ([1]).

(43) All Member States have adopted further specific measures concerning the advertising of medicinal products. There are disparities between these measures. These disparities are likely to have an impact on the functioning of the internal market, since advertising disseminated in one Member State is likely to have effects in other Member States.

(44) Council Directive 89/552/EEC of 3 October 1989 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the pursuit of television broadcasting activities ([2]) prohibits the television advertising of medicinal products which are available only on medical prescription in the Member State within whose jurisdiction the television broadcaster is located. This principle should be made of general application by extending it to other media.

(45) Advertising to the general public, even of non-prescription medicinal products, could affect public health, were it to be excessive and ill-considered. Advertising of medicinal products to the general public, where it is permitted, ought therefore to satisfy certain essential criteria which ought to be defined.

(46) Furthermore, distribution of samples free of charge to the general public for promotional ends must be prohibited.

(47) The advertising of medicinal products to persons qualified to prescribe or supply them contributes to the information available to such persons. Nevertheless, this advertising should be subject to strict conditions and effective monitoring, referring in particular to the work carried out within the framework of the Council of Europe.

(48) Advertising of medicinal products should be subject to effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 84/450/EEC.

(49) Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.

(50) Persons qualified to prescribe medicinal products must be able to carry out these functions objectively without being influenced by direct or indirect financial inducements.

(51) It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarize themselves with new products and acquire experience in dealing with them.

(52) Persons qualified to prescribe or supply medicinal products must have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.

([1]) OJ L 250, 19.9.1984, p. 17. Directive as amended by Directive 97/55/EC (OJ L 290, 23.10.1997, p. 18).

([2]) OJ L 298, 17.10.1989, p. 23. Directive as amended by Directive 97/36/EC (OJ L 202, 30.7.1997, p. 60).

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(53) Each undertaking which manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product conforms with the approved conditions of use.

(54) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Community are continually adapted to take account of scientific and technical progress.

(55) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(56) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Community is intended to allow competent authorities to share the information at the same time.

(57) It is the interest of the Community to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(58) Holders of marketing authorisations should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.

(59) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission ([1]).

(60) The Commission should be empowered to adopt any necessary changes to Annex I in order to take into account scientific and technical progress.

(61) This Directive should be without prejudice to the obligations of the Member States concerning the time-limits for transposition of the Directives set out in Annex II, Part B.

HAVE ADOPTED THIS DIRECTIVE:

TITLE I

DEFINITIONS

Article 1

For the purposes of this Directive, the following terms shall bear the following meanings:

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2. *Medicinal product:*

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

([1]) OJ L 184, 17.7.1999, p. 23.

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3. *Substance:*

Any matter irrespective of origin which may be:

— human, e.g.

human blood and human blood products;

— animal, e.g.

micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products;

— vegetable, e.g.

micro-organisms, plants, parts of plants, vegetable secretions, extracts;

— chemical, e.g.

elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

4. *Immunological medicinal product:*

Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) 'allergen product' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

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5. *Homeopathic medicinal product:*

Any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States. A homeopathic medicinal product may contain a number of principles.

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6. *Radiopharmaceutical:*

Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

7. *Radionuclide generator:*

Any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical.

8. ►M4 *Kit* ◄*:*

Any preparation to be reconsitituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.

9. *Radionuclide precursor:*

Any other radionuclide produced for the radio-labelling of another substance prior to administration.

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10. *Medicinal products derived from human blood or human plasma:*

Medicinal products based on blood constitutents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin.

11. *Adverse reaction:*

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

12. *Serious adverse reaction:*

An adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

13. *Unexpected adverse reaction:*

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.

14. *Periodic safety update reports:*

The periodical reports containing the records referred to in Article 104.

15. *Post-authorisation safety study:*

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

16. *Abuse of medicinal products:*

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effets.

17. *Wholesale distribution of medicinal products:*

All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorized or entitled to supply medicinal products to the public in the Member State concerned.

18. *Public service obligation:*

The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.

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18a *Representative of the marketing authorisation holder:*

The person, commonly known as local representative, designated by the marketing authorisation holder to represent him in the Member State concerned.

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19. *Medicinal Prescription:*

Any medicinal prescription issued by a professional person qualified to do so.

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20. *Name of the medicinal product:*

The name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trade mark or the name of the marketing authorisation holder.

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21. *Common name:*

The international non-proprietary name recommended by the World Health Organization, or, if one does not exist, the usual common name.

22. *Strength of the medicinal product:*

The content of the active substances expressed quantitatively per dosage unit, per unit of volume or weight according to the dosage form.

23. *Immediate packaging:*

The container or other form of packaging immediately in contact with the medicinal product.

24. *Outer packaging:*

The packaging into which is placed the immediate packaging.

25. *Labelling:*

Information on the immediate or outer packaging.

26. *Package leaflet:*

A leaflet containing information for the user which accompanies the medicinal product.

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27. *Agency:*

The European Medicines Agency established by Regulation (EC) No 726/2004 ([1]).

28. *Risks related to use of the medicinal product:*

— any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;

— any risk of undesirable effects on the environment.

28a. *Risk-benefit balance:*

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28, first indent.

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29. *Traditional herbal medicinal product:*

A herbal medicinal product that fulfils the conditions laid down in Article 16a(1).

([1]) OJ L 136, 30.4.2004, p. 1.

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30. *Herbal medicinal product:*

Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

31. *Herbal substances:*

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

32. *Herbal preparations:*

Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

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TITLE II

SCOPE

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Article 2

1. This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process.

2. In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.

3. Notwithstanding paragraph 1 and Article 3(4), Title IV of this Directive shall apply to medicinal products intended only for export and to intermediate products.

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Article 3

This Directive shall not apply to:

1. Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the magistral formula).

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2. Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula).

3. Medicinal products intended for research and development trials, but without prejudice to the provisions of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1].

[1] OJ L 121, 1.5.2001, p. 34.

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4. Intermediate products intended for further processing by an authorized manufacturer.

5. Any radionuclides in the form of sealed sources.

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6. Whole blood, plasma or blood cells of human origin, except for plasma which is prepared by a method involving an industrial process.

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Article 4

1. Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionizing radiation.

2. This Directive shall be without prejudice to Council Decision 86/346/EEC of 25 June 1986 accepting on behalf of the Community the European Agreement on the Exchange of Therapeutic Substances of Human Origin ([1]).

3. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

4. This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission.

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Article 5

1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

2. Member States may temporarily authorise the distribution of an unauthorised medicinal product in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

3. Without prejudice to paragraph 1, Member States shall lay down provisions in order to ensure that marketing authorisation holders, manufacturers and health professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised indications or from the use of an unauthorised medicinal product, when such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not national or Community authorisation has been granted.

4. Liability for defective products, as provided for by Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products ([2]), shall not be affected by paragraph 3.

([1]) OJ L 207, 30.7.1986, p. 1.

([2]) OJ L 210, 7.8.1985, p. 29. Directive as last amended by Directive 1999/34/EC of the European Parliament and of the Council (OJ L 141, 4.6.1999, p. 20).

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TITLE III

PLACING ON THE MARKET

CHAPTER 1

Marketing authorization

Article 6

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

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When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1).

1a The marketing authorisation holder shall be responsible for marketing the medicinal product. The designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

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2. The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, ►M4 kits ◄, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals.

Article 7

A marketing authorization shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorized, according to national legislation, to use such medicinal products in an approved health care establishment exclusively from authorized radionuclide generators, ►M4 kits ◄ or radionuclide precursors in accordance with the manufacturer's instructions.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

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(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the WHO, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

(ca) Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged.

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(d) Description of the manufacturing method.

(e) Therapeutic indications, contra-indications and adverse reactions.

(f) Posology, pharmaceutical form, method and route of administration and expected shelf life.

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(g) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

(h) Description of the control methods employed by the manufacturer.

(i) Results of:

— pharmaceutical (physico-chemical, biological or microbiological) tests,

— pre-clinical (toxicological and pharmacological) tests,

— clinical trials.

(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.

(ib) A statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

(j) A summary, in accordance with Article 11, of the product characteristics, a mock-up of the outer packaging, containing the details provided for in Article 54, and of the immediate packaging of the medicinal product, containing the details provided for in Article 55, together with a package leaflet in accordance with Article 59.

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(k) A document showing that the manufacturer is authorised in his own country to produce medicinal products.

(l) Copies of any authorisation obtained in another Member State or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination. Copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61. Details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.

This information shall be updated on a regular basis.

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(m) A copy of any designation of the medicinal product as an orphan medicinal product under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products [1], accompanied by a copy of the relevant Agency opinion.

(n) Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials referred to in point

[1] OJ L 18, 22.1.2000, p. 1.

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(i) of the first subparagraph shall be accompanied by detailed summaries in accordance with Article 12.

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Article 9

In addition to the requirements set out in Articles 8 and 10(1), an application for authorization to market a radionuclide generator shall also contain the following information and particulars:

— a general description of the system together with a detailed description of the components of the system which may affect the composition or quality of the daughter nucleid preparation,

— qualitative and quantitative particulars of the eluate or the sublimate.

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Article 10

1. By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of preclinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.

2. For the purposes of this Article:

(a) ‘reference medicinal product’ shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;

(b) ‘generic medicinal product’ shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not be required of the applicant if he can

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demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

3. In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.

4. Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

5. In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

Article 10a

By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature.

Article 10b

In the case of medicinal products containing active substances used in the composition of authorised medicinal products but not hitherto used in combination for therapeutic purposes, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance.

Article 10c

Following the granting of a marketing authorisation, the authorisation holder may allow use to be made of the pharmaceutical, pre-clinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

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Article 11

The summary of the product characteristics shall contain, in the order indicated below, the following information:

1. name of the medicinal product followed by the strength and the pharmaceutical form.
2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.
3. pharmaceutical form.
4. clinical particulars:
   - 4.1. therapeutic indications,
   - 4.2. posology and method of administration for adults and, where necessary for children,
   - 4.3. contra-indications,
   - 4.4. special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such products and administering them to patients, together with any precautions to be taken by the patient,
   - 4.5. interaction with other medicinal products and other forms of interactions,
   - 4.6. use during pregnancy and lactation,
   - 4.7. effects on ability to drive and to use machines,
   - 4.8. undesirable effects,
   - 4.9. overdose (symptoms, emergency procedures, antidotes).
5. pharmacological properties:
   - 5.1. pharmacodynamic properties,
   - 5.2. pharmacokinetic properties,
   - 5.3. preclinical safety data.
6. pharmaceutical particulars:
   - 6.1. list of excipients,
   - 6.2. major incompatibilities,
   - 6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,
   - 6.4. special precautions for storage,
   - 6.5. nature and contents of container,
   - 6.6. special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product, if appropriate.
7. marketing authorisation holder.
8. marketing authorisation number(s).
9. date of the first authorisation or renewal of the authorisation.
10. date of revision of the text.
11. for radiopharmaceuticals, full details of internal radiation dosimetry.
12. for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

For authorisations under Article 10, those parts of the summary of product characteristics of the reference medicinal product referring to

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indications or dosage forms which were still covered by patent law at the time when a generic medicine was marketed need not be included.

Article 12

1. The applicant shall ensure that, before the detailed summaries referred to in the last subparagraph of Article 8(3) are submitted to the competent authorities, they have been drawn up and signed by experts with the necessary technical or professional qualifications, which shall be set out in a brief curriculum vitae.

2. Persons having the technical and professional qualifications referred to in paragraph 1 shall justify any use made of scientific literature under Article 10a in accordance with the conditions set out in Annex I.

3. The detailed summaries shall form part of the file which the applicant submits to the competent authorities.

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CHAPTER 2

Specific provisions applicable to homeopathic medicinal products

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Article 13

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market within the Community are registered or authorised in accordance with Articles 14, 15 and 16, except where such medicinal products are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993. In case of registrations, Article 28 and Article 29(1) to (3) shall apply.

2. Member States shall establish a special simplified registration procedure for the homeopathic medicinal products referred to in Article 14.

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Article 14

1. Only homeopathic medicinal products which satisfy all of the following conditions may be subject to a special, simplified registration procedure:

— they are administered orally or externally,

— no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto,

— there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

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If new scientific evidence so warrants, the Commission may amend the third indent of the first subparagraph by the procedure referred to in Article 121(2).

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At the time of registration, Member States shall determine the classification for the dispensing of the medicinal product.

2. The criteria and rules of procedure provided for in Article 4(4), Article 17(1) and Articles 22 to 26, 112, 116 and 125 shall apply by analogy to the special, simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

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Article 15

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

— scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,

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— dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography,

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— manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,

— manufacturing authorization for the medicinal product concerned,

— copies of any registrations or authorizations obtained for the same medicinal product in other Member States,

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— one or more mock-ups of the outer packaging and the immediate packaging of the medicinal products to be registered,

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— data concerning the stability of the medicinal product.

Article 16

1. Homeopathic medicinal products other than those referred to in Article 14(1) shall be authorized and labelled in accordance with ►M4 Articles 8, 10, 10a, 10b, 10c and 11 ◄.

2. A Member State may introduce or retain in its territory specific rules for the ►M4 pre-clinical tests ◄ and clinical trials of homeopathic medicinal products other than those referred to in Article 14(1) in accordance with the principles and characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Title IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 14(1).

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CHAPTER 2a

Specific provisions applicable to traditional herbal medicinal products

Article 16a

1. A simplified registration procedure (hereinafter ‘traditional-use registration’) is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

(b) they are exclusively for administration in accordance with a specified strength and posology;

(c) they are an oral, external and/or inhalation preparation;

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(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

2. Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

3. However, in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 or registration pursuant to Article 14, the provisions of this chapter shall not apply.

Article 16b

1. The applicant and registration holder shall be established in the Community.

2. In order to obtain traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

Article 16c

1. The application shall be accompanied by:

(a) the particulars and documents:

(i) referred to in Article 8(3)(a) to (h), (j) and (k);

(ii) the results of the pharmaceutical tests referred to in the second indent of Article 8(3)(i);

(iii) the summary of product characteristics, without the data specified in Article 11(4);

(iv) in case of combinations, as referred to in Article 1(30) or Article 16a(2), the information referred to in Article 16a(1)(e) relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients;

(b) any authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to refuse to grant an authorisation or registration, whether in the Community or a third country, and the reasons for any such decision;

(c) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;

(d) a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.

Annex I shall apply by analogy to the particulars and documents specified in point (a).

2. A corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the

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excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for.

3. The requirement to show medicinal use throughout the period of 30 years, referred to in paragraph 1(c), is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the medicinal product has been reduced during that period.

4. Where the product has been used in the Community for less than 15 years, but is otherwise eligible for simplified registration, the Member State where the application for traditional-use registration has been submitted shall refer the product to the Committee for Herbal Medicinal Products. The Member State shall submit relevant documentation supporting the referral.

The Committee shall consider whether the other criteria for a simplified registration as referred to in Article 16a are fully complied with. If the Committee considers it possible, it shall establish a Community herbal monograph as referred to in Article 16h(3) which shall be taken into account by the Member State when taking its final decision.

Article 16d

1. Without prejudice to Article 16h(1), Chapter 4 of Title III shall apply by analogy to registrations granted in accordance with Article 16a, provided that:

(a) a Community herbal monograph has been established in accordance with Article 16h(3), or

(b) the herbal medicinal product consists of herbal substances, preparations or combinations thereof contained in the list referred to in Article 16f.

2. For other herbal medicinal products as referred to in Article 16a, each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by another Member State in accordance with this chapter.

Article 16e

1. Traditional-use registration shall be refused if the application does not comply with Articles 16a, 16b or 16c or if at least one of the following conditions is fulfilled:

(a) the qualitative and/or quantitative composition is not as declared;

(b) the indications do not comply with the conditions laid down in Article 16a;

(c) the product could be harmful under normal conditions of use;

(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

(e) the pharmaceutical quality is not satisfactorily demonstrated.

2. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 16f

1. A list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products shall be established in accordance with the procedure referred to in Article 121(2). The list shall contain, with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product.

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2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided. Article 16e(1)(c) and (d) shall not apply.

3. If a herbal substance, preparation or a combination thereof ceases to be included in the list referred to in paragraph 1, registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documents referred to in Article 16c(1) are submitted within three months.

Article 16g

1. Articles 3(1) and (2), 4(4), 6(1), 12, 17(1), 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108, 111(1) and (3), 112, 116 to 118, 122, 123, 125, 126, second subparagraph, and 127 of this Directive as well as Commission Directive 91/356/EEC ([1]) shall apply, by analogy, to traditional-use registration granted under this chapter.

2. In addition to the requirements of Articles 54 to 65, any labelling and user package leaflet shall contain a statement to the effect that:

(a) the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use; and

(b) the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.

A Member State may require that the labelling and the user package leaflet shall also state the nature of the tradition in question.

3. In addition to the requirements of Articles 86 to 99, any advertisement for a medicinal product registered under this chapter shall contain the following statement: Traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.

Article 16h

1. A Committee for Herbal Medicinal Products is hereby established. That Committee shall be part of the Agency and shall have the following competence:

(a) as regards simplified registrations, to:

— perform the tasks arising from Article 16c(1) and (4),

— perform the tasks arising from Article 16d,

— prepare a draft list of herbal substances, preparations and combinations thereof, as referred to in Article 16f(1), and

— establish Community monographs for traditional herbal medicinal products, as referred to in paragraph 3 of this Article;

(b) as regards authorisations of herbal medicinal products, to establish Community herbal monographs for herbal medicinal products, as referred to in paragraph 3 of this Article;

(c) as regards referrals to the Agency under Chapter 4 of Title III, in relation to herbal medicinal products as referred to in Article 16a, to perform the tasks set out in Article 32;

(d) where other medicinal products containing herbal substances are referred to the Agency under Chapter 4 of Title III, to give an opinion on the herbal substance where appropriate.

Finally, the Committee for Herbal Medicinal Products shall perform any other task conferred upon it by Community law.

([1]) OJ L 193, 17.7.1991, p. 30.

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The appropriate coordination with the Committee for Human Medicinal Products shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 57(2) of Regulation (EEC) No 2309/93.

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Herbal Medicinal Products.

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent national authorities.

The said Committee may coopt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

With a view to the coopting of such members, the said Committee shall identify the specific complementary scientific competence of the additional member(s). Coopted members shall be chosen among experts nominated by Member States or the Agency.

The members of the said Committee may be accompanied by experts in specific scientific or technical fields.

3. The Committee for Herbal Medicinal Products shall establish Community herbal monographs for herbal medicinal products with regard to the application of Article 10(1)(a)(ii) as well as traditional herbal medicinal products. The said Committee shall fulfil further responsibilities conferred upon it by provisions of this chapter and other Community law.

When Community herbal monographs within the meaning of this paragraph have been established, they shall be taken into account by the Member States when examining an application. Where no such Community herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Community herbal monographs are established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. The general provisions of Regulation (EEC) No 2309/93 relating to the Committee for Human Medicinal Products shall apply by analogy to the Committee for Herbal Medicinal Products.

Article 16i

Before 30 April 2007, the Commission shall submit a report to the European Parliament and to the Council concerning the application of the provisions of this chapter.

The report shall include an assessment on the possible extension of traditional-use registration to other categories of medicinal products.

▼B

CHAPTER 3

Procedures relevant to the marketing authorization

▼M4

Article 17

1. Member States shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 210 days after the submission of a valid application.

▼**M4**

Applications for marketing authorisations in two or more Member States in respect of the same medicinal product shall be submitted in accordance with Articles 27 to 39.

2. Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that Articles 27 to 39 apply.

Article 18

Where a Member State is informed in accordance with Article 8(3)(1) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it was submitted in compliance with Articles 27 to 39.

▼**B**

Article 19

In order to examine the application submitted in accordance with ►**M4** Articles 8, 10, 10a, 10b and 10c ◄, the competent authority of the Member State:

1. must verify whether the particulars submitted in support of the application comply with the said ►**M4** Articles 8, 10, 10a, 10b and 10c ◄ and examine whether the conditions for issuing an authorization to place medicinal products on the market (marketing authorization) are complied with.
2. may submit the medicinal product, its starting materials and, if need be, its intermediate products or other constituent materials, for testing by ►**M4** an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose ◄ in order to ensure that the control methods employed by the manufacturer and described in the particulars accompanying the application in accordance with Article 8(3)(h) are satisfactory.
3. may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the ►**M4** Articles 8(3), 10, 10a, 10b and 10c ◄. Where the competent authority avails itself of this option, the time limits laid down in Article 17 shall be suspended until such time as the supplementary information required has been provided. Likewise, these time limits shall be suspended for the time allowed the applicant, where appropriate, for giving oral or written explanation.

Article 20

Member States shall take all appropriate measures to ensure that:

(a) the competent authorities verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to Article 8(3)(d), and/or to carry out controls according to the methods described in the particulars accompanying the application in accordance with Article 8(3)(h);

(b) the competent authorities may allow manufacturers and importers of medicinal products coming from third countries, ►**M4** in justifiable cases ◄, to have certain stages of manufacture and/or certain of the controls referred to in (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.

Article 21

1. When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.

▼B

2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.

▼M4

3. The competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which they have authorised.

4. The competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests and the clinical trials of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The competent authorities shall make publicly accessible without delay the assessment report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each indication applied for.

Article 22

In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. This authorisation may be granted only for objective, verifiable reasons and must be based on one of the grounds set out in Annex I. Continuation of the authorisation shall be linked to the annual reassessment of these conditions. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

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Article 23

After an authorization has been issued, the authorization holder must, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

These changes shall be subject to the approval of the competent authority of the Member State concerned.

▼M4

The authorisation holder shall forthwith supply to the competent authority any new information which might entail the amendment of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11, or 32(5), or Annex I.

In particular, he shall forthwith inform the competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned.

In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

▼M4

Article 23a

After a marketing authorisation has been granted, the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.

The holder shall also notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. Such notification shall, otherwise than in exceptional circumstances, be made no less than 2 months before the interruption in the placing on the market of the product.

Upon request by the competent authority, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in his possession relating to the volume of prescriptions.

Article 24

1. Without prejudice to paragraphs 4 and 5, a marketing authorisation shall be valid for five years.

2. The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.

To this end, the marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months before the marketing authorisation ceases to be valid in accordance with paragraph 1.

3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with paragraph 2.

4. Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.

5. When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.

6. The competent authority may, in exceptional circumstances and on public health grounds grant exemptions from paragraphs 4 and 5. Such exemptions must be duly justified.

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Article 25

Authorization shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorization holder.

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Article 26

1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that:

(a) the risk-benefit balance is not considered to be favourable; or

(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.

▼M4

2. Authorisation shall likewise be refused if any particulars or documents submitted in support of the application do not comply with Articles 8, 10, 10a, 10b and 10c.

3. The applicant or the holder of a marketing authorisation shall be responsible for the accuracy of the documents and the data submitted.

CHAPTER 4

Mutual recognition procedure and decentralised procedure

Article 27

1. A coordination group shall be set up for the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in this Chapter. The Agency shall provide the secretariat of this coordination group.

2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of three years. Members of the coordination group may arrange to be accompanied by experts.

3. The coordination group shall draw up its own Rules of Procedure, which shall enter into force after a favourable opinion has been given by the Commission. These Rules of Procedure shall be made public.

Article 28

1. With a view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10b, 10c and 11. The documents submitted shall include a list of Member States concerned by the application.

The applicant shall request one Member State to act as 'reference Member State' and to prepare an assessment report on the medicinal product in accordance with paragraphs 2 or 3.

2. Where the medicinal product has already received a marketing authorisation at the time of application, the concerned Member States shall recognise the marketing authorisation granted by the reference Member State. To this end, the marketing authorisation holder shall request the reference Member State either to prepare an assessment report on the medicinal product or, if necessary, to update any existing assessment report. The reference Member State shall prepare or update the assessment report within 90 days of receipt of a valid application. The assessment report together with the approved summary of product characteristics, labelling and package leaflet shall be sent to the concerned Member States and to the applicant.

3. In cases where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall request the reference Member State to prepare a draft assessment report, a draft summary of product characteristics and a draft of the labelling and package leaflet. The reference Member State shall prepare these draft documents within 120 days after receipt of a valid application and shall send them to the concerned Member States and to the applicant.

4. Within 90 days of receipt of the documents referred to in paragraphs 2 and 3, the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the reference Member State accordingly. The reference Member State shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

5. Each Member State in which an application has been submitted in accordance with paragraph 1 shall adopt a decision in conformity with

▼M4

the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved, within 30 days after acknowledgement of the agreement.

Article 29

1. If, within the period laid down in Article 28(4), a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group.

2. Guidelines to be adopted by the Commission shall define a potential serious risk to public health.

3. Within the coordination group, all Member States referred to in paragraph 1 shall use their best endeavours to reach agreement on the action to be taken. They shall allow the applicant the opportunity to make his point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly. Article 28(5) shall apply.

4. If the Member States fail to reach an agreement within the 60-day period laid down in paragraph 3, the Agency shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34. The Agency shall be provided with a detailed statement of the matters on which the Member States have been unable to reach agreement and the reasons for their disagreement. A copy shall be forwarded to the applicant.

5. As soon as the applicant is informed that the matter has been referred to the Agency, he shall forthwith forward to the Agency a copy of the information and documents referred to in the first subparagraph of Article 28(1).

6. In the circumstances referred to in paragraph 4, Member States that have approved the assessment report, the draft summary of product characteristics and the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.

Article 30

1. If two or more applications submitted in accordance with Articles 8, 10, 10a, 10b, 10c and 11 have been made for marketing authorisation for a particular medicinal product, and if Member States have adopted divergent decisions concerning the authorisation of the medicinal product or its suspension or revocation, a Member State, the Commission or the applicant or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use, hereinafter referred to as 'the Committee', for the application of the procedure laid down in Articles 32, 33 and 34.

2. In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up.

The coordination group shall lay down a list taking into account the proposals from all Member States and shall forward this list to the Commission.

The Commission or a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer these products to the Committee in accordance with paragraph 1.

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Article 31

1. The Member States or the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary, in particular to take account of the information collected in accordance with Title IX.

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the applicant or the marketing authorisation holder.

The Member States and the applicant or the marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

2. Where the referral to the Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation.

In that event, Article 35 shall apply to those medicinal products only if they were covered by the authorisation procedures referred to in this Chapter.

Article 32

1. When reference is made to the procedure laid down in this Article, the Committee shall consider the matter concerned and shall issue a reasoned opinion within 60 days of the date on which the matter was referred to it.

However, in cases submitted to the Committee in accordance with Articles 30 and 31, this period may be extended by the Committee for a further period of up to 90 days, taking into account the views of the applicants or the marketing authorisation holders concerned.

In an emergency, and on a proposal from its Chairman, the Committee may agree to a shorter deadline.

2. In order to consider the matter, the Committee shall appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee shall define their tasks and specify the time-limit for the completion of these tasks.

3. Before issuing its opinion, the Committee shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations within a time limit which it shall specify.

The opinion of the Committee shall be accompanied by a draft summary of product characteristics for the product and a draft text of the labelling and package leaflet.

If necessary, the Committee may call upon any other person to provide information relating to the matter before it.

The Committee may suspend the time-limits referred to in paragraph 1 in order to allow the applicant or the marketing authorisation holder to prepare explanations.

4. The Agency shall forthwith inform the applicant or the marketing authorisation holder where the opinion of the Committee is that:

(a) the application does not satisfy the criteria for authorisation; or

(b) the summary of the product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 11 should be amended; or

▼M4

(c) the authorisation should be granted subject to certain conditions, in view of conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance; or

(d) a marketing authorisation should be suspended, varied or revoked.

Within 15 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of his intention to request a re-examination of the opinion. In that case, he shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee shall re-examine its opinion in accordance with the fourth subparagraph of Article 62(1) of Regulation (EC) No 726/2004. The reasons for the conclusion reached shall be annexed to the assessment report referred to in paragraph 5 of this Article.

5. Within 15 days after its adoption, the Agency shall forward the final opinion of the Committee to the Member States, to the Commission and to the applicant or the marketing authorisation holder, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining an authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the opinion:

(a) a draft summary of the product characteristics, as referred to in Article 11;

(b) any conditions affecting the authorisation within the meaning of paragraph 4(c);

(c) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

(d) the proposed text of the labelling and leaflet.

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Article 33

Within ►M4 15 days ◄ of the receipt of the opinion, the Commission shall prepare a draft of the decision to be taken in respect of the application, taking into account Community law.

In the event of a draft decision which envisages the granting of marketing authorization, the documents referred to in ►M4 Article 32(5), second subparagraph ◄ shall be annexed.

Where, exceptionally, the draft decision is not in accordance with the opinion of the Agency, the Commission shall also annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to the Member States and the applicant ►M4 or the marketing authorisation holder ◄.

▼M4

Article 34

1. The Commission shall take a final decision in accordance with, and within 15 days after the end of, the procedure referred to in Article 121(3).

2. The rules of procedure of the Standing Committee established by Article 121(1) shall be adjusted to take account of the tasks incumbent upon it under this Chapter.

Those adjustments shall entail the following provisions:

(a) except in cases referred to in the third paragraph of Article 33, the opinion of the Standing Committee shall be given in writing;

(b) Member States shall have 22 days to forward their written observations on the draft decision to the Commission. However, if a decision has to be taken urgently, a shorter time-limit may be set by the Chairman according to the degree of urgency involved.

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This time-limit shall not, otherwise than in exceptional circumstances, be shorter than 5 days;

(c) Member States shall have the option of submitting a written request that the draft Decision be discussed in a plenary meeting of the Standing Committee.

Where, in the opinion of the Commission, the written observations of a Member State raise important new questions of a scientific or technical nature which have not been addressed in the opinion delivered by the Agency, the Chairman shall suspend the procedure and refer the application back to the Agency for further consideration.

The provisions necessary for the implementation of this paragraph shall be adopted by the Commission in accordance with the procedure referred to in Article 121(2).

3. The decision as referred to in paragraph 1 shall be addressed to all Member States and reported for information to the marketing authorisation holder or applicant. The concerned Member States and the reference Member State shall either grant or revoke the marketing authorisation, or vary its terms as necessary to comply with the decision within 30 days following its notification, and they shall refer to it. They shall inform the Commission and the Agency accordingly.

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Article 35

1. Any application by the marketing authorization holder to vary a marketing authorization which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorized the medicinal product concerned.

The Commission shall, in consultation with the Agency, adopt appropriate arrangements for the examination of variations to the terms of a marketing authorization.

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These arrangements shall be adopted by the Commission in the form of an implementing Regulation in accordance with the procedure referred to in Article 121(2).

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 32, 33 and 34 shall apply by analogy to variations made to marketing authorizations.

Article 36

1. Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.

2. Without prejudice to the provisions of Article 31, in exceptional cases, where urgent action is essential to protect public health, until a definitive decision is adopted a Member State may suspend the marketing and the use of the medicinal product concerned on its territory. It shall inform the Commission and the other Member States no later than the following working day of the reasons for its action.

Article 37

Articles 35 and 36 shall apply by analogy to medicinal products authorized by Member States following an opinion of the Committee given in accordance with Article 4 of Directive 87/22/EEC before 1 January 1995.

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Article 38

1. The Agency shall publish an annual report on the operation of the procedures laid down in this Chapter and shall forward that report to the European Parliament and the Council for information.

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2. At least every ten years the Commission shall publish a report on the experience acquired on the basis of the procedures described in this Chapter and shall propose any amendments which may be necessary to improve those procedures. The Commission shall submit this report to the European Parliament and to the Council.

Article 39

Article 29(4), (5) and (6) and Articles 30 to 34 shall not apply to the homeopathic medicinal products referred to in Article 14.

Articles 28 to 34 shall not apply to the homeopathic medicinal products referred to in Article 16(2).

▼B

TITLE IV

MANUFACTURE AND IMPORTATION

Article 40

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required nothwithstanding that the medicinal products manufactured are intended for export.

2. The authorization referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

However, such authorization shall not be required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorized in the Member States to carry out such processes.

3. Authorization referred to in paragraph 1 shall also be required for imports coming from third countries into a Member State; this Title and Article 118 shall have corresponding application to such imports as they have to manufacture.

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4. The Member States shall forward to the Agency a copy of the authorisation referred to in paragraph 1. The Agency shall enter that information on the Community database referred to in Article 111(6).

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Article 41

In order to obtain the manufacturing authorization, the applicant shall meet at least the following requirements:

(a) specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled;

(b) have at his disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements which the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 20;

(c) have at his disposal the services of at least one qualified person within the meaning of Article 48.

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The applicant shall provide particulars in support of the above in his application.

Article 42

1. The competent authority of the Member State shall issue the manufacturing authorization only after having made sure of the accuracy of the particulars supplied pursuant to Article 41, by means of an inquiry carried out by its agents.

2. In order to ensure that the requirements referred to in Article 41 are complied with, authorization may be made conditional on the carrying out of certain obligations imposed either when authorization is granted or at a later date.

3. The authorization shall apply only to the premises specified in the application and to the medicinal products and pharmaceutical forms specified in that same application.

Article 43

The Member States shall take all appropriate measures to ensure that the time taken for the procedure for granting the manufacturing authorization does not exceed 90 days from the day on which the competent authority receives the application.

Article 44

If the holder of the manufacturing authorization requests a change in any of the particulars referred to in points (a) and (b) of the first paragraph of Article 41, the time taken for the procedure relating to this request shall not exceed 30 days. In exceptional cases this period of time may be extended to 90 days.

Article 45

The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 41 and concerning the qualified person referred to in Article 48; where the competent authority concerned exercises this right, application of the time-limits referred to in Article 43 and 44 shall be suspended until the additional data required have been supplied.

Article 46

The holder of a manufacturing authorization shall at least be obliged:

(a) to have at his disposal the services of staff who comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

(b) to dispose of the authorized medicinal products only in accordance with the legislation of the Member States concerned;

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant to Article 41; the competent authority shall, in any event, be immediately informed if the qualified person referred to in Article 48 is replaced unexpectedly;

(d) to allow the agents of the competent authority of the Member State concerned access to his premises at any time;

(e) to enable the qualified person referred to in Article 48 to carry out his duties, for example by placing at his disposal all the necessary facilities;

▼M4

(f) to comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.

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This point shall also be applicable to certain excipients, the list of which as well as the specific conditions of application shall be established by a Directive adopted by the Commission in accordance with the procedure referred to in Article 121(2).

Article 46a

1. For the purposes of this Directive, manufacture of active substances used as starting materials shall include both total and partial manufacture or import of an active substance used as a starting material as defined in Part I, point 3.2.1.1 (b) Annex I, and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabelling, such as are carried out by a distributor of starting materials.

2. Any amendments necessary to adapt paragraph 1 to new scientific and technical developments shall be laid down in accordance with the procedure referred to in Article 121(2).

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Article 47

The principles and guidelines of good manufacturing practices for medicinal products referred to in Article 46(f) shall be adopted in the form of a directive, in accordance with the procedure referred to in Article 121(2).

Detailed guidelines in line with those principles will be published by the Commission and revised necessary to take account of technical and scientific progress.

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The principles of good manufacturing practice for active substances used as starting materials referred to in point (f) of Article 46 shall be adopted in the form of detailed guidelines.

The Commission shall also publish guidelines on the form and content of the authorisation referred to in Article 40(1), on the reports referred to in Article 111(3) and on the form and content of the certificate of good manufacturing practice referred to in Article 111(5).

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Article 48

1. Member States shall take all appropriate measures to ensure that the holder of the manufacturing authorization has permanently and continuously at his disposal the services of at least one qualified person, in accordance with the conditions laid down in Article 49, responsible in particular for carrying out the duties specified in Article 51.

2. If he personally fulfils the conditions laid down in Article 49, the holder of the authorization may himself assume the responsibility referred to in paragraph 1.

Article 49

1. Member States shall ensure that the qualified person referred to in Article 48 fulfils the ►M4 ———— ◄ conditions of qualification set out in paragraphs 2 and 3.

2. A qualified person shall be in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course of study, or a course recognized as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study in one of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology.

However, the minimum duration of the university course may be three and a half years where the course is followed by a period of theoretical and practical training of a minimum duration of one year and including

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a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university courses or two courses recognized by the State as equivalent co-exist in a Member State and where one of these extends over four years and the other over three years, the three-year course leading to a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course or its recognized equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as the diplomas, certificates or other evidence of formal qualifications awarded on completion of both courses are recognized as equivalent by the State in question.

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

— ►M4 Experimental physics ◄
— General and inorganic chemistry
— Organic chemistry
— Analytical chemistry
— Pharmaceutical chemistry, including analysis of medicinal products
— General and applied biochemistry (medical)
— Physiology
— Microbiology
— Pharmacology
— Pharmaceutical technology
— Toxicology
— Pharmacognosy (study of the composition and effects of the natural active substances of plant and animal origin).

Studies in these subjects should be so balanced as to enable the person concerned to fulfil the obligations specified in Article 51.

In so far as certain diplomas, certificates or other evidence of formal qualifications mentioned in the first subparagraph do not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.

3. The qualified person shall have acquired practical experience over at least two years, in one or more undertakings which are authorized to manufacture medicinal products, in the activities of qualitative analysis of medicinal products, of quantitative analysis of active substances and of the testing and checking necessary to ensure the quality of medicinal products.

The duration of practical experience may be reduced by one year where a university course lasts for at least five years and by a year and a half where the course lasts for at least six years.

Article 50

1. A person engaging in the activities of the person referred to in Article 48 from the time of the application of Directive 75/319/EEC, in a Member State without complying with the provisions of Article 49 shall be eligible to continue to engage in those activities ►M4 within the Community ◄.

2. The holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course — or a course recognized as equivalent by the Member State concerned — in a scientific discipline allowing him to engage in the activities of the person referred to in Article 48 in accordance with the laws of that State may — if he began his course prior to 21 May 1975 — be considered as qualified to carry out in that State the duties of the person referred to in Article 48 provided that he has previously engaged in the following activities for at least two years before 21 May 1985 following notification of this directive in one or more undertakings authorized to manufacture: production supervision and/or

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qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of the person referred to in Article 48 to ensure the quality of the medicinal products.

If the person concerned has acquired the practical experience referred to in the first subparagraph before 21 May 1965, a further one year's practical experience in accordance with the conditions referred to in the first subparagraph will be required to be completed immediately before he engages in such activities.

Article 51

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing:

(a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization;

▼M4

(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the Community, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

▼B

The batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph of paragraph 1 have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person must certify in a register or equivalent document provided for that purpose, that each production batch satisfies the provisions of this Article; the said register or equivalent document must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years.

Article 52

Member States shall ensure that the duties of qualified persons referred to in Article 48 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

Member States may provide for the temporary suspension of such a person upon the commencement of administrative or disciplinary procedures against him for failure to fulfil his obligations.

▼B

Article 53

The provisions of this Title shall also apply to homeopathic medicinal products.

TITLE V

LABELLING AND PACKAGE LEAFLET

Article 54

The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:

▼M4

(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults; where the product contains up to three active substances, the international non-proprietary name (INN) shall be included, or, if one does not exist, the common name;

▼B

(b) a statement of the active substances expressed qualitatively and quantitatively per dosage unit or according to the form of administration for a given volume or weight, using their common names;

(c) the pharmaceutical form and the contents by weight, by volume or by number of doses of the product;

(d) a list of those excipients known to have a recognized action or effect and included in the ►M4 detailed guidance ◄ published pursuant to Article 65. However, if the product is injectable, or a topical or eye preparation, all excipients must be stated;

▼M4

(e) the method of administration and, if necessary, the route of administration. Space shall be provided for the prescribed dose to be indicated;

(f) a special warning that the medicinal product must be stored out of the reach and sight of children;

▼B

(g) a special warning, if this is necessary for the medicinal product;

(h) the expiry date in clear terms (month/year);

(i) special storage precautions, if any;

▼M4

(j) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products, where appropriate, as well as reference to any appropriate collection system in place;

(k) the name and address of the marketing authorisation holder and, where applicable, the name of the representative appointed by the holder to represent him;

▼B

(l) the number of the authorization for placing the medicinal product on the market;

(m) the manufacturer's batch number;

▼M4

(n) in the case of non-prescription medicinal products, instructions for use.

▼B

Article 55

1. The particulars laid down ►M4 in Article 54 ◄ shall appear on immediate packagings other than those referred to in paragraphs 2 and 3.

▼B

2. The following particulars at least shall appear on immediate packagings which take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 54 and 62.

▼M4

— the name of the medicinal product as laid down in point (a) of Article 54,

▼B

— the name of the holder of the authorization for placing the product on the market,

— the expiry date,

— the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 54 and 62 cannot be displayed:

▼M4

— the name of the medicinal product as laid down in point (a) of Article 54 and, if necessary, the route of administration,

▼B

— the method of administration,

— the expiry date,

— the batch number,

— the contents by weight, by volume or by unit.

Article 56

The particulars referred to in Articles 54, 55 and 62 shall be easily legible, clearly comprehensible and indelible.

▼M4

Article 56a

The name of the medicinal product, as referred to in Article 54, point (a) must also be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package information leaflet is made available on request from patients' organisations in formats appropriate for the blind and partially-sighted.

▼B

Article 57

Notwithstanding Article 60, Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

— the price of the medicinal product,

— the reimbursement conditions of social security organizations,

— the legal status for supply to the patient, in accordance with Title VI,

— identification and authenticity.

▼M4

For medicinal products authorised under Regulation (EC) No 726/2004, Member States shall, when applying this Article, observe the detailed guidance referred to in Article 65 of this Directive.

▼B

Article 58

The inclusion in the packaging of all medicinal products of a package leaflet shall be obligatory unless all the information required by Articles 59 and 62 is directly conveyed on the outer packaging or on the immediate packaging.

▼M4

Article 59

1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:

(a) for the identification of the medicinal product:

(i) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the product contains only one active substance and if its name is an invented name;

(ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;

(b) the therapeutic indications;

(c) a list of information which is necessary before the medicinal product is taken:

(i) contra-indications;

(ii) appropriate precautions for use;

(iii) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, foodstuffs) which may affect the action of the medicinal product;

(iv) special warnings;

(d) the necessary and usual instructions for proper use, and in particular:

(i) the dosage,

(ii) the method and, if necessary, route of administration;

(iii) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

and, as appropriate, depending on the nature of the product:

(iv) the duration of treatment, where it should be limited;

(v) the action to be taken in case of an overdose (such as symptoms, emergency procedures);

(vi) what to do when one or more doses have not been taken;

(vii) indication, if necessary, of the risk of withdrawal effects;

(viii) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product;

(e) a description of the adverse reactions which may occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case; the patient should be expressly asked to communicate any adverse reaction which is not mentioned in the package leaflet to his doctor or pharmacist;

(f) a reference to the expiry date indicated on the label, with:

(i) a warning against using the product after that date;

(ii) where appropriate, special storage precautions;

(iii) if necessary, a warning concerning certain visible signs of deterioration;

(iv) the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances, using common names, for each presentation of the medicinal product;

(v) for each presentation of the product, the pharmaceutical form and content in weight, volume or units of dosage;

(vi) the name and address of the marketing authorisation holder and, where applicable, the name of his appointed representatives in the Member States;

(vii) the name and address of the manufacturer;

(g) where the medicinal product is authorised in accordance with Articles 28 to 39 under different names in the Member States concerned, a list of the names authorised in each Member State;

▼M4

(h) the date on which the package leaflet was last revised.

2. The list set out in point (c) of paragraph 1 shall:

(a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women, the elderly, persons with specific pathological conditions);

(b) mention, if appropriate, possible effects on the ability to drive vehicles or to operate machinery;

(c) list those excipients knowledge of which is important for the safe and effective use of the medicinal product and which are included in the detailed guidance published pursuant to Article 65.

3. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

▼B

Article 60

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Title.

Article 61

▼M4

1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the draft package leaflet, shall be submitted to the authorities competent for authorising marketing when the marketing authorisation is requested. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.

▼B

2. The competent authority shall refuse the marketing authorization if the labelling or the package leaflet do not comply with the provisions of this Title or if they are not in accordance with the particulars listed in the summary of product characteristics.

3. All proposed changes to an aspect of the labelling or the package leaflet covered by this Title and not connected with the summary of product characteristics shall be submitted to the authorities competent for authorizing marketing. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

4. The fact that the competent authority do not refuse a marketing authorization pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer ►M4 and ◄ the marketing authorization holder.

Article 62

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information mentioned in Articles 54 and 59(1) and other information compatible with the summary of the product characteristics which is useful ►M4 for the patient ◄, to the exclusion of any element of a promotional nature.

Article 63

1. The particulars for labelling listed in Articles 54, 59 and 62 shall appear in the official language or languages of the Member State where the product is placed on the market.

The first subparagraph shall not prevent these particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

▼M4

In the case of certain orphan medicinal products, the particulars listed in Article 54 may, on reasoned request, appear in only one of the official languages of the Community.

2. The package leaflet must be written and designed to be clear and understandable, enabling the users to act appropriately, when necessary with the help of health professionals. The package leaflet must be clearly legible in the official language or languages of the Member State in which the medicinal product is placed on the market.

The first subparagraph shall not prevent the package leaflet from being printed in several languages, provided that the same information is given in all the languages used.

3. When the product is not intended to be delivered directly to the patient, the competent authorities may grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State in which the product is placed on the market.

▼B

Article 64

Where the provisions of this Title are not complied with, and a notice served on the person concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorization, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Title.

▼M4

Article 65

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

(a) the wording of certain special warnings for certain categories of medicinal products;

(b) the particular information needs relating to non-prescription medicinal products;

(c) the legibility of particulars on the labelling and package leaflet;

(d) the methods for the identification and authentication of medicinal products;

(e) the list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated;

(f) harmonised provisions for the implementation of Article 57.

▼B

Article 66

1. The outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars mentioned in Article 54. In addition, the labelling on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information:

— the name or code of the medicinal product, including the name or chemical symbol of the radionuclide,

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— the batch identification and expiry date,

— the international symbol for radioactivity,

▼M4

— the name and address of the manufacturer,

▼B

— the amount of radioactivity as specified in paragraph 2.

Article 67

The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with the provisions of Article 59. In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 68

Without prejudice to the provisions of Article 69, homeopathic medicinal products shall be labelled in accordance with the provisions of this title and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 69

1. In addition to the clear mention of the words ‘homeopathic medicinal product’, the labelling and, where appropriate, the package insert for the medicinal products referred to in Article 14(1) shall bear the following, and no other, information:

▼M4

— the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 1(5); if the homeopathic medicinal product is composed of two or more stocks, the scientific names of the stocks on the labelling may be supplemented by an invented name,

▼B

— name and address of the registration holder and, where appropriate, of the manufacturer,

— method of administration and, if necessary, route,

— expiry date, in clear terms (month, year),

— pharmaceutical form,

— contents of the sales presentation,

— special storage precautions, if any,

— a special warning if necessary for the medicinal product,

— manufacturer's batch number,

— registration number,

— ‘homeopathic medicinal product without approved therapeutic indications’,

▼M4

— a warning advising the user to consult a doctor if the symptoms persist.

▼B

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

— the price of the medicinal product,

— the conditions for refunds by social security bodies.

▼B

TITLE VI

CLASSIFICATION OF MEDICINAL PRODUCTS

Article 70

1. When a marketing authorization is granted, the competent authorities shall specify the classification of the medicinal product into:

— a medicinal product subject to medical prescription,

— a medicinal product not subject to medical prescription.

To this end, the criteria laid down in Article 71(1) shall apply.

2. The competent authorities may fix sub-categories for medicinal products which are available on medical prescription only. In that case, they shall refer to the following classification:

▼M4

(a) medicinal products on medical prescription for renewable or non-renewable delivery;

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(b) medicinal products subject to special medical prescription;

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(c) medicinal products on 'restricted' medical prescription, reserved for use in certain specialised areas.

▼B

Article 71

1. Medicinal products shall be subject to medical prescription where they:

— are likely to present a danger either directly or indirectly, even when used correctly, if utilized without medical supervision, or

— are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or

— contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or

— are normally prescribed by a doctor to be administered parenterally.

2. Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:

— the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971, or

— the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or

— the medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.

3. Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:

— the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment,

— the medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere, or

— the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

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4. A competent authority may waive application of paragraphs 1, 2 and 3 having regard to:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; and/or

(b) other circumstances of use which it has specified.

5. If a competent authority does not designate medicinal products into sub-categories referred to in Article 70(2), it shall nevertheless take into account the criteria referred to in paragraphs 2 and 3 of this Article in determining whether any medicinal product shall be classified as a prescription-only medicine.

Article 72

Medicinal products not subject to prescription shall be those which do not meet the criteria listed in Article 71.

Article 73

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of classification. They shall update this list annually.

▼M4

Article 74

When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the classification of a medicinal product by applying the criteria listed in Article 71.

Article 74a

Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised.

▼B

Article 75

Each year, Member States shall communicate to the Commission and to the other Member States, the changes that have been made to the list referred to in Article 73.

TITLE VII

WHOLESALE DISTRIBUTION OF MEDICINAL PRODUCTS

Article 76

►M4 1. ◄ Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorization has been granted in accordance with Community law are distributed on their territory.

▼M4

2. In the case of wholesale distribution and storage, medicinal products shall be covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.

3. Any distributor, not being the marketing authorisation holder, who imports a product from another Member State shall notify the marketing authorisation holder and the competent authority in the Member State to which the product will be imported of his intention to import it. In the case of products which have not been granted an authorisation pursuant to Regulation (EC) No 726/2004, the notification to the competent authority shall be without prejudice to

▼M4

additional procedures provided for in the legislation of that Member State.

▼B

Article 77

1. Member States shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to the possession of an authorization to engage in activity as a wholesaler in medicinal products, stating the place for which it is valid.

2. Where persons authorized or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorization provided for in paragraph 1.

3. Possession of a manufacturing authorization shall include authorization to distribute by wholesale the medicinal products covered by that authorization. Possession of an authorization to engage in activity as a wholesaler in medicinal products shall not give dispensation from the obligation to possess a manufacturing authorization and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. At the request of the Commission or any Member State, Member States shall supply all appropriate information concerning the individual authorizations which they have granted under paragraph 1.

5. Checks on the persons authorized to engage in the activity of wholesaler in medicinal products and the inspection of their premises, shall be carried out under the responsibility of the Member State which granted the authorization.

6. The Member State which granted the authorization referred to in paragraph 1 shall suspend or revoke that authorization if the conditions of authorization cease to be met. It shall forthwith inform the other Member States and the Commission thereof.

7. Should a Member State consider that, in respect of a person holding an authorization granted by another Member State under the terms of paragraph 1, the conditions of authorization are not, or are no longer met, it shall forthwith inform the Commission and the other Member State involved. The latter shall take the measures necessary and shall inform the Commission and the first Member State of the decisions taken and the reasons for those decisions.

Article 78

Member States shall ensure that the time taken for the procedure for examining the application for the distribution authorization does not exceed 90 days from the day on which the competent authority of the Member State concerned receives the application.

The competent authority may, if need be, require the applicant to supply all necessary information concerning the conditions of authorization. Where the authority exercises this option, the period laid down in the first paragraph shall be suspended until the requisite additional data have been supplied.

Article 79

In order to obtain the distribution authorization, applicants must fulfil the following minimum requirements:

(a) they must have suitable and adequate premises, installations and equipment, so as to ensure proper conservation and distribution of the medicinal products;

(b) they must have staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

(c) they must undertake to fulfil the obligations incumbent on them under the terms of Article 80.

▼B

Article 80

Holders of the distribution authorization must fulfil the following minimum requirements:

(a) they must make the premises, installations and equipment referred to in Article 79(a) accessible at all times to the persons responsible for inspecting them;

(b) they must obtain their supplies of medicinal products only from persons who are themselves in possession of the distribution authorization or who are exempt from obtaining such authorization under the terms of Article 77(3);

(c) they must supply medicinal products only to persons who are themselves in possession of the distribution authorization or who are authorized or entitled to supply medicinal products to the public in the Member State concerned;

(d) they must have an emergency plan which ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorization holder for the medicinal product concerned;

(e) they must keep records either in the form of purchase/sales invoices, or on computer, or in any other form, giving for any transaction in medicinal products received or dispatched at least the following information:

— date,

▼M4

— name of the medicinal product,

▼B

— quantity received or supplied,

— name and address of the supplier or consignee, as appropriate;

(f) they must keep the records referred to under (e) available to the competent authorities, for inspection purposes, for a period of five years;

(g) they must comply with the principles and guidelines of good distribution practice for medicinal products as laid down in Article 84.

▼M4

Article 81

With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a distribution authorisation which has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

The holder of a marketing authorisation for a medicinal product and the distributors of the said medicinal product actually placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

▼B

Article 82

For all supplies of medicinal products to a person authorized or entitled to supply medicinal products to the public in the Member State

▼B

concerned, the authorized wholesaler must enclose a document that makes it possible to ascertain:

— the date,

▼M4

— the name and pharmaceutical form of the medicinal product,

▼B

— the quantity supplied,

— the name and address of the supplier and consignor.

Member States shall take all appropriate measures to ensure that persons authorized or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 83

The provisions of this Title shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

— narcotic or psychotropic substances within their territory,

— medicinal products derived from blood,

— immunological medicinal products,

— radiopharmaceuticals.

▼M4

Article 84

The Commission shall publish guidelines on good distribution practice. To this end, it shall consult the Committee for Medicinal Products for Human Use and the Pharmaceutical Committee established by Council Decision 75/320/EEC ([1]).

Article 85

This Title shall apply to homeopathic medicinal products.

▼B

TITLE VIII

ADVERTISING

Article 86

1. For the purposes of this Title, 'advertising of medicinal products' shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products; it shall include in particular:

— the advertising of medicinal products to the general public,

— advertising of medicinal products to persons qualified to prescribe or supply them,

— visits by medical sales representatives to persons qualified to prescribe medicinal products,

— the supply of samples,

— the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal,

— sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products,

— sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith.

([1]) OJ L 147, 9.6.1975, p. 23.

▼B

2. The following are not covered by this Title:

— the labelling and the accompanying package leaflets, which are subject to the provisions of Title V,

— correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product,

— factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims,

▼M4

— information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products.

▼B

Article 87

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorization has not been granted in accordance with Community law.

2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product:

— shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties,

— shall not be misleading.

▼M4

Article 88

1. Member States shall prohibit the advertising to the general public of medicinal products which:

(a) are available on medical prescription only, in accordance with Title VI;

(b) contain substances defined as psychotropic or narcotic by international convention, such as the United Nations Conventions of 1961 and 1971.

2. Medicinal products may be advertised to the general public which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.

3. Member States shall be entitled to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.

4. The prohibition contained in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes.

TITLE VIIIa

INFORMATION AND ADVERTISING

Article 88a

Within three years of the entry into force of Directive 2004/726/EC, the Commission shall, following consultations with patients' and consumers' organisations, doctors' and pharmacists' organisations, Member States and other interested parties, present to the European Parliament

▼M4

and the Council a report on current practice with regard to information provision — particularly on the Internet — and its risks and benefits for patients.

Following analysis of the above data, the Commission shall, if appropriate, put forward proposals setting out an information strategy to ensure good-quality, objective, reliable and non-promotional information on medicinal products and other treatments and shall address the question of the information source's liability.

▼B

Article 89

1. Without prejudice to Article 88, all advertising to the general public of a medicinal product shall:

(a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;

(b) include the following minimum information:

— the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance,

— the information necessary for correct use of the medicinal product,

— an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.

▼M4

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its international non-proprietary name, where this exists, or the trademark if it is intended solely as a reminder.

▼B

Article 90

The advertising of a medicinal product to the general public shall not contain any material which:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;

(b) suggests that the effects of taking the medicine are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicine;

(d) suggests that the health of the subject could be affected by not taking the medicine; this prohibition shall not apply to the vaccination campaigns referred to in Article 88(4);

(e) is directed exclusively or principally at children;

(f) refers to a recommendation by scientists, health professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a foodstuff, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

▼B

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof.

▼M4

▼B

Article 91

1. Any advertising of a medicinal product to persons qualified to prescribe or supply such products shall include:

— essential information compatible with the summary of product characteristics;

— the supply classification of the medicinal product.

Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.

▼M4

2. Member States may decide that the advertising of a medicinal product to persons qualified to prescribe or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

▼B

Article 92

1. Any documentation relating to a medicinal product which is transmitted as part of the promotion of that product to persons qualified to prescribe or supply it shall include, as a minimum, the particulars listed in Article 91(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 93

1. Medical sales representatives shall be given adequate training by the firm which employs them and shall have sufficient scientific knowledge to be able to provide information which is precise and as complete as possible about the medicinal products which they promote.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 91(1).

3. Medical sales representatives shall transmit to the scientific service referred to in Article 98(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 94

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

▼M4

2. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than health-care professionals.

▼B

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3.

▼M4

Article 95

The provisions of Article 94(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes; such hospitality shall always be strictly limited to the main scientific objective of the event; it must not be extended to persons other than health-care professionals.

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Article 96

1. Free samples shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

(a) the number of samples for each medicinal product each year on prescription shall be limited;

(b) any supply of samples shall be in response to a written request, signed and dated, from the prescribing agent;

(c) those supplying samples shall maintain an adequate system of control and accountability;

▼M4

(d) each sample shall be no larger than the smallest presentation on the market;

▼B

(e) each sample shall be marked ‘free medical sample — not for sale’ or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing psychotropic or narcotic substances within the meaning of international conventions, such as the United Nations Conventions of 1961 and 1971, may be supplied.

2. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 97

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organizations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Title, may take legal action against such advertisement, or bring such advertisement before an administrative authority competent either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or administrative authorities powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

— to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising, or

▼B

— if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication,

even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in the second subparagraph to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or administrative authorities powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

— to require publication of that decision in full or in part and in such form as they deem adequate,

— to require in addition the publication of a corrective statement.

5. Paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 98

1. The marketing authorization holder shall establish, within his undertaking, a scientific service in charge of information about the medicinal products which he places on the market.

2. The marketing authorization holder shall:

— keep available for, or communicate to, the authorities or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from his undertaking together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination,

— ensure that advertising of medicinal products by his undertaking conforms to the requirements of this Title,

— verify that medical sales representatives employed by his undertaking have been adequately trained and fulfill the obligations imposed upon them by Article 93(2) and (3),

— supply the authorities or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities,

— ensure that the decisions taken by the authorities or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

▼M4

3. The Member States shall not prohibit the co-promotion of a medicinal product by the holder of the marketing authorisation and one or more companies nominated by him.

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Article 99

Member States shall take the appropriate measures to ensure that the provisions of this Title are applied and shall determine in particular what penalties shall be imposed should the provisions adopted in the execution of Title be infringed.

▼M4

Article 100

Advertising of the homeopathic medicinal products referred to in Article 14(1) shall be subject to the provisions of this Title with the exception of Article 87(1).

However, only the information specified in Article 69(1) may be used in the advertising of such medicinal products.

▼B

TITLE IX

PHARMACOVIGILANCE

Article 101

The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the competent authorities.

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The Member States may impose specific requirements on doctors and other health-care professionals in respect of the reporting of suspected serious or unexpected adverse reactions.

Article 102

In order to ensure the adoption of appropriate and harmonised regulatory decisions concerning the medicinal products authorised within the Community, having regard to information obtained about adverse reactions to medicinal products under normal conditions of use, the Member States shall operate a pharmacovigilance system. This system shall be used to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, and to evaluate such information scientifically.

Member States shall ensure that suitable information collected within this system is communicated to the other Member States and the Agency. The information shall be recorded in the database referred to in point (l) of the second subparagraph of Article 57(1) of Regulation (EC) No 726/2004 and shall be permanently accessible to all Member States and without delay to the public.

This system shall also take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks.

Article 102a

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities in order to guarantee their independence.

▼B

Article 103

The marketing authorization holder shall have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance.

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That qualified person shall reside in the Community and shall be responsible for the following:

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(a) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the company, and to medical representatives, is collected and collated in order to be accessible at least at one point within the Community;

▼B

(b) the preparation for the competent authorities of the reports referred to in Article 104, in such form as may be laid down by those authorities, in accordance with the guidance referred to in Article 106(1);

(c) ensuring that any request from the competent authorities for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;

(d) the provision to the competent authorities, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorization safety studies.

▼M4

Article 104

1. The marketing authorisation holder shall be required to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country.

Save in exceptional circumstances, these reactions shall be communicated electronically in the form of a report in accordance with the guidelines referred to in Article 106(1).

2. The marketing authorisation holder shall be required to record all suspected serious adverse reactions which are brought to his attention by a health-care professional and to report them promptly to the competent authority of the Member State on whose territory the incident occurred, and no later than 15 days following the receipt of the information.

3. The marketing authorisation holder shall be required to record and report all other suspected serious adverse reactions which meet the notification criteria in accordance with the guidelines referred to in Article 106(1), of which he can reasonably be expected to have knowledge, promptly to the competent authority of the Member State in whose territory the incident occurred, and no later than 15 days following the receipt of the information.

4. The marketing authorisation holder shall ensure that all suspected serious unexpected adverse reactions and any suspected transmission via a medicinal product of any infectious agent occurring in the territory of a third country are reported promptly in accordance with the guidelines referred to in Article 106(1), so that the Agency and the competent authorities of the Member States in which the medicinal product is authorised are informed of them, and no later than 15 days following the receipt of the information.

5. By way of derogation from paragraphs 2, 3 and 4, in the case of medicinal products which are covered by Directive 87/22/EEC or which have qualified for the procedures laid down in Articles 28 and 29 of this Directive or which have been the subject of the procedures under Articles 32, 33 and 34 of this Directive, the marketing authorisation holder shall also ensure that all suspected serious adverse reactions occurring in the Community are reported in such a way as to be accessible to the reference Member State or to any competent authority acting as reference Member State. The reference Member State shall assume the responsibility of analysing and monitoring such adverse reactions.

6. Unless other requirements have been laid down as a condition for the granting of the marketing authorisation, or subsequently as indicated in the guidelines referred to in Article 106(1), reports of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, immediately upon request or at least every six months after authorisation and until the placing on the market. Periodic safety update reports shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year

▼M4

for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.

The periodic safety update reports shall include a scientific evaluation of the risk-benefit balance of the medicinal product.

7. The Commission may lay down provisions to amend paragraph 6 in view of experience gained through its operation. The Commission shall adopt the provisions in accordance with the procedure referred to in Article 121(2).

8. Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in paragraph 6 in accordance with the procedure laid down by Commission Regulation (EC) No 1084/2003 ([1]).

9. The holder of a marketing authorisation may not communicate information relating to pharmacovigilance concerns to the general public in relation to its authorised medicinal product without giving prior or simultaneous notification to the competent authority.

In any case, the marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

Member States shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge these obligations is subject to effective, proportionate and dissuasive penalties.

Article 105

1. The Agency, in collaboration with the Member States and the Commission, shall set up a data-processing network to facilitate the exchange of pharmacovigilance information regarding medicinal products marketed in the Community in order to allow all competent authorities to share the information at the same time.

2. Making use of the network referred to in paragraph 1, Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are promptly made available to the Agency and the other Member States, and in any case within 15 days after their notification at the latest.

3. The Member States shall ensure that reports of suspected serious adverse reactions that have taken place on their territory are promptly made available to the marketing authorisation holder, and in any case within 15 days after their notification at the latest.

Article 106

1. In order to facilitate the exchange of information on pharmacovigilance within the Community, the Commission, after consulting the Agency, the Member States and interested parties, shall draw up guidelines on the collection, verification and presentation of adverse reaction reports, including technical requirements for electronic exchange of pharmacovigilance information in accordance with internationally agreed formats, and shall publish a reference to an internationally agreed medical terminology.

Acting in accordance with the guidelines, marketing authorisation holders shall use internationally agreed medical terminology for the reporting of adverse reactions.

These guidelines shall be published in Volume 9 of The Rules governing Medicinal Products in the European Community and shall take account of international harmonisation work carried out in the field of pharmacovigilance.

2. For the interpretation of the definitions referred to in points (11) to (16) of Article 1 and of the principles outlined in this Title, the

([1]) OJ L 159, 27.6.2003, p. 1.

▼M4

marketing authorisation holder and the competent authorities shall follow the guidelines referred to in paragraph 1.

Article 107

1. Where, as a result of the evaluation of pharmacovigilance data, a Member State considers that a marketing authorisation should be suspended, revoked or varied in accordance with the guidelines referred to in Article 106(1), it shall forthwith inform the Agency, the other Member States and the marketing authorisation holder.

2. Where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation of a medicinal product, provided that the Agency, the Commission and the other Member States are informed no later than the following working day.

When the Agency is informed in accordance with paragraph 1 in relation to suspensions and revocation, or the first subparagraph of this paragraph, the Committee shall prepare an opinion within a time-frame to be determined depending on the urgency of the matter. In relation to variations, the Committee may upon request from a Member State prepare an opinion.

Acting on the basis of this opinion, the Commission may request all Member States in which the product is being marketed to take temporary measures immediately.

The final measures shall be adopted in accordance with the procedure referred to in Article 121(3).

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Article 108

Any amendments which may be necessary to update provisions of Articles 101 to 107 to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

TITLE X

SPECIAL PROVISIONS ON MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

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Article 109

For the collection and testing of human blood and human plasma, Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC ([1]) shall apply.

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Article 110

Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma. For this purpose, they shall encourage the voluntary unpaid donation of blood and plasma and shall take the necessary measures to develop the production and use of products derived from human blood or human plasma coming from voluntary unpaid donations. They shall notify the Commission of such measures.

([1]) OJ L 33, 8.2.2003, p. 30.

▼B

TITLE XI

SUPERVISION AND SANCTIONS

Article 111

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1. The competent authority of the Member State concerned shall ensure, by means of repeated inspections, and if necessary unannounced inspections, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples, that the legal requirements governing medicinal products are complied with.

The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice referred to in Article 47. These inspections may also be carried out at the request of a Member State, the Commission or the Agency.

In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia ([1]) (European Directorate for the quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.

The competent authority of the Member State concerned may carry out inspections of starting material manufacturers at the specific request of the manufacturer himself.

Such inspections shall be carried out by officials representing the competent authority who shall be empowered to:

(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products or of active substances used as starting materials, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;

(b) take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;

(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;

(d) inspect the premises, records and documents of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX, and in particular Articles 103 and 104.

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2. Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch-to-batch consistency.

▼M4

3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good manufacturing practice laid down in Article 47 or, where appropriate, with the requirements laid down in Articles 101 to 108. The content of such reports shall be communicated to the manufacturer or marketing authorisation holder who has undergone the inspection.

([1]) OJ L 158, 25.6.1994, p. 19.

▼M4

4. Without prejudice to any arrangements which may have been concluded between the Community and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1.

5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice shall be issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by Community legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6. Member States shall enter the certificates of good manufacturing practice which they issue in a Community database managed by the Agency on behalf of the Community.

7. If the outcome of the inspection as referred to in paragraph 1 is that the manufacturer does not comply with the principles and guidelines of good manufacturing practice as provided for by Community legislation, the information shall be entered in the Community database as referred to in paragraph 6.

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Article 112

Member States shall take all appropriate measures to ensure that the holder of the marketing authorization for a medicinal product and, where appropriate, the holder of the manufacturing authorization, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Article 113

For the purpose of implementing Article 112, Member States may require manufacturers of immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 51.

Article 114

1. Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:

— live vaccines,
— immunological medicinal products used in the primary immunization of infants or of other groups at risk,
— immunological medicinal products used in public health immunization programmes,
— new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,

to submit samples from each batch of the bulk and/or the medicinal product for examination ►M4 by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose ◄ before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority of that Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities may require the marketing

▼B

authorization holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk and/or the medicinal product for testing ►M4 by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose ◄ before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

▼M4

Article 116

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out.

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Article 117

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1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

(a) the medicinal product is harmful under normal conditions of use; or

(b) it lacks therapeutic efficacy; or

(c) the risk-benefit balance is not favourable under the authorised conditions of use; or

(d) its qualitative and quantitative composition is not as declared; or

(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

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2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

▼B

Article 118

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

▼M4

Article 119

The provisions of this Title shall apply to homeopathic medicinal products.

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TITLE XII

STANDING COMMITTEE

Article 120

Any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

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Article 121

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, hereinafter called 'the Standing Committee', in the task of adapting to technical progress the directives on the removal of technical barriers to trade in the medicinal products sector.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Articles 4 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 4(3) of Decision 1999/468/EC shall be set at one month.

4. The Standing Committee shall adopt its own rules of procedure which shall be made public.

▼B

TITLE XIII

GENERAL PROVISIONS

▼M4

Article 122

1. Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Articles 40 and 77, on the certificates referred to in Article 111(5) or on the marketing authorisations are fulfilled.

2. Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111(3) to the competent authorities of another Member State.

▼M4

3. The conclusions reached in accordance with Article 111(1) shall be valid throughout the Community.

However, in exceptional cases, if a Member State is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 111(1), that Member State shall forthwith inform the Commission and the Agency. The Agency shall inform the Member States concerned.

When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States which are not parties to the disagreement.

▼B

Article 123

1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith.

2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 124

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 122 and 123.

Article 125

Every decision referred to in this Directive which is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

Such decision shall be notified to the party concerned, together with information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress.

▼M4

Decisions to grant or revoke a marketing authorisation shall be made publicly available.

▼B

Article 126

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

▼M4

Article 126a

1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI.

3. Before granting such an authorisation a Member State shall:

(a) notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant an authorisation under this Article in respect of the product concerned; and

(b) request the competent authority in that State to furnish a copy of the assessment report referred to in Article 21(4) and of the marketing authorisation in force in respect of the said medicinal product.

4. The Commission shall set up a publicly accessible register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the authorisation holder. The Commission shall amend the register of medicinal products accordingly and make this register available on their website.

5. No later than 30 April 2008, the Commission shall present a report to the European Parliament and the Council concerning the application of this provision with a view to proposing any necessary amendments.

Article 126b

In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry which could affect their impartiality. These persons shall make an annual declaration of their financial interests.

In addition, the Member States shall ensure that the competent authority makes publicly accessible its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

▼B

Article 127

1. At the request of the manufacturer, the exporter or the authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of the manufacturing authorization. When issuing such certificates Member States shall comply with the following conditions:

(a) they shall have regard to the prevailing administrative arrangements of the World Health Organization;

(b) for medicinal products intended for export which are already authorized on their territory, they shall supply the summary of the product characteristics as approved in accordance with Article 21.

2. When the manufacturer is not in possession of a marketing authorization he shall provide the authorities responsible for establishing the certificate referred to in paragraph 1, with a declaration explaining why no marketing authorization is available.

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Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004 and the Scientific Committee in its opinion refers to recommended conditions or restrictions with regard to the safe and effective use of the medicinal product as provided for in Article 9(4)(c) of that Regulation, a decision addressed to the Member States shall be adopted in accordance with the procedure provided for in Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.

Article 127b

Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

▼**B**

TITLE XIV

FINAL PROVISIONS

Article 128

Directives 65/65/EEC, 75/318/EEC, 75/319/EEC, 89/342/EEC, 89/343/EEC, 89/381/EEC, 92/25/EEC, 92/26/EEC, 92/27/EEC, 92/28/EEC and 92/73/EEC, amended by the Directives referred to in Annex II, Part A, are repealed, without prejudice to the obligations of the Member States concerning the time-limits for implementation set out in Annex II, Part B.

References to the repealed Directives shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex III.

Article 129

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Communities*.

Article 130

This Directive is addressed to the Member States.

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ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

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Introduction and general principles

(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10 (1) shall be presented in accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in The rules governing medicinal products in the European Community, Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).

(2) The particulars and documents shall be presented as five modules: Module 1 provides European Community specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH [1] regions (European Community, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to above.

(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full or abridged application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products (CPMP) and published by the European Medicine Evaluation Agency (EMEA) and the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

(6) The manufacturing process shall comply with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use [2] and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4.

(7) All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [3]. To be taken into account during the assessment of an application, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.

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[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[2] OJ L 193, 17.7.1991, p. 30.
[3] OJ L 121, 1.5.2001, p. 34.

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(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Council Directives 87/18/EEC on the harmonisation of regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their application for tests in chemical substances [1] and 88/320/EEC on the inspection and verification of good laboratory practice (GLP) [2].

(10) Member States shall also ensure that all tests on animals are conducted in accordance with Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulation and administrative provisions of the Member States regarding the protection of animals for experimental and other scientific purposes.

(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulations (EC) No 1084/2003 [3] and (EC) No 1085/2003 [4] of the Commission or, if relevant, in accordance with national provisions, as well as the requirements in Volume 9 of Commission publication The rules governing medicinal products in the European Community.

This Annex is divided in four different parts:

— Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).

— Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).

— Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.

— Part IV deals with 'Advanced therapy medicinal products' and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

1.1. Table of contents

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.

1.2. Application form

The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

(1) OJ L 15, 17.1.1987, p. 29.
(2) OJ L 145, 11.6.1988, p. 35.
(3) See p. 1 of this Official Journal.
(4) See p. 24 of this Official Journal.

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Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 40, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 11 as approved by Member States and a list of countries in which an application has been submitted.

As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.

1.3. **Summary of product characteristics, labelling and package leaflet**

1.3.1. *Summary of product characteristics*

The applicant shall propose a summary of the product characteristics, in accordance with Article 11.

1.3.2. *Labelling and package leaflet*

A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Title V on the labelling of medicinal products for human use (Article 63) and on package leaflet (Article 59).

1.3.3. *Mock-ups and specimens*

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.

1.3.4. *Summaries of product characteristics already approved in the Member States*

Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Articles 11 and 21 as approved by Member States, where applicable and a list of countries in which an application has been submitted.

1.4. **Information about the experts**

In accordance with Article 12 (2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. **Specific requirements for different types of applications**

Specific requirements for different types of applications are addressed in Part II of the present Annex.

1.6. **Environmental risk assessment**

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products containing or consisting of GMOs (Genetically Modified Organisms) within the meaning of Article 2 of Directive 2001/18/EC of the European

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Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of modified organisms and repealing Council Directive 90/220/EEC ([1]) shall be addressed.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of the said Directive.

The information shall consist of:

— an introduction;

— a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;

— the information requested in Annexes II to IV of the Directive 2001/18/EC, including detection and identification methods as well as unique code of the GMO, plus any additional information on the GMO or the product of relevance to evaluating the environmental risk;

— an environment risk assessment (ERA) report prepared on basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of Directive 2001/18/EC;

— taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the Summary of Product Characteristics, labelling and package leaflet;

— appropriate measures in order to inform the public.

A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

2. MODULE 2: SUMMARIES

This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 12 of this Directive.

Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

Information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. **Overall table of contents**

Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. **Introduction**

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.

2.3. **Quality overall summary**

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

([1]) OJ L 106, 17.4.2001, p. 1.

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Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. **Non-clinical overview**

An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.

For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. **Clinical overview**

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. **Non-clinical summary**

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/in vitro shall be provided as factual written and tabulated summaries which shall be presented in the following order:

— Introduction
— Pharmacology Written Summary
— Pharmacology Tabulated Summary
— Pharmaco-kinetics Written Summary
— Pharmaco-kinetics Tabulated Summary
— Toxicology Written Summary
— Toxicology Tabulated Summary.

2.7. **Clinical Summary**

A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarised clinical information shall be presented in the following order:

— Summary of Bio-pharmaceutics and Associated Analytical Methods
— Summary of Clinical Pharmacology Studies
— Summary of Clinical Efficacy
— Summary of Clinical Safety

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— Synopses of Individual Studies

3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. **Format and presentation**

The general outline of Module 3 is as follows:

— Table of contents
— Body of data
  — *Active substance*

    General Information

    — Nomenclature
    — Structure
    — General Properties

    Manufacture

    — Manufacturer(s)
    — Description of Manufacturing Process and Process Controls
    — Control of Materials
    — Controls of Critical Steps and Intermediates
    — Process Validation and/or Evaluation
    — Manufacturing Process Development

    Characterisation

    — Elucidation of Structure and other Characteristics
    — Impurities

    Control of Active Substance

    — Specification
    — Analytical Procedures
    — Validation of Analytical Procedures
    — Batch Analyses
    — Justification of Specification

    Reference Standards or Materials

    Container Closure System

    Stability

    — Stability Summary and Conclusions
    — Post-approval Stability Protocol and Stability Commitment
    — Stability Data
  — *Finished Medicinal Product*

    Description and Composition of the Medicinal Product

    Pharmaceutical Development

    — Components of the Medicinal Product
      — Active Substance
      — Excipients
    — Medicinal Product
      — Formulation Development
      — Overages
      — Physicochemical and Biological Properties
    — Manufacturing Process Development
    — Container Closure System
    — Microbiological Attributes
    — Compatibility

    Manufacture

    — Manufacturer(s)
    — Batch Formula
    — Description of Manufacturing Process and Process Controls
    — Controls of Critical Steps and Intermediates
    — Process Validation and/or Evaluation

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Control of Excipients

— Specifications
— Analytical Procedures
— Validation of Analytical Procedures
— Justification of Specifications
— Excipients of Human or Animal Origin
— Novel Excipients

Control of Finished Medicinal Product

— Specification(s)
— Analytical Procedures
— Validation of Analytical Procedures
— Batch Analyses
— Characterisation of Impurities
— Justification of Specification(s)

Reference Standards or Materials

Container Closure System

Stability

— Stability Summary and Conclusion
— Post-approval Stability Protocol and Stability Commitment
— Stability Data

— *Appendices*

— Facilities and Equipment (Biological Medicinal Products only)
— Adventitious Agents Safety Evaluation
— Excipients

— *European Community Additional Information*

— Process Validation Scheme for the Medicinal Product
— Medical Device
— Certificate(s) of Suitability
— Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)

— Literature References

3.2. **Content: basic principles and requirements**

(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a

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method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

(6) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines.

(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the

(i) detailed description of the manufacturing process,

(ii) quality control during manufacture, and

(iii) process validation

to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.

In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines or by the supply of scientific data to substantiate this compliance.

(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well

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as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.

(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.

(12) Where applicable and if needed, a CE marking which is required by Community legislation on medical devices shall be provided.

Special attention shall be paid to the following selected elements.

3.2.1. *Active substance(s)*

3.2.1.1. General information and information related to the starting and raw materials

a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, chemical name(s).

The structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

b) For the purposes of this Annex, starting materials shall mean all the materials from which the active substance is manufactured or extracted.

For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

A biological medicinal product is a product, the active substance of which is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma as defined, respectively in paragraphs (4) and (10) of Article 1; medicinal products falling within the scope of Part A of the Annex to Regulation (EEC) No 2309/93; advanced therapy medicinal products as defined in Part IV of this Annex.

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing process of the active substance(s)

a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Raw materials shall be listed and their quality and controls shall also be documented.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) For biological medicinal products, the following additional requirements shall apply.

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The origin and history of starting materials shall be described and documented.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond.

Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.

The manufacturing facilities and equipment shall be described.

d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3. Characterisation of the active substance(s)

Data highlighting the structure and other characteristics of the active substance(s) shall be provided.

Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.

The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5. Reference standards or materials

Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.

3.2.1.6. Container and closure system of the active substance

A description of the container and the closure system(s) and their specifications shall be provided.

3.2.1.7. Stability of the active substance (s)

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised

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b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format

c) The post authorisation stability protocol and stability commitment shall be provided

3.2.2. *Finished medicinal product*

3.2.2.1. Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

— the active substance(s),

— the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,

— the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),

— these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in Article 8 (3) (c):

— in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

— in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

— in respect of colouring matter, designation by the 'E' code assigned to them in Council Directive 78/25/EEC of 12 December 1977 on the approximation of the rules of the Member States concerning the colouring matters authorised for use in medicinal products [1] and/or European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs [2].

In order to give the 'quantitative composition' of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.

For medicinal products containing an active substance, which is the subject of an application for marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological

(1) OJ L 11, 14.1.1978, p. 18.
(2) OJ L 237, 10.9.1994, p. 13.

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activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.2.2. Pharmaceutical development

This chapter shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.

The studies described in this chapter are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant chapters of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.

a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.

b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.

c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.

d) Any overages in the formulation(s) shall be warranted.

e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.

f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.

g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.

h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.

i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.2.3. Manufacturing process of the finished medicinal product

a) The description of the manufacturing method accompanying the application for Marketing Authorisation pursuant to Article 8 (3) (d), shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

— mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

— in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,

— experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,

— for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,

— a detailed batch formula.

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The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.

c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipients

a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Colouring matter shall, in all cases, satisfy the requirements of Directives 78/25/EEC and/or 94/36/EC. In addition, colouring matter shall meet purity criteria as laid down in Directive 95/45/EC, as amended.

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.

c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the Official Journal of the European Union.

Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

d) Novel excipients:

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance(s) of Module 3.

Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.

Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.

Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and

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have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.2.7. Container and closure of the finished medicinal product

A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finished medicinal product

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in case of vaccines, information on cumulative stability shall be provided where appropriate;

c) The post authorisation stability protocol and stability commitment shall be provided.

4. MODULE 4: NON-CLINICAL REPORTS

4.1. **Format and Presentation**

The general outline of Module 4 is as follows:

— Table of contents
— Study reports
  — *Pharmacology*
    — Primary Pharmaco-dynamics
    — Secondary Pharmaco-dynamics
    — Safety Pharmacology
    — Pharmaco-dynamic Interactions
  — *Pharmaco-kinetics*
    — Analytical Methods and Validation Reports
    — Absorption
    — Distribution
    — Metabolism
    — Excretion
    — Pharmaco-kinetic Interactions (non-clinical)
    — Other Pharmaco-kinetic Studies
  — *Toxicology*
    — Single-Dose Toxicity
    — Repeat-Dose Toxicity
    — Genotoxicity
      — In vitro
      — In vivo (including supportive toxico-kinetics evaluations)
    — Carcinogenicity
      — Long-term studies
      — Short- or medium-term studies
      — Other studies

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- — Reproductive and Developmental Toxicity
  - — Fertility and early embryonic development
  - — Embryo-fetal development
  - — Prenatal and postnatal development
  - — Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
  - — Local Tolerance
- — *Other Toxicity Studies*
  - — Antigenicity
  - — Immuno-toxicity
  - — Mechanistic studies
  - — Dependence
  - — Metabolites
  - — Impurities
  - — Other
- — Literature references

4.2. **Content: basic principles and requirements**

Special attention shall be paid to the following selected elements.

(1) The pharmacological and toxicological tests must show:

a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;

examination of reproductive function, of embryo/foetal and perinatal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

(4) Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. *Pharmacology*

Pharmacology study shall follow two distinct lines of approach.

— Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both in vivo and in vitro, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.

— Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the

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anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2. *Pharmaco-kinetics*

Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmaco-kinetic program shall be design to allow comparison and extrapolation between animal and human.

4.2.3. *Toxicology*

a) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.

b) Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.

c) Geno-toxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

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d) Carcino-genicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.
2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies.
3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.

e) Reproductive and developmental toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

f) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.

The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. **Format and Presentation**

The general outline of Module 5 is as follows:

— Table of contents for clinical study reports

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- Tabular listing of all clinical studies
- Clinical study reports
  - *Reports of Bio-pharmaceutical Studies*
    - Bio-availability Study Reports
    - Comparative Bio-availability and Bio-equivalence Study Reports
    - In vitro — In vivo Correlation Study Report
    - Reports of Bio-analytical and Analytical Methods
  - *Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials*
    - Plasma Protein Binding Study Reports
    - Reports of Hepatic Metabolism and Interaction Studies
    - Reports of Studies Using Other Human Bio-materials
  - *Reports of Human Pharmaco-kinetic Studies*
    - Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports
    - Patient Pharmaco-kinetics and Initial Tolerability Study Reports
    - Intrinsic Factor Pharmaco-kinetics Study Reports
    - Extrinsic Factor Pharmaco-kinetics Study Reports
    - Population Pharmaco-kinetics Study Reports
  - *Reports of Human Pharmaco-dynamic Studies*
    - Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports
    - Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports
  - *Reports of Efficacy and Safety Studies*
    - Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - Study Reports of Uncontrolled Clinical Studies
    - Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses
    - Other Study Reports
  - *Reports of Post-marketing Experience*
- Literature references

5.2. **Content: basic principles and requirements**

Special attention shall be paid to the following selected elements.

a) The clinical particulars to be provided pursuant to Articles 8 (3) (i) and 10 (1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:

   — for at least 15 years after completion or discontinuation of the trial,

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— or for at least two years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,

— or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the European Community, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of Directive 2001/20/EC and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

— the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used

— audit certificate(s), if available

— the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject

— final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

e) The particulars of clinical trials referred to above shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:

1) the number and sex of subjects treated;

2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;

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3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

4) where controlled trials were carried out under the above conditions, whether the control group:

— received no treatment

— received a placebo

— received another medicinal product of known effect

— received treatment other than therapy using medicinal products

5) the frequency of observed adverse reactions;

6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;

7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;

8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

g) In addition, the investigator shall always indicate his observations on:

1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

2) any interactions that have been observed with other medicinal products administered concomitantly;

3) the criteria determining exclusion of certain patients from the trials;

4) any deaths which occurred during the trial or within the follow-up period.

h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.

i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.

j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1. *Reports of bio-pharmaceutics studies*

Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on in vitro and in vivo correlation study, and bio-analytical and analytical methods shall be provided.

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10 (1) (a).

5.2.2. *Reports of studies pertinent to pharmaco-kinetics using human bio-materials*

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmaco-kinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. *Reports of human pharmaco-kinetic studies*

a) The following pharmaco-kinetic characteristics shall be described:

— absorption (rate and extent),

— distribution,

— metabolism,

— excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk,

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and differences between man and animal species used in the pre clinical studies, shall be described.

In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. *Reports of human pharmaco-dynamic studies*

a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:

— the dose-response relationship and its time course,

— justification for the dosage and conditions of administration,

— the mode of action, if possible.

The pharmaco-dynamic action not related to efficacy shall be described.

The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. *Reports of efficacy and safety studies*

5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

In general, clinical trials shall be done as ‘controlled clinical trials’ if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.

(2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

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5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

5.2.6. *Reports of post-marketing experience*

If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. *Case reports forms and individual patient listings*

When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.

PART II

SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a 'well-established medicinal use' as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

— the time over which a substance has been used,

— quantitative aspects of the use of the substance,

— the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and

— the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the provisions on 'well-established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level

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of safety and/or efficacy can be supported although some studies are lacking.

d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.

b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

— the grounds for claiming essential similarity;

— a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;

— an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';

— an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;

— every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

— if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

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When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

— Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

— Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

— the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

— in the present state of scientific knowledge, comprehensive information cannot be provided, or

— it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

— the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,

— the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,

— the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.

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PART III

PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. **Plasma-derived medicinal product**

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Annex:

— Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma ([1]).

— Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.

— The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.

— The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.

— Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

b) Content

In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

(1) Plasma origin

(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.

(iii) selection/exclusion criteria for blood/plasma donors.

(iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.

(2) Plasma quality and safety

(i) compliance with European Pharmacopoeia Monographs.

([1]) OJ L 313, 13.12.2000, p. 22.

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(ii) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.

(iv) conditions of storage and transport of plasma.

(v) procedures for any inventory hold and/or quarantine period.

(vi) characterisation of the plasma pool.

(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

c) Evaluation and Certification

— For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.

— The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.

— The Plasma Master File shall be updated and re-certified on an annual basis.

— Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95 ([1]) concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products ([2]). Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003.

— As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

— By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

1.2. **Vaccines**

For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

([1]) OJ L 55, 11.3.1995, p. 15.
([2]) OJ L 214, 24.8.1993, p. 1.

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a) Principles

For the purposes of this Annex:

— Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

— A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

— A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

— A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:

Active Substance

1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.
2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.
3. Characterisation of the active substance
4. Quality control of the active substance
5. Reference standard and materials
6. Container and closure system of the active substance
7. Stability of the active substance.

c) Evaluation and Certification

— For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Community.

— The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.

— Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.

— By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.

— As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted

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the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).

2. RADIO-PHARMACEUTICALS AND PRECURSORS

2.1. **Radio-pharmaceuticals**

For the purposes of this chapter, applications based upon Articles 6 (2) and 9 shall provide a full dossier in which the following specific details shall be included:

Module 3

a) In the context of a radio-pharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radio-nuclide. The description of the manufacturing method of radio-pharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radio-nuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia . In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

   For radio-nuclides, the nuclear reactions involved shall be discussed.

   In a generator, both mother and daughter radio-nuclides shall be considered as active substances.

b) Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

c) Starting materials include irradiation target materials.

d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.

e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.

f) For generators, details on the testing for mother and daughter radio-nuclides are required. For generator-eluates, tests for mother radio-nuclides and for other constituents of the generator system shall be provided.

g) The requirement to express the content of active substances in terms of the mass of active entities shall onlyapply to radio-pharmaceutical kits. For radio-nuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radio-nuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

i) Information on stability shall be given for radio-nuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. **Radio-pharmaceutical precursors for radio-labelling purposes**

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present

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information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

In particular, the following information where applicable shall be provided:

Module 3

The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Council Directives 87/18/EEC and 88/320/EEC shall be provided, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 1(5).

Module 3

The provisions of Module 3 shall apply to the documents submitted in accordance with Article 15 in the simplified registration of homeopathic medicinal products referred to in Article 14(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in Article 16(1) with the following modifications.

a) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

b) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.

In case dilutions are involved, these dilution steps should be done in accordance with the homeopathicmanufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.

c) Control tests on the finished medicinal product

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The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

d) Stability tests

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Module 4

The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 14(1) with the following specifications.

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

4. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be considered:

(1) Herbal substances and herbal preparations

For the purposes of this Annex the terms ‘herbal substances and preparations’ shall be considered equivalent to the terms ‘herbal drugs and herbal drug preparations’, as defined in the European Pharmacopoeia.

With respect to the nomencRlature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved

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in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

(2) Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

5. ORPHAN MEDICINAL PRODUCTS

— In the case of an orphan medicinal product in the meaning of Regulation (EC) No 141/2000, general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

— When an applicant for an marketing authorisation for an orphan medicinal product invokes the provisions of Article 10 (1)(a)(ii)

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and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer — as way of derogation — to the use of that substance in accordance with the provisions of Article 5 of this Directive.

PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

Modules 1 to 5 shall apply. For Genetically Modified Organisms deliberate release in the environment, attention shall be paid to the persistence of the Genetically Modified Organisms in the recipient and to the possible replication and/or modification of the Genetically Modified Organisms when released in the environment. The information concerning the environmental risk should appear in the Annex to Module 1.

1. GENE THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, gene therapy medicinal product shall mean a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either in vivo or ex vivo, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression in vivo. The gene transfer involves an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. The vector can also be included in a human or animal cell.

1.1. **Diversity of gene therapy medicinal products**

a) Gene therapy medicinal products based on allogeneic or xenogeneic cells

The vector is ready-prepared and stored before its transfer into the host cells.

The cells have been obtained previously and may be processed as a cell bank (bank collection or bank established from procurement of primary cells) with a limited viability.

The cells genetically modified by the vector represent an active substance.

Additional steps may be carried out in order to obtain the finished product. By essence, such a medicinal product is intended to be administered to a certain number of patients.

b) Gene therapy medicinal products using autologous human cells

The active substance is a batch of ready-prepared vector stored before its transfer into the autologous cells.

Additional steps may be carried out in order to obtain the finished medicinal product.

Those products are prepared from cells obtained from an individual patient. The cells are then genetically modified using a ready-prepared vector containing the appropriate gene that has been prepared in advance and that constitutes the active substance. The preparation is re-injected into the patient and is by definition intended to a single patient. The whole manufacturing process from the collection of the cells from the patient up to the re-injection to the patient shall be considered as one intervention.

c) Administration of ready-prepared vectors with inserted (prophylactic, diagnostic or therapeutic) genetic material

The active substance is a batch of ready-prepared vector.

Additional steps may be carried out in order to obtain the finished medicinal product. This type of medicinal product is intended to be administered to several patients.

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Transfer of genetic material may be carried out by direct injection of the ready-prepared vector to the recipients.

1.2. **Specific requirements regarding Module 3**

Gene therapy medicinal products include:

— naked nucleic acid
— complex nucleic acid or non viral vectors
— viral vectors
— genetically modified cells

As for other medicinal products, one can identify the three main elements of the manufacturing process, i.e.:

— starting materials: materials from which the active substance is manufactured such as, gene of interest, expression plasmids, cell banks and virus stocks or non viral vector;
— active substance: recombinant vector, virus, naked or complex plasmids, virus producing cells, in vitro genetically modified cells;
— finished medicinal product: active substance formulated in its final immediate container for the intended medical use. Depending on the type of gene therapy medicinal product, the route of administration and conditions of use may necessitate an ex vivo treatment of the cells of the patient (see 1.1.b).

A special attention shall be paid to the following items:

a) Information shall be provided on the relevant characteristics of the gene therapy medicinal product including its expression in the target cell population. Information concerning the source, construction, characterisation and verification of the encoding gene sequence including its integrity and stability shall be provided. Apart from therapeutic gene, the complete sequence of other genes, regulatory elements and the vector backbone shall be provided.

b) Information concerning the characterisation of the vector used to transfer and deliver the gene shall be provided. This must include its physico-chemical characterisation and/or biological/immunological characterisation.

   For medicinal products that utilise a micro-organism such as bacteria or viruses to facilitate gene transfer (biological gene transfer), data on the pathogenesis of the parental strain and on its tropism for specific tissues and cell types as well as the cell cycle-dependence of the interaction shall be provided.

   For medicinal products that utilise non-biological means to facilitate gene transfer, the physico-chemical properties of the constituents individually and in combination shall be provided.

c) The principles for cell banking or seed lot establishment and characterisation shall apply to gene transfer medicinal products as appropriate.

d) The source of the cells hosting the recombinant vector shall be provided.

   The characteristics of the human source such as age, sex, results of microbiological and viral testing, exclusion criteria and country of origin shall be documented.

   For cells of animal origin, detailed information related to the following items shall be provided:

   — Sourcing of the animals
   — Animal husbandry and care
   — Transgenic animals (methods of creation, characterisation of transgenic cells, nature of the inserted gene)
   — Measures to prevent and monitor infections in the source/donor animals
   — Testing for infectious agents
   — Facilities
   — Control of starting and raw materials.

   Description of cell collection methodology including location, type of tissue, operating process, transportation, storage and traceability as well as controls carried out during the collection process shall be documented.

e) The evaluation of the viral safety as well as the traceability of the products from the donor to the finished medicinal product, are an essential part of the documentation to be supplied. E.g., the presence

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of replication competent virus in stocks of non-replication competent viral vectors must be excluded.

2. SOMATIC CELL THERAPY MEDICINAL PRODUCTS (HUMAN AND XENOGENEIC)

For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, biodegradable or not).

Specific requirements for cell therapy medicinal products regarding Module 3

Somatic cell therapy medicinal products include:

— Cells manipulated to modify their immunological, metabolic or other functional properties in qualitative or quantitative aspects;

— Cells sorted, selected and manipulated and subsequently undergoing a manufacturing process in order to obtain the finished medicinal product;

— Cells manipulated and combined with non-cellular components (e.g. biological or inert matrixes or medical devices) and exerting the principle intended action in the finished product;

— Autologous cell derivatives expressed in vitro under specific culture conditions;

— Cells genetically modified or otherwise manipulated to express previously unexpressed homologous or non-homologous functional properties.

The whole manufacturing process from the collection of the cells from the patient (autologous situation) up to the re-injection to the patient shall be considered as one single intervention.

As for other medicinal products, the three elements of the manufacturing process are identified:

— starting materials: materials from which the active substance is manufactured, i.e., organs, tissues, body fluids or cells;

— active substance: manipulated cells, cell lysates, proliferating cells and cells used in conjunction with inert matrixes and medical devices;

— finished medicinal products: active substance formulated in its final immediate container for the intended medical use.

a) General information on active substance(s)

The active substances of cell therapy medicinal products consist of cells which as a consequence of in vitro processing display prophylactic, diagnostic or therapeutic properties different from the original physiological and biological one.

This section shall describe the type of cells and culture concerned. Tissues, organs or biological fluids from which cells are derived as well as the autologous, allogeneic, or xenogeneic nature of the donation and its geographical origin shall be documented. Collection of the cells, sampling and storage prior further processing shall be detailed. For allogeneic cells, special attention shall be paid to the very first step of the process, which covers selection of donors. The type of manipulation carried out and the physiological function of the cells that are used as active substance shall be provided.

b) Information related to the starting materials of active substance(s)

1. Human somatic cells

Human somatic cell therapy medicinal products are made of a defined number (pool) of viable cells, which are derived from a manufacturing process starting either at the level of organs or tissues retrieved from a human being, or, at the level of a well defined cell bank system where the pool of cells relies on continuous cell lines. For the purposes of this chapter, active substance shall mean the seed pool of human cells and finished medicinal product shall

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mean seed pool of human cells formulated for the intended medical use.

Starting materials and each step of the manufacturing process shall be fully documented including viral safety aspects.

(1) Organs, tissues, body fluids and cells of human origin

The characteristics of the human source such as age, sex, microbiological status, exclusion criteria and country of origin shall be documented.

Description of sampling including site, type, operating process, pooling, transportation, storage and traceability as well as controls carried out on sampling shall be documented.

(2) Cell banking systems

Relevant requirements depicted in part I shall apply for the preparation and quality control of cell banking systems. This may essentially be the case for allogeneic or xenogeneic cells.

(3) Ancillary materials or ancillary medical devices

Information shall be provided on the use of any raw materials (e.g., cytokines, growth factors, culture media) or of possible ancillary products and medical devices e.g., cell sorting devices, biocompatible polymers, matrix, fibres, beads in terms of bio-compatibility, functionality as well as the risk of infectious agents.

2. Animal somatic cells (xenogeneic)

Detailed information related to the following items shall be provided:

— Sourcing of the animals
— Animal husbandry and care
— Genetically modified animals (methods of creation, characterisation of transgenic cells, nature of the inserted or excised (knock out) gene)
— Measures to prevent and monitor infections in the source/donor animals
— Testing for infectious agents including vertically transmitted micro-organisms (also endogenous retro viruses)
— Facilities
— Cell banking systems
— Control of starting and raw materials.

a) Information on the manufacturing process of the active substance(s) and the finished product

The different steps of the manufacturing process such as organ/tissue dissociation, selection of the cell population of interest, in vitro cell culture, cell transformation either by physico-chemical agents or gene transfer shall be documented.

b) Characterisation of active substance(s)

All of the relevant information on the characterisation of the cell population of interest in terms of identity (species of origin, banding cytogenetics, morphological analysis), purity (adventitious microbial agents and cellular contaminants), potency (defined biological activity), and suitability (karyology and tumorigenicity tests) for the intended medicinal use shall be provided.

c) Pharmaceutical development of finished medicinal product

Apart from the specific method of administration used (intravenous infusion, site-injection, transplantation surgery), information shall also be provided on the use of possible ancillary medical devices (bio-compatible polymers, matrix, fibres, beads) in terms of bio-compatibility and durability.

d) Traceability

A detailed flow chart shall be provided insuring the traceability of the products from the donor to the finished medicinal product.

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3. SPECIFIC REQUIREMENTS FOR GENE THERAPY AND SOMATIC CELL THERAPY (HUMAN AND XENOGENEIC) MEDICINAL PRODUCTS REGARDING MODULES 4 AND 5

3.1. **Module 4**

For gene and somatic cell therapy medicinal products, it is recognised that conventional requirements as laid down in Module 4 for non-clinical testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of the products in question, including high degree of species specificity, subject specificity, immunological barriers and differences in pleiotropic responses.

The rationale underpinning the non-clinical development and the criteria used to choose relevant species and models shall be properly captioned in Module 2.

It may be necessary to identify or develop new animal models in order to assist in the extrapolation of specific findings on functional endpoints and toxicity to in vivo activity of the products in human beings. The scientific justification for the use of these animal models of disease to support safety and proof of concept for efficacy shall be provided.

3.2. **Module 5**

The efficacy of advanced therapy medicinal products must be demonstrated as described in Module 5. For some products and for some therapeutic indications, however, it may not be possible to perform conventional clinical trials. Any deviation from the existing guidelines shall be justified in Module 2.

The clinical development of advanced therapy medicinal products will have some special features owing to the complex and labile nature of the active substances. It requires additional considerations because of issues related to viability, proliferation, migration and differentiation of cells (somatic cell therapy), because of the special clinical circumstances where the products are used or because of the special mode of action through gene expression (somatic gene therapy).

Special risks associated with such products arising from potential contamination with infectious agents must be addressed in the application for marketing authorisation for advanced therapy medicinal products. Special emphasis should be put on both the early stages of development in one hand, including the choice of donors in the case of cell therapy medicinal products, and on the therapeutic intervention as a whole, including the proper handling and administration of the product on the other hand.

Furthermore, Module 5 of the application should contain, as relevant, data on the measures to surveying and control of the functions and development of living cells in the recipient, to prevent transmission of infectious agents to the recipient and to minimise any potential risks to public health.

3.2.1. *Human pharmacology and efficacy studies*

Human pharmacology studies should provide information on the expected mode of action, expected efficacy based on justified endpoints, bio-distribution, adequate dose, schedule, and methods of administration or modality of use desirable for efficacy studies.

Conventional pharmaco-kinetic studies may not be relevant for some advanced therapy products. Sometimes studies in healthy volunteers are not feasible and the establishment of dose and kinetics will be difficult to determine in clinical trials. It is necessary, however, to study the distribution and in vivo behaviour of the product including cell proliferation and long-term function as well as the extent, distribution of the gene product and duration of the desired gene expression. Appropriate tests shall be used and, if necessary, developed for the tracing of the cell product or cell expressing the desired gene in the human body and for the monitoring of the function of the cells that were administered or transfected.

The assessment of the efficacy and safety of an advanced therapy medicinal product must include the careful description and evaluation of the therapeutic procedure as a whole, including special ways of administration, (such as transfection of cells ex vivo, in vitro manipulation, or use of interventional techniques), and testing of the possible associated regimens (including immuno-suppressive, antiviral, cytotoxic treatment).

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The whole procedure must be tested in clinical trials and described in the product information.

3.2.2. *Safety*

Safety issues arising from immune response to the medicinal products or to the expressed proteins, immune rejection, immuno-suppression, and breakdown of immuno-isolation devices shall be considered.

Certain advanced gene therapy and somatic cell therapy medicinal products (e.g. xenogeneic cell therapy and certain gene transfer products) may contain replication-competent particles and/or infectious agents. The patient may have to be monitored for the development of possible infections and/or their pathological sequelae during pre- and/or post-authorisation phases; this surveillance may have to be extended to close contacts of the patient including health-care workers.

The risk of contamination with potentially transmissible agents cannot be totally eliminated in the use of certain somatic cell therapy medicinal products and certain gene transfer medicinal products. The risk can be minimised, however, by appropriate measures as described in Module 3.

The measures included in the production process must be complemented with accompanied testing methods, quality control processes and by appropriate surveillance methods that must be described in Module 5.

The use of certain advanced somatic cell therapy medicinal products may have to be limited, temporarily or permanently, to establishments that have documented expertise and facilities for assuring a specific follow up of the safety of the patients. A similar approach may be relevant for certain gene therapy medicinal products that are associated with a potential risk of replication-competent infectious agents.

The long term monitoring aspects for the development of late complications shall also be considered and addressed in the submission, where relevant.

Where appropriate, the applicant has to submit a detailed risk management plan covering clinical and laboratory data of the patient, emerging epidemiological data, and, if relevant, data from archives of tissue samples from the donor and the recipient. Such a system is needed to ensure the traceability of the medicinal product and the rapid response to suspicious patterns of adverse events.

4. SPECIFIC STATEMENT ON XENO-TRANSPLANTATION MEDICINAL PRODUCTS

For the purposes of this Annex, xeno-transplantation shall mean any procedure that involves the transplantation, implantation, or infusion into a human recipient of either live tissues or organs retrieved from animals, or, human body fluids, cells, tissues or organs that have undergone ex vivo contact with live non-human animal cells, tissues or organs.

Specific emphasis shall be paid to the starting materials.

In this respect, detailed information related to the following items shall be provided according to specific guidelines:

— Sourcing of the animals
— Animal husbandry and care
— Genetically modified animals (methods of creation, characterisation of transgenic cells, nature of the inserted or excised (knock out) gene)
— Measures to prevent and monitor infections in the source/donor animals
— Testing for infectious agents
— Facilities
— Control of starting and raw materials
— Traceability.

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ANNEX II

PART A

Repealed Directives, with their successive amendments (referred to by Article 128)

Council Directive 65/65/EEC (OJ 22, 9. 2. 1965, p. 369/65)

Council Directive 66/454/EEC (OJ 144, 5. 8. 1966, p. 2658/66)

Council Directive 75/319/EEC (OJ L 147, 9. 6. 1975, p. 13)

Council Directive 83/570/EEC (OJ L 332, 28. 11. 1983, p. 1)

Council Directive 87/21/EEC (OJ L 15, 17. 1. 1987, p. 36)

Council Directive 89/341/EEC (OJ L 142, 25. 5. 1989, p. 11)

Council Directive 92/27/EEC (OJ L 113, 30. 4. 1992, p. 8)

Council Directive 93/39/EEC (OJ L 214, 24. 8. 1993, p. 22)

Council Directive 75/318/EEC (OJ L 147, 9. 6. 1975, p. 1)

Council Directive 83/570/EEC

Council Directive 87/19/EEC (OJ L 15, 17. 1. 1987, p. 31)

Council Directive 89/341/EEC

Commission Directive 91/507/EEC (OJ L 270, 26. 9. 1991, p. 32)

Council Directive 93/39/EEC

Commission Directive 1999/82/EC (OJ L 243, 15. 9. 1999, p. 7)

Commission Directive 1999/83/EC (OJ L 243, 15. 9. 1999, p. 9)

Council Directive 75/319/EEC

Council Directive 78/420/EEC (OJ L 123, 11. 5. 1978, p. 26)

Council Directive 83/570/EEC

Council Directive 89/341/EEC

Council Directive 92/27/EEC

Council Directive 93/39/EEC

Commission Directive 2000/38/EC (OJ L 139, 10. 6. 2000, p. 28)

Council Directive 89/342/EEC (OJ L 142, 25. 5. 1989, p. 14)

Council Directive 89/343/EEC (OJ L 142, 25. 5. 1989, p. 16)

Council Directive 89/381/EEC (OJ L 181, 28. 6. 1989, p. 44)

Council Directive 92/25/EEC (OJ L 113, 30. 4. 1992, p. 1)

Council Directive 92/26/EEC (OJ L 113, 30. 4. 1992, p. 5)

Council Directive 92/27/EEC

Council Directive 92/28/EEC (OJ L 113, 30. 4. 1992, p. 13)

Council Directive 92/73/EEC (OJ L 297, 13. 10. 1992, p. 8)

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PART B

Time-limits for transposition into national law (referred to by Article 128)

Directive	Deadline for transposition
Directive 65/65/EEC	31 December 1966
Directive 66/454/EEC	—
Directive 75/318/EEC	21 November 1976
Directive 75/319/EEC	21 November 1976
Directive 78/420/EEC	—
Directive 83/570/EEC	31 October 1985
Directive 87/19/EEC	1 July 1987
Directive 87/21/EEC	1 July 1987
	1 January 1992 (1)
Directive 89/341/EEC	1 January 1992
Directive 89/342/EEC	1 January 1992
Directive 89/343/EEC	1 January 1992
Directive 89/381/EEC	1 January 1992
Directive 91/507/EEC	1 January 1992 (2)
	1 January 1995 (3)
Directive 92/25/EEC	1 January 1993
Directive 92/26/EEC	1 January 1993
Directive 92/27/EEC	1 January 1993
Directive 92/28/EEC	1 January 1993
Directive 92/73/EEC	31 December 1993
Directive 93/39/EEC	1 January 1995 (4)
	1 January 1998 (5)
Directive 1999/82/EC	1 January 2000
Directive 1999/83/EC	1 March 2000
Directive 2000/38/EC	5 December 2001

(1) Deadline for transposition applicable to Greece, Spain and Portugal.
(2) Except Section A, point 3.3 in Part II of the Annex.
(3) Deadline for transposition applicable to Section A, point 3.3 in Part II of the Annex.
(4) Except with regard to Article 1(6).
(5) Deadline for transposition applicable to Article 1(7).

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ANNEX III

CORRELATION TABLE

This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 1(1) to (3)	Art. 1(1) to (3)										
Art. 1(4)			Annex	Art. 1(1) and (2)							
Art. 1(5)											Art. 1
Art. 1(6) to (9)					Art. 1(2)						
Art. 1(10)						Art. 1(1)					
Art. 1(11) to (16)			Art. 29b, 1st paragraph								
Art. 1(17) and (18)							Art. 1(2)				
Art. 1(19)								Art. 1(2), 2nd sentence			
Art. 1(20) to (26)									Art. 1(2)		
Art. 1(27)			Art. 8(1)								
Art. 1(28)			Art. 10(1)								
Art. 2	Art. 2(1)										
Art. 3(1) and (2)	Art. 1(4) and (5) Art 2(3), 1st indent										

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This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 3(3) and (4)	Art.2(3), 2nd and 3rd indents										
Art. 3(5)					Art. 1(1)						
Art. 3(6)						Art. 1(2)					
Art. 4(1)					Art. 1(3)						
Art. 4(2)						Art. 1(3)					
Art. 4(3)	Art. 3, 2nd subparagraph										
Art. 4(4)	Art. 6										
Art. 5	Art. 2(4)										
Art. 6(1)	Art. 3(1)										
Art. 6(2)					Art. 2, 1st sentence						
Art. 7					Art. 2, 2nd sentence						
Art. 8(1) and (2)	Art. 4(1) and (2)										
Art. 8(3)(a) to (e)	Art. 4, 3rd para., points 1 to 5	Art. 1, 1st paragraph									
Art. 8(3)(f) to (i)	Art. 4, 3rd para., points 6 to 8.1										
Art. 8(3)(j) to (l)	Art. 4, 3rd para., points 9 to 11										

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This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Art. 9					Art. 3						
Art. 10(1)	Art. 4, 3rd paragraph, point 8.2										
Art. 10(2)		Art. 1, 2nd paragraph									
Art. 11, points 1 to 5.3	Art. 4a, points 1 to 5.3										
Art. 11, point 5.4	Art. 4a, point 5.4			Art. 3							
Art. 11, points 5.5 to 6.4	Art. 4a, points 5.5 to 6.4										
Art. 11, point 6.5	Art. 4a, point 6.6										
Art. 11, point 7	Art. 4a, point 6.5										
Art. 11, points 8 to 9					Art. 4						
Art. 12(1)			Art. 1								
Art. 12(2) and (3)			Art. 2								
Art. 13											Art. 6(1) and (2)
Art. 14(1) and (2)											Art. 7(1) and (4)
Art. 14(3)											Art. 4, 2nd paragraph

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Art. 15											Art. 8
Art. 16											Art. 9
Art. 17	Art. 7										
Art. 18	Art. 7a										
Art. 19			Art. 4								
Art. 20			Art. 5								
Art. 21	Art. 4b										
Art. 22	Art. 10(2)										
Art. 23	Art. 9a										
Art. 24	Art. 10(1)										
Art. 25	Art. 9										
Art. 26	Art. 5										
Art. 27			Art. 8								
Art. 28(1)			Art. 9(3)								
Art. 28(2)			Art. 9(1)								
Art. 28(3)			Art. 9(2)								
Art. 28(4)			Art. 9(4)								
Art. 29			Art. 10								
Art. 30			Art. 11								
Art. 31			Art. 12								

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Art. 34			Art. 14(2) to (4)								
Art. 35			Art. 15								
Art. 36			Art. 15a								
Art. 37			Art. 15b								
Art. 38			Art. 15c								
Art. 39			Art. 14(5)								
Art. 40			Art. 16								
Art. 41			Art. 17								
Art. 42			Art. 18								
Art. 43			Art. 20(1)								
Art. 44			Art. 20(2)								
Art. 45			Art. 20(3)								
Art. 46			Art. 19								
Art. 47			Art. 19a								
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Art. 49			Art. 23								
Art. 50			Art. 24								

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Art. 51(1) and (2)			Art. 22(1)								
Art. 51(3)			Art. 22(2)								
Art. 52			Art. 25								
Art. 53											Art. 3
Art. 54									Art. 2(1)		
Art. 55									Art. 3		
Art. 56									Art. 4(1)		
Art. 57									Art. 5(2)		
Art. 58									Art. 6		
Art. 59									Art. 7(1) and (2)		
Art. 60									Art. 5(1) and Art. 9		
Art. 61									Art. 10(1) to (4)		
Art. 62									Art. 2(2) and Art. 7(3)		
Art. 63(1)									Art. 4(2)		
Art. 63(2)									Art. 8		
Art. 63(3)									Art. 10(5)		
Art. 64									Art. 11(1)		

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Art. 65									Art. 12		
Art. 66					Art. 5						
Art. 67					Art. 6(1)						
Art. 68											Art. 2(2)
Art. 69											Art. 7(2) and (3)
Art. 70								Art. 2			
Art. 71								Art. 3			
Art. 72								Art. 4			
Art. 73								Art. 5(1)			
Art. 74								Art. 5(2)			
Art. 75								Art. 6(2)			
Art. 76							Art. 2				
Art. 77							Art. 3				
Art. 78							Art. 4(1)				
Art. 79							Art. 5				
Art. 80							Art. 6				
Art. 81							Art. 7				
Art. 82							Art. 8				
Art. 83							Art. 9				

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Art. 84							Art. 10				
Art. 85											Art. 9
Art. 86										Art. 1(3) and (4)	
Art. 87										Art. 2	
Art. 88										Art. 3(1) to (6)	
Art. 89										Art. 4	
Art. 90										Art. 5	
Art. 91										Art. 6	
Art. 92										Art. 7	
Art. 93										Art. 8	
Art. 94										Art. 9	
Art. 95										Art. 10	
Art. 96										Art. 11	
Art. 97(1) to (4)										Art. 12(1) and (2)	
Art. 97(5)										Art. 12(4)	
Art. 98										Art. 13	
Art. 99										Art. 14	
Art. 100											Art. 6(3)

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Art. 101			Art. 29e								
Art. 102			Art. 29a								
Art. 103			Art. 29c								
Art. 104			Art. 29d								
Art. 105			Art. 29f								
Art. 106(1)			Art. 29g								
Art. 106(2)			Art. 29b, 2nd paragraph								
Art. 107			Art. 29h								
Art. 108			Art. 29i								
Art. 109						Art. 3(1) to (3)					
Art. 110						Art. 3(4)					
Art. 111(1)			Art. 26, 1st and 2nd paragraph								
Art. 111(2)				Art. 4(1)							
Art. 111(3)			Art. 26, 3rd paragraph								
Art. 112	Art. 8		Art. 27								
Art. 113				Art. 4(2)		Art. 4(2)					
Art. 114(1)				Art. 4(3)							
Art. 114(2)						Art. 4(3)					

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Art. 115						Art. 4(1)					
Art. 116	Art. 11										
Art. 117			Art. 28								
Art. 118			Art. 29								
Art. 119											Art. 4(1)
Art. 120		Art. 2a, 1st paragraph									
Art. 121		Art. 2b	Art. 37a								
Art. 122			Art. 30								
Art. 123			Art. 33								
Art. 124											Art. 5
Art. 125	Art. 12		Art. 31				Art. 4(2)		Art. 11(2)	Art. 12(3)	
Art. 126, 1st paragraph	Art. 21										
Art. 126, 2nd paragraph			Art. 32								
Art. 127			Art. 28a								
Art. 128	—	—	—	—	—	—	—	—	—	—	—
Art. 129	—	—	—	—	—	—	—	—	—	—	—
Art. 130	—	—	—	—	—	—	—	—	—	—	—
Annex I		Annex									

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This Dir.	65/65/EEC	75/318/EEC	75/319/EEC	89/342/EEC	89/343/EEC	89/381/EEC	92/25/EEC	92/26/EEC	92/27/EEC	92/28/EEC	92/73/EEC
Annex II	—	—	—	—	—	—	—	—	—	—	—
Annex III	—	—	—	—	—	—	—	—	—	—	—