Annex. Medicinal Products to be Authorised by the Community

1. Medicinal products developed by means of one of the following biotechnological processes:
- recombinant DNA technology,
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
- hybridoma and monoclonal antibody methods.

1a. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.

2. Medicinal products for veterinary use intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

3. Medicinal products for human use containing a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community, for which the therapeutic indication is the treatment of any of the following diseases:
- acquired immune deficiency syndrome,
- cancer,
- neurodegenerative disorder,
- diabetes,

and with effect from 20 May 2008
- auto-immune diseases and other immune dysfunctions,
- viral diseases.

After 20 May 2008, the Commission, having consulted the Agency, may present any appropriate proposal to amend this point and the European Parliament and the Council shall take a decision thereon in accordance with the Treaty.

4. Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No. 141/2000.

Practical Commentary on Regulation No. 726/2004

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A. Introduction

The authorisation and marketing of medicinal products is highly regulated at EU level with the dual aim of protecting public health and ensuring the free movement of medicinal products. A marketing authorisation for such products may be issued either by the competent authority of an EC Member State for its own territory (national authorisation) or by the European Commission (the "Commission") for the entire European Community ("EC") (Community authorisation).[1]

Most conventional medicinal products require national marketing authorisations. If the product in question has received a marketing authorisation in any Member State at the time of application, the applicant may rely on the mutual recognition procedure to obtain such authorisation in the other Member States as well. If not, he may resort to the decentralised procedure and simultaneously submit an application, based on an identical dossier, in every Member State where he intends to obtain a marketing authorisation, designating one of them as reference Member State.[2] Both the mutual recognition and decentralised procedures are governed by Directive 2001/83/EC on the Community code relating to medicinal products for human use.[3] Finally, independent national procedures are also possible, but only for medicinal products to be marketed in one Member State only.

In contrast, certain types of medicinal products are subject to a centralised Community procedure ("centralised procedure") pursuant to Regulation No. 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency ("Regulation 726/2004")[4]. The centralised

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1 Through the EEA Agreement, Iceland, Liechtenstein and Norway have adopted the entire "acquis communautaire" with respect to medicinal products. It follows that any reference to Member States should be read to include Iceland, Liechtenstein and Norway. The only exception to this rule is that legally binding acts from the EC, such as Commission decisions, do not directly confer rights and obligations in Iceland, Liechtenstein and Norway, but first have to be transposed into legally binding acts in these states. Pursuant to Decision No. 74/1999 of 28 May 1999 of the EEA Joint Committee, Iceland, Liechtenstein and Norway have undertaken to take corresponding decisions simultaneously when decisions on the approval of medicinal products are taken by the EC.

2 In principle, all Member States involved have to recognise the marketing authorisation granted or assessment made by the competent authority of the reference Member State, unless they duly justify that there are reasons to suppose that the medicinal product concerned presents a potentially serious risk to public health.

3 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 2001 L311/67 (Directive 2001/83/EC).

4 Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L136/1. This Regulation replaces 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.

procedure is in some cases mandatory and in others optional.[5] Under the centralised procedure, the applicant should submit a single application to the European Medicines Agency ("EMEA"). If, after evaluation, a marketing authorisation is granted, this authorisation will be valid for the entire EC, conferring the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State.[6]

B. Scope

The categories of medicinal products that fall within the scope of Regulation 726/2004 are listed in Article 3 and in the Annex to Regulation 726/2004. For products listed in Article 3(1) and in the Annex, applicants are obliged to use the centralised procedure (mandatory scope), whereas for products referred to in Articles 3(2) and 3(3), applicants may decide at their own discretion to resort to that procedure (optional scope).

1. Mandatory Scope

a) Human or Veterinary Medicinal Products derived from Biotechnology

In order to fall within the mandatory scope of the centralised procedure, the products must have been developed by means of one of the following biotechnological processes:

- recombinant DNA technology;
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells;
- hybridoma and monoclonal antibody methods.

Similar biological ("biosimilar") medicinal products that are developed by one of these processes also enter into the mandatory scope of the centralised procedure.[7]

b) Advanced Therapy Medicinal Products for Human Use

Since 30 December 2008, applications for advanced therapy medicinal products also fall within the mandatory scope of the centralised procedure.[8] The notion "advanced therapy medicinal products" includes gene and somatic cell therapy medicinal products as defined in Part IV of Annex I to Directive 2001/83/EC as well as tissue engineered products as defined in Article 2(1)(b) of Regulation No. 1394/2007.

Before 30 December 2008, advanced therapy medicinal products were only obliged to follow the centralised procedure if they entered into one of the other categories.[9]

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[5] *See*, below, B. It is important to note that penalties may be applied for infringement of the provisions of Regulation 726/2004, both by the Member States and at EC level (See, Article 84 of Regulation 726/2004 and Commission Regulation (EC) No. 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No. 726/2004 of the European Parliament and of the Council, OJ 2007 L 155/10).

[6] *See*, Article 13(1) of Regulation 726/2004.

[7] Commission's Notice to Applicants ("NTA"), volume 2A, chapter 4, section 1.5, p. 6 (human medicines) and volume 6A, chapter 4, section 1.4, p. 5 (veterinary medicines).

[8] *See*, amendments to the Annex by Article 27 of Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004, OJ 2007 L324/121.

c) Performance Enhancers for Veterinary Use

This category comprises veterinary medicinal products intended primarily for use as performance enhancers in order to promote the growth of treated animals or to increase yields from treated animals.

d) Human Medicinal Products containing a new Active Substance for the Treatment of certain Specific Diseases

Applications for medicinal products for human use containing a new active substance[10], which was not authorised in the EC before 20 November 2005, must also use the centralised procedure if the therapeutic indication of these products is the treatment of one of the following diseases:

- acquired immune deficiency syndrome;
- cancer;
- neurodegenerative disorder;
- diabetes;
- auto-immune diseases and other immune dysfunctions;
- viral diseases.

The EMEA Committee for Medicinal Products for Human Use ("CHMP") provided working definitions of these diseases in a document entitled "Scientific aspects and working definitions for the mandatory scope of the centralised procedure"[11], which is based on the tenth version of the International Classification of Diseases (ICD-10)[12] and the third edition of the International Classification of Diseases for Oncology (ICD-O)[13]. It is important to note that the indication for the medicinal products concerned must be the "treatment" of one of these diseases, which refers to interventions that are specifically targeted at altering their natural course. It follows that only products with causal or curative action will fall within the compulsory scope, contrary to those intended for prevention or diagnosis.[14]

e) Orphan Medicinal Products for Human Use

Medicinal products for human use that are designated as orphan medicinal products pursuant to Regulation No. 141/2000[15] also fall within the mandatory scope of the centralised procedure.

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[9] For instance, NTA, volume 2A, chapter 4, section 1.1, p. 3 (human medicines) and volume 6A, chapter 4, section 1.1, p. 3 (veterinary medicines) list "*products intended for gene therapy*" amongst those which are considered to be derived from biotechnology. It also refers to cell therapy products derived from any of the above-mentioned biotech processes.

[10] As defined in Annex III to the NTA, volume 2A, chapter 1.

[11] Doc. Ref. EMEA/CHMP/121944/2007.

[12] International Statistical Classification of Diseases and Related Health Problems – Tenth revision, World Health Organization, Geneva.

[13] International Classification of Diseases for Oncology – Third edition, World Health Organization, Geneva.

[14] NTA, volume 2A, chapter 4, section 1.2, p.4.

[15] Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ 2000 L18/1.