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Pharmaceutical Licensing

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This chapter discusses key procedural aspects of the European Community pharmaceutical regime. The regime is complex because of the variety of the issues it addresses, many of which involve a delicate scientific and technical assessment based on the available data and the broader policy principles that underpin the system. Broadly speaking, it involves a scientific evaluation of medicines, based on a risk-benefit assessment, and takes into account both the need to protect patients (and other persons) – by ensuring that medicines are of sufficient quality, safety and efficacy – as well as the need to ensure availability of new therapeutic methods. In addition, the regime must strike balances between protecting and encouraging innovation and stimulating competition through simplified approval procedures for medicines, and between providing information to patients and controlling promotional activities by companies.

Only the pharmaceutical regime regulates products in such minute detail, including full details on composition, therapeutic indications, prescription status, persons involved in the manufacturing and regulatory processes, method of packaging and package sizes, the wording of package leaflets and labeling on containers, and required information for physicians. Any amendment to these details is also subject to regulatory review. This, combined with the high variability of products and the significance of many specific characteristics of the products, means that the regime necessarily relies heavily on administrative decision making. While these decisions in general aim to protect public health, they can also have significant economic impact. Thus, adequate procedural guarantees are of major importance to the pharmaceutical sector.

The Community pharmaceutical regime covers medicines for human use and veterinary medicines. The procedures for both types of medicines are fairly similar, so for the sake of simplicity, this chapter discusses only the procedures that apply to medicines for human use.

This chapter discusses the law as it currently stands – on November 1, 2005 – including major amendments that were made to the legislation in 2004, most of which take effect in October and November 2005. These legislative revisions will be further clarified in European Commission guidelines and to some extent also in formal implementing legislation. Implementation documents that currently exist only in draft form are generally not discussed in this chapter.[1] One exception is, however, made. In light of the significance and novelty of the new powers of the European Commission to impose financial penalties on pharmaceutical companies, a first draft of a Commission Regulation establishing a more detailed penalties regime has been included in the discussion.

Finally, because the pharmaceutical licensing system is currently in a transitional phase where new legislation is being implemented, this Chapter unavoidably represents a mixture of older and revised principles and procedures.

1. Introductory Note on the Difference Between Adversary and Inquisitorial Administrative Process

As is generally the case for adjudications by European Community institutions, administrative decisions in the pharmaceutical sector are taken on the basis of a mainly investigatory or inquisitorial procedure and not pursuant to an adversary process. There is no

[1] Key documents, including the Notice to Applicants ("NtA"), can be found on the website of the Commission's pharmaceutical unit, http://pharmacos.eudra.org/F2/eudralex/index.htm , and on the website of the European Medicines Agency, http://www.emea.eu.int.

clear separation between the investigatory phase and the adjudicatory step by an independent decision maker. There are often different administrative bodies involved in the decision making process (see below point 3.(c)). Moreover, these steps, which typically occur sequentially, can allow for specific aspects to be assessed afresh, but the practical impact of this remains limited: None of the procedures in the pharmaceutical field provide for a real adversary approach.

The investigatory procedure is based to a larger extent on data provided by the interested party and not so much on independent fact-finding by the authorities. This is the clearest with regard to applications for marketing authorizations, where the applicant pharmaceutical company must produce adequate data, in line with the legal requirements and principles expressed in regulatory guidance to demonstrate the quality, safety and efficacy of the product. This is also true when products are reviewed later on, for instance because of concerns of inadequate safety or efficacy, as the authorities will expect companies to produce the key data. Still, in all cases, the authorities do take into account other data that are available. Moreover, the Community pharmaceutical system is also based on a pooling of regulatory and scientific expertise from throughout Europe at the European Medicines Evaluation Agency (EMEA).[2]

A specific opportunity for establishing an adversary approach is offered by the need for a new sanctions system at the Community level. This results from the major overhaul of the EC pharmaceutical rules adopted in 2004 of which most changes took effect in October and November 2005. The new rules place a much stronger emphasis on enforcement and, for the first time, grant the European Commission the power to impose penalties on pharmaceutical companies. Details of the penalties regime will be provided in a Commission Regulation

[2] The EMEA is also known as "the Agency".

which is currently in preparation (see below point 9). A first proposal for such a regulation was released for consultation in February 2005. It envisaged a two-step procedure, where the EMEA conducts the main investigation, and then Commission takes the final decision based on an assessment of the EMEA's investigation report.

The system being specifically designed to impose sanctions when the pharmaceutical rules are not complied with, it would be easy initiate an adversary procedure – involving, for instance, an independent administrative adjudicator appointed within the Commission's Legal Service. Such an approach was reflected in stakeholder responses to the consultation.

2. Narrative

As will be discussed in section 3, there are various types of administrative decisions that are taken pursuant to the EC pharmaceutical legislation. This section summarizes three "case study" procedures, as an illustration of the EC pharmaceutical licensing system. The examples were chosen to demonstrate the variety of issues that can arise during particular administrative procedures, and because they have been the subject of court proceedings. The first two examples were eventually the subject of judicial review before the Community courts in Luxemburg, while the third example was extensively discussed in a judgment in a national product liability case before the Queen's Bench Division of the High Court of Justice of England and Wales.

a) Community Review of a Class of Anorectic Medicines (The Anorectics Cases (Joined cases T-74/00; T-76/00; T-83/00 to T-85/00; T-132/00; T-137/00 and T-141/00))

- *Factual Background*

Anorectic medicines are divided in three substance groups:

- Type I Substances: amfepramone, clobenzorex, fenproporex, mazindole, mefenorex, norpseudoephedrine, phendimetrazine, phenmetrazine, and phentermine;

- Type II Substances: dexfenfluramine and fenfluramine ;

- Type III Substances: fenbutrazate and propylhexedrine.

Products containing these active substances had been authorized nationally and had not undergone the mutual recognition procedure (a procedure for obtaining parallel approvals in other EU Member States which has been operational since early 1995).

In 1995, Germany triggered a Community interest referral (under Article 12 of the EC Directive 75/319[3], now Article 31 of Directive 2001/83/EC[4] (the "EC Human Use Directive")) to obtain a binding Community conclusion "on the risks and benefit of chemically defined, centrally acting anorectics and on their authorization status." The referral resulted from concerns about the risk of patients developing primary pulmonary hypertension when using anorectic agents for treatment of obesity. On 15 February 1996, the CPMP[5] issued initial opinions (separately for each substance type) which proposed amendments to the SmPCs[6] of the products in question. The amendments mainly regarded

[3] Second Council Directive f 20 May 1975 on the Approximation of Provisions laid down by Law, Regulation or Administrative Action Relating to Proprietary Medicinal Products, as subsequently amended.

[4] 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, as subsequently amended.

[5] The CPMP, Committee for Proprietary Medicinal Products was renamed in 2004 the "CHMP," Committee for Human Medicinal Products. This Chapter generally refers to CHMP even if the Committee at the relevant time was called the CPMP:

[6] The Summary of Product Characteristics (SmPC) summarizes the main characteristics of the product and contains the main information for prescribing physicians. It is drafted in scientific terms and forms the basis for (continued…)

the therapeutic indications, contra-indications, undesirable effects, and the implementation of detailed special warnings and precautions for use in a "black box." Some of the marketing authorization holders appealed the opinions and, as a consequence, the CPMP modified its proposal for amending the SmPCs. Notably, during these reviews, the positive risk-benefit assessments – carried out as part of the marketing authorization process – of the medicines involved went generally unquestioned.

During a judicial review procedure, the European Court of First Instance (CFI) summarized the CPMP's assessment report as follows:

> *"In its assessment report of 18 July 1996 on all anorectic agents, the CPMP essentially explained inter alia that the International Primary Pulmonary Hypertension Study (hereinafter the IPPH Study), which had been the subject of a report of 7 March 1995, had proven a causal link between the use of anorectics and the occurrence of PPH. The risk of PPH was higher when the treatment duration exceeded three months. The CPMP noted that the reported cases showed that this was a class effect common to all anorectics. As regards the efficacy of those substances, the CPMP found that the weight-loss obtained after short-term treatment was 2 to 5 kg on average, that long-term efficacy had not been established, and that weight-regain occurred immediately after the pharmacological treatment was discontinued. In those circumstances, it considered the benefit/risk balance for the anorectic*

preparing a patient leaflet. Both the SmPC and the leaflet have to be officially approved. The SmPC is the European equivalent of the U.S. package insert. Sometimes it is also referred to as "SPC".

compounds to be favourable, subject to amendment of the summaries of product characteristics for the medicinal products in question."[7]

Based on the CPMP's final opinions, the Commission adopted two decisions on December 9, 1996 that required Member States to oblige marketing authorization holders to make the relevant changes to their products' SmPCs (Commission decisions C(96)3608 final/1 and C(96)3608 final/3).

In 1998, Austria and other Member States requested a new Community referral for the substances in question because of safety concerns following several cases of cardiac valve disorders. The procedure was initiated pursuant to Article 15a of Directive 75/319 (now Article 36 of the Human Use Directive), which governs products whose approval status was already determined by a Community procedure.[8] The request generally questioned the risk-benefit balance of anorectic products in the light of the requirements set out by new guidelines on the efficient treatment of obesity, such as the CPMP Note for Guidance on Clinical Investigation of Drugs Used in Weight Control, the guidance from the Royal College of Physicians, and guidelines of the American Society for Clinical Nutrition. On this basis, the CPMP reviewed the following anorectic substances: clobenzorex, fenproporex, fenbutrazate, propylhexedrine; mazindole, mefenorex, norpseudoephedrine, phendimetrazine and phenmetrazine (resulting in Commission Decision C(2000)608); amfepramone (resulting in Commission Decision C(2000)453); and phentermine (resulting in Commission Decision C(2000)452). During the review, the marketing authorizations for medicines containing fenbutrazate and phenmetrazine were withdrawn; and marketing authorizations for medicines

[7] No. 24 CFI, Judgment 26 November 2002, Joined cases T-74/00; T-76/00; T-83/00 to T-85/00; T-132/00; T-137/00 and T-141/00.

[8] The exact scope of application of Article 15a was highly disputed before the Community courts (see below).

containing propylhexedrine and mazindole had already disappeared by the time the referral started or were withdrawn shortly after it had started.

The first report of the Pharmacovigilance Working Party to the CPMP in 1998 concluded that the risk-benefit assessment of the products remained unchanged. However, a later report concluded that the substances do not fulfill the criteria of effective therapy in obesity treatment as they were effective only in short-term treatment and that clinical evidence on their long-term effect was not available. This was based on the new CPMP Note for Guidance (issued in 1997) and new national guidelines, which required a long-term weight-loss effect in the treatment of obesity. Based on these findings, the CPMP issued opinions recommending the withdrawal of the marketing authorizations for these anorectic medicines because the risk-benefit balance of the products was now considered negative. Again, some marketing authorization holders appealed but were unsuccessful. Based on the final CPMP opinions, the Commission adopted three decisions on March 9, 2000, ordering the Member States to withdraw the marketing authorizations for the products concerned. Several marketing authorization holders sought judicial review before the CFI, which led to the decisions being annulled. The annulment was later confirmed by the European Court of Justice (ECJ), but on very different legal grounds.

- *Legal Issues Addressed*

In the anorectics cases, the CFI discussed two different aspects. First, it reviewed whether the 2000 decisions were validly based on Article 15a, and consequently whether the 1996 decisions triggered the application of Article 15a. Second, the Court reviewed in great detail the criteria for withdrawing marketing authorizations and the burden of proof of the authorities when they decide on a withdrawal.

The CFI found that the Commission was not competent to make the contested decisions of March 9, 2000 that ordered the withdrawal of marketing authorizations granted for anorectic medicines. The Court held that the Article 12 procedure in 1996 could not result in binding Commission decisions,[9] and that the marketing authorizations for the anorectic products were not really harmonized, so that there could be no valid referral under Article 15a.

In addition, the Court held that the decision was also illegal because it did not meet the substantive requirements for withdrawing marketing authorizations. The Court stated that a competent authority can, at any time, re-evaluate the risk-benefit balance, and may take appropriate action, particularly in cases of scientific uncertainty. The latter is an application of the "precautionary principle", a general principle of Community law that allows actions to protect public health early on in an evaluation procedure without changing the general burden of proof.

However, according to the Court, the withdrawal of a marketing authorization cannot be based on mere changes in the scientific criteria for the risk-benefit assessment if no new data underpin a revised assessment of the risk-benefit balance of a product:

> *"(…)the withdrawal of a marketing authorization must in principle be regarded as justified only where a new potential risk or the lack of efficacy is substantiated by new, objective, scientific and/or medical data or information. In particular, it is entirely logical that the application of a new assessment criterion, which reflects a current consensus in the medical community, is justifiable during the period of the*

[9] Articles 12 and following of Directive 75/319 were badly drafted and did not clearly state that an Article 12 referral resulted in a binding Commission decision. The same defect existed with regard to the mutual recognition procedure, but there the Court held that the clear intention of that procedure was to result in a binding arbitration. The defects were in the meantime corrected by Directive 2004/27, amending Directive 2001/83, which codifies Directive 75/319 and other directives.

authorization's validity only if that development is based on new data or information."

The CPMP also did not refer to new products available on the market with a better risk-benefit balance, which would have had an impact on the evaluation of the products in question. As a result, the decisions were unlawful also with regard to their content as they were not based on any new data, which in any case would not have yet been available for the evaluation carried out in 1996.

The Commission appealed the CFI decision, but the ECJ held that the SmPC changes imposed in 1996 did not harmonize the old national decisions and that a subsequent referral therefore could not be based on Article 15a. The ECJ thus avoided having to decide on key issues raised by the CFI.

b) Community Review of Third Generation Oral Contraceptives

- *Review at the Community Level*

In 1995, the CPMP started a review of third generation oral contraceptives containing desogene or desogestrel. The review was based on epidemiological studies, including studies that were close to completion or publication at that time and that indicated a slightly higher risk for non-fatal venous thromboembolism. The review was informal and not based on the Community interest procedure under Article 12 of Directive 75/319.

Following hearings with the investigators, the CPMP invited the three companies affected – Schering, Organon, and Wyeth – to provide scientific material related to the risk of third generation contraceptives and to present it at a hearing with the CPMP and an ad-hoc working party. After assessing the available information, the CPMP concluded in a position statement that it was not appropriate to order the withdrawal of marketing authorizations on

the basis of ensuring public health as the available data did not show significant differences in the risks for cardiovascular mortality and stroke, and showed only slight increases in venous thromboembolism when compared with second generation oral contraceptives (containing levonorgestrel). The CPMP also found that a better risk profile for myocardial infarction could not be substantiated. It did, however, require the companies to supply further information and suggested that specific information be included in communications to physicians and users.

In April 1996, based on more scientific input from the companies affected and further studies becoming available, the CPMP issued a second position statement stating that third generation oral contraceptives, at that time, seemed to have a slightly higher risk of venous thromboembolism. It also stated that a better risk profile concerning myocardial infarction could not yet be confirmed, and asked for further studies to clarify this issue. In addition, the CPMP requested that information for physicians and users be supplemented.

Later on, the CPMP requested that clinical trials be initiated to address the differences between combined oral contraceptives of the second and third generations, such as differences with regard to common side effects, and information about haemostatic factors. In addition, the CPMP asked for further information from the investigators who had conducted the epidemiological studies that first triggered the review. This was addressed in an updated position statement of early 1997.

In 2001, the CPMP issued a public assessment report on combined oral contraceptives and venous thromboembolism (EMEA/CPMP/2201/01/en/Final). It stated that the risk assessment of venous thromboembolism remained favorable for all combined oral contraceptives but that the third generation oral contraceptives reviewed carried a slightly increased risk of venous thromboembolism when compared to second generation products. A

favorable risk profile concerning myocardial infarction again could not be proved. As a safety measure, the CPMP recommended reflecting the risk differences in the SmPCs and the package leaflets and providing additional information to prescribers and users. The proposals for change concerned the SmPC sections "Special Warnings and Special Precautions for Use" and "Undesirable Effects."

- *Product Liability Litigation in the United Kingdom*

In the U.K., women who had taken third generation oral contraceptives brought a product liability class action against Schering Health Care Limited, Organon Laboratories Limited, and John Wyeth & Brother Limited. The plaintiffs claimed that they had suffered various cardio-vascular injuries, such as venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral venous thrombosis (CVT), and strokes as a consequence of using the oral contraceptives. The court decided to dismiss the claims holding that there was "*not as a matter of probability any increased relative risk of VTE carried out by any of the third generation oral contraceptives supplied to these Claimants by the Defendants as compared with second generation products containing Levonorgestrel.*" (High Court of Justice Queen's Bench Division, Judgment of the Honorable Mr. Justice Mackay, July 29, 2002). In its judgment the judge stated that he did not feel bound by the review carried out by the regulators and their conclusions.

Based on witness examinations of the key assessors who had conducted the CPMP review, the judge held that the review did not support any finding of increased risk. He did, however, add that his decision was one merely on product liability and not a judicial review of the CPMP assessment.

c) Community Marketing Authorization for Ferriprox

(The Ferriprox Case (T-326/99)

- *Factual Background*

Ferriprox is an iron chelating product, approved for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate. It contains the active substance deferiprone.[10]

In February 1998, Apotex filed an application for a marketing authorization for Ferriprox and following the review by the CPMP rapporteur and co-rapporteur and the responses to follow-up questions both in writing and in oral explanations, the CPMP issued a positive opinion on January 28, 1999.

On April 28, 1999, Dr. Nancy Fern Olivieri, a key opinion leader in the treatment of iron-overload in thalassaemia patients, informed the EMEA of what she claimed to be new safety information on deferiprone, particularly concerning hepatic fibrosis and cardiac disease. Dr. Olivieri was in the past involved as investigator in the clinical trials conducted to support the application for marketing authorization, but her collaboration with Apotex had ceased due to disagreement over the interpretation of the study results. She submitted information based on

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[10] Ferriprox is in reality an orphan medicine but went through the approval process before the orphan medicines rules took effect and, thus, does not benefit from the specific market exclusivity protection, although it could qualify for orphan medicine status for another indication. A medicine is eligible for orphan designation if it can be established

"(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or (…)

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition."

(Art. 3 No. 1 of Regulation 141/2000) Ferriprox would fulfil these criteria as only 10,000 to 20,000 people in the European Community suffer from this disease and the medicine allows for a much easier administration of the product than the competing medicine available for the treatment of thalassaemia major. It therefore offers a significant additional benefit to patients suffering from the disease. The application for a marketing authorization of Ferriprox was based on "exceptional circumstances" (as it was not possible to provide comprehensive information on the safety and efficacy of the medicine), allowing the submission on fewer clinical data than normally required. The clinical data that were submitted resulted mainly from a Phase II and a Phase III trial and data from compassionate use of the medicine.

the clinical trials she was involved in and also data resulting from a separate trial she conducted after stopping the collaboration with Apotex. She also referred to a publication of her findings in the New England Journal of Medicine in August 1998.

The CPMP Chairman informed the Commission of this development on May 20, 1999 and Apotex was "requested to supplement the file with any additional information in his possession or to confirm that all currently available information relevant to the issue had been supplied during the evaluation process." The Commission suspended its decision making process and asked the CPMP to clarify the impact of the new information on its earlier opinion. The EMEA created an ad-hoc experts group, which reviewed the submissions by Dr. Olivieri and subsequent submissions by Apotex. The group discussed these new materials without the presence of Dr. Olivieri or Apotex (but one of the members of the experts group had openly chosen the side of Dr. Olivieri).

Ultimately, on June 23, 1999 the CPMP issued a revised positive opinion for granting marketing authorization under exceptional circumstances. The Commission adopted a decision on August 25, 1999 which reflected the recommendations of the CPMP. The decision to grant the marketing authorization for Ferriprox was justified on the following grounds:

> *"- first, the indication of deferiprone is strictly limited to the treatment of iron overload in patients who present thalassaemia major and for whom treatment by deferoxamine is counter-indicated or is accompanied by severe toxicity;*
>
> *- second, deferiprone is relatively effective, in the sense that it promotes elimination of iron and may prevent its accumulation in certain patients treated with it, as is shown by the results obtained by reference to the concentration of serum ferritin in the course of trials LA-01, LA-02 and LA-03 in particular;*

- third, despite the information indicating the lower efficacy of deferiprone compared with deferoxamine and the lack of information showing that a negative iron balance is achieved in the long-term, the marketing authorization for deferiprone is explained by the absence of another therapeutic solution able to preserve the life of the patients concerned by the indication;

- fourth, in order to obtain the information deemed necessary to complete the scientific assessment of deferiprone, the marketing authorization is subject to a number of specific obligations requiring Apotex to supply additional information."[11]

Dr. Olivieri brought an action before the CFI seeking annulment of the CPMP opinion and the Commission decision and also to apply for immediate suspension of the decision pending the litigation on the merits.

- *Legal Issues Addressed*

The Ferriprox case addresses third party involvement in marketing authorization procedures. It reviews whether third parties have the right to provide information and have this information assessed during the evaluation procedure, and under what circumstances they can challenge a Commission decision granting a marketing authorization before the Community courts.

The CFI held that, under the specific circumstances of the case, Dr. Olivieri did not have an interest in bringing an action in order to protect public health in general or to defend her professional reputation. The Court did, however, confirm that the Commission was allowed

[11] Decision of the CFI in its Judgment of 18 December 2003 - T-326/99), par. 83.

(For further details on the procedural steps, see http://www.emea.eu.int/humandocs/Humans/EPAR/ferriprox/ferriprox.htm; further details on the evaluation of the application can be found in the scientific discussion document http://www.emea.eu.int/humandocs/Humans/EPAR/ferriprox/ferriprox.htm.)

to gather relevant information on the product from third parties, and was obliged to examine information that calls into question the scientific assessment already made by the CPMP. In the Ferriprox case, that had happened by asking the CPMP to reassess the file. Only when the information had not adequately been examined would Dr. Olivieri have had standing.

The Court concluded:

> *"Therefore, the Court finds that, although the applicant was entitled to make sure that the CPMP and the Commission examined the information which she had sent directly to the CPMP in order to contribute to the scientific assessment of deferiprone and to ensure the authenticity of the results obtained in the course of trial LA-01, that right ended at the moment when that information was examined and taken into account in the course of that assessment procedure.*
>
> *Consequently, the applicant no longer has an interest in bringing proceedings to contest the legality of the contested decision is so far as concerns the examination of the correctness and completeness of the scientific information relating to deferiprone." (par. 91-92)*

The Court also clearly held that third parties do not have the right to participate or be heard in the administrative procedure of evaluating and granting a marketing authorization. It stated in this context:

> *"Unlike other Community administrative procedures, in particular those in the area of the competition rules, during which third parties, that is to say parties interested in or potentially affected by any Commission decision, are entitled to be heard by the Commission before the decision is adopted, Regulation No 2309/93 establishes a purely bilateral procedure. It is a procedure between the applicant for marketing*

authorisation and the administration, during which the administration must take into account the applicant's interest in obtaining marketing authorisation and the public interest in the protection of human health. Dr Olivieri, in her capacity as third party, is not entitled to participate in that procedure or set herself up as interlocutor of the CPMP and of the Commission in regard to the assessment of the scientific data relating to the product in question." (par. 94)

3. Substantive Background

a) Overview of the Community Pharmaceutical Legislation

- *Main Developments*

The Community pharmaceutical legislation was gradually developed over the last four decades. The first step was the adoption of Directive 65/65 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products in January 1965. It was adopted in the wake of the thalidomide scandal and required all Member States of the European Economic Community at that time to impose a pre-market approval system for branded medicines. Such approval requirement did already exist in, for instance, France and Belgium but not yet in Germany. Directive 65/65 contained a definition of a medicinal product, which is important for borderline issues, and established general principles for the pre-market approval, in the form of a marketing authorization. The directive has proven to be well designed and the key concepts remain applicable today. The definition of a medicine, for instance, remained in essence unchanged until 2004 and even then was only fine-tuned.

Similarly, the basic concept of a marketing authorization has remained in effect, the subsequent legislation defining the standards for approval in further detail and broadening the

scope of the approval system to non-branded (generic) products, as well as specific types of products, such as vaccines, allergens, radiopharmaceuticals, and blood-derived products. Over the years, more detailed rules were also added on the manufacturing procedures and labeling requirements, and in 1992 specific rules were issued on wholesale distribution, advertising, and classification of products with regard to prescription status.

Almost all these rules were adopted on the basis of the old Articles 100 and, later on 100a of the EEC Treaty. Article 100a is now Article 95 of the EC Treaty. These provisions allow for Community legislation to be adopted to harmonize the national rules and administrative practices so as to allow for the free movement of products between the Member States. However, in the context of a regulatory regime that is based on product specific approvals and that has to take into account complex scientific and technical issues, a free movement of products cannot be guaranteed by merely harmonizing the principles upon which decisions must be based but also the decisions themselves need to be streamlined. This was first attempted via non-binding consultation of a scientific advisory group that pooled national experts of the medicines agencies (the Committee for Proprietary Medicinal Products or CPMP), mainly for more innovative products, but was not sufficiently successful. Consequently, a binding system for harmonized decisions was decided upon in 1993, in the context of the broad Simple Market initiative that was started by a Commission White Paper in 1985 and resulted in broad reforms in many sectors, abolishing, for instance, customs controls between Member States. These new medicines rules took effect in 1995 and provide for (i) a Community marketing authorization, issued by the European Commission and valid in all Member States, for biotechnology medicines and on an optional basis also for other innovative products (the so-called “centralized procedure”); and (ii) harmonized national decisions in all Member States where approval is sought for new products (the so-called “mutual recognition” or “decentralized procedure”, which became binding beginning in

1998). These systems remain in place and the key directives were codified in 2001 in the "Human Use Directive" 2001/83. The system was further strengthened by a major review of the pharmaceutical legislation, which was adopted in 2004 and reflects important new policy orientations.

- *Protection of Public Health*

From the beginning in 1965, a major consideration of the pharmaceutical legislation obviously was the protection of public health. This is expressed in the recitals to Directive 65/65:

> *"Whereas the primary purpose of any rules concerning the production and distribution of proprietary medicinal products must be to safeguard public health; (…)"*

This has remained the key criterion for regulatory decisions. The CFI, for instance, clearly stated:

> *"The general principle that precedence must be given to the protection of public health is, as regards medicinal products for human use, expressly enshrined in the first recital in the preamble to Directive 65/65 (recital 2 in the preamble to the Code), which states that the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health, and in the third recital in the preamble to Directive 93/39, which provides that in the interest of public health and of the consumer of medicinal products, it is necessary that decisions on the authorization to place medicinal products on the market be exclusively based on the criteria of quality, safety and efficacy ... extensively harmonised by ... Directive 65/65 ....*

Those provisions confirm that only requirements related to the protection of public health must be taken into consideration when a marketing authorization is granted under Article 5 of Directive 65/65 (Article 26 of the Code), when such an authorization is renewed under Article 10(1) of that directive (Article 24 of the Code), and in the management of marketing authorizations in accordance with Article 11 of that directive (Article 116 of the Code)."[12]

- *2004 Revision*

This emphasis on the protection of public health is further strengthened in the 2004 revisions to the pharmaceutical legislation. The revisions broaden the power of the regulators to take action against existing marketing authorizations and grant them more discretion in this context.

At the same time, the revisions strengthen the regulatory obligations of pharmaceutical companies and in particular require more detailed and more specific pharmacovigilance activities. Combined with the recent post-marketing experiences with certain classes of medicines, the new rules will result in a more controlled regulatory environment for medicines and more detailed supervision. This is reinforced by a second policy consideration underlying the revised legislation, which is the stronger emphasis on inspections (for instance pharmacovigilance inspections) and enforcement. A specific example of the latter is the new provision giving the European Commission the power to impose financial penalties on companies that do not comply with their obligations in connection with marketing authorizations that are granted under the centralized procedure. The Commission has issued

[12] Cases T-74/00, T-76/00, T-83/00 to T-85/00, T-132/00, T-137/00 and T-141/00: Artegodan GmbH and Others v Commission of the European Communities(so-called "Anorectics cases"), Judgment of the CFI of 26 November 2002, par. 175-176.

a first draft of a Commission Regulation establishing a specific penalties procedure and is currently reworking the draft. A final Regulation may be issued by the end of 2005.

Finally, the revision of the legislation introduces very important changes to the regulatory data protection rules. As part of this, it now also requires medicines regulators to take decisions that have a predominantly economic effect. Obviously, decisions on the approval status of a medicine can have a very significant financial impact for the company concerned and its competitors in the market, but these decisions must uniquely be taken on the basis of public health criteria. Under the new pharmaceutical rules, however, regulators must now also assess whether a new therapeutic indication for an existing product (not approved for more than eight years) provides a "*significant clinical benefit in comparison with existing therapies*" so as to merit an additional year of regulatory data exclusivity, which provides protection against the approval of generic copies.[13] A similar provision applies to new indications that are developed for already well-known substances.[14]

b) Legislation and Guidance Texts

The current Community pharmaceutical legislation mainly consists of the following pieces of legislation (with respect to human medicines):[15]

[13] Article 10.1 of the amended Directive 2001/83.

[14] *Ibid.* Similar regulatory decisions with mainly economic effect are taken under the rules governing orphan medicines. These rules are designed to create financial incentives for companies to develop therapies for rare diseases. The key incentive is a ten-year market exclusivity for an approved medicine. This period can, however, be reduced to six years in certain cases when the product "is sufficiently profitable not to justify maintenance of market exclusivity" (Article 8.2 of Regulation 147/2000) on orphan medicinal products). This provision will become relevant beginning in mid-2006 and risks being controversial. Very recently, the COMP has granted orphan designation for the first time based on the "insufficient return on investment" criterion (20 September 2005).

[15] We have not listed the amending directives or Regulations but have indicated when the law has been subject to amendment.

- 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 as amended (often referred to as the “Human Use Directive”);

- 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;

- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use;

- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products;

- Council Directive 89/105/EEC, of 21 December 1988, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion within the scope of national health insurance systems;

- 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 Evaluation of Medicinal Products, which will be replaced by 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 in November 2005;

- Council Regulation (EC) No 297/95, of 10 February 1995, on fees payable to the European Agency for the Evaluation of Medicinal Products, as amended;

- Commission Regulation (EC) No 540/95, of 10 March 1995, laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with the provisions of Council Regulation (EEC) No 2309/93;

- Commission Regulation (EC) No 1662/95, of 7 July 1995, laying down certain detailed arrangements for implementing the Community decision-making procedures in respect of marketing authorizations for products for human or veterinary use;

- Commission Regulation (EC) No 2141/96, of 7 November 1996, concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EEC) No 2309/93;

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products;

- Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’;

- Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorization for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State;

- Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorization for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93.

These provisions are supplemented by guidance texts that are issued by the European Commission (including detailed guidelines on the operation of the regulatory procedures, contained in the Notice to Applicants) and by the EMEA.

These texts are accessible on the website of the Pharmaceutical Unit of the Commission (http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm) and of the EMEA (http://www.emea.eu.int/index/indexh1.htm; mainly under "Guidance documents").

c) Institutions Involved in the Decision Making Process[16]

The Community pharmaceutical regime is a complex system that combines national and Community systems. The key institutions involved at the Community level are the following:

- *European Commission*

[16] As stated in the introduction, only the regime on medicines for human use is discussed. There are also specific bodies for veterinary medicines.

The Commission is, as general "guardian of the Treaty," responsible for supervising general compliance with the pharmaceutical rules and can be called upon by other institutions for guidance when the rules are not clear. In addition, under the pharmaceutical rules the Commission is the main body that is empowered to issue decisions, such as granting or refusing marketing authorizations, suspensions or withdrawals under the centralized procedure, or ordering Member States to grant or withdraw marketing authorizations under the decentralized procedures.

- *European Medicines Evaluation Agency (EMEA)*

The European Medicines Evaluation Agency is responsible for the scientific evaluation of medicinal products and provides, through its Committees, the scientific assessment of medicines, on which Commission decisions are based. The EMEA[17] only has limited powers to issue decisions on its own. Most important issues are formally decided upon by the Commission, based on the scientific opinions rendered by the EMEA committees. However, the EMEA sometimes takes a decision. It can, for instance, refuse the validation of an application for marketing authorization or for variation of a marketing authorization, and decides whether or not a product qualifies for the centralized procedure.[18] It also takes fee decisions (including fee waivers), can ask for further pharmacovigilance data, appoints product managers and rapporteurs/co-rapporteurs, etc. Internally it will also take decisions as to the participation of members of the committees in scientific evaluations of products when conflicts of interests are at stake.

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[17] Originally, the agency was called the "European Agency for the Evaluation of Medicinal Products", but was often referred to as the "European Medicines Agency" or "EMEA". Effective on May 20, 2004, the name was officially changed to the "European Medicines Agency", in part to stress its functions beyond the evaluation of medicines. The acronym EMEA has, however, been maintained.

[18] Medicines falling within the scope of List B of the Annex to Regulation 2309/93 can optionally be approved under the centralized procedure. Beginning on November 20, 2005, the criteria for optional centralized approval are contained in Art. 3 of Regulation 726/2004.

- *Specialized Committees within the EMEA*

The EMEA comprises several specific committees for the evaluation of medicines. Details on their tasks and composition are provided for in Article 56 and 61 of Regulation No. 726/2004 (previously in Article 50 and 61 of Regulation No. 2309/93). Those committees have to install rules for procedures.

The main committees are:

- The CHMP (Committee for Medicinal Products for Human Use, the successor to the CPMP beginning in May 2004), which is responsible for preparing the opinion of the EMEA on any question relating to the evaluation of medicinal products for human use.[19]

- The HMPC (Committee on Herbal Medicinal Products), which is in charge of the evaluation of herbal medicinal products.

- The COMP (Committee for Orphan Medicinal Products), which, among other, examines orphan drug designations and further supports the Commission in policy matters concerning orphan medicinal products.

The committees can form their own standing and temporary working parties. Furthermore, the committees are to establish a standing working party for providing scientific advice to companies. The CHMP may also establish scientific advisory groups in connection with the evaluation of specific types of medicines or treatments and can request advice on general scientific and ethical questions.

[19] The CVMP or Committee for Medicinal Products for Veterinary Use exercises the parallel function for veterinary products.

- *Coordination Group (formerly the Mutual Recognition Facilitation Group)*

The Coordination Group (of representatives of national regulators) acts as a mediating committee between Member States in case of disagreements concerning marketing authorization applications under the decentralized and mutual recognition procedures. The Coordination Group's primary task is to achieve agreement between Member States to avoid an arbitration procedure. The Coordination Group was formally established on October 30, 2005, by Article 27 of Directive 2004/27 amending the Human Use Directive. Its predecessor, the informal Mutual Recognition Facilitation Group (MRFG), however, was already carrying out these activities on an informal basis since the beginning of the new authorization regime in 1995 for the purpose of facilitating the smooth functioning of the decentralized procedures.

- *Standing Committee*

The Standing Committee on Medicinal Products for Human Use assists the Commission in its tasks and is involved in the Commission's decision making process concerning medicines. From a procedural perspective, the Standing Committee forms part of the "comitology process" as laid down in Decision 1999/468/EC and allows for the participation of the Member States in the procedure. The Standing Committee's involvement generally is in writing. However, under specific circumstances, meetings may be required. The Commission must submit a draft decision (e.g., granting a Community marketing authorization) to the Standing Committee, which can adopt an opinion by a qualified majority. If the opinion approves the proposal, the Commission can adopt the decision. In case of a negative opinion, or if no opinion can be adopted, the matter is referred to the European Union's Council of Ministers.

The Notice to Applicants, Volume 2A, Chapter 6, describes the following circumstances in which the Standing Committee must be consulted:

"(a) - *new application (Article 10 of Regulation (EC) No 726/2004);*

- *application for an extension (Article 2 and Annex II to Commission Regulation (EC) No 1085/2003);*

- *conditional marketing authorization (Article 14(7) of Regulation (EC) No 726/2004 and Commission Regulation (EC) No …/2005);*

- *annual reassessment of a marketing authorization granted under exceptional circumstances (Article 14(8) of Regulation (EC) No 726/2004);*

- *renewal of the marketing authorisation (Article 14 of Regulation (EC) No 726/2004);*

- *suspension and revocation (Article 10 of Regulation (EC) No 726/2004);*

- *provisional measures (Article 20 of Regulation (EC) No 726/2004).*

(b) Decisions adopted in Community referral procedures

- *where Member States fail to reach an agreement in the framework of a mutual recognition or decentralised procedure (Article 29 of Directive 2001/83/EC);*

- *where divergent decisions have been taken by Member States (Article 30 of Directive 2001/83/EC);*

- *in cases of Community interest (Article 31 of Directive 2001/83/EC);*

- *where mutual recognition of variation has not been accepted (Article 35 of Directive 2001/83/EC);*

- *where a Member State considers that the variation of a marketing authorization or its suspension or withdrawal is necessary for the protection of public health (Article 36 of Directive 2001/83/EC);*

- *where a medicinal product is to be authorized in accordance with Regulation (EC) No 726/2004 and the scientific opinion by the EMEA contains conditions or restrictions with regard to the safe and effective use of the product (Article 127a of Directive 2001/83/EC).*

(c) Decisions concerning designation of a medicinal product as an orphan where the draft Commission decision is not in accordance with the opinion of the Committee on Orphan Medicinal Products."

Further details on the procedures of the Standing Committee can be found in its revised Rules of Procedure, which were recently published. These rules contain detailed information about the organization of the Committee's meetings, the preparation of decisions, and other significant procedures (Rules of Procedure for the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products, published September 14, 2005; http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/09_05/Post%20Stand%20Cttee%20clean%20version%20-%20%20RoP%20Standing%20Cttees%202005%85.pdf).

d) Types of Decisions

The key decisions in the pharmaceutical sector relate to (i) the granting of marketing authorizations, (ii) variations to existing authorizations (at the request of the pharmaceutical

company, for instance to have a new therapeutic indication approved), or (iii) the variation, suspension or withdrawal of a marketing authorization when regulators consider specific measures are needed (often in light of pharmacovigilance data that suggest a different risk-benefit ratio for the product). The latter two categories often overlap when companies take the initiative to restrict the approval, or agree with recommendations of the regulators.

Most of the decisions are taken by the European Commission, after consultation with the Standing Committee under the above mentioned comitology procedure. They are typically taken on the basis of a scientific and technical assessment by the CHMP within the EMEA.

Sometimes, preliminary decisions are taken by the EMEA and if they are negative, they do not result in Commission decisions. Typical examples are the denial of access to the centralized procedure (under the current rules, so-called "List B status" for high-technology products, other than biotechnology products), or refusals to validate applications.

The following are examples of typical adjudication procedures under the Community pharmaceutical rules:

- *Decision on an application for a marketing authorization under the centralized procedure*

Decisions on the granting or refusal of marketing authorizations are taken by the Commission on the basis of a scientific opinion of the CHMP. While, generally, the Commission will adopt a decision in accordance with the opinion of the CHMP, the CFI is currently dealing with a Commission refusal to grant a marketing authorization despite the issuance of a positive opinion by the CHMP (Case T-15/04, *Sandoz GmbH vs. Commission of the European Union*, concerning the medicine Omnitrop.). In addition, the Commission may request the EMEA to resolve a specific issue before a decision is taken. For instance, this

was the case in the above mentioned Ferriprox case, where the CPMP reviewed specific information submitted by a third party.

An application can also be refused without the file reaching the stage of a Commission decision. The Notice to Applicants provides that each application for a marketing authorization must first be validated by the EMEA. This step implies an administrative review of the file and a preliminary check of its completeness. It should be done within ten working days. In case of a negative validation, the application is considered invalid and is refused.

It is also possible that an application under the centralized procedure is not accepted because the product does not fall within one of the categories of products that can be centrally approved. This can in particular arise for products for which the applicant has the option to seek a Community marketing authorization or one or more national authorizations. This applies, for instance, to products that are produced with new manufacturing techniques that "*in the opinion of the Agency, demonstrate a significant technical advance*"[20] and, under the new centralized procedure, products that "constitute a significant therapeutic, scientific or technical innovation" or when a centralized marketing authorization is "*in the interest of patients*."[21]

There is an informal administrative procedure for obtaining "List B status" (now "Article 3.2(b) status") for specific products and in practice that status is discussed well in advance of filing a marketing authorization application. The Notice to Applicants, Volume 2, Chapter 4, Centralized Procedure, contains further information on this part of the procedure.

[20] Part B of the Annex to Regulation 2309/93.

[21] Article 3.2(b) of Regulation 726/2004.

The CHMP can require the applicant to undergo a GMP inspection of the manufacturing plant if it is necessary for the evaluation of the application (Article 8 Regulation No. 726/2004; Details in the Notice to Applicants, Volume 2, Chapter 4) or request GCP inspections.

- *Application for a variation to a centralized marketing authorization*

Subject to the type of variation, as further defined in Article 3 of Regulation No. 1085/2003, the application requirements and the procedure for evaluating the admissibility of a variation to a marketing authorization differ. The regulation covers three types of variations. Minor "Type IA" variations only require a notification procedure and receive an acknowledgement of validity by the EMEA, if the legal prerequisites are fulfilled. Such variations include, for instance, a change in the name and/or address of the marketing authorization holder or a change in the name and/or address of the manufacturer. Minor "Type IB" variations are subject to a more detailed review by the EMEA and the applicant may be required to amend its application according to the proposal of the EMEA or otherwise risk having the application rejected. Examples of these variations include a change in the name of the medicine or a minor change in the manufacturing process of the active substance. Finally, a stricter review procedure applies to major "Type II" variations, which are always reviewed by the CHMP and may be subject to an arbitration procedure in the case of a disagreement between the applicant and the CHMP. Major Type II variations cover, for instance, significant changes in the manufacturing process, new indications, and important labeling changes. The Regulation also excludes certain changes that are too important to be treated as variations. Instead, they are treated as extension applications and are subject to the authorization procedure. Examples include a change in a salt, ester, or isomer of the active substance without a significant change in safety and efficacy, a new strength, or a new

pharmaceutical form. Finally, the Regulation does not regulate transfers of marketing authorizations, which are subject to separate rules.

Again, in certain circumstances, an application can be denied without a formal intervention of the Commission.

Examples of variation procedures that have resulted in litigation before the CFI are:

- Case T-123/00: *Dr. Karl Thomae GmbH v Commission of the European Communities*

  The EMEA refused to validate a minor variation applied for under Regulation 542/95 (the predecessor of Regulation 1085/2003), by which the applicant wanted to add two product names to its centrally approved product in order to be able to use different names in several member states (for trade mark reasons), and to have a different layout of the package in one country. The EMEA took the view that a centrally approved product could only be marketed in the Community under one name (the so-called "single trademark" policy) and with an identical package layout throughout the Community. The Court held that such a refusal cannot be based purely on a policy statement and requires specific justification.

- Case T-133/03: *Schering-Plough Ltd. v. Commission of the European Communities and the European Agency for the Evaluation of Medicinal Products ("EMEA")*

  The EMEA refused a minor variation to a marketing authorization concerning the change of the name of one of the three pharmaceutical forms covered by the marketing authorization. The applicant wanted to use the name "Allex Reditabs" for a specific oral lyophilisate form of the Allex product. The EMEA refused the application. The case is still pending.

- Case T-179/00: *A. Menarini - Industrie Farmaceutiche Riunite Srl v Commission of the European Communities*

  This case does not relate to a variation procedure but presents similar issues in the context of an administrative review of the final packaging of a centrally approved product. The marketing authorization holder had concluded a co-marketing agreement with the Italian company Menarini and the parties wanted to include the Menarini logo in the so-called "blue box" -- a specific area on the outer packaging -- where country specific information, such as local representatives, can be displayed. The EMEA, taking a critical view, referred the matter to the Commission, where it was discussed with the Member States within the Pharmaceutical Committee. While the Commission did not object to the inclusion of the logo of the marketing authorization holder on the package, the Commission objected to the inclusion of the logo of the distributor on the box and issued a negative decision in the form of a letter. The Commission's decision was annulled by the court.

- *Imposed variation, suspension or withdrawal of the marketing authorization*

Marketing authorizations are subject to permanent review in the interest of public health, such as based on data gathered under a pharmacovigilance system. This can result in decisions concerning the suspension or withdrawal of a marketing authorization, or specific changes (e.g. labeling changes) after the re-assessment of a medicine. Such decisions are taken at the centralized and decentralized levels and, despite the procedural differences in achieving such a decision, the substantial criteria for the decisions are identical. While suspensions are appropriate in cases of uncertainty, withdrawals result from a negative risk-benefit assessment. Imposed variations, ordered by the Commission or by the Member

States, are another, less restrictive, instrument in dealing with new information about the product, especially safety data. They typically consist of restrictions in the indication and additions of new warnings and precautions.

- *Arbitration under the decentralized procedure*

Since 1995, products that are not centrally approved are subject to the mutual recognition procedure, which became mandatory in 1998. The procedure is based on the assessment by one Member State, the "Reference Member State", which is then reviewed by the other Member States where approval is sought, the "Concerned Member States". In case of disagreement, the matter is referred to the CHMP. The company seeking authorization has the right to be heard by the CHMP and the CHMP's opinion results in a binding Commission decision, which has to be transposed into national decisions by the affected Member States. This arbitration procedure is based on Article 2a and Articles 32 through 36 of Directive 2001/83.

- *Specific Community referrals*

In addition to the arbitration procedure mentioned in the previous section, Community pharmaceutical law provides for the following types of Community referrals:

- Article 30 of Directive 2001/83/EC as amended ("Divergent Decision Referral");

- Article 31 of Directive 2001/83/EC as amended ("Community Interest Referral").

These procedures can also, and in most cases mainly do, apply to older products. They result in binding Commission decisions. A "divergent decision referral" is intended to reconcile the SmPCs, or key parts thereof, of older products. This can be done at the request of the pharmaceutical company -- as was the case for the first referral, relating to alfa interferon --

but now this is mainly done to harmonize SmPCs so as to provide a common reference product for generic versions in all Member States.

"Community interest referrals" on the other hand mainly deal with serious safety or efficacy concerns. The CFI ruled in Anorectics that an Article 31 procedure does not result in a binding Commission decision and the same reasoning applies to Article 30 decisions. The 2004 revision of the legislation rectifies this situation, effective beginning in April 2004.

- *Fee decisions*

Fees for EMEA services are laid down in Council Regulation No. 297/95/EC as amended (currently being further amended, for details see draft: http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/04_05/com2005_0106en01.pdf). Fee decisions are taken by the EMEA itself through the Executive Director, who also has the power to decide on fee waivers. Fee waivers or reductions may be granted for orphan medicines or under circumstances further specified in the Regulation No. 297/95. The Management Board of the EMEA has adopted implementing rules on fees.

- *Penalty decisions (under the Draft Penalties Regulation)*

Under the revised legislation, the Commission has the power to impose penalties in case of infringement of the obligations of a marketing authorization holder of a centrally approved product. Details on the penalties regime and the relevant procedure will be laid down in a Commission Regulation, which is currently being prepared. It is envisaged that the Commission will decide on penalties after the EMEA has conducted an investigation, either at its own initiative or at the request of the Commission or a Member State.

- *Miscellaneous acts or decisions by the EMEA*

- Request for pharmacovigilance data

The EMEA can order a marketing authorization holder to provide pharmacovigilance data at any time during the life cycle of a medicinal product in order to assess the risk-benefit balance of the product and to be able to supervise marketed medicines sufficiently (Article 16 (2) Regulation No. 726/2004).

- EPAR (European Public Assessment Report) Decision

The CHMP produces the EPAR, which is publicly available on the Internet. The EMEA is required to publish the assessment report supplemented by the reasons in favor of granting an authorization at the same time that the marketing authorization is issued. Confidential information must not be made available. To ensure the latter, the pharmaceutical company receives a draft EPAR in advance and must indicate the information that it considers confidential.

- Decision to put information on the Internet

Regulation No. 726/2004 places much more emphasis on transparency and requires the EMEA to provide the general public with non-confidential regulatory, scientific or technical information concerning the authorization and supervision of medicines. This will have to be done in accordance with specific rules of procedure to be adopted pursuant to Article 80 of the Regulation. Information can be made available via the Internet. The EMEA also has a Standard Operating Procedure (SOP) on the "Publication and External Dissemination produced by the EMEA" (EMEA/SOP/T/1040).

- Decision to request access to documents under Regulation 1049/2001

Regulation 1049/2001 granting access to documents held by the European Parliament, Council and Commission also applies to documents held by EMEA and is further implemented by rules set up by the EMEA's Management Board. The difficult rule is that access can be granted unless one of the exceptions or restrictions to the right of access applies (see below point 4.9). Negative decisions can be challenged. For further details, see the section entitled "Access to Commission documents."

- *In the discussions below, only four of these decisions will be discussed:*

1. decision on a marketing authorization under the centralized procedure.

2. decision on the application for a variation to a centralized marketing authorization.

3. decision issued after a Community interest referral based on Article 31 of Directive 2001/83 as amended.

4. decision on issuing a penalty under the Draft Penalties Regulation.

4. Application or investigation phase

4.1 Application phase

Of the four types of centralized decisions discussed, only the first two (marketing authorization decision and variation thereto) typically start with an application. The others typically start at the initiative of the regulators, possible after a complaint (for penalties) or when safety or efficacy concerns are raised.

This section only describes marketing authorization applications under the centralized procedure because it is the most complex procedure. Similar principles apply to voluntary variations.

a) Dossier Requirements

In accordance with Article 8 (3) of Directive 2001/83/EC, the applicant for a marketing authorization has to provide comprehensive information about the product, such as:

- the product name,
- composition of the product,
- manufacturing method,
- therapeutic indications and contraindications as well as adverse reactions,
- pharmaceutical form,
- dose,
- route of administration,
- precautionary and safety measures,
- description of control methods,
- results of pharmaceutical, preclinical and clinical trials (which is the core part of the dossier),
- a proposed SmPC,
- description of the packaging materials,

This information has to be provided in the form of the so-called Common Technical Document (CTD) as described in the amended Annex to Directive 2001/83/EC (Annex

amended by Directive 2003/63/EC). The CTD consists of five modules and comprises all of the information required by Article 8 (3) of Directive 2001/83/EC. The five modules are:

- Module 1: Administrative information;
- Module 2: Summaries;
- Module 3: Chemical, pharmaceutical and biological information for medicinal products containing chemical and/or biological active substances;
- Module 4: Non-clinical reports;
- Module 5: Clinical study reports.

The Annex to Directive 2001/83 contains detailed information about the content and presentation of the dossier. In addition, the "Notice to Applicants Volume 2B", "Presentation and content of the dossier" and particularly the document on "Incorporating the Common Technical Document (CTD) (June 2004)" (http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm) contains implementation guidance for applicants and provides details for different application situations, such as marketing authorizations, variations, abridged applications, etc.

If an Active Substance Master File for an active ingredient exists, the applicant must ensure that it is fully accessible to the CHMP. In case of medicines containing genetically modified organisms (GMO), the information on environmental risk assessment needs to be included. An applicant should carefully check the dossier requirements for its product and may address specifics in pre-filing meetings with the EMEA (see below).

For some types of applications, such as abridged applications (the main approval route for generic medicines), or applications for similar biological products (which are follow-on

products of biological medicines), different dossier requirements apply. Abridged applications, for example, are exempted from the requirement to provide pre-clinical and clinical studies (Article 10 (1) Directive 2001/83/EC as amended). For similar biological products, specific rules were adopted in 2003 and 2004. The Directive 2001/83, in Article 10.4 and in the Annex, establishes a basic framework, which is being supplemented with CHMP guidelines. As a general rule, follow-on biological medicines require more comprehensive data to allow for a valid risk-benefit assessment. The products are not well characterized and their properties very much depend on the selection methods for starting materials and the manufacturing process. There is also a case pending before the CFI relating to the refusal of a marketing authorization for Omnitrop, a "biosimilar" genotropin product. The Commission refused the approval although the CPMP had issued a positive opinion and the refusal seems to be mainly based on the fact "that the performance of "comparability studies" implied that the legal conditions for the application of the procedure were not met."[22]

b) Forms to be filed

Application forms for the different procedures are available on the Internet and can be found at the following link: http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm.

c) Submission to the EMEA

Applications in the centralized procedure have to be sent to the EMEA. The address is

EMEA; 7 Westferry Circus; Canary Wharf; London E14 4HB; United Kingdom.

The dossier can be delivered to the following address:

[22] Case 15/04. Sandoz is also suing the FDA for failure to adopt a decision on the application for approval, which it filed in 2003 (*Scrip*, 16 September 2005, page 15).

EMEA Loading Dock; Ontario Way; Canary Wharf; London E 14 4HB; United Kingdom,[23] or can be submitted electronically. The EMEA has set up a Q&A document, dealing with the formal and substantial parts to be dealt with prior to submission (http://www.emea.eu.int/htms/human/presub/list.htm), which also contains information about electronic submission, number of copies, timing aspects, etc.

d) Notifications about filing for application

The EMEA requests that applicants make a pre-filing announcement at least six months in advance in order to assist the members of the committees in organizing their workload and to allow for an efficient review of the application.

Third parties are generally not notified about the lodging of marketing authorization applications. However, the EMEA posts positive opinions of the CHMP on its website. Pending applications are made public once the CHMP makes a positive opinion publicly available. In the Ferriprox case, Dr. Olivieri notified the CPMP shortly after the first opinion had been made public; hence it is likely that she found out that way about the application and its positive assessment. The higher emphasis on transparency under the revised rules may also result in earlier disclosure of information, but this is still under review.

[23] The Notice to Applicants, Volume 2, Chapter 7 contains further details for the dossier delivery, such as maximum weight of boxes, etc. In addition, it contains a fax form to be send to the EMEA before the actual delivery of the dossier. Applications under the national or decentralized procedures have to be submitted to the Member State Authorities in charge for the issuing of marketing authorizations. The Notice to Applicants, Volume 2, Chapter 7 contains further details on the requirements to be complied with in different Member States, such as numbers of copies in the different procedures, exact addresses, etc. The addresses can also be found on the "Heads of Agencies" website (http://heads.medagencies.org/). Member States act either as Reference Member States, taking the lead in the evaluation of an application, or as Concerned Member States, recognizing the marketing authorization granted by the Reference Member state. Details can be found in the "Notice to Applicants, Volume 2A Chapter 2 Mutual Recognition". In addition, the local procedures in the Member States become crucial.

A specific additional step applies to applicants who want to use the centralized procedure where it is optional (previously, "List B" product, as from November 20, 2005 pursuant to Article 3 of Regulation 726/2004). They should indicate this in a letter of intention that includes the following information for the EMEA's use in evaluating the product's eligibility for the centralized procedure:

- a draft Summary of Product Characteristics (SMPC);
- a justification of the product's eligibility for evaluation under the Centralized Procedure;
- in case of a product falling under the scope of Part B, a concise document, preferably not more than 2 pages, stating why the product should be eligible for a marketing authorization through the Centralized Procedure;
- an indication of the number of strengths/pharmaceutical forms/pack sizes (if already known);
- an indication of the intended legal basis for submission of the application; (…).[24]

e) Pre-filing meeting

"The EMEA emphasises the importance of Pre-Submission Meetings with applicants. Pre-Submission Meetings (which should take place approximately 6 months prior to the anticipated date of submission of the application) are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMEA."[25]

[24] http://www.emea.eu.int/htms/human/presub/q01.htm.

[25] http://www.emea.eu.int/htms/human/presub/index.htm.

An applicant can ask for a pre-filing meeting to discuss legal and procedural steps, including preferences for rapporteurs and the appointment of "project managers" within the EMEA. The project manager, who is appointed in the pre-filing phase, has a crucial role in the organization of the application and evaluation procedure and serves as a contact point for the parties involved in the process. The pre-filing meeting is also intended to help the applicant preparing the application, in accordance with the legal requirements and so as to allow prompt validation.

The application form for a pre-filing meeting as well as a "Q&A" document about the pre-application phase can be obtained on the EMEA website. The "Notice to Applicants, Chapter 4, Centralized Procedure" contains details about the information to be included in the request.

Furthermore, the EMEA offers scientific advice through its working parties if guidelines on a specific topic (Notice to Applicants - Volume 3) or pharmacopoeias are not sufficient, or if the company wants to deviate from them. Scientific advice can be obtained at all stages during the process of development of the product and typically is requested well in advance of an actual application because it is used to steer the development of the data package. Scientific advice is not binding for the final decision about a marketing authorization application. The EMEA has issued a guidance document and a SOP for the processing of scientific advice through its committees.

f) Time limits for consideration[26]

There are specific time limits for the review of an application for marketing authorization. The procedure consists of (i) a scientific evaluation, which results in an opinion by the committee in charge (the CHMP in case of human medicines), and (ii) the final decision

[26] The following information relates to an application procedure only.

(which is taken by the Commission, although it is possible that it would have to be taken by the Council of Ministers, but this has not yet happened).[27]

Before an evaluation procedure starts, the application first needs to be validated. The validation of an application should normally be completed ten days after the EMEA has sent an acknowledgement of receipt to the applicant. However, if further information or clarification is needed, the validation phase may take longer.

The evaluation procedure begins after the rapporteur and co-rapporteur confirm that they have received a dossier. It should be completed and an opinion issued within 210 days, but there are various steps where that period is suspended (so-called "clock stops"). The Commission has provided tables that describe the time structure of the evaluation and decision making process. This will be discussed further in point 4.7, Conduct of the Investigation. Under Regulation 726/2004, there is also specific provision built in for accelerated assessment, or, where needed, an assessment taking more than 210 days.

g) Negative decision

An application may be denied without reaching the Commission level when it cannot be validated or when the medicine is not eligible for the central approval procedure. This is, however, exceptional.

A marketing authorization application is also denied if the medicine does not fulfill the authorization criteria, such as safety, efficacy and quality.[28] Generally, the CHMP will have

[27] This section discusses the time limits under Regulation 726/2004.

[28] Article 12 Regulation 726/2004 provides: "*1. The marketing authorisation shall be refused if, after verification of the particulars and documents submitted in accordance with Article 6, it appears that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product. Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with* (continued…)

issued a negative opinion and the Commission will then accordingly adopt a negative decision. However, the Commission is not bound by the CHMP opinion and can refuse an application despite a positive opinion of the CHMP (which happened in the aforementioned Omnitrop case).

4.2 Applications—investigatory phase

The project manager is in charge for the administrative organization of the entire evaluation process of the application. He is appointed in the pre-submission phase and will therefore already assist the applicant before the actual filing of an application. After filing, he has to coordinate the validation, assessment by the rapporteurs, review by the CHMP as a group, involvement of scientific advisory groups and experts, etc. He must make sure that the time frames are kept and that necessary steps are taken at the foreseen points in time.

With the validation of an application, the CHMP checks whether the application is complete and complies with the formal legal requirements. Then follows the main part of the procedure, i.e., the substantial evaluation of whether the medicine fulfills the criteria of safety, efficacy, and quality in order to be authorized.

The CHMP will appoint a rapporteur and co-rapporteur for the assessment of the application. They have to evaluate the application on the basis of the dossier submitted by the applicant and to provide the CHMP with a preliminary assessment. The CHMP can request scientific advisory committees to provide scientific input on the basis of the assessment of the

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Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.

2. The refusal of a Community marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Community.

3. Information about all refusals and the reasons for them shall be made publicly accessible."

rapporteur and/or co-rapporteur, which then has to be reflected in the CHMP´s assessment of the application.

The preliminary assessment is discussed within the CHMP and will normally lead to a list of questions and a recommendation being provided to the applicant together with the scientific discussion. *"The CHMP recommendation will state whether:*

- *the product could be approvable provided satisfactory answers are given to the "other concerns" and the indications, other elements of the SPC or other conditions for the marketing authorization are amended as outlined in the list of questions;*

- *the provisional view of the CHMP is that the product is unlikely to be satisfactory since there are "major objections" which have been identified in the detailed questions."*[29]

The applicant has up to six months to answer the CHMP´s questions and to provide additional information. During this time, the clock for the evaluation of the application is stopped (one of the so-called "clock stops"). The applicant can liaise with the project manager, rapporteur and co-rapporteur in order to clarify issues concerning the questions and the further processing of the application. The applicant's answers are submitted in writing. The applicant can also withdraw the application with a view to filing a stronger dossier at a later stage, which often happens when new data are needed and cannot be compiled within the six-month period.

[29] Notice to Applicants, Volume 2A, Chapter 4, page 16.

On the basis of the response, both rapporteurs draft a joint response to the questions and provide it to the CHMP and EMEA, which then may comment on it. The applicant also receives a copy for information purposes. At that point, the CHMP may decide to request oral explanations from the applicant, who can also ask for the oral hearing on his own. If there is a hearing, the clock stops again. Then, the final draft of the SMPC, package leaflet, etc. are provided and on the 210th day at the latest, the CHMP opinion together with the assessment report are issued. The CHMP tries to decide on the basis of scientific consensus, but if no consensus can be reached, a majority vote will prevail and the diverging opinions have to be reflected in the assessment report.

In case of an unfavorable opinion, the applicant has to be informed immediately and provided with the CHMP assessment report, which states the reasons for a negative opinion and dissenting votes of members of the CHMP if any. The same applies when the CHMP requires the SmPC to be changed, considers that the labeling or package leaflet is not in accordance with the legal requirements, or that the authorization can only be granted subject to conditions. In these cases, the applicant may request in writing (within 15 days after the receipt of the opinion) that the opinion be reassessed. The request has to be supported by a written explanation within 60 days after the receipt of the opinion. The CHMP then has to reassess its opinion within 60 days after the receipt of the written explanation through newly appointed rapporteurs. However, the review is restricted to the questions raised by the applicant in its appeal and may only be based on scientific information that had already been provided to the CHMP when issuing its first opinion. The applicant may also request to involve a scientific advisory committee at that point. The CHMP must draft a final opinion, which includes the conclusions of the reassessment.

The "reassessment" thus involves reevaluation of the application by the same body, based on the same data. Therefore, it is not an administrative appeal procedure as it is usually understood.

The CHMP opinion together with the assessment report are then forwarded to the Commission for the adoption of a decision (see below), with a copy to the Member States and the applicant.

4.3 Complaints—pre-complaint phase

There is no formal complaint procedure, except indirectly under the proposed Penalties Regulation. The following sections discuss regulatory intervention with respect to products that are already approved. This includes variations to approved marketing authorizations that the Commission may impose based on safety or efficacy concerns raised by a national regulatory authority or through the Community referral process.

a) Variation of a centrally approved product

A variation procedure may be preceded by the Commission imposing an "urgent safety restriction" on a marketing authorization holder in cases where there is a risk to human or animal health. The marketing authorization holder is then obliged not only to implement the urgent safety restriction but also to initiate a variation procedure reflecting the urgent safety restriction.[30] The application must include appropriate documentation in support of the proposed change within 15 days at the latest after the initiation of the urgent safety restriction. Details about the processing of variation procedures can be obtained from the

[30] Urgent safety restriction is*" an interim change, due to new information having a bearing on the safe use of the medicinal product, to the product information concerning particularly one or more of the following items in the summary of product characteristics: the indications, posology, contraindications, warnings, target species and withdrawal periods."*

Notice to Applicants, Volume 2A, Chapter 5, Variations and on the EMEA website http://www.emea.eu.int/htms/human/postguidance/index.htm. The EMEA has also adopted SOPs for variation procedures.

b) Community Referrals

Specific guidance is given by the Commission (Notice to Applicants, Volume 2A, Chapter 3) on Community referrals, such as the Community Interest Referral based on Article 31 of Directive 2001/83. Before the actual referral is lodged, the Commission advises the referring party (a Member State, the Commission or the marketing authorization holder) to send a notification to the EMEA to announce that a referral will be initiated and provide clear and concise information as to the question to be referred to the CHMP together with details on the concerned product, marketing authorization holder, etc. In this context, it is possible to request a meeting with the EMEA to discuss the regulatory and procedural issues connected with the intended referral. This pre-submission coordination is intended to streamline the conduct of the formal Community referral procedure.

c) Draft Penalties Regulation Article 7 (2) and (3)

Under the Draft Penalties Regulation, the EMEA may request information from a marketing authorization holder about a possible infringement before initiating a formal infringement proceeding. Thus, the target of a complaint will have a chance to provide a statement with regard to the allegations before it is confronted with a formal investigation.

In addition, once the EMEA has decided to initiate an infringement proceeding, the EMEA must notify the marketing authorization holder and the concerned Member States of its decision in writing. The notification must include a description of the alleged infringement

and the relevant facts substantiating the allegations together with a request to stop the infringement.

4.4 Opening of investigation

4.4.1 How is an investigation triggered? Through a notification or an application? By a third party complaint or information from another government agency or a court case? Or by information identified by the Commission staff itself?

a) Variation of a centrally approved product

Variations can be triggered by the marketing authorization holder, who lodges an application, or they can be imposed by the Commission. A specific case is an urgent safety restriction, which is an interim change to the product information concerning one or more core parts of the SmPC (e.g., indications, posology, contra-indications and warnings -- and for veterinary products, target species and withdrawal periods) due to new information that has a bearing on the safe use of the medicinal product. An urgent safety restriction can be implemented by the marketing authorization holder or imposed by the competent authorities. It needs to be followed by an application for a variation to formally implement the restriction in the marketing authorization.

New information leading to the implementation of urgent safety restrictions can arise from different sources. Marketing authorizations are subject to continuous review by the EMEA and the authorities of the Member States. This is reflected not only in the right to ask the marketing authorization holder for data to assess whether the risk-benefit balance of a product remains positive (Article 16 Regulation 726/2004) but also by the operation of a detailed pharmacovigilance system. The latter imposes information and notification obligations on the marketing authorization holder, allows for the systematic collection and

reporting of adverse events, and ensures the proper exchange of information across the border on the basis of an agreed terminology. New information may also be gained through new studies conducted with the medicine, new therapeutic options in the treatment of a disease, and other means.

New information can result in an updated risk-benefit assessment becoming negative. This can result in the withdrawal of the marketing authorization, but often variations will be sufficient. They can consist in stricter information (warnings, contraindications, etc), a limitation of the indications, etc. The urgent safety restriction allows to implement the measure quickly to protect public health and the subsequent variation procedure then implements, or if needed refines or corrects, the measure based on a concrete scientific assessment.

b) Community Referral Article 31 Directive 2001/83

The Community interest referral can be triggered by a Member State, the Commission, an applicant for a marketing authorization or the holder of an already-issued authorization in cases where the Community interest is at stake. Community interest has a very broad meaning and covers not only public health issues but also the promotion of the European internal market[31] for medicines and consumer protection concerns. The Community interest must be demonstrated by the referring party, but there seems to be limited review, especially when an authority makes the referral.

The person who triggers the referral, must refer the matter to the CHMP (using an official notification form) and clearly identify the referred question together with a detailed explanation.

[31] I.e. the Common Market between the different EU Member States.

c) Draft Penalties Regulation

The EMEA can initiate an infringement proceeding itself or at the request of the Commission or a competent authority of a Member State (Article 7 (1) of the draft Regulation). The EMEA is not obliged to start an investigation, except when requested by the Commission. The Commission must always be informed. In addition, the EMEA is required to contact the marketing authorization holder and may ask that it provide information about the alleged infringement. For further details on the scope of the Draft Penalties Regulation, see Section 9 of this Chapter on "Enforcement action".

4.4.2 Are there checks on the investigation process? Any requirements that probable cause be established before an investigation takes place? Any other protective requirements? How about requirements of approval (such as the requirement that lower level staff get higher-level approval in order to proceed)?

a) Variation Procedures

Generally, the EMEA´s Code of Conduct requires EMEA to take certain measures to ensure that proper administrative procedures are observed. While the Code would apply to the EMEA's conduct of an investigation, the Code's requirements are of a general nature and do not provide for specific safeguards on the investigative process in the event that EMEA seeks a variation to a marketing authorization. In addition, the EMEA has developed SOPs on the handling of variation procedures within the context of a centralized marketing authorization.

- EMEA/SOP/H/3005 on Type II Variation to a Marketing Authorization granted under the Centralized Procedure;

- EMEA/SOP/H/3002/01 on Type IB variations Supersedes SOP on type I variations (17/01/05);

- EMEA/SOP/H/3001/01 on Type IA variations Supersedes SOP on type I variations (17/01/05).

These SOPs are not accessible on the website of the EMEA.

b) Community Referral (Article 31)

The referral procedures generally require a clear identification of the issues and questions that are being referred to the CHMP. In case of an Article 31 referral, the referring party must establish that a Community interest is involved, but there seems to be limited review, especially when an authority makes the referral. There are no further checks or protective measures that specifically limit or control the investigative measures that the EMEA may employ.

c) Draft Penalties Regulation

The Draft Penalties Regulation requires the EMEA to disclose details of the alleged infringements together with the available evidence showing the infringement when it notifies the marketing authorization holder, the Commission and other authorities of the beginning of the infringement proceeding. This requirement to disclose the factual basis for an infringement is designed to ensure that procedures are not initiated without sufficient prima facie evidence to support the allegations. It can therefore be regarded as a protective mechanism. However, there is no need for prior approval by the Commission or another Community Organization.

4.4.3 Are there ways by which a private party can push forward or expedite Commission action on an application or a complaint against a competitor? How about ways to slow down an investigation?

There is no specific procedure for a third party to provide scientific input during the review of an application for approval or a re-evaluation of a marketed product. While third parties do not have any legal basis for formally intervening in the evaluation process, input from third parties is not excluded. In the *Olivieri* case, the CFI clarified the role a third party may have:

> *"Therefore, the Court finds that, although the applicant was entitled to make sure that the CPMP and the Commission examined the information which she had sent directly to the CPMP in order to contribute to the scientific assessment of deferiprone and to ensure the authenticity of the results obtained in the course of trial LA-01, that right ended at the moment when that information was examined and taken into account in the course of that assessment procedure."*[32]

In that case, Dr. Olivieri's special role as a former investigator in clinical trials sponsored by the pharmaceutical company in question was clearly of relevance. The main purpose of the marketing authorization application and re-assessment processes in the pharmaceutical licensing context is to safeguard public health, not to protect competitors. Therefore, third party involvement remains limited. This may be different in cases where generic approvals are at stake, because the generic applicant typically relies on data from the marketing authorization holder for the original medicine, which then has a significant interest in protecting its data from being used for the review of the generic application during the data

[32] No. 91 of the Findings of the CFI in its Judgment of 18 December 2003 - T-326/99.

exclusivity period and in avoiding improper use of such data in general. We are, however, not aware of specific precedents before the EMEA in the context of generics.

4.5 Personnel and committees:

4.5.1 What staff are involved in application reviews and investigations?

a) EMEA

Under the centralized procedure, the CHMP (Article 61 Regulation 726/2004) is in charge of the evaluation of human medicines. A list of the CHMP members with contact details and information on their scientific profile can be found on the EMEA website (http://www.emea.eu.int/htms/general/contacts/CHMP.html).

The requirements for the composition of the CHMP are laid down in Article 61 of Regulation 726/2004. The members are appointed for a renewable period of three years by the Member States after consultation with the EMEA's Management Board. They must be selected on the basis of their experience in the evaluation of medicines. They represent the national authorities but are required to base their findings on the requirements of public health and should not serve as points of influence for the interests of national authorities. The CHMP can also include up to five additional members, appointed by the CHMP on the basis of their scientific qualifications. The CHMP has set up its own rules of procedure as required by the Regulation.

For the evaluation of a medicine, an EMEA official is normally appointed as project manager in the pre-application phase. The CHMP has to appoint one of its members as rapporteur and another one as co-rapporteur. In case of a required re-evaluation of an opinion, different members have to act as rapporteur and co-rapporteur.

Depending on the medicine to be reviewed, the CHMP may involve additional groups or experts in the evaluation of a product. Generally, the following bodies may become involved:

- Standing working parties (such as the group for "scientific advice for companies"),
- Temporary working parties, such as ad-hoc working groups set up to answer specific needs (such as in the oral contraceptives review), or
- Scientific advisory groups.

Ad-hoc working groups and scientific advisory groups are composed of experts with relevant knowledge who are drawn from a list supplied to EMEA by the Member States.

For specific medicines, the following committees also play an important regulatory role:[33]

- COMP (Committee on Orphan Medicinal Products), which reviews applications for orphan medicine status; orphan medicines now have to be approved under the centralized procedure;
- HMPC (Herbal Medicinal Products Committee), which reviews herbal medicines and plays a special role in the simplified approval procedures for herbal products (but this is less likely to be significant under the centralized procedure).

[33] The draft Paediatrics Regulation (…) also foresees the installation of a specific paediatric committee, which would combine specific knowledge in the paediatric sector and therefore would be involved in the evaluation procedure of paediatric data. In the future, such data will under specific conditions may have to be submitted with new marketing authorization applications and applications for line extensions. In exchange, a six-month SmPC extension will be granted.

There are also plans to set up a Committee on Advanced Therapies (CAT) for evaluating advanced therapy products (for details, see the Draft Regulation on Advanced Therapy Products). The CAT may be subordinated to the CHMP, which can adopt a different scientific opinion.

EMEA staff are generally required to comply with the EMEA code of conduct (http://www.emea.eu.int/pdfs/general/admin/Conduct/647003en.pdf).

b) Coordination Group / MRFG (http://heads.medagencies.org/)

Since October 30, 2005, the Coordination Group has been an official part of the decentralized process for marketing authorizations. Replacing the previous informal Mutual Recognition Facilitation Group (MRFG), the Coordination Group aims to reach agreements among Member States when there are dissenting opinions concerning marketing authorization applications or variation applications and thereby avoid formal arbitration proceedings. The Coordination Group was first introduced in 2004, when the pharmaceutical law underwent a major revision, pursuant to Article 27 of Directive 2001/83. The group consists of one representative per Member State who is appointed for a renewable period of three years with the EMEA providing the Secretariat for the Group. The Coordination Group is still in the process of setting up its rules of procedure.

The MRFG stated the following on its website:

> *"The Member states recognised that there needed to be a group that could coordinate and facilitate the operation of the decentralized mutual recognition procedure. (…) The Group is chaired by the country which holds the Presidency of the European Union.*

The Group has no formal position in EC legislation, but has established itself as a major player in the new European system. The Group provides a forum where procedural issues can be discussed and problems resolved. It is able to undertake an overview of individual applications. However, scientific discussions related to individual applications are not discussed within the Group, but rather are handled through "breakout sessions" which are organised and chaired by the specific reference member states (the RMS). (…)

The European Commission attends the MRFG meetings and this permits many procedural matters to be resolved at the MRFG. For more complex issues are referred formally to the Commission for further work."

c) Commission

DG Enterprise's Unit F2 deals with pharmaceuticals regulation. The Head of the Unit is Dr. Martin Terberger. The Unit is structured into the following five subgroups:

- Legal, Economic and Horizontal Affairs, which covers decision making procedures, paediatrics, penalties, orphan regulation, pharmacovigilance, enlargement, borderline products, etc. The group consists of Irene Sacristan-Sanchez, Claire Joan Scharf-Kröner, Erik Helstad, Sandrine Planisi Llobera and Fanny Deneyer.

- Decision Making Process, which covers marketing authorizations, designation of orphan medicine status, etc. The group consists of Mélanie Cailleret, Rosa Galvano, Monika Jaros-Lanquetot, Maryse Robert, Brigitte Schauterden and Aurélien Perez.

- Medicinal Products for Human Use, which covers the decision making process for human medicines, coordination with the different bodies involved in the authorization process, clinical trials, Notice to Applicants, pharmaceutical law review, etc. The group consists of. Birka Lehmann, Peter Arlett, Marie-Claire Dubrunfaut, Nicolas Rossignol, Fanny Deneyer, Elena Prats and Nadia Boukhenfouf.

- Veterinary Medicinal Products, which covers Notice to Applicants, pharmaceutical law review, Maximum Residue Limits, GMP, etc. The group consists of Karin Krauss, Anne Gautrais, Sabine Atzor and Erika Maffessoni.

- Telematics, which covers the EUDRA system, IT standardization, Pharmacos websites. Rochus de Raat deals with Telematics.

For details, please see http://pharmacos.eudra.org/F2/commit/profile.htm.

d) Standing Committee on Medicinal Products for Human Use

The Standing Committee on Medicinal Products for Human Use comprises representatives of the Member States and is chaired by the Commission. It plays a role in the decision making process in accordance with Article 121 Directive 2001/83 and Article 87 of Regulation No. 726/2004, which allows input from Member States into the adoption of a Commission decision under a typical comitology procedure (see below). The Standing Committee is listed in the "List of Committees that assist the Commission in the conduct of its implementing measures" (2000/C 225/02) and has its own rules of procedure.

> *"The Standing Committee is chaired by the Commission representative, who does not vote. Member States representatives' votes are weighted as described in Article 205(2) of the EC Treaty (decision by a qualified majority of 232 out of 321 votes).*

The opinion of the Standing Committee relating to Commission decisions concerning Community marketing authorisations and referral procedures is adopted in accordance with the management procedure of Articles 4 and 7 of Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission. The period laid down in Article 4(3) of 1999/468/EC is set at one month. (See Articles 87(3) of Regulation (EC) No 726/2004 and 121(3) of Directive 2001/83/EC).

The Rules of Procedure of the Committee can be consulted in [insert link once RoP adopted and published]

In the cases where the consultation of the Standing Committee is not necessary, the decision is adopted by the Commission within 15 calendar days of receipt of the opinion of the EMEA.

(…)

The opinion of the Standing Committee will normally be given by written procedure.

The draft decision is forwarded by the Commission to the competent national authorities designated by each Member State (in their own language) by electronic telecommunication or in written form.

Member States shall have 22 calendar 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 Commission according to the degree of urgency involved. This time-limit shall not, otherwise than in exceptional circumstances, be shorter than 5 calendar days. Within this time-limit, Member States must inform the Commission whether they approve the draft, reject it, or abstain. Any Member State

failing to respond within the time-limit to express its opposition or intention to abstain from voting is deemed to have approved the draft.

Member States may forward written comments during the written procedure. (…)"[34]

4.5.2 Involvement of an advisory committee? Comitology process? Member States?

a) Advisory committees within the EMEA and other parts of the Commission

The CHMP can use standing or temporary working groups to provide scientific advice if such expertise is required in the evaluation of a particular product. The decision to involve such groups is made by the CHMP as part of its general responsibility for the scientific evaluation of medicines. The CHMP rules of procedure describe how these working groups may be used in the evaluation process, including how members of such groups are appointed.

Regulation No. 141/2000 on orphan medicines established the COMP (Committee on Orphan Medicinal Products), which is responsible for evaluating applications for orphan drug designations. The COMP also has a major role in advising the Commission on the development of its policies on orphan medicines, including assisting in the drafting of Commission guidelines on orphan medicines and in international negotiations related to such medicines (Article 4 of Regulation 141/2000).

The Pharmaceutical Committee was established by Council Decision 75/320 as another advisory body to the Commission. Its main tasks are the examination of *"any question relating to the application of Directives on proprietary medicinal products, which are brought up by its Chairman (…)*" (Article 2 of the Decision) and "*any other question in the field of proprietary medicinal products brought up by its Chairman (…)*" (Article 2 of the

[34] Notice to Applicants, Volume 2A, Chapter 6 (November 2005).

Decision). The Committee also is consulted by the Commission in the preparation of proposals for Directives in the field of medicines or amendments to such legislation.

The Scientific Committee on Medicinal Products and Medical Devices is a separate scientific advisory body that deals with scientific and technical questions relating to Community legislation concerning medicines for human and veterinary use. The Committee is not involved in the evaluation of individual medicines and its responsibilities therefore do not overlap with the specific authority given to the CHMP for medicine evaluation and the development of related guidelines and policies. The Committee has issued opinions on a variety of topics, including the use of blood and blood products, the safety of blood used for transfusion and organs used for transplantation, the safety of human-derived products as regards TSE, and "clinical superiority" and "similarity" in the context of the orphan medicines legislation.

Directive 78/25/EC established a committee dealing with the adaptation to technical progress of the directives on the elimination of technical barriers to trade in the coloring which may be added to medicinal products. That committee consists of representatives of the Member States with a representative of the Commission as chairman and has its own rules of procedure.

b) Comitology process

The general rules on the comitology process are laid down in Commission Decision 1999/468/EC and are relevant for pharmaceutical regulation decision making. The body involved in the comitology procedure other than the Commission and Council is the Standing Committee already mentioned above. The relevant procedures are the management procedure (Article 4 of the Decision) in case of the centralized procedure and the regulatory procedure (Article 5 of the Decision) in case of the decentralized procedure. The Comitology

procedure provides the Member States agencies the possibility to exercise influence in the decision making process as they can issue written remarks to the draft decision of the Commission and they can ask for a oral hearing in the Standing Committee (for details see above "Standing Committee for Medicines for Human Use"). The comitology procedure thus is an instrument to integrate Member States in the decision making process of the Commission and to balance the fact that they will be bound by the decision issued by the Commission. In case of disagreement, the issue can be referred to the Council. However, to our knowledge, the comitology procedure has never become crucial in the adoption of decisions on marketing authorization for medicines.

4.6 Notice:

4.6.1 Is a complaint issued before an investigation begins or does the investigation precede the complaint?

a) Variation of a Centrally Approved Product

If the Commission imposes urgent safety restrictions, no complaint will precede the actual order requiring urgent safety restrictions.

b) Referral

A referral does not involve a formal complaint but the marketing authorization applicant or the marketing authorization holder is notified when the referral is made (see below).

c) Draft Penalties Regulation

Pursuant to Article 7 of the Draft Penalties Regulation, a target company must be notified in writing when the EMEA decides to start an infringement procedure against it. The EMEA

has the authority "where appropriate" to include in its notice an order that the target company stop the allegedly infringing activities.

4.6.2 What are the requirements for notifying the target of a pending investigation or of the decision to issue a complaint? What information is conveyed in the notice? How specific must the notice be?

a) Community Referral (Article 31)

If a Member State or the Commission starts a referral procedure, the applicant or marketing authorization holder must be informed about the referral and the questions identified by the referring party (Commission or a Member State).

b) Draft Penalties Regulation

As discussed above, the target company must be notified in writing when the EMEA decides to start an infringement procedure. In the notification, the EMEA must indicate the details of the allegations against the marketing authorization holder and any factual and legal elements on which such allegations are based. The notification must indicate that penalty payments may be imposed. The EMEA also has the authority "where appropriate" to include in its notice an order that the target company stop the alleged infringement.

On the basis of a report of the EMEA, the Commission will issue a statement of objections, which must include a description of the alleged infringement and the supporting evidence as well as a warning that penalties may be imposed. The Commission also has the authority "where appropriate" to include in its statement of objections an order that the target company stop the alleged infringement.

4.6.3 Are third parties notified of such action? What public notice is provided? Are complaints confidential?

Generally, third parties are not notified of actions taken against a company. However, in cases where public health is at stake, the EMEA or Member State authorities may inform the public about the measures taken. Article 26 of Regulation 726/2004 also provides for the possibility to provide the information on pharmacovigilance issues to the general public.

In addition, the EMEA website contains a section with "Product Safety Announcements", where information about safety concerns together with information for physicians and patients can be found.

4.7 Conduct of the investigation

4.7.1 Time Limits

The pharmaceutical legislation contains detailed rules providing time limits on the conduct of the scientific evaluation at the EMEA level and for the Commission decision making process. The time limits are mandatory and may only be extended when the law specifically permits it, but the new legislation does not allow the CHMP when assessing a centralized application to extend the time limit for the review of the dossier (Article 6 (3) of Regulation 726/2004).

Different procedures will follow different timelines depending on the scope of the review, the complexity of the issues involved and, in the case of pharmacovigilance measures, the urgency of the matter. The typical evaluation and decision making process for a centralized marketing authorization application as well as for a community referral are provided below as illustrations of the typical timing for an investigation.

The current version of the Notice to Applicants, Volume 2A Chapter 4 (page 15p.) describes the timetable for central marketing authorizations. This is provided as practical guidance, but the timetable can be revised as a consequence of the adoption of Regulation 726/2004, which, among other things, provides for the possibility of an accelerated review (in 150 days) and, where justified, additional review time beyond the usual 210-day limit..

DAY	ACTION
1	Start of the procedure
70	Receipt of the Assessment Reports from Rapporteur and Co-Rapporteur by CHMP members and EMEA. EMEA sends Rapporteur and Co-Rapporteur Assessment Report to the applicant, making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CHMP.
100	Rapporteur, Co-Rapporteur, other CHMP members and EMEA receive comments from Members of the CHMP.
115	Receipt of draft list of questions (including the CHMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur by CHMP members and EMEA.
120	CHMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA. Clock stop. At the latest by Day 120, adoption by CHMP of request for GMP / GCP inspection, if necessary (Inspection procedure starts).

121*	Submission of the responses, including revised SPC, labeling and package leaflet texts in 13 languages, and restart of the clock. Submission of mock-ups in color for each strength/form in the smallest pack-size covering all EU official languages, Norwegian and Icelandic and language combinations.

* Target dates for the submission of the responses are published on the EMEA website (http://www.emea.eu.int/ – documents 'Pre-Submission Guidance').

After receipt of the responses, the CHMP will adopt a timetable for the evaluation of the responses. In general the following standard timetable will apply:

DAY	ACTION
150	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP members and the EMEA. EMEA sends joint Assessment Report to the applicant making it clear that it only sets out their preliminary conclusions and that it is sent for information only and does not yet represent the position of the CHMP. Where applicable, Inspection to be carried out.
170	Deadline for comments from CHMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP Members.
180	CHMP discussion and decision on the need for an oral explanation by the applicant. If oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Submission of final inspection report

	to EMEA, Rapporteur and Co-Rapporteur by the inspections team (at the latest by Day 180).
181	Restart the clock and oral explanation (if needed).
181 to 210	Final draft of English SPC, labelling and package leaflet sent by applicant to the Rapporteur and Co-Rapporteur, EMEA and other CHMP members.
by 210	Adoption of CHMP Opinion + CHMP Assessment Report (and timetable for the provision of revised translations)

After adoption of a CHMP opinion, the preparation of the annexes to the Commission decision and in case of a positive CHMP opinion, the preparation of the European Public Assessment Report (EPAR) are carried out in accordance with the following timetable:

DAY	ACTION
215 at the latest	Applicant provides the CHMP members with SPC, package leaflet and labeling in the 13 languages. A copy of the cover letter to be sent to the EMEA for information.
225	Preparation by the applicant of final revised translations of SPC, labeling and package leaflets taking account comments received from EMEA and CHMP.
230 at the latest	Applicant provides EMEA with final translations of SPC, package leaflets and labeling in the 13 languages. Revised full color mock-ups covering all countries

	should also be submitted.
by 240	CHMP Assessment Report to be transmitted to the applicant. Transmission of Opinion in all EU languages to applicant, Commission, Member States and Norway and Iceland.
By 300	Finalization of EPAR in consultation with Rapporteur, Co-Rapporteur, CHMP and applicant (the latter for confidentiality aspects).

Following the receipt of the EMEA opinion, the Commission enters into the decision making process, which is described in the Notice to Applicants, Volume 2A, Chapter 6. The following table displays the decision making process and a typical timeline. After the receipt of the input of the Standing Committee, the Commission generally must adopt a decision within 15 days, unless the matter is referred to the Council of Ministers due to a dissenting opinion from the Standing Committee.

EMEA opinion

15 days	***Reception by the European Commission services of the appropriate documentation*** - Documentation checking - Generation of the draft Commission decision - Inter-service consultation (around 10 days)

22 days	***Written Procedure (22[35] days according to Regulation (EEC) No 726/2004)*** - Draft Commission decision with the annexes sent in the 19 Community linguistic versions[36] to the member states and marketing authorization holder
15 days	***Adoption Phase*** - Receipt of the amended version of the annexes if required - Generation of the final Commission decision - Sending of the final Commission decision with annexes in the authentic language (language of the marketing authorization holder) to the Secretariat General - Signature of the Director General of DG Enterprise on behalf of the Commissioner: sub-delegation procedure
	Notification phase - Notification by paper copy to the marketing authorization holder of the final Commission decision with the annexes in the authentic language only for decisions concerning centralized marketing authorization - Notification for referral procedure: the decisions with annexes are

[35] 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. This time-limit shall not otherwise than in exceptional circumstances , be shorter than 5 days.

[36] Council Regulation (EC) No 930/2004 of 1 May 2004 on temporary derogation measures relating to the drafting in Maltese of the acts of the institutions of the European Union.

	notified to the Permanent Representatives who are in charge of their transmission to the National Authorities - Sending of the final Commission decisions with Annexes in the 11 Community linguistic versions to the member states, EMEA, marketing authorization holder and EFTA by electronic way (Eudrasafe)

For Community referrals, time limits are also laid down in Directive 2001/83 and are explained in the Notice to Applicants, Volume 2A, Chapter 3, Community Referrals and also in Volume 9, Pharmacovigilance. The evaluation and decision making process in those cases is as follows:

DAY	ACTION
0	Notification of a referral to the CPMP
1	First meeting of the CPMP following the referral to discuss the question(s) referred to the CPMP and the appointment of the Rapporteur/(Co)-Rapporteur, where appropriate). Adoption by the CPMP of the question(s) to be addressed by the applicant(s)/Marketing Authorization Holder(s).
Clock Stop	For the applicant(s)/Marketing Authorization Holder(s) to answer the list of questions raised by the CPMP.
Clock re-Start (Day	First CPMP meeting after submission of responses (including

2)	proposed English SPC, if applicable). Translation into English of the Reference Member State Assessment Report should also be submitted with the responses, if applicable. Adoption by the CPMP of timetable for the rest of the procedure
45	(Co-) Rapporteur(s) prepare(s) a report on the written comments from the applicant(s)/Marketing Authorization Holder(s) together, if applicable, with the draft SPC to be annexed to the opinion.
55	Comments from CPMP members on the (Co-) Rapporteur(s) assessment report(s) plus draft SPC (if applicable).
60	Discussion at the CPMP Need to have an oral explanation: (Co-) Rapporteur(s) and EMEA to liaise with the applicant(s)/Marketing Authorization Holder(s) Applicant(s)/Marketing Authorization Holder(s) should submit the translations of draft SPC in all official languages* (if applicable).
Clock Stop	If necessary, for the preparation and submission of oral explanations
Clock re-start	If necessary, oral explanations

90	Adoption of the CPMP opinion with annexes, if applicable as provided in Article 32 of Directive 2001/83/EC as amended

If the applicant / marketing authorization holder appeals the opinion, time limits for the appeal procedure are as follows:

DAY	ACTION
0	Receipt of CPMP's proposed opinion, acknowledged receipt by the applicant(s)/Marketing Authorization Holder(s)
Until Day 15	Applicant(s)/Marketing Authorization Holder(s) shall notify EMEA of intention to appeal
Until Day 60	Applicant(s)/Marketing Authorization Holder(s) forward to EMEA detailed grounds for appeal
Within the following 60 days	CPMP considers the appeal and adopts final opinion

4.7.2 Information-gathering and other investigatory powers

The EMEA and the Commission have different regulatory responsibilities, which can lead to different issues in investigations. As a preliminary matter, however, it is important to note that the primary responsibility for enforcing pharmaceutical regulations, in particular as they relate to the manufacturing, importing, distribution and advertising of medicines, rests with

the Member States. The latter have their own investigatory powers, including broad rights to request information and documents, inspect plants and take samples, that are only partially harmonized at the EC level. Such rights may also be relevant in authorization and referral procedures and, more generally, for pharmacovigilance procedures, but they are not discussed in this report.

a) Centralized Marketing Authorization Application

- *Application Form*

The main means for gathering information during the application process is the application itself, which must include a detailed dossier about the medicine. The dossier is evaluated against the requirements for issuing a marketing authorization as set out in Article 12 of Regulation 726/2004 (safety, efficacy and quality of the medicine). Obviously, the CHMP can also rely on other available data, but each decision is primarily based upon the dossier that has been submitted. The CHMP may also ask the applicant to supplement the dossier, which can be done either orally or in writing.

- *List of Questions*

The CHMP will normally also produce a list of questions based on the initial assessment of the application by the rapporteur and co-rapporteur. The applicant may answer these questions in writing and, at its request, in an oral hearing before the CHMP. While the applicant prepares its answers, the clock will be stopped for the purpose of the deadlines for evaluating the medicine, but this period may not exceed 6 months.

- *Laboratory Check of Medicines*

The CHMP can also request that an official laboratory performs an analysis of the medicine, its starting materials, intermediate products and other compounds in order to assure the validity of the control methods applied in the manufacture of the product (Article 7 b of the Regulation).

- *GMP or GCP Inspection*

If necessary for the evaluation of the medicine, the CHMP will ask for a GMP inspection of the manufacturing plant. Information about the manufacturer or importer may also be obtained from Member States upon CHMP's written request. Similarly, the CHMP can request a GCP inspection. The CHMP would typically make such requests in relation to the pivotal clinical trial.

- *Scientific Committees*

The CHMP is also entitled to seek specific scientific advice from its standing or temporary working groups, which consist of scientific experts. The details for setting up and involving such working groups are comprised in the CHMP's rules of procedure (Article 56 of Regulation 726/2004).

b) Variation of centrally approved medicines

Variation procedures may be preceded by an urgent safety restriction that can be triggered by new data becoming available to the marketing authorization holder or the EMEA through pharmacovigilance measures (for further details see 4.7.2. (c) below). However, the variation procedure itself is started by the marketing authorization holder's notification (Type IA) or application (Type IB or Type II) for variation. The seriousness of the requested variation determines which procedure must be used.. The notification procedure for Type IA minor variations requires the applicant to (i) submit all necessary documents, including those

amended as result of the variation, and (ii) pay the relevant fee. The notification procedure for Type IB minor variations requires the marketing authorization holder to (i) submit all documents amended as a result of the variation, (ii) submit all documents necessary to demonstrate that the conditions laid down in Annex I (of the variation regulation) are satisfied in relation to the requested variation, and (ii) pay the relevant fee. In case of a Type II Variation, the applicant is required to (i) submit the relevant particulars and supporting documents, (ii) submit supporting data relating to the variation applied for, (iii) submit all documents amended as a result of the application, (iv) submit an addendum to existing expert reports/overviews/summaries to take account of the variation applied for, and (v) pay the relevant fee. The documents to be submitted to the EMEA give an indication of the information sources the EMEA uses when considering the notification or application. However, a Type II Variation requires a CHMP opinion, which means the CHMP may use further sources of information and involve scientific working parties or experts in the evaluation of the medicine. In addition, the CHMP is entitled to ask the applicant for supplementary information (Article 6 (7) of Regulation 1085/2003).

c) Community Referral Article 31 Directive 2001/83

- *Information from the Referring Person*

The referring person must provide the CHMP with all available information relating to the matter in question, which must be clearly described because it also limits the review conducted by the CHMP. In any event, the marketing authorization holder or the applicant must supply the CHMP with all available information relating to the matter in question.

The CHMP must take into account all relevant factors in evaluating the ongoing validity of an existing marketing authorization and determining whether amendments, suspension or withdrawal are necessary. The following documents are of major importance when gathering

information about the safety, efficacy and quality of a marketed product (see also Notice to Applicants, Volume 9 Pharmacovigilance - Medicinal Products for Human Use and Veterinary Medicinal Products):

- *Periodic Safety Update Reports (PSURs)*

The marketing authorization holder is obliged to provide periodic reports about the safety of its product to the EMEA and Member States either on request or after specific time periods fixed by the law (Article 104 of the Human Use Directive). The frequency at which these reports are required depends on the length of time the product has been on the market. PSURs must include a scientific risk-benefit-assessment.

- *Specific Data Request (Article 23 of the Human Use Directive)*

The EMEA can at any time request data from the marketing authorization holder to enable it to check if the risk-benefit assessment remains positive.

- *Notifications of adverse events*

The marketing authorization holder must establish a pharmacovigilance system and report adverse events to the Member States and the EMEA. The reporting obligations depend on the event involved (expected or unexpected serious events; within the Community or in third countries). The reporting and documentation requirements are laid down in the Notice to Applicants on Pharmacovigilance (Volume 9).

- *Information generated through official pharmacovigilance systems*

Member States are obliged to operate a pharmacovigilance system and to ensure information is exchanged with other Member States and the EMEA. Pharmacovigilance systems were in place in individual Member States before the harmonized EC rules came into force and

involved, for example, reports by health care professionals and pharmacovigilance centers for the collection of reports. The current system includes harmonized institutional requirements in the Member States, electronic data exchange and a European Database for Pharmacovigilance information. These systems for gathering information about medicines are important for signal generation concerning risks with medicines and can be further used in the re-assessment of a medicine.

- *Scientific Material, Studies*

New scientific material, publications of studies in specialized journals, new studies conducted by the company, and studies conducted by competitors may provide information that is relevant for a re-assessment of a marketing authorization.[37]

- *Expert Advice*

The CHMP may request expert advice with respect to specific questions. In the case of such a request, the CHMP must specify the questions to be answered by the experts.

- *Written and Oral Explanations*

The applicant or marketing authorization holder may provide written or oral explanations before the CHMP adopts its opinion.

- *Information from third parties*

The CHMP may request information from third parties. Third parties may also, on their own initiative, approach the EMEA and submit additional information about a medicine. In the *Olivieri* case, the CFI held that the EMEA needs to take into account all information that is

[37] See Notice to Applicants, Volume 9, Pharmacovigilance, page 88.

relevant for the evaluation of a medicine as the main purpose of the legislation is to protect public health.

- *Other information available*

The Notice to Applicants, Volume 2A, Chapter 3, states that "*[t]he CPMP may also take into account any other information at its disposal which concerns the quality, safety and efficacy of the medicinal product and which may help in arriving at its opinion.*"

Finally, as mentioned previously, the Member States' authorities have to supervise pharmaceutical companies and manufacturers and have powers to enable them to do so, including the right to inspect plants, request records, require the cooperation of companies and their staff, and take samples.

d) Draft Penalties Regulation

The EMEA has the right to ask for (i) written or oral explanations; (ii) the submission of particular documents; (iii) the testing of a medicinal product in accordance with Article 7 b of Regulation 726/2004; and (iv) the cooperation of national competent authorities (such as requests for inspections or the performance of supervisory measures).

The Commission may ask the marketing authorization holder, the EMEA, or the national authorities to provide any relevant information and it may hear other natural or legal persons. The Commission may also decide to send the matter back to the EMEA, if it considers that additional information is needed to issue a decision.

4.8 Rights and duties of target

4.8.1 Duty to disclose information that is subject to privilege? Attorney-client? Self-incrimination? Work product? Pharmaceutical Law does not provide for any specifics that supplement or amend the general rules.

4.8.2 Duty to cooperate?

a) Cooperation in General

In the pharmaceutical sector, the marketing authorization holder has an obligation to cooperate with the authorities. Under Article 23 of Directive 2001/83, the marketing authorization holder is required to supply the competent authority with any new information which might entail the amendment of documents, such as the dossier of the marketing authorization. In addition, as described above, it must provide PSURs, notify adverse events and, if requested by the EMEA, provide data needed for the risk-benefit assessment of a medicine. There are also obligations to cooperate with the national authorities responsible for the supervision of the manufacturing, distribution, etc. of medicines (but these obligations may, depending on the facts, rest on certain affiliates or commercial partners of the marketing authorization holder). The different procedures allow the authorities, particularly the CHMP, to request, among other things, further information and inspections, with which the marketing authorization holder must comply.

For Community referrals, Article 31 of Directive 2001/83 specifically states that the company must supply the CHMP with "*all available information relating to the matter in question.*"

b) Draft Penalties Regulation

The Draft Penalties Regulation expressly requires the marketing authorization holder to cooperate with the EMEA and the Commission during the investigation procedure (Article 16 (2)). It also requires holders of centralized marketing authorizations to update the dossiers.

4.8.3 Must the target be notified when third parties are questioned regarding the target?

a) Community Referral Article 31 of Directive 2001/83

The CHMP may call upon any other person to provide information relating to the referral (Article 32 (3)). However, the law does not impose any specific notification requirements on the applicant or marketing authorization holder.

b) Draft Penalties Regulation

Under the Draft Penalties Regulation, the Commission may hear any legal or individual person who can provide information on the alleged infringement. The draft does not impose a specific obligation to notify the target concerned if the Commission questions a third party.

4.8.4 What are the mechanisms whereby the target can raise issues about pending investigations?

a) General remarks

Generally, the marketing authorization holder's notification obligations and duty to cooperate with the EMEA (and other national bodies) means that it may provide to the EMEA information about the product and new scientific data at any time. In the context of an ongoing investigation, the main opportunity to raise specific points is either through written or oral explanations or through specific hearings. Nevertheless, informal contact with the

EMEA is possible at any time. The EMEA code of conduct contains a specific provision about hearings (see below) and the right to make statements, which reads as follows:

> *"Article 16 - Right to be heard and to make statements*
>
> *In cases where the rights or interests of individuals are involved, the agent or other servant shall ensure that, at every stage in the decision-making procedure, the rights of defense are respected.*
>
> *Every member of the public shall have the right, in cases where a decision affecting his rights or interests has to be taken, to submit written comments and, when needed, to present oral observations before the decision is taken."*

b) Community Referral

The CHMP must provide the applicant or marketing authorization holder with the opportunity to present written or oral explanations. As already mentioned, the company may appeal the opinion, which requires written submissions.

c) Draft Penalties Regulation

The draft Regulation permits oral or written explanations by the marketing authorization holder. With respect to the first stage of the investigation, the EMEA's investigative procedure, this is provided for in Article 8 of the draft Regulation. With respect to the second part of the procedure, the Commission's review and decision, it is set out in Article 11 of the draft Regulation. In addition, the target may submit specific arguments when it receives from the Commission a request for information (Article 12 of the draft regulation). Article 16 of the draft regulation enshrines the target's rights of participation, which includes the right to submit any documents, books, or records.

4.8.5 Are there any defenses against investigation? Harassment? Selective complaints, etc.

There are no specific defenses against investigation in the pharmaceutical legislation, as investigations are triggered for public health reasons. However, the EMEA's code of conduct, which is an implementation of good administrative behavior, lays down some principles that must be respected by the agents when assessing a medicine. In particular, the code of conduct deals with discrimination and abuse of powers.

> *"Article 5 - Absence of discrimination*
>
> *In dealing with requests from the public and in taking decisions, the agent or other servant of the Agency shall ensure that the principle of equality of treatment is respected. Members of the public who are in the same situation shall be treated in a similar manner.*
>
> *If any difference in treatment is made, the agent or other servant of the Agency shall ensure that it is justified by the objective relevant features of the particular case.*
>
> *The agent or other servant of the Agency shall in particular avoid any unjustified discrimination between members of the public based on nationality, sex, racial or ethnic origin, religion or belief, disability, age, or sexual orientation.*
>
> *(…)*
>
> *Article 7 - Absence of abuse of power*
>
> *Powers shall be exercised solely for the purposes for which they have been conferred by the relevant provisions. The agent or other servant of the Agency shall in*

particular avoid using those powers for purposes which have no basis in the law or which are not motivated by any public interest."

4.9 Access to information in Commission files

4.9.1 Rights of access? Who? What? Limitations?

a) Commission: Access to its files in general

Access to Commission documents is governed by Regulation No. 1049/2001 on public access to documents of the European Parliament, the Council and the Commission. The aim of this Regulation is transparency and participation by Community citizens in decision-making in order to achieve broader legitimacy, efficiency, and responsibility of the administration towards the citizens. The Regulation governs (i) the right to access; (ii) grounds for restricting access (such as the protection of public interest, business secrets, or to ensure the proper completion of a decision-making process); (iii) criteria for classifying documents; (iv) application and review procedures; and (v) ways of exercising of the right to access (copies, electronic access, etc.). If the documents come from third parties or Member States, the Commission must involve those parties in considering whether or not to grant access (Article 4 of the Regulation). The Community bodies are required to establish an administrative procedure for granting access to documents that they have produced or are in their possession and to include provisions about access in their rules of procedure. In addition, the bodies must install document registers that are intended to facilitate access, mainly via electronic means. The Commission has amended its rules of procedure (see http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_345/l_34520011229en00940098.pdf) to comply with the right to access. It operates different registers with publicly available documents, including the document register, the comitology document register (see http://europa.eu.int/documents/comm/index_en.htm) and, of particular relevance for the

pharmaceutical sector, the "Community register of medicinal products"(see http://pharmacos.eudra.org/F2/register/index.htm). For detailed information about access to documents see the Commission's website at:http://europa.eu.int/comm/secretariat_general/sgc/acc_doc/index_en.htm.

The Pharmaceutical Unit of the European Commission provides for access to its decisions through the register of medicines, which includes details of marketing authorizations, refusals, variation decisions, withdrawals, suspensions, and decisions under the decentralized procedures. However, documents can only be accessed if they do not contain confidential information.

The "Access to European Commission Documents - A Citizen's Guide" states that internal documents can also be requested. Internal documents are documents that are either not finalized or not intended for publication. The guide provides examples, including preparatory documents of Commission decisions and policy initiatives (such as preliminary drafts, interim reports, draft legislative proposals or decisions), explanatory documents, and correspondence between the Commission and Member States or third parties.

b) Commission: Access to the files by involved parties

Parties that are directly involved obviously benefit from the general access rules but they can also use certain procedural guarantees that are specific to them. For instance, the Regulation 726/2004 provides that a draft Commission decision on a marketing authorization application or following a Community referral must be made available to the marketing authorization holder at the same time as it is sent to the Member States. Therefore, access is granted automatically. However, access to the written remarks of the Standing Committee is not expressly granted in the law.

Specific problems may arise if several marketing authorization holders are concerned, for example in the case of an Article 31 review procedure for a group of medicines. The reports may contain business secrets that must be kept confidential and thus cannot be shared with all participants. In such cases, different information may be disclosed to the different companies.

As mentioned above, internal documents are not excluded from access and an involved party can seek access if no restrictions apply to the documents being sought .

Draft Penalties Regulation Article 16 (3)

The target of an investigation has the right to access the documents and other materials compiled by the EMEA, the Commission or a national competent authority serving as evidence of an alleged infringement.

c) EMEA: Access to the files by third parties

Access to EMEA documents is also regulated by Regulation 1049/2001, and specific implementing rules have been adopted by the EMEA. In addition, the rules governing the centralized procedure contain specific transparency provisions.

- *Access to documents in general*

The "Rules on the Implementation of Council Regulation (EC) No 1647/2003 on Access to EMEA Documents"[38] contain details about accessing EMEA documents. The rules were adopted in 2004 by the management board of the EMEA.

[38] Council Regulation (EC) No 1647/2003 amended regulation 2309/93 and made the general Regulation 1049/2001 on access applicable to the EMEA.

They grant access to documents that are produced or received by the EMEA, or held in its possession, unless access is restricted. Reasons for refusing access include the protection of commercial interests of a natural or legal person, such as intellectual property (Article 3 of the Rules), or if disclosure would seriously undermine the decision-making process. If the documents originate from a third party, the EMEA must consider whether access must be refused on the basis of Article 3. If in doubt, the third party should be consulted in order to determine whether any exceptions to the right of access apply.

In addition, Article 57 of Regulation 726/2004 provides other instruments for disseminating or providing access to information to the general public. For example, there are publicly available databases on adverse events and pharmacovigilance information is made available to the public.

- *Transparency under Regulation 726/2004*

Regulation 726/2004 contains several provisions that seek to ensure a higher level of transparency in the regulatory system. For example, there is an obligation to establish public databases of medicines. A key aspect of transparency, however, has existed since the centralized procedure began, in the form of the European Public Assessment Report (EPAR). The EPAR is a general assessment report of a centrally-approved product, which is published after commercially confidential information is deleted (Article 13 (3) Regulation 726/2004). They are available on the EMEA's website. Before an EPAR is published, the applicant may comment on what he considers to be confidential. The project manager then prepares a draft EPAR, which must be approved by the CHMP.

d) EMEA: Access to files by directly involved parties

Parties directly involved in the regulatory procedure can also access other documents.

- *Rapporteur reports*

The initial assessment report is made available to the applicant. The EMEA provides this report both for information purposes and to enable the company to respond to questions and concerns.

- *List of questions and overall conclusions of the CHMP*

After a first discussion of the rapporteur reports, the CHMP adopts a list of questions and overall conclusions, which is made available to the applicant.

- *Joint Response Assessment Report (Rapporteur / Co-Rapporteur)*

This joint report is also provided to the applicant. The Notice to Applicants states that this is for information purposes only.

- *Final opinion and assessment report*

These documents will be sent to the applicant within 15 days of the adoption of the CHMP's opinion.

- *Access to reports when more than one company is involved*

Access to reports can be problematic when reports discuss different medicines and include commercial secrets of the individual companies. In such cases, access must also be restricted between the different companies. The fact that companies are subject to the same review procedure does not entitle them to access the business secrets of competitors. For example, in the Cisapride review (an Article 31 referral), the detailed assessment reports were restricted to certain parties for confidentiality reasons.

- *Draft Penalties Regulation Article 16 (3)*

See above, point (b).

4.9.2 How is this right exercised & when must it be exercised? When must the information be provided?

a) Access to Commission documents by third parties

The Rules of procedure of the Commission, as amended, implement the Regulation on access to documents (http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_345/l_34520011229en00940098.pdf). They set out access to Commission documents for third parties. The Secretariat-General deals with requests for access.

Third parties must make a written application for access to documents (by mail, e-mail, or fax). The applicant does not have to provide reasons but it must specifically identify document it wishes to access. The Commission may help with the identification of the document.

An acknowledgement of receipt of the application should be sent to the applicant and the application has to be processed within fifteen days. If access is granted, it can be exercised in different ways, for example by providing hard copies, electronic versions, or access to a file where the document is stored. If access is refused, the Commission must provide the applicant with reasons. The Commission must also inform the applicant about the possibility of having the application reconsidered by the Commission. This second application is called a confirmatory application and follows the same procedure as the initial application. If access is denied again, the Commission must inform the applicant about the right to appeal to the CFI and the European Ombudsman complaints procedure. If the document originates

from a third party, the latter must be consulted before access can be granted as any objections by such third party must be taken into account.

b) Access to Commission documents by involved parties

As mentioned above, directly involved parties will automatically receive the relevant Commission documents: the draft and the final Commission decisions. No application is necessary.

c) Access to EMEA documents by third parties

Third parties may request access to documents by lodging a written or electronic application to the executive director of the EMEA identifying accurately the particular document sought. The procedure within the EMEA is essentially the same as the Commission's (as described above). Details about the procedure can be found in the Rules for the Implementation of Council Regulation (EC) No. 1647/2003 on Access to EMEA Documents (EMEA/MB/91992/2004/adopted).

d) Access to EMEA documents by involved parties

EMEA documents, such as the rapporteur and co-rapporteur report and the draft assessment report, will be sent to an applicant or marketing authorization holder directly without any requirement to apply for it. In some cases, however, companies have not received draft assessment reports that have been prepared for the CHMP but were superseded by later reports. This was the case in the informal review of oral contraceptives.

4.9.3 Can affected third parties such as competitors have access to the Commission's files?

Pharmaceutical law does not contain any specific rules granting to third parties access to documents that affect a party to a procedure. The general rules of access to Commission or EMEA documents (see above) apply. They provide access to a certain extent but there are restrictions. For instance, Article 4 of Regulation 1049/2001 allows the Commission to refuse access if disclosure would undermine (i) the protection of the public interest, privacy and integrity of an individual, or the commercial interests of natural or legal persons, including intellectual property; (ii) court proceedings or legal advice; or (iii) inspections, investigations or audits, unless there is an overriding interest in favor of disclosure. In addition, access may be restricted when the internal documents concerned relate to a matter on which a decision has not yet been taken. If the document comes from a third party, the latter must be consulted before a access is granted.

Competitors may therefore not have access to Commission files that contain commercial secrets and, even where commercial secrets are not involved, the Commission may turn down an application if the documents relate to a decision that has not yet been taken.

The same principles apply to EMEA documents and this is reflected in the EMEA rules on access to documents:

> *"Article 22 - Requests for information*
>
> *The agent or other servant shall, when he has responsibility for the matter concerned, provide members of the public with the information that they request. The agent or other servant shall take care that the information communicated is clear and understandable. If an oral request for information is too complicated or too comprehensive to be dealt with, the agent or other servant shall advise the person concerned to formulate his demand in writing. If, because of its confidentiality, an agent or other servant may not disclose the information requested, he or she shall, in*

accordance with Article 18 of this Code, indicate to the person concerned the reasons why he cannot communicate the information.

Further to requests for information on matters for which he has no responsibility, the agent or other servant shall direct the requester to the competent person and indicate his name and telephone number.

Further to requests for information concerning another Community institution or body, the agent or other servant shall direct the requester to that institution or body.

Where appropriate, the agent or other servant shall, depending on the subject of the request, direct the person seeking information to the unit or sector responsible for providing information to the public.

Article 23 - Requests for public access to documents

Further to requests for access to documents of the Agency, the agent or other servant shall give access to these documents in accordance with the Decision on access to EMEA documents. If the agent or other servant cannot comply with an oral request for access to documents, the citizen shall be advised to formulate it in writing."

However, after a marketing authorization is granted, the EPAR is publicly available without any confidential material. In addition, the EMEA may provide information to the public, such as the refusal to grant a marketing authorization together with its reasons (Article 12 (3) of Regulation 726/2004), or pharmacovigilance information (Article 26 of the Regulation). Article 80 of Regulation 726/2004 allows for the provision of regulatory, scientific and technical information on the authorization and supervision of medicines as far as it does not comprise confidential information. The transparency strategy of the EMEA is further detailed at http://www.emea.eu.int/htms/human/postguidance/q91.htm.

Finally, specific problems may arise when third parties claim they represent the public interest in seeking access to documents. This issue arose in the *Olivieri* case, where Dr. Olivieri intervened in the approval process of Ferriprox and unsuccessfully sought the annulment of the marketing authorization. In principle, third parties will not have special access rights when they assert representation of patients or other special categories of persons, because the public interest is primarily represented by the EMEA and the Commission. There are, however, certain opportunities for patient organizations and physician associations to be consulted under the new rules of the centralized procedure.

4.9.4 What information in the files is unavailable, because of trade secrets, for example?

- *EMEA and Commission Documents*

The Citizen's Guide on the Access of European Commission Documents explains the restrictions of access as follows:

> *"Exceptions to the right of access are clearly set out in the rules:*
>
> *1) refusal is justified where disclosure could undermine the protection of:*
>
> *- the public interest (in particular public security, defence and military matters, international relations, or the financial, monetary or economic policy of the Community or a Member State);*
>
> *- privacy and the integrity of the individual, in particular in accordance with Community legislation regarding the protection of personal data;*
>
> *2) unless there is an overriding public interest in disclosure, refusal is justified where such disclosure could undermine the protection of:*

- the commercial interests of a specific natural or legal person, including intellectual property;

- court proceedings and legal advice;

- the purpose of inspections, investigations and audits;

3) unless there is an overriding public interest in disclosure, refusal is justified where such disclosure could seriously undermine the Commission's decision-making process in respect of any document:

- drawn up by the Commission for internal use or received by it, which relates to a matter where the decision has not yet been taken;

- containing opinions for internal use as part of deliberations and preliminary consultations within the Commission, even after the decision has been taken."

If the exemptions apply only to parts of a document, the rest of that document must be disclosed.

The EMEA rules on access to documents contain the same restrictions. Therefore these practical rules on access to Commission documents should also apply to documents held by the EMEA.

- *Draft Penalties Regulation - restrictions of access (Article 17 (2))*

The draft Regulation restricts the target's right to access documents relating to the infringement procedure if the documents or material are deemed to be confidential with regard to third parties or to the EMEA, the Commission, or the national competent authorities.

4.9.5 Consequences if Commission fails to provide access to information?

If the Commission or the EMEA fail to provide information, the applicant is entitled to bring the matter before the CFI (Article 8 of Regulation 1049/2001) or lodge a complaint with the European Ombudsman.

4.10 Settlement or compromise

An applicant for a marketing authorization who faces a refusal of his application, or a marketing authorization holder whose product is subject to review and whose marketing authorization may be suspended or withdrawn, may often avoid such a negative outcome by agreeing changes to be made to the marketing authorization application or the issued marketing authorization. Amendments concerning the therapeutic indications of the product, contraindications, special warnings and precautions may balance concerns about safety or efficacy and render the risk-benefit assessment positive. During an application procedure, an applicant may be presented with recommendations by the CHMP informing him that "*the product could be approvable provided satisfactory answers are given to the "other concerns" and the indications, other elements of the SPC or other conditions for the marketing authorization are amended as outlined in the list of questions.*"[39]

5. The individualized / generalized (or adjudicative-legislation) distinction

The Commission and the EMEA do not only fulfill executive functions, such as assessing medicines and taking marketing authorization decisions, but also play a crucial role in developing the legislation and its administrative implementation. They do this by drafting guidance documents, such as the Notice to applicants or the CHMP guidelines.

[39] Notice to Applicants, Volume 2A, Chapter 3.

The Commission plays a key part in preparing legislation. It often seeks reports on specific issues before preparing legislative proposals and organizes public consultations, the results of which are taken into account when drafting legislative proposals. Current examples are the Paediatrics Regulation and the Advanced Therapies Regulation (for details on the proposals, see http://pharmacos.eudra.org/F2/home.html), which are in different stages of preparation but take into account feedback from the public, including industry, on concept papers and earlier drafts. The Commission also has extensive powers to adopt implementing legislation, mainly in the form of a Commission Directive or a Commission Regulation. These texts are typically adopted under the comitology procedure but are frequently preceded by consultations. A current example is the Draft Penalties Regulation, which is in the process of being finalized.

In addition, the Commission issues many important guidance documents, such as the Notice for Applicants and Guidance documents, including those on GMPs, SmPCs and patient leaflets. The EMEA also issues guidelines on its website. Guidelines are not binding but are of major importance for the practical implementation of the legislation. They assist in planning the research intended to be used in applications as well as the applications themselves and provide detailed procedural guidance relating to various areas of Community law.

The Notice to Applicants is a general Commission guideline on the procedures and requirements for authorization of pharmaceutical products. It has its legal basis in Article 6 Regulation 2309/93 (Article 6 of Regulation 726/2004 in the future) and in the Annex to Directive 2001/83. Directive 2001/83 also provides the legal basis for guidelines on both GMPs (including guidance on GMPs for active substances used as starting materials) (Article 47) and the concept of a potential serious risk to public health (Article 29 (2)).

An example of the legal basis for EMEA guidance documents is in Directive 2003/63, which replaced the Annex to the Human Use Directive and, at Part II point 4, requires specific guidelines data requirements for similar biological products ("*[t]he 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*").

To align the Notice to Applicants and other guidance documents with the recent regulatory changes, the Commission and the EMEA are in the process of revising and supplementing their current guidance and will publish updates accordingly.

Finally, the distinction between an adjudication and a legislative decision is not always clear. An example (from outside the human medicines sector) is presented by the CFI case T-13/99 *Pfizer Animal Health SA v. The Council of the European Union*. That case concerned an application for annulment of a Council Regulation that contained provisions for the withdrawal of the authorization to use certain antibiotics as additives in feeding stuffs. This authorization procedure can appear to relate to one company while formally relating to the inclusion of a substance in a legislative list regarding additives that can be used in feeding stuffs and has effect *erga omnes*.[40] Nevertheless, the Court held that Pfizer had standing because it was the only producer of virginiamycin and had gone through the specific and detailed regulatory approval procedure.

Guidelines are developed on the basis of regulatory experience obtained in specific dossiers. However, a new policy approach is sometimes adopted during the review of a specific dossier. This policy is subsequently reflected in draft, and later final, general guidance. This occurred with respect to the level of detail that can be included in the therapeutic indication

[40] The feed additives rules have been amended since and now also include company specific approvals.

section of the SmPC. In the above-mentioned *Capoten* case, the CHMP applied what was later described a "clean indication" policy. This policy meant omitting specific outcome data from the therapeutic indication section and moving them to another part of the SmPC. That new policy was also adopted in the *Renitec* case, and is now reflected in revised general SmPC guidelines. In *Capoten*, the Commission withdrew the decision. The *Renitec* case is still pending before the CFI.

6. Hearing phase

6.1 Rights to an administrative hearing

(The following covers points 6.1.1 to 6.1.7, without distinguishing the points. We adopted this structure for consistency and readability reasons)

The different procedures allow the applicant (or otherwise affected entity) to give written or oral explanations to the bodies involved in the evaluation of medicines. For the centralized marketing authorization procedure, the variation procedure, Community referrals, and the infringement procedure under the proposed Draft Penalties Regulation, the rules contain explicit provisions that grant a right to be heard during these procedures. However, these "hearings" form part of the investigation process and are conducted together with the scientific evaluation of a medicine.

a) Centralized marketing authorization procedure

The marketing authorization application requires the applicant to disclose all relevant information about the medicine (for details see Article 6 (1) of the Regulation, Article 8 of Directive 2001/83, as well as the dossier requirements as discussed earlier).

- *Article 7 c Regulation 726/2004*

The CHMP may, after a first discussion of the assessment report, ask the applicant to supplement the data that were submitted. This is reflected in the time limits (see above), and there is a ”stopping of the clock” at day 120 if further information is requested. The applicant may provide written and oral explanations in reply. This “hearing” takes place while the application is still under consideration within the CHMP. The Notice to Applicants, Volume 2A, Chapter 3 discusses the procedure for oral explanations:

> *“Oral explanations will usually be conducted in the following sequence:*
>
> *The Chairman will invite the applicant’s representatives to briefly introduce themselves; to confirm that all pertinent data have been submitted to the CPMP, whether favourable or unfavourable to the case and whether there is any further or additional information to be given to the CPMP.*
>
> *The Chairman will invite the applicant representatives to make their presentation (usually not more than 30 minutes) and will then ask the Rapporteur to put any outstanding questions to the applicant.*
>
> *An opportunity will also be given to all members of the CPMP to add supplementary questions or comments; At the conclusion of the oral explanation, the representatives of the applicant will be invited to withdraw while the CPMP discusses its recommendations on the application.”*

The CHMP and the applicant can, independently of the request for supplementing information, ask for an oral hearing to provide further explanations. The CHMP has issued a guidance paper containing practical information about the conduct of hearings and a

schematic overview of the different steps of the hearings. Applicants who are subjected to hearings should prepare in accordance with these recommendations.[41]

- *Article 9 (2) 726/2004*

If the CHMP opinion is not entirely positive, the applicant may, within fifteen days of receiving it, request a re-evaluation of the opinion by way of a notice to the EMEA. It must then support this request with comprehensive reasoning within 60 days of the receipt of opinion. The re-assessment may, again, include a hearing for an oral explanation if it is required to clarify the issues raised in the appeal.

- *Article 20 (2) 726/2004*

When a centrally-approved product comes up for review because, for example, a Member State raises safety or efficacy concerns, the marketing authorization holder should be given the opportunity to provide oral or written submissions about the questions raised.

- *Article 8 (2), 11, 16 Draft Penalties Regulation*

The Draft Penalties Regulation grants each marketing authorization holder the right to be heard by the EMEA during the investigation procedure to enable it to present its defense. The draft Regulation also contains a right for the marketing authorization holder to request an oral hearing when it submits its written explanations in response to the Commission's statement of objections. The marketing authorization holder can request third parties to attend the hearing to support its written submissions. The hearing will be conducted by the Commission on its premises and will not be made public.

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[41] http://www.emea.eu.int/pdfs/human/regaffair/239001en.pdf.

b) Referral procedures

- *Article 32 (3) of Directive 2001/83*

In referral procedures, the marketing authorization holder can provide written or oral explanations to the CHMP. The right to an oral hearing was previously limited to referrals pursuant to Articles 29, 30, 35, 36 and 37, while in Article 31 ("Community interest") referrals provided no such right. Nevertheless, marketing authorization holders were typically offered the opportunity to make oral submissions, in addition to its written arguments. The Notice to Applicants, Volume 2A, Chapter 3 recommends that hearings should be held even if they are not legally required. It states: *"Even though the right for a hearing is not obligatory in all cases, the CPMP should, as a matter of good administrative practice, always grant applicant(s)/Marketing Authorization Holder(s) the right to present his/their views.*"

- *Article 32 (4) of Directive 2001/83*

In case of an unfavorable opinion, the company can request a re-examination. The requirements are the same as described above (see Section 4.2).

c) General Comments on third party information

The CHMP may request information from third parties if it considers it necessary to carry out the scientific evaluation of the medicine. This right is found in Article 32 (3) of Directive 2001/83 and, with regard to penalties, in Article 12 of the Draft Penalties Regulation. It was also confirmed in the *Olivieri* case, where the court held that the Commission had to take into account information obtained from third persons:

"72. the application of those provisions must, in principle, enable the Commission to comply with its obligations under Article 11 of Regulation No 2309/93 without, as a rule, having to obtain or verify information relating to the scientific evaluation of the medicinal product in question from or by persons other than the applicant for marketing authorization.

73. Nevertheless, the Court notes that none of the provisions of the applicable Community rules prohibits the Commission, prior to granting a marketing authorization, from following a procedure during which persons other than the applicant for marketing authorization are able to submit their observations so as to enable it to fulfill its duty to check, in the interest of public health, that all the information relating to the scientific evaluation of the product in question, whether it be favourable or unfavourable to the product, has indeed been made available to it. The fact that those rules do not contain any provision to that effect cannot prevent the Commission from obtaining information from a third party where such a course of action is indispensable in order to safeguard public health. "

In addition, the EMEA code of conduct states that information from third parties may be taken into account at every stage of the procedure.

6.2 Hearing officer

6.2.1 Who is the hearing officer or officers? How are those persons qualified and trained? Is the person a full-time hearing officer or does he/she have other tasks? How many hearing officers are present at a hearing (that is, is there just one hearing officer or is there a panel of hearing officers)?

Oral submissions are presented to the CHMP. No specific officers are appointed for hearings and no specific training is given to the persons conducting hearings.

6.2.2 What is the role of the hearing officer or officers? To serve as independent administrative judges (as would occur in an adversarial system) or as officials gathering information as part of an administrative investigation (as would occur in an inquisitorial system). [See part 1. of these guidelines for further background on this distinction] Or do they serve some other function or functions?

This is not relevant.

6.2.3 Bias / conflict of interest / disclosure of financial interests etc.

This section only discusses the specific rules applicable to the EMEA and persons active within the EMEA. For the Commission, the general principles relating to independence and conflicts of interest apply.

a) Conflicts of interests

Regulation 726/2004 (like the predecessor 2309/93) contains rules about the handling of conflicts of interest. Article 63 requires that members of the administrative body, members of the committees, rapporteurs and experts must not have any financial interests in the pharmaceutical industry that could impact their neutrality. They are obliged to act in the public interest and, therefore. they need to disclose information annually about their financial interests. The EMEA holds a register of each person's direct or indirect interests that may relate to the pharmaceutical industry.. This register is publicly available on request , although it can only be accessed at the EMEA's premises. In addition, members of administrative

bodies, members of committees, rapporteurs and experts need to report any interests they may have in the topics discussed at meetings.

The EMEA code of conduct contains further provisions in this respect:

> *"Integrity and high standards of professional conduct by members of the Management Board, scientific committees and working parties, European experts and EMEA staff are crucial for the independence of the EMEA and for its reputation vis-à-vis the public regarding its execution of European Union policy in the field of public health." and stresses the importance of independence and impartiality to properly conduct their tasks:*
>
> *We strongly believe that in order to ensure the success of the EMEA mission we need to:*
>
> *- assure the highest personal standards of integrity, honesty and independence*
>
> *- foster the spirit of loyalty and commitment to the goals of the EMEA*
>
> *- assure impartiality and discretion to applicants*
>
> *- develop public confidence in the transparency of the evaluation process."*

The code of conduct requires the agents to be impartial and independent (Article 8). It clarifies who should declare interests and defines direct and indirect interests as financial interests, work carried out for the pharmaceutical industry, other links with the pharmaceutical industry and links with other industries relevant to the nature of the work. It also sets out the procedure for declaring interests and the evaluation of such interests, as well as forms for the declaration of interests.

In addition, the EMEA has issued the "EMEA policy on the handling of conflicts of interests for EMEA scientific committees members and experts" (EMEA/H/5475/04/Final), which sets out further details relating to the criteria and procedure for assessing risk levels. the outcome of this assessment determines the extent to which a person can participate in a specific procedure (such as drafting general guidelines as a member of the CHMP or a working group or acting as a rapporteur or co-rapporteur). The EMEA has a special body, the "Declaration of Interests Assessment Group" (DIAG) to deal with conflicts of interests issues.

b) Are there any limitations on off-the-record ("ex parte") communications between the decision-makers and by parties outside the Commission?

This is not relevant.

c) Is there any separation of functions of Commission staff members? In other words, can persons who have played roles as investigators, prosecutors, or advocates serve as hearing officers or advisers to hearing officers?

This is not relevant.

d) Are there any rules prohibiting or relating to legislative or political pressure on decision makers?

In addition to the rules on independence and impartiality, Article 61 of Regulation 726/2004 seeks to prevent Member States from influencing the work of the EMEA and its Committees by prohibiting them from giving orders to the national representatives that could conflict with their duties and tasks within the EMEA. It also requires the CHMP's opinion to be science-based. In general, the EMEA must make scientific, and not political, decisions. Article 61 (6) and (7) read as follows:

"(6) Members of the committees and experts responsible for evaluating medicinal products shall rely on the scientific evaluation and resources available to national marketing authorization bodies. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of nominated committee members and experts. Member States shall refrain from giving committee members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.

(7) When preparing the opinion, each committee shall use its best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based."

When exercising their judicial review powers, the EC Courts have stressed that decisions in the pharmaceutical sector must be taken on public health grounds, which implies that they need to be free from political considerations and influence as well as economic interests. In the *Anorectics* cases, the CFI held:

"175. The general principle that precedence must be given to the protection of public health is, as regards medicinal products for human use, expressly enshrined in the first recital in the preamble to Directive 65/65 (recital 2 in the preamble to the Code), which states that the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health, and in the third recital in the preamble to Directive 93/39, which provides that in the interest of public health and of the consumer of medicinal products, it is necessary that decisions on the authorization to place medicinal products on the market be exclusively based on the

criteria of quality, safety and efficacy ... extensively harmonised by ... Directive 65/65 ....

176. Those provisions confirm that only requirements related to the protection of public health must be taken into consideration when a marketing authorization is granted under Article 5 of Directive 65/65 (Article 26 of the Code), when such an authorization is renewed under Article 10(1) of that directive (Article 24 of the Code), and in the management of marketing authorizations in accordance with Article 11 of that directive (Article 116 of the Code)."

6.3 Conduct of the hearing

Points 6.3.1 to 6.3.11 are jointly discussed under this heading.

As indicated earlier, the applicant or marketing authorization holder has various opportunities to provide input into the investigation and assessment procedures. The ways of providing input vary depending on the procedure concerned. As stated above, submissions can be provided in writing or by way of oral hearings. As for the initiation procedure and practical requirements, the Notice to Applicants, Volume 2A, Chapter 3, summarizes as follows:

"Oral explanations will be provided at the request of either the applicant or the CPMP. When the applicant wishes to have the opportunity of an oral explanation, they should present a written request to the CPMP preferably one month before the anticipated date of the oral explanation and certainly prior to Day 180.

The CPMP may also invite the applicant to provide oral explanations on aspects of the dossier requiring clarification. A list of outstanding issues, to be addressed at the oral explanation will be adopted by the CPMP (usually at Day 180) and sent to the

applicant. The applicant would then liaise with the Rapporteur and the EMEA project manager regarding details of the presentation.

In order to maximise the benefit of an oral explanation, it is important that applicants preparing for and attending oral explanations bear in mind that they are held to only allow clarification of outstanding issues. The applicant should remember: That the oral proceedings of the CPMP are in English. For the presentation, slide projectors, overhead projectors and computerised systems are available at the EMEA. Applicants should consult in advance with the EMEA project manager on the facilities they would like to use.

Any written explanation which the applicant wishes to present in order to support and elaborate on outstanding issues to be addressed during the oral explanation should be received by the EMEA project manager and all CPMP members at least 14 days before the CPMP meeting.

Copies of any audio/visual aid material, including paper copies of projector slides/overheads, must preferably be sent to the CPMP Secretariat and the EMEA project manager in advance or be brought to the meeting, for distribution prior to the oral explanation. At least one week before the oral explanation, the applicant should provide the project manager with the definitive list of names and a short curriculum vitae of the persons who will be attending the oral explanation. The applicant's delegation attending the hearing should be limited to a maximum of 10 persons

Oral explanations will usually be conducted in the following sequence:

The Chairman will invite the applicant’s representatives to briefly introduce themselves; to confirm that all pertinent data have been submitted to the CPMP,

whether favourable or unfavourable to the case and whether there is any further or additional information to be given to the CPMP. The Chairman will invite the applicant representatives to make their presentation (usually not more than 30 minutes) and will then ask the Rapporteur to put any outstanding questions to the applicant. An opportunity will also be given to all members of the CPMP to add supplementary questions or comments; At the conclusion of the oral explanation, the representatives of the applicant will be invited to withdraw while the CPMP discusses its recommendations on the application."

This may serve as an example of the way oral hearings will be conducted within the EMEA.

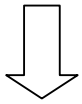
The CHMP guideline on the conduct of a hearing (http://www.emea.eu.int/pdfs/human/regaffair/239001en.pdf) details the hearing as follows:

STEP 1 (Day 180)

List of Outstanding issues adopted by CPMP

Applicant requires clock-stop

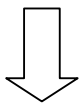
(30 days as default, 60 or 90 days to be agreed at CPMP level)



Step II (clock stop)

OE written preparatory documents by applicants

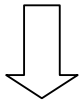
and feed back from Rapporteur/EMEA



Step III (clock stop)

CPMP plenary discussion

Feed back to the Applicant



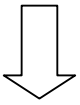
Step IV

Final OE Slides (electronic + hard copies) submitted

Oral explanation

Applicant de-briefing

[if positive CPMP trend]



Step V

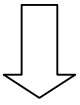
Finalisation of CPMP scientific opinion

Revised product information (+ draft letter of undertaking, if appropriate)

Revised CPMP AR

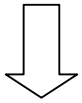
Draft CPMP Opinion

Draft SMOP



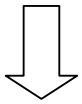
Day +5

Applicant provides Rapporteurs, CPMP and EMEA PTL with revised product information (draft letter of undertaking, if appropriate)



Day +10

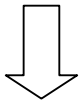
EMEA PTL provides Rapporteur/Co-Rapporteur with revised draft CPMP AR, draft CPMP opinion and SMOP for final comments



Day +20-25

Rapporteur/Co-Rapporteur feedback to EMEA PTL

Pre-final drafts in the CPMP pack circulated to CPMP Members in advance of the next CPMP plenary meeting



Adoption of CPMP opinion

- *Hearings in the context of the Draft Penalties Regulation*

The Draft Penalties Regulation requires the hearing to be held by the persons appointed by the CHMP for that purpose at the Commission's premises and . The hearing is not public, although the marketing authorization holder may request that third parties be heard if they may be able to corroborate any aspects of the marketing authorization holder's written submissions. However, to prevent an abuse of process, such requests must be reasonable and may only relate to the written comments the marketing authorization holder has submitted.

7. Decisional phase

7.1 Type of decision? Are we correct in assuming that the officials who conducted the hearing do not write a "proposed" decision? Our assumption is that there is only a single final decision at the conclusion of the process, not a series of tentative decisions.

- *General*

The CHMP is the body that scientifically evaluates medicines and that conducts the hearing. It publishes an opinion relating to each marketing authorization application and adopts an assessment report, a draft summary of the product characteristics (SmPC), any conditions affecting the authorization, details of any recommended conditions or restrictions on the safe and effective use of the medicinal product, and the proposed labeling and package leaflet texts. The Commission drafts the decision, to which is attached all key documents appended to the CHMP's opinion. Generally, the decision is taken by the Commission based on the comitology procedure, but in case of disagreement between the Commission and the Standing Committee, the Council of Ministers would decide. This has not happened to date.

If the Standing Committee raises new questions concerning the safety, efficacy, or quality of the product, or if new issues arise within the CHMP or are notified to the Commission, the Commission may stop the decision-making process and refer the issue back to the CHMP for further evaluation. An interesting example is the *Olivieri* case, where the Commission, after having been informed by the EMEA that there were new data submitted by Dr. Olivieri, decided to refer the application back to the CHMP.

The Commission also declined to proceed with the decision-making procedure and decided to send the opinion back to the CHMP in the *Omnitrop* case. In that case, the Commission

disagreed with the CHMP's recommendation to approve the product as a follow-on biological medicine. The refusal was apparently based exclusively on legal reasons, namely the proper legal basis for approval of a similar biological product without a full dossier. Currently, Sandoz is challenging this decision before the CFI, claiming that the Court should

> *"annul the Commission decision, notified to the applicant by letter dated 14 November 2003, not to proceed with the decision for a marketing authorization of Omnitrop under Article 10(1)(a)(ii) of Directive 2001/83 and to send the CPMP opinion of 26 June 2003 back to the EMEA; (…)"*

The Commission will usually only issue one decision. However, where there is review of a whole product class, comprising different substances and different products, the Commission may issue several decisions even if they have the same or a similar content. This occurred in the *Anorectics* cases. The Commission issued several decisions, covering Clobenzorex, Fenproporex, Fenbutrazate, Propylhexedrine, Mazindole, Mefenorex, Norpseudoephedrine, Phendimetrazine, and Phenmetrazine (Commission Decision C(2000)608); Amfepramone (C(2000)453); and Phentermine (C(2000)452).

The addressee of a decision is provided with a hard copy of the Commission's decision. The addressee will be the pharmaceutical company under the centralized procedure. Under the mutual recognition/decentralized procedure, the relevant Member State will receive the decision and it will then have to issue national decisions directed to the companies involved.

- *Exceptionally, EMEA decision*

As described earlier, the EMEA's role lies primarily in the scientific evaluation of medicines through the CHMP. This results in an opinion, which forms the basis for a formal Commission decision. However, some decisions are taken by the EMEA. We have already

mentioned that fee decisions are taken by the EMEA's Executive Director himself. In addition, the decision to start an infringement procedure under the Draft Penalties Regulation will be taken by the EMEA. It will carry out the factual investigation for this procedure, although it will not be competent to issue the final penalties decision.

In case of a centralized variation procedure concerning a minor variation of Type IA, the EMEA independently determines the validity of the notification and informs the marketing authorization holder accordingly. Therefore, the Commission is not actively participating in this decision, although, if necessary, it must formalize the variation by issuing an amended decision.

The decision as to whether a product is eligible for optional centralized review (previously Part B of the Annex to Regulation 2309/93, currently pursuant to Article 3 of Regulation 726/2004) is also taken by the EMEA.

The Notice to Applicants states: "*Based on the draft SPC and on the summary document, the EMEA will then inform the applicant of the CPMP position as to whether the product falls within the scope of Part B of the Annex to the Regulation.*"

This decision is taken before the actual application procedure starts as filing an application is dependent on selection of the correct procedure.

7.2 Decisions and findings, substantiation

What is the nature of the decision-maker's obligation to find facts (how detailed must fact findings be)? Must the decision maker provide and justify legal interpretations and conclusions? Must the decision-maker furnish reasons for discretionary decisions? How detailed a statement of reasons must be provided? [Art 253] Must the statement of reasons cover all of the factors that the agency is required to consider?

a) Article 81 of Regulation 726/2004 -- Substantiation obligation

Article 81 of Regulation 726/2004 requires that "*1. All decisions to grant, refuse, vary, suspend, withdraw or revoke a marketing authorization which are taken in accordance with this Regulation shall state in detail the reasons on which they are based. Such decisions shall be notified to the party concerned.*"

Commission decisions must therefore discuss the reasons for the decision in detail. However, where applications are denied or authorizations are withdrawn or restricted, the requirement to state the reasons for the decision is more crucial than in cases where the decision is in favor of the addressee.

b) Statement of reasons in the CHMP opinion

The CHMP is obliged to provide the reasons that underlie the conclusions in its opinion. In addition, the assessment report must be made available to the applicant (Article 9 Regulation No. 726/2004 and Article 32 (5) of Directive 2001/83). The EMEA code of conduct requires that "*[e]very decision or recommendation of the Agency which may adversely affect the rights or interests of a private person shall state the grounds on which it is based by indicating clearly the relevant facts and the legal basis of the decision The agent or other servant shall avoid making decisions which are based on brief or vague grounds or which do not contain individual reasoning.*"[42]

It further provides that the public agent must ensure the lawfulness of the administrative actions:

> "*Article 4 - Lawfulness*

[42] Art. 18 of the Code of Conduct.

The agent or other servant of the Agency shall act according to law and apply the rules and procedures laid down in Community legislation. The agent or other servant of the Agency shall in particular take care that decisions which affect the rights or interests of individuals have a basis in law and that their content complies with the law.

In addition, the agent is bound by its duty to be objective, which means that when taking decisions he "shall take into consideration the relevant factors (only) and give each of them its proper weight in the decision, whilst excluding any irrelevant element from consideration."[43]

c) Special substantiation obligations for Commission in cases of different opinion to EMEA

If the Commission wants to deviate from the CHMP opinion when making its decision, it must provide a detailed explanation of its reasons. The law treats this as an exceptional case and imposes strict conditions. The Notice to Applicants confirms that any deviation from the EMEA opinion must be exceptional but that the Commission must be allowed to deviate from the CHMP's opinion, provided that it gives an explanation as "*the Commission is responsible, politically and legally, for its decision, and it would therefore be inconceivable for it to be unable to influence the content of that decision.*"

Recently, the Commission chose not follow the CHMP's opinion and refused to grant a marketing authorization for the medicine Omnitrop. This seems to have been based more on technical legal grounds than on a disagreement on the science and the quality, safety and

[43] Art. 8 of the Code of Conduct..

efficacy of the product (see Case T-15/04, *Sandoz GmbH vs. Commission of the European Union*).

d) Substantiation requirements under the Draft Penalties Regulation

The Draft Penalties Regulation requires the Commission to state reasons, which must be communicated in writing to the marketing authorization holder (Article 14).

7.3 Dialogue requirement

Is there a duty of care imposed on decision makers to consider and respond to all relevant submissions by the parties (a dialogue requirement)?

The evaluation of medicines must be based on the conditions for granting a marketing authorization as laid down in law. The CHMP (and the Commission) must take into account all relevant information provided by the applicant as well as relevant information coming from third parties (as held in *Olivieri*). Inadequate response to relevant arguments can imply that the decision is invalid.

In case of an appeal against a CHMP opinion, the legislation specifically states that the review is limited to data that were already available during the original review (Article 62 (1) of Regulation 726/2004).

7.4 Is there a reasonableness requirement imposed on discretionary decisions?

The EMEA code of conduct requires the EMEA to act in accordance with the principle of proportionality. Article 6 of the Code of Conduct reads:

> *"When taking decisions, the agent or other servant of the Agency shall ensure that the measures taken are proportional to the aim pursued. The agent or other servant shall*

in particular avoid restricting the rights of the citizens or imposing charges on them, when those restrictions or charges are not in a reasonable relation with the purpose of the action pursued. When taking decisions, the agent or other servant of the Agency shall strike a fair balance between the interests of private persons and the general public interest."

This is relevant when restrictions are imposed on the marketing of a medicine, including, for instance, limiting the approved indications or strengthening the warnings required, as well as in the decision-making process for marketing authorization suspensions or withdrawals. In these contexts, the authorities can also rely on the precautionary principle. In the *Anorectics* case, the CFI made the following general considerations:

"181. In addition, where there is scientific uncertainty, it is for the competent authority to assess the medicinal product in question in accordance with the precautionary principle. It is therefore appropriate to recall the origin and content of that principle before explaining its effect on the rules of evidence in connection with the system of prior authorisation of medicinal products.

182. As regards environmental matters, the precautionary principle is expressly enshrined in Article 174(2) EC, which establishes the binding nature of that principle. Furthermore, Article 174(1) includes protecting human health among the objectives of Community policy on the environment.

183. Therefore, although the precautionary principle is mentioned in the Treaty only in connection with environmental policy, it is broader in scope. It is intended to be applied in order to ensure a high level of protection of health, consumer safety and the environment in all the Community's spheres of activity. In particular, Article 3(p) EC includes a contribution to the attainment of a high level of health protection

among the policies and activities of the Community. Similarly, Article 153 EC refers to a high level of consumer protection and Article 174(2) EC assigns a high level of protection to Community policy on the environment. Moreover, the requirements relating to that high level of protection of the environment and human health are expressly integrated into the definition and implementation of all Community policies and activities under Article 6 EC and Article 152(1) EC respectively.

184. It follows that the precautionary principle can be defined as a general principle of Community law requiring the competent authorities to take appropriate measures to prevent specific potential risks to public health, safety and the environment, by giving precedence to the requirements related to the protection of those interests over economic interests. Since the Community institutions are responsible, in all their spheres of activity, for the protection of public health, safety and the environment, the precautionary principle can be regarded as an autonomous principle stemming from the abovementioned Treaty provisions.

185. It is settled case-law that, in the field of public health, the precautionary principle implies that where there is uncertainty as to the existence or extent of risks to human health, the institutions may take precautionary measures without having to wait until the reality and seriousness of those risks become fully apparent (Case C-180/96 United Kingdom v Commission [1998] ECR I-2265, paragraph 99, and Case T-199/96 Bergaderm and Goupil v Commission [1998] ECR II-2805, paragraph 66). Prior to the enshrinement in case-law of the precautionary principle, on the basis of the Treaty provisions, that principle was implicitly applied in the review of proportionality (see, to that effect, order in Case C-180/96 R United Kingdom v Commission, paragraphs 73 to 78, and the order of the President of the Court of First

Instance in Case T-76/96 R National Farmers' Union and Others v Commission [1996] ECR II-815, paragraphs 82 to 93, in particular paragraph 89).

186. Where scientific evaluation does not make it possible to determine the existence of a risk with sufficient certainty, whether to have recourse to the precautionary principle depends as a general rule on the level of protection chosen by the competent authority in the exercise of its discretion (on the distinction between scientific advice, on the one hand, and that discretionary assessment of the competent authority, on the other, see the judgment in Case C-405/92 Mondiet [1993] ECR I-6133, paragraph 31, and the Opinion of Advocate General Gulmann in that case, point 28). That choice must, however, comply with the principle that the protection of public health, safety and the environment is to take precedence over economic interests, as well as with the principles of proportionality and non-discrimination.

187. In the Community system of prior authorisation of medicinal products the competent authority, when considering an application for authorisation of a medicinal product, in principle exercises its discretion in weighing up the benefits and risks of that medicinal product - reserving the right subsequently to revise its assessment of that benefit/risk balance in the light of new scientific data.

188. As regards, more specifically, the rules of evidence applicable to that system, it is for the undertaking seeking marketing authorisation of a medicinal product to prove, first, the efficacy of the medicinal product and, second, its safety, that proof being based, in particular, on trials in accordance with the provisions of Directive 75/318.

189. Subsequently, when an application for renewal of an authorisation, the validity of which is limited to five years under Article 10(1) of Directive 65/65, is considered,

the assessment of the medicinal product is to be carried out, according to that article, on the basis of the details of pharmacovigilance data and other information relevant to the monitoring of medicinal products.

190. Furthermore, it is clear from Article 10(2) of that directive that it is only [i]n exceptional circumstances, and following consultation with the applicant that an authorisation may be made subject to certain specific obligations, including, in particular, the carrying out of further studies following the granting of authorisation. Those exceptional decisions may be adopted only for objective and verifiable reasons, referred to in Part 4(G) of the Annex to Directive 75/318, that is in particular where in the present state of scientific knowledge the applicant cannot provide comprehensive information on the efficacy and safety of the medicinal product in question under normal conditions of use.

191. In that system, save in the special situation provided for in Article 10(2) of Directive 65/65, the holder of the marketing authorisation of a medicinal product is not required to provide evidence of the efficacy and/or safety of that medicinal product during the period of that authorisation's validity. As the Commission acknowledges, the onus is indisputably on the competent authority to prove that just one of the conditions for withdrawal, variation or suspension of a marketing authorisation, which are set out in Article 11 of Directive 65/65, is met. Contrary to the applicants' contentions, acceptance that in cases of scientific uncertainty reasonable doubts as to the efficacy or safety of a medicinal product are capable of justifying a precautionary measure cannot be treated as equivalent to a reversal of the burden of proof.

192. The precautionary principle requires the suspension or withdrawal of a marketing authorisation where new data give rise to serious doubts as to either the safety or the efficacy of the medicinal product in question and those doubts lead to an unfavourable assessment of the benefit/risk balance of that medicinal product (see above, paragraph 178). Against that background, the competent authority need do no more than provide, in accordance with the general rules of evidence, solid and convincing evidence which, while not resolving the scientific uncertainty, may reasonably raise doubts as to the safety and/or efficacy of the medicinal product.

193. In addition, the passages in the legislation which highlight the relative nature of the assessment of a medicinal product, in particular the seventh and eighth recitals in the preamble to Directive 75/318, refer to the progress of scientific knowledge and to new discoveries. It is also clear from the introduction of the Annex to Directive 75/318 that the benefit/risk balance is to be assessed continuously on the basis of any new information or data submitted to the competent authorities.

194. Against that background, leaving aside the exceptional situation in which the competent authority makes a detailed acknowledgement that it had incorrectly assessed a medicinal product when taking the decision to grant or, as the case may be, maintain or renew the authorisation, the withdrawal of a marketing authorisation must in principle be regarded as justified only where a new potential risk or the lack of efficacy is substantiated by new, objective, scientific and/or medical data or information. In particular, it is entirely logical that the application of a new assessment criterion, which reflects a current consensus in the medical community, is justifiable during the period of the authorisation's validity only if that development is based on new data or information.

195. Those requirements are clearly compatible with the need to ensure the highest level of health protection in the management of marketing authorisations of medicinal products. Before obtaining the marketing authorisation of a medicinal product, the applicant is required to prove that that medicinal product has a favourable benefit/risk balance. In addition, the validity of the authorisation is in principle limited to a renewable period of five years. In those circumstances, the system of prior authorisation allows the presumption that, during that period, in the absence of any solid evidence to the contrary, the medicinal product in question has a favourable benefit/risk balance, subject always to the possibility of suspending the authorisation in cases of emergency. Where there is no such evidence, the need not to reduce the range of medicinal products available for the treatment of a particular disorder argues in favour of keeping the medicinal product on the market so that, in every case, the most appropriate medicinal product may be prescribed."

Decisions relating to medicines have to be taken on the basis of the public health criteria that are contained in the legislation. This means a broad range of considerations must be taken into account. Only very rarely will a situation be unequivocal from a scientific point of view. This does not, however, mean that the CHMP and the Commission have discretionary powers. The exact limits of the powers of the authorities are not yet clearly defined and are raised, for instance, in the *Renitec* case (Case T-273/03, *Merck Sharp & Dohme v the Commission*). In the *Renitec* case, consideration was given to the criteria to be applied when SmPCs of older products are harmonized. The case is still pending and may be decided on a different issue (the absence of powers to formally harmonize SmPCs, in line with the *Anorectics* ruling).

7.5 What remedies are available to the Commission?

As discussed in earlier passages, the Commission may withdraw, suspend or amend marketing authorizations if required for public health reasons. In addition, it may now issue penalties in cases of infringements by marketing authorization holders of their legal obligations and compel the marketing authorization holder to comply with the measures of inquiry imposed by the EMEA (Article 8 of the Draft Penalties Regulation).

In addition, the Commission may ask Member States to conduct investigations.

7.6 Is the full decision publicly available? How is it publicized?

a) Marketing Authorization and Variation Decisions concerning the Centralized Procedure

Decisions about the granting, variation, or refusal of marketing authorizations are publicly available on the Commission's website (http://pharmacos.eudra.org/F2/register/index.htm). The website grants access to all decisions relating to medicinal products, including the Annexes to the decisions, which comprise the SmPC, identification of the manufacturer, specific conditions for the marketing authorization, and the labeling and package leaflet in all languages. In case of a refusal to grant a marketing authorization, the decision, scientific conclusions, and grounds for refusal are made available. Article 12 (3) of Regulation 726/2004 requires the Commission to make publicly available information about the refusal to grant an authorization, including its reasons for refusal. Article 13 (2) of the Regulation requires the notification on the issuance of a marketing authorization to be published in the Official Journal of the European Union, but the information on the websites of the Commission and the EMEA are the main tools of communication. In addition, Article 13 (3) obliges the EMEA to release a public assessment report (EPAR), once confidential

information has been removed, and to publish its reasons for granting a marketing authorization.

The EMEA's website (http://www.emea.eu.int/index/indexh1.htm) contains a register of the EPARs, SmPCs and labeling information for all authorized products. The register also contains information about the procedural steps taken before marketing authorizations were issued and an overview of steps taken later. In addition, the site provides access to product safety announcements and public statements of the EMEA concerning suspensions or withdrawals.

If a marketing authorization is granted subject to conditions, the list of conditions must also be published (Article 14 (7) of the Regulation).

b) Decisions concerning referrals

Decisions resulting from referral procedures are also available on the Commission's website (http://pharmacos.eudra.org/F2/register/index.htm). Usually, the decision itself is published along with annexed documents, such as the findings of the CHMP and SmPCs.

The EMEA's website (http://www.emea.eu.int/index/indexh1.htm) contains a list of products that have been the subject of referrals. The website provides background information on the referral as well as the annexes to the marketing authorizations, which include the SmPC, labeling and package leaflet.

c) Draft Penalties Regulation

The Commission's decision requiring an infringement to be stopped and imposing fines on a marketing authorization holder will have to be published in accordance with Article 84 (3) of Regulation 726/2004 (Article 14 of the Draft Penalties Regulation). This allows the

Commission to publish the names of the marketing authorization holders, the amount of the fine, and the reasons for the decision.

7.7 Process resulting in a rule instead of a decision

This is not relevant.

8. Administrative reconsideration

8.1 Reconsideration of the Commission's decision?

It is possible for the Commission to reconsider its decision. This is rare, but it does happen. On 9 September 2002, the Commission issued a decision following an Article 30 (of Directive 2001/83) procedure to harmonize SmPCs in order to allow generic companies to have a common reference product in all Member States. The decision ordered the Member States to amend the listed marketing authorizations and to produce the harmonized SmPCs for the medicine Capoten and associated names (captopril). This decision was contested before the CFI, but the proceeding was stopped as the Commission revoked its prior decision on 11 June 2003 conceding:

> *"(3) It appears that the scientific evaluation procedure leading to the opinion of 30 May 2002, on which Decision C(2002) 3370 of 9 September 2002 is based, did not respect some procedural requirements, in particular as regards the obligation to provide proper reasons."*

However, no pharmaceutical laws provide for circumstances under which the Commission must reconsider its decision.

8.2 Administrative appeal

In certain circumstances, a party can ask for reconsideration. A CHMP opinion can be "appealed" (to the same body) by filing a "request for reexamination" within 15 days.

Regarding access to documents, the law provides for reconsideration of administrative decisions of both the Commission and the EMEA. For instance, the "Rules for the implementation of Council Regulation (EC) No. 1647/2003 on access to EMEA documents" contain a provision for administrative reconsideration if access is partly or fully denied after the initial application (Article 6 and 7 of the Rules).

There are no other formal appeal procedures. Decisions can, however, be challenged before the Community Courts, provided that the applicant has appropriate standing and the act is one that can be appealed.

9. Enforcement actions

The enforcement of pharmaceutical law and compliance with the conditions of marketing authorizations is primarily a responsibility of the Member States. This is reflected in Articles 18 and 19 of Regulation No. 726/2004/EC (former Article 17 and 18 of Regulation No. 2309/93/EC). The Commission or the EMEA are generally not directly involved in such enforcement actions. They may, however, become involved, either by adopting regulatory measures concerning the marketing authorization itself, or, in the future, by imposing penalties on marketing authorization holders for infringement of their obligations.

As already mentioned above, when Member States notify the CHMP and the Commission, in accordance with Article 20 of Regulation 726/2004/EC, that manufacturers or importers are not fulfilling their obligations, or when a Member State or the Commission considers that

measures provided for in Chapter IX and XI of Directive 2001/83 should be adopted, the Commission requests the CHMP to issue an opinion, and then takes a preliminary and a final decision The CHMP and the Commission may be involved accordingly in decentralized procedures on the basis of Article 36 or Article 107 (pharmacovigilance measures), if a Member State considers that it is appropriate to suspend, withdraw or amend an existing marketing authorization. The CHMP is typically required to issue an opinion on what measures are appropriate, but the Member States and the Commission can impose preliminary measures to safeguard public health.

In the future, the Draft Penalties Regulation will provide for a special enforcement measure for the Commission in relation to centrally approved products. If the holder of a centralized marketing authorization infringes one of its obligations, the Commission will be able to impose penalties. The specific obligations will be listed in a Commission Regulation that will probably be adopted in the near future. The draft released for consultation in February 2005 has a very broad scope and it is likely that it will be significantly curtailed:

> *"Article 1*
>
> *Scope*
>
> *The provisions of this Regulation shall apply to the infringement of obligations related to marketing authorizations granted in accordance with Regulation (EC) No 726/2004 which concern:*
>
> *(a) the establishment of the marketing authorization holder in the Community in accordance with Article 2 of Regulation (EC) No 726/2004;*
>
> *(b) the completeness, veracity and accuracy of the particular and documents contained in an application for marketing authorization or of any other documents*

and data submitted to the European Medicines Agency established by Regulation (EC) No 726/2004 (the Agency) by a marketing authorization holder in accordance with the provisions of Regulation (EC) No 726/2004;

(c) the conditions or restrictions included in the marketing authorization in accordance with Article 9(4)(b) of Regulation (EC) No 726/2004;

(d) the conditions or restrictions included in the marketing authorization in accordance with Article 9(4)(c) of Regulation (EC) No 726/2004 and Article 127a of Directive 2001/83/EC;

(e) the supply of information concerning the medicinal product in accordance with Articles 16 and 41 of Regulation (EC) No 726/2004;

(f) the detection of residues in the case of veterinary medicinal products in accordance with Article 41 of Regulation (EC) No 726/2004;

(g) the labelling and package leaflet in accordance with Title V of Directive 2001/83/EC and Title V of Directive 2001/82/EC;

(h) the specific obligations, specific procedures and conditions referred to in Article 14(7) and (8) of Regulation (EC) No 726/2004 and in any other provisions adopted pursuant to it;

(i) notification to the Agency of the dates of actual marketing and of the date when the product ceases to be on the market in accordance with Articles 13(4) and 38(4) of Regulation (EC) No 726/2004;

(j) pharmacovigilance and market surveillance, in accordance with Chapter 3 of Title II, Chapter 3 of Title III of Regulation (EC) No 726/2004 and any other provisions adopted pursuant to them and with Article 9(1) of Regulation (EC) 1085/2003;

(k) compassionate use in accordance with Article 83 of Regulation (EC) No 726/2004;

(l) manufacturing and import in accordance with Title IV of Directive 2001/83/EC, Title IV of Directive 2001/82/EC and any other provisions adopted pursuant to them;

(m) information and advertising in accordance with Titles VIII and VIIIa of Directive 2001/83/EC and Article 85(3) of Directive 2001/82/EC."

The scope of the Commission's powers to impose penalties will be very broad, but it does not prevent Member States from enforcing infringements themselves. This could lead to parallel actions based on the same infringement, which would be against the *non bis in idem* rule. To limit the risk, the draft Regulation includes communication obligations and a mechanism for coordination between the Member States, the EMEA and the Commission.

The Commission may impose two types of penalties: one-off fines for the infringement of obligations connected to a marketing authorization; periodic penalties for the enforcement of measures of inquiry; and decisions ordering an infringement to be ceased.

The Draft Penalties Regulation contains a two-step procedure for imposing penalties:

- first, a stage of inquiry conducted by the EMEA; and

- second, a decision-making stage conducted by the Commission.

The explanatory memorandum to the Draft Penalties Regulations explains:

- *"The decision to initiate an infringement procedure under the implementing Regulation shall be taken by the Agency, having informed the Commission and national competent authorities.*

- *The Agency will equally conduct an inquiry, and to that effect it shall be empowered to require such information to be supplied as is necessary to detect any infringement and to rely on the cooperation of national competent authorities.*

- *The decisions by the Commission imposing penalties under this Regulation will be based on the opinion of the Agency, following the inquiry, the observations by the marketing authorization holder concerned and, where appropriate, other information submitted to it.*

- *When carrying out an infringement procedure, the Agency and the Commission will ensure the respect of the rights of defence and of the principle of the confidentiality of the infringement procedure.*"

10. Strategic concerns

It is very important for pharmaceutical companies, and for lawyers advising them, to take into account certain basic principles.

First, pharmaceutical law is primarily guided by the general principle of public health. The need to protect public health is the overarching consideration underpinning the regulatory system and it must be taken into account when individual decisions are taken. The CFI stressed this principle in the *Anorectics* decision:

> *"175. The general principle that precedence must be given to the protection of public health is, as regards medicinal products for human use, expressly enshrined in the*

first recital in the preamble to Directive 65/65 (recital 2 in the preamble to the Code), which states that the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health, and in the third recital in the preamble to Directive 93/39, which provides that in the interest of public health and of the consumer of medicinal products, it is necessary that decisions on the authorization to place medicinal products on the market be exclusively based on the criteria of quality, safety and efficacy ... extensively harmonised by ... Directive 65/65 ....

176. Those provisions confirm that only requirements related to the protection of public health must be taken into consideration when a marketing authorization is granted under Article 5 of Directive 65/65 (Article 26 of the Code), when such an authorization is renewed under Article 10(1) of that directive (Article 24 of the Code), and in the management of marketing authorizations in accordance with Article 11 of that directive (Article 116 of the Code).

177. In particular, in view of the precedence thereby accorded to the protection of public health, where, on the basis of the progress of scientific knowledge and new data collected in particular in the context of pharmacovigilance, the competent authority proves to the requisite legal standard that a medicinal product no longer meets one of the criteria set out in Article 11 of the directive, the holder of the marketing authorization of that medicinal product, which is valid for five years and renewable for five-year periods pursuant to Article 10 of Directive 65/65, may not claim that he is entitled, by virtue of the principle of legal certainty, to specific protection of his interests during the period of the authorization's validity. "

Companies must ensure that their products are safe. This applies to the marketing authorization application phase but is equally relevant once the product is on the market. It is not only the authorities that may request follow-up information on the product to allow for a continued risk-benefit assessment of the product. The companies are themselves responsible for the safety of their product and cannot refer to an issued marketing authorization to avoid civil or criminal liability.

It is therefore crucial that a company shows responsibility for its product and demonstrates reliability and credibility, which will build the regulators' confidence in the company.

Responding to regulators' questions in an open and direct way, as well as open cooperation with them on issues that are raised, will help create an environment for an efficient management of a product in dialogue with the regulators.

The need to protect public health also requires new therapies being made available to treat patients, which can require certain risks to be taken. This is demonstrated by the ability to allow conditional marketing authorizations to be granted under the centralized procedure, and in the emphasis on the role of risk management systems.

At the same time, pharmaceutical law also regulates highly valuable rights and assets of pharmaceutical companies. The cost to develop new products (and support existing ones) keeps rising and data and market exclusivity are crucial to protect the interests of this innovative industry.

Finally, the regulatory authorities exercise wide powers over medicines and pharmaceutical companies. This makes transparent administrative procedures, with adequate procedural rights and checks and balances, all the more important. The existing procedures and rights are typically based on express rules, but partially result from the application of general

principles by way of guidelines and practices. A detailed administrative procedural code for Community institutions would be most welcome.

11. Related Questions

Concerning the following aspects, pharmaceutical law does not contain specific rules but the general Community rules apply. Therefore, we will not further discuss general principles applicable to the pharmaceutical sector but mainly point out if there are specifics.

11.1 Is there a doctrine of exhaustion of administrative remedies so that a party must raise all issues at the agency level in order to raise them on judicial review? Must a party request reconsideration of decision before seeking judicial review?

In pharmaceutical law, there is no specific exhaustion of administrative remedies doctrine that requires a party to raise all issues at the agency level in order to be able to raise them in judicial review proceedings. As a practical matter, however, all relevant information should be made available in due time so that it can be taken into account during the scientific review. In addition, procedural irregularities are best objected to during the procedure so as to allow the institutions to take corrective action.

Finally, although a request for reconsideration of -- “appeal” against -- an initial CHMP opinion is not a prerequisite for seeking judicial review of the final decision, it is clearly advisable to request a reconsideration if it can be expected that a judicial review will at least in part be based on issues that can be adequately addressed during the reconsideration by the CHMP.

11.2 If a party raises an argument during the investigation or the hearing and the Commission fails to respond to it, could this failure be an issue on judicial review?

In line with the general principles of Community law, failure to address a relevant argument can render the decision void for lack of adequate reasoning. This will, however, not automatically be the case and will depend on the circumstances.

11.3 Is a duty of care imposed on the Commission to fully and impartially discover all of the relevant facts?

The primary interest that must be taken into account is the protection of public health. The pharmaceutical licensing system is, however, mainly based on applications for marketing authorizations and there is no duty on the EMEA or the CHMP to collect new data on their own. The review is based on data submitted by the applicant and on data that are otherwise available, such as the scientific literature and experience held by regulators (supplemented occasionally with data submitted by third parties).

11.4 Is there a principle of res judicata?

In line with the general principles, decisions of the ECJ or the CFI result in *res judicata* and administrative decisions that are not challenged in time by interested parties become definitive towards them. There is, however, no broader principle of *res judicata* by administrative practices or guidelines, which can be tested on their legality each time they are being followed.

11.5 Is there a principle of equitable estoppel? For example, assume a Commission staff member gave a private party erroneous advice which caused the private party to detrimentally rely on the advice. Any relief in such a case?

It is a clear principle of Community law that legitimate expectations must be respected. However, the primary interest of decisions in the pharmaceutical field is to protect public health and this will override expectations of private parties, even if they result from actions of the EMEA or the Commission. In very clear cases, the latter could give rise to a claim for damages but could not prevent the adoption of measures that are needed to protect public health.

11.6 Is there an obligation of consistency, meaning Commission must follow existing precedent or explain why it has been departed from?

In *Thomae* (referred to above), the CFI stressed the need for consistency in the context of allowing different trade names for a centrally approved product:

> *"77. The Court finds that in the contested decision the EMEA did not adopt the interpretation set out in the Communication of 22 July 1998 and did not consider whether the applicant could rely on exceptional circumstances such as to justify the addition of names in respect of the medicinal product Daquiran. By contrast, the EMEA relied on another interpretative publication from the Commission, namely the Guideline on dossier requirements for Type I variations (November 1999). That document is intended to provide applicants for minor variations to a Community MA with clarification of a practical nature. Following an introductory section, the document is presented as a table which sets out, for 34 kinds of variations, the conditions to be met and the documents which the applicant must provide. The name is one of the terms of the MA which may be varied only by substitution. By implication, the guideline rules out the possibility of variation of a Community MA consisting of the addition of a name. That interpretation is thus inconsistent with the Communication of 22 July 1998, although there was no suggestion that the guideline*

was intended to amend the communication. That inconsistency is regrettable from the point of view of legal certainty, since the Communication of 22 July 1998 and the guideline at issue both seek to interpret Regulations No 2309/93 and No 542/95.

78. Third, it is necessary to add that it is apparent from the Commission's practice in taking decisions that on at least two occasions the Commission authorised a variation of a Community MA consisting of the addition of a name (medicinal products Refludin and Refludan; Infergen and Inferax)."

11.7 Are hearings or other proceedings open to the public?

Hearings are not open to the public because they typically involve discussion of business secrets. Public hearings are sometimes organized by the Commission and the EMEA on broader policy issues.

11.8 Is the Commission obliged to follow its procedural rules even if those rules were not otherwise legally required?

As a rule, the Commission and the EMEA have to follow these rules. There may be exceptions when clearly needed to protect public health.

11.9 Is there a "harmless error" rule with regard to all of the various procedural requirements discussed above? (A "harmless error" rule means that a court will not overturn the administrative decision even though procedural errors were committed if those errors did not affect the result)

Procedural errors only invalidate a decision when they concern an "essential procedural requirement" and the error at least potentially affected the outcome of the procedure.

12. Other remedies for private parties

12.1 What remedies exist in the case of alleged mal-administration aside from judicial review?

Judicial review is the main remedy for pharmaceutical companies that believe an administrative decision has not been taken properly.

In the *Capoten* case, the Commission withdrew its decision after the company lodged its application for annulment with the CFI. This case demonstrates that litigation may lead to quick corrections. This is exceptional, however, and litigation before the Community courts is markedly slow.

The codes of conduct of the EMEA and the Commission require these bodies to operate good administrative practices. The Commission's code of conduct also provides for a complaints procedure to investigate alleged acts of misadministration. This allows for more informal administrative action. Details of the code, together with practical information on its "enforcement", can be found at http://europa.eu.int/comm/secretariat_general/code/index_en.htm.

Occasionally, third parties have tried to challenge a specific aspect of a centralized marketing authorization before a national court through unfair competition litigation. We are not aware, of cases where this has been effective.

Finally, an applicant or marketing authorization holder may start a new procedure at any time.

12.2 Ombudsman

The European Ombudsman plays a crucial role in the context of access to documents (see above). To the best of our knowledge, the Ombudsman has not yet played a crucial role in any administrative procedure in the pharmaceutical sector.

12.3 Quashing evidence

There are no specific rules under the pharmaceutical legislation allowing certain evidence to be excluded from regulatory dossiers. On the contrary, there is a general principle that all relevant information should be reviewed, even if certain conditions are not satisfied in relation to certification of the reliability of the data. In the *Olivieri* case, the CFI held:

> *"70. To enable the Commission to comply with those obligations [i.e. to assess the quality, safety and efficacy of the product in the interest of public health], Regulation No 2309/93 and the documents to which it refers lay down precise rules for the presentation of applications for marketing authorisation, their investigation and subsequent decisions. In particular, Article 6(1) of Regulation No 2309/93 provides that an application for authorisation for a medicinal product for human use must be accompanied by the particulars and documents referred to in Articles 4 and 4a of Directive 65/65/EEC, in the Annex to Directive 75/318/EEC and in Article 2 of Directive 75/319/EEC. Pursuant to that provision, an applicant for marketing authorisation must annex to his application all the information relating to the scientific evaluation of the medicinal product in question, and in particular information concerning the results of all the clinical trials, whether favourable or unfavourable to the product (see the third paragraph in the introduction and Part 4 A of the Annex to the Directive). Compliance with the requirements set out in Article 6(1) of that regulation is vital to ensure attainment of the essential objective of*

safeguarding public health (interim order, paragraph 66, see also, by analogy, Norbrook Laboratories, paragraphs 40 and 41).

…

90. Similarly, the applicant cannot claim that there is a formal defect solely because she did not sign the report of clinical trial LA-01 (or the report of clinical trial LA-03) sent with the application for marketing authorisation submitted by Apotex. Although the applicable rules provide that the final report of a clinical trial must be signed by the investigators or the principal investigator (see Part 4 C.1 of the Annex to the Directive), it is also apparent from those rules that in the event of an incomplete or interrupted trial all the relevant information relating to that trial must be supplied with the application for marketing authorisation (see the introduction to the Annex to the Directive). Having regard to the termination of trials LA-01 and LA-03, the applicant's signature on the reports of those trials - which were accompanied by explanations as to why Apotex had decided to terminate them - was not formally required by the relevant rules. Moreover, it is clear from the data in the present case that the applicant provided the CPMP with all the particulars necessary to guarantee the authenticity of the results obtained in the course of trial LA-01. "

The situation is different under the proposed Penalties Regulation. Evidence may have to be excluded in order to ensure the fairness of the procedure.

12.4 Damages

In principle, a company can claim damages if it is improperly refused a marketing authorization, variation, suspension or withdrawal. However, the threshold is high and claims for damages against Community institutions are rarely successful. In addition, there

are no specific rules relating to liability in the pharmaceutical sector.[44] The standards for entitlement to damages vary according to whether the act that caused the damage was discretionary.

In the case of discretionary acts, liability on the basis of Article 288 of the EC Treaty only arises if:

- the claimant can show a violation of superior rules of law for the protection of individuals;
- the violation was manifest and grave, or sufficiently serious; and
- the violation has caused damages.

The courts have a great deal of discretion in determining if there has been a sufficiently serious violation.

In relation to non-discretionary acts, a claimant merely needs to show that:

- the act was illegal; and
- the act caused damages.

Claims for damages are more frequent in the veterinary medicines sector. In the *Pharos* case (see above), the claim for damages concerned the failure of the Commission to include a substance in Annex II of the MRL Regulation in a timely manner. The claim was unsuccessful because the court could not find that the Commission acted illegally.

[44] Article … of Regulation 726/2004 does provide that the EMEA must, "in the case of non-contractual liability, … shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or by its servants in the performance of their duties", but this copies the language of non-contractual liability of the Community through the European Commission, etc. of the EC Treaty.

In *CEVA and Pharmacia v. Commission*, the CFI held that the Commission had not acted in accordance with the principle of sound administration by failing to act for 18 months to propose the classification of progesterone under the MRL Regulation.[45] This decision was appealed by the Commission and overturned by the ECJ. The ECJ held that the CFI had not adequately justified its decision and had not applied the correct criteria for non-contractual liability, which it summarized as follows:

> *"61 The second paragraph of Article 288 EC requires the Community, in the case of non-contractual liability, to make good, in accordance with the general principles common to the laws of the Member States, any damage caused by its institutions or servants in the performance of their duties.*
>
> *62 The system of rules which the Court has worked out with regard to that provision takes into account, inter alia, the complexity of the situations to be regulated, difficulties in the application or interpretation of the texts and, more particularly, the margin of discretion available to the author of the act in question (Joined Cases C-46/93 and C-48/93 Brasserie du Pêcheur and Factortame [1996] ECR I 1029, paragraph 43; Case C-352/98 P Bergaderm and Goupil v Commission [2000] ECR I 5291, paragraph 40; Case C-312/00 P Commission v Camar and Tico [2002] ECR I 11355, paragraph 52; and Case C-472/00 P Commission v Fresh Marine [2003] ECR I 7541, paragraph 24).*

[45] This delay followed a long scientific review period, where the CVMP (the veterinary medicines committee with the EMEA) provided a positive advice but the Commission sought advice from the Scientific Committee on Veterinary Measures Relating to Public Health, which reached a different conclusion. Such succession of scientific input is not exceptional in the veterinary sector, where the regulatory regime is also politically sensitive. The relevant steps are clearly described in the decisions of the CFI and the ECJ.

63 The Court has ruled that Community law confers a right to reparation where three conditions are met: the rule of law infringed must be intended to confer rights on individuals; the breach must be sufficiently serious; and, finally, there must be a direct causal link between the breach of the obligation devolving on the institution and the damage sustained by the injured parties (Brasserie du Pêcheur and Factortame, paragraph 51; Bergaderm and Goupil v Commission, paragraphs 41 and 42; Commission v Camar and Tico, paragraph 53; and Commission v Fresh Marine, paragraph 25, all cited above).

64 With regard to the second condition, the Court has stated that the decisive test for determining whether a breach of Community law is sufficiently serious is whether the Community institution concerned manifestly and gravely disregarded the limits on its discretion (Brasserie du Pêcheur and Factortame, paragraph 55; Bergaderm and Goupil v Commission, paragraph 43; Commission v Camar and Tico, paragraph 54; and Commission v Fresh Marine, paragraph 26).

65 Where that institution has only a considerably reduced, or even no, discretion, the mere infringement of Community law may be sufficient to establish the existence of a sufficiently serious breach (Bergaderm and Goupil v Commission, paragraph 44; Commission v Camar and Tico, paragraph 54; and Commission v Fresh Marine, paragraph 26).

66 The determining factor in deciding whether there has been such an infringement is therefore the discretion available to the institution concerned (Bergaderm and Goupil v Commission, paragraph 46; Commission v Camar and Tico, paragraph 55; and Commission v Fresh Marine, paragraph 27)."

The ECJ then decided the case on the merits and held that no damages were due. The Court reasoned as follows:

> *"73 In this case, it is first necessary to determine whether the Commission's conduct between 1 January 2000 and 25 July 2001, the period in respect of which the Court of First Instance found that there had been inaction of such kind as to give rise to liability on the part of the Community, constitutes a clear and serious disregard of the limits imposed on the Commission's discretion.*
>
> *74 It is thus necessary to determine the extent of that discretion.*
>
> *75 It must be remembered in this regard that the Court, ruling in relation to a legal procedure similar to that provided for under Regulation No 2377/90, held that, in delicate and controversial cases, the Commission must have a sufficiently broad discretion and enough time to submit for re-examination the scientific questions which determine its decision (see Bergaderm and Goupil v Commission, paragraph 66).*
>
> *76 That case-law is germane to the present case in the light of the recitals in the preamble to Regulation No 2377/90.*
>
> *77 It follows from the third recital in the preamble to Regulation No 2377/90 that the establishment of MRLs for veterinary medicinal products administered to food-producing animals is intended to protect public health.*
>
> *78 The third recital also states that MRLs are to be established in accordance with generally recognised principles of safety assessment, taking into account any other scientific assessment of the safety of the substances concerned which may have been undertaken by international organisations.*

79 The sixth recital in the preamble states that the procedure for the establishment of MRLs at Community level must involve a single scientific assessment of the highest possible quality.

80 It follows that the Commission must be given a discretion which is sufficient to allow it to determine, on a fully informed basis, the measures that are necessary and appropriate for the protection of public health.

81 As the Court of First Instance properly recognised in paragraph 100 of the judgment under appeal, the progesterone file is one that is particularly complex.

82 That complexity is attributable, inter alia, to the facts, as noted by the Court of First Instance in paragraph 100 of the judgment under appeal, that progesterone is an endogenous substance and that there are at present no reliable analytical methods by which to check abuse of that substance. It is apparent from the documents before the Court of First Instance that, although an application to have an MRL established for progesterone had been before it since 1993, the Commission found itself facing a situation of continuing scientific uncertainty characterised by divergences between the scientific opinions adopted between 1996 and 1999 by the CVMP, on the one hand, and, on the other, the SCVPH and other international scientific bodies, which the Commission, in accordance with the third recital in the preamble to Regulation No 2377/90, takes into account.

83 In those circumstances, the Commission was entitled to seek an additional opinion from the CVMP (Case C-151/98 P Pharos v Commission [1999] ECR I 8157, paragraph 26), as the Court of First Instance, moreover, recognised in paragraph 99 of the judgment under appeal.

84 In its second opinion of December 1999 the CVMP had maintained its recommendation in favour of including progesterone in Annex II to Regulation No 2377/90, which is reserved for substances in respect of which it does not appear necessary to establish an MRL. In its report of April 1999 the SCVPH had concluded that greater exposure to hormones might be associated with an increased risk of cancer and negative effects on development and that continued exposure, even at small dosages, appeared likely to increase that risk further, even though no quantification was possible at that stage.

85 In those circumstances, it does not appear unreasonable for the Commission to have awaited the adoption by the SCVPH in May 2000 of a re-evaluation of its report of April 1999 prior to taking a decision on the authorisation in principle of the use of progesterone for therapeutic purposes.

86 The Commission adopted a position on that issue on 24 May 2000 when it adopted a draft directive amending Directive 96/22, which provided inter alia for Member States to prohibit on a temporary basis the administration of progesterone to food-producing animals, while maintaining the possibility of derogating in the case of administration for therapeutic or zootechnical purposes.

87 That position on the maintenance of the use of progesterone for therapeutic or zootechnical purposes constituted a stage which necessarily had to precede the taking of a position on the establishment of an MRL for that substance, since an MRL may be established for a pharmacologically active substance only if that substance is intended to be placed on the market (Case C 248/99 P France v Monsanto and Commission [2002] ECR I 1, paragraph 80).

88 In its opinion of December 1999 the CVMP had recommended that progesterone be included in Annex II to Regulation No 2377/90 and, as a consequence, that opinion did not contain any recommendation as to the establishment of an MRL. The Commission explained that, in view of the opinion of the SCVPH, it considered that that direction did not amount to an acceptable risk management measure and that, as a result, it decided to propose that progesterone be included in Annex I to that regulation. That meant that an MRL would be established in the draft regulation to be submitted. According to the Commission, in the light of the continuing scientific uncertainties, that operation was complex in nature, a fact which explains why the Commission was not able to submit the draft regulation until 25 July 2001.

89 Regard being had to the extent of the discretion available to the Commission and to all of the factual circumstances, it does not appear that, in taking that decision on the basis of public-health considerations, the Commission disregarded in a clear and serious manner the limits on its discretion.

90 In paragraph 102 of the judgment under appeal, the Court of First Instance ruled that, even if the scientific and political complexities of the file were such as to prevent the Commission from adopting, shortly after the CVMP had issued its second opinion, a draft regulation conforming to that opinion, the Commission ought none the less to have adopted measures to safeguard the interests of CEVA and Pfizer.

91 With regard to the first measure referred to by the Court of First Instance, that is to say, the Commission's adoption of draft measures establishing a provisional MRL on the basis of Article 4 of Regulation No 2377/90, it must be borne in mind that that article applies only 'provided that there are no grounds for supposing that residues of the substance concerned at the level proposed present a hazard for the health of the

consumer', a condition which precisely was not satisfied in a situation of scientific uncertainty and disquiet in regard to public health.

92 With regard to the second measure referred to by the Court of First Instance by way of alternative argument, that is to say, a new deferral by the Commission of the time-limit laid down in Article 14 of Regulation No 2377/90, suffice it to point out that the deferral of that time-limit would also not have been an appropriate measure for safeguarding public health.

93 In the light of all those considerations, it therefore does not appear that, in not submitting a draft regulation prior to 25 July 2001, the Commission breached Community law in a sufficiently serious way as to give rise to liability on the part of the Community.

94 Accordingly, without it being necessary to examine the other conditions necessary for the establishment of non-contractual liability on the part of the Community, the actions must be dismissed."[46]

[46] Cases T-344/00 and T-345/00, *CEVA and Pharmacia v. Commission*, decision of the CFI of 26 February 2003; on appeal, Case C-198/03P, *Commission v. CEVA and Pfizer Enterprises*, decision of 12 July 2005.