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DRAFT
PRELIMINARY

Pharmaceutical Licensing

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. It broadly speaking involves a scientific evaluation of medicines, based on a benefit-risk assessment and taking 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 stimulating 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 among others full details on composition, therapeutic indications, prescription status, persons involved in the manufacturing and the regulatory process, method of packaging and package sizes, the wording of the package leaflet and of labeling on the containers, and prescribing information for physicians. Any amendment to these detail is also subject to regulatory review. This, combined with the high variability of products and the significance of many specific characteristics of the products, requires the regime to heavily rely on administrative decision making. These decisions in general aim at protecting public health but can also have a significant economic impact and adequate procedural guarantees are thus of major significance in this sector.

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

This chapter discusses the law as it currently stands – on 1 October 2005 -- including major amendments that were made to the legislation in 2004 and that mainly take effect in October and November 2005. The revisions in the legislation will be further clarified in guidelines and to some extent also in formal implementing legislation. Implementation documents that currently only exist 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 is already discussed.

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 investigational or inquisitorial procedure and not pursuant to an adversary process. There is no clear separation between an investigational phase and an adjudicatory step by an independent decision maker. There are often different administrative bodies involved in the decision making process (see below […]) and these steps, which typically occur in succession, can allow for specific aspects to

[1] Key documents, including the Notice to Applicants ("NtA"), can be found on the web site of the Commission's pharmaceutical unit, http://dg3.eudra.org/F2/eudralex/index.htm , and on the web site of the European Medicines Agency, http://www.emea.eu.int.

be assessed afresh, but the practical impact of this remains limited and none of the procedures in the pharmaceutical field provide for a real adversary approach.

To a great extent, the investigatory procedure is based 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. It is, however, also true when products are reviewed later on, for instance because of concerns of inadequate safety or lack of efficacy, as the authorities will expect the companies to produce the key data. In all cases, however, the authorities do take into account other data that are available and the Community pharmaceutical system is also based on a pooling of regulatory and scientific expertise from throughout Europe at the European Medicines Agency (EMEA).

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, which was adopted in 2004 and mainly takes effect in October and November 2005. The new rules place a much stronger emphasis on enforcement of the pharmaceutical rules and provide that for the first time the European Commission can impose penalties on pharmaceutical companies. Details of the penalties regime have to be provided in a Commission Regulation which is currently in preparation (see below […]). A first proposal for regulation was released for consultation in February 2005. It envisages a two-step procedure, where the EMEA conducts the main investigation and the Commission assesses this review in light of the relevant legal provisions and takes the final decision.

The system being specifically designed to impose sanctions when the pharmaceutical rules are not being complied with, it would be easy to provide for an adversary procedure – involving, for instance, an independent administrative adjudicator appointed within the Commission's Legal Service -- and this was reflected in comments in response to the consultation procedure.

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 provides a succinct summary of three procedures, as an illustration of the system. The examples were chosen to illustrate the variety of issues that can arise, but were also selected because each was later discussed before a court. The first two resulted in actions for judicial review before the Community courts in Luxemburg, while the latter was extensively discussed in a judgment of the UK Queen's Bench in a national product liability case.

2.1. 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))

2.1.1. 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, where authorized nationally and had not undergone any mutual recognition procedure (a procedure for obtaining parallel approvals in various EU Member States, operational since early 1995).

In 1995, Germany triggered a Community interest referral (under Art. 12 of Directive 75/319, now Art. 31 of the 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. The CPMP[2] issued initial opinions (separately for each substance type) on 15 February 1996. The opinions proposed amendments to the SmPCs[3] of the products in question, mainly with regard to 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 However, during these reviews, the positive risk-benefit assessment of the medicines involved was not generally questioned.

The assessment was summarized as follows by the Court of First Instance (in the judicial review procedure mentioned below):

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[2] The CPMP, Committee for Proprietary Medicinal Products, has been renamed in 2004 and is now the CHMP (Committee for Human Medicinal Products).

[3] 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 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.

"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 compounds to be favourable, subject to amendment of the summaries of product characteristics for the medicinal products in question."[4]

Based on the CPMP's final opinions, the Commission adopted two decisions on 9 December 1996 that required Member States to impose the relevant changes to the SmPCs on marketing authorization holders (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 after the occurrence of several cases of cardiac valve disorders. The procedure was initiated pursuant to Article 15a of Directive 75/319 (now Art. 36 of the Human Use Directive), which governs products whose approval status was

[4] (No. 24 Court of First Instance, 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)

already determined by a Community procedure.[5] The request generally questioned the risk-benefit balance of anorectic products in the light the requirements set out by the 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. In light of this, 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 containing propylhexedrine and mazindol 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 came to the conclusion that the risk-benefit assessment of the products remained unchanged, but a later report concluded that the substances (?) do not fulfill the criteria of effective therapy in obesity treatment as they only were effective in short term treatment and 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

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

balance of the products was now considered negative. Again, some marketing authorization holders appealed but were not successful. Based on the final CPMP opinions, the Commission adopted three decisions on 9 March 2000, ordering the Member States to withdraw the marketing authorizations for the products concerned. Several marketing authorization holders sought judicial review before the Court of First Instance, which annulled the decisions. The annulment was later confirmed by the European Court of Justice (ECJ), but on very different legal grounds.

2.1.2. Legal issues addressed

In the anorectics cases, the Court of First Instance discussed two different aspects. First, it reviewed whether the 2000 decisions were validly based on Article 15a, and in that light reviewed whether the 1996 decisions were valid so as to trigger the applicability of Article 15a. Second, the Court in great detail reviewed the criteria for withdrawing marketing authorizations and the burden of proof of the authorities when they decide on a withdrawal.

The European Court of First Instance found that the Commission was not competent to adopt the contested decisions of 9 March 2000 that ordered the withdrawal of marketing authorizations granted for anorectic medicines. It held that the Article 12 procedure in 1996 could not result in binding Commission decisions[6] and that the marketing authorizations for the anorectic products were not really harmonized, so that there could be no valid referral under Article1 15a.

In addition, the Court held that the decision was also illegal because it did not meet

[6] Article 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.

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 the 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 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 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 also unlawful with regard to their content as they were not based on any new data, which 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 could thus not be based on Article 15a. The ECJ thus avoided having to decide on key issues raised by the CFI.

2.2. Community Review of Third Generation Oral Contraceptives

2.2.1. Review on 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.

After 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 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 in communications to doctors and users be included.

In April 1996, after further scientific input from the companies affected and further studies made 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 information for physicians and users was supplemented.

Further 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. The CPMP communicated this in an updated position statement in 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 with all combined oral contraceptives but that the third generation oral contraceptives reviewed had a slight increase in risk of venous thromboembolism when compared to second generation products. A favorable risk profile concerning myocardial infarction could again not be proved. As a safety measure, the CPMP recommended reflecting the differences in the risk in the SmPCs and the Package leaflets and providing that information to prescribers and users. The proposals for change concerned the SPC sections “Special warnings and special precautions for use” and “Undesirable effects.”

[Discussion of 1995 - 1996 will be shortened and instead the various sequences of the review in 2000-2001 discussed.]

2.2.2. Product Liability Litigation in the United Kingdom

In the UK, 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 Levonorgesterel.*" ((High Court of Justice Queens Bench Division, Judgment of the Honorable Mr. Justice Mackay, 29 July 2002). In its judgment the Judge stated that he did not feel bound by the review carried out by the regulators and by their conclusions. In fact, 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. **[to be expanded]**

2.3. Community Marketing Authorization for Ferriprox (The Ferriprox Case (T-326/99)

2.3.1. 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 inadequately. It contains the active substance deferiprone.[7]

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

On 28 April 1999, Dr. Nancy Fern Olivieri, a key opinion leader in the treatment of iron-overload in thalassaemia patients informed the Agency 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 the clinical trails 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.

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[7] 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. **Check details** The application for a marketing authorization was based on "exceptional circumstances" (it not being 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 submitted resulted mainly from a Phase II and a Phase III trial and data from compassionate use of the medicine.

The CPMP Chairman informed the Commission on this development on 20 May 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 called an ad-hoc expert group, which reviewed the submissions by Dr. Olivieri and subsequent submissions by Apotex, and discussed them without the presence of Dr. Olivieri or Apotex (but one of the members of the expert group had openly chosen the side of Dr. Olivieri).

Ultimately, the CPMP on 23 June 1999 issued a revised positive opinion for granting marketing authorization under exceptional circumstances. Based on this opinion, the Commission adopted a corresponding decision on 25 August 1999. In light of the new information, the granting of the marketing authorization 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."[8]

Challenging both the CPMP opinion and the Commission decision granting a marketing authorization for Ferriprox, Dr. Olivieri brought this case to the CFI.

2.3.2. Legal issues addressed

The Ferriprox case addresses third party involvement in marketing authorization procedures and whether third parties have the right to provide information and be heard during the evaluation procedure as well as challenge a CPMP opinion or the corresponding Commission decision in court proceedings.

The Court of First Instance denied the applicant Dr. Olivieri the right to challenge both the CPMP opinion and the Commission decision granting marketing authorization to Ferriprox and dismissed the claims as inadmissible. The Court held that, under the specific circumstances of the case did not have an interest in bringing an action (i) in order to protect public health nor (ii) to defend her professional reputation. The Court also clearly stated that the Commission was allowed to gather information on the product from third parties.

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[8] No. 83 of the Findings of the Court of First Instance in its Judgment of 18 December 2003 - T-326/99)
(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)

The Ferriprox case limits third party rights in the course of issuing a marketing authorization in a two ways: first, the third party must have had an important role in the context of the development and research of the product; second, a third party can only challenge a Commission decision if the information provided was not taken into account in issuing the decision.

The Court also clearly declined a right of a third party to participate on basis of an own right to be heard in the administrative procedure of evaluating and granting a marketing authorization, stating that:

> *"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 authorization and the administration, during which the administration must take into account the applicant's interest in obtaining marketing authorization 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."*

3. Substantive Background

3.1. European Community Pharmaceutical Law

3.1.1. Overview of the Community Pharmaceutical Legislation

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 only then was fine-tuned.

Similarly, the basic concept of a marketing authorization remains 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 on labeling requirements, and in 1992 specific rules were signed on wholesale distribution, advertising and classification of products with regard to prescription status. These rules were adopted successively between 1975 and mainly 1992 and the bulk of them were codified in November 2001 in what is typically called the Human Use Directive 2001/83.

All these rules were adopted on the basis of Article 95 of the EC Treaty (formerly Article 100a) or, in the beginning, Article 100. 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 is binding as from 1998). These systems remain in place but are further strengthened by a major review of the pharmaceutical legislation, which was adopted in 2004 and also reflects important new policy orientations.

Obviously, already from the beginning in 1965, a major consideration of the pharmaceutical legislation 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; (...)"

and has remained the key criterion for regulatory decisions. The European Court of First Instance, 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)."[9]

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

At the same time, the package strengthens the regulatory obligations of pharmaceutical companies and in particular requires 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 granting the European Commission to impose financial penalties on companies that do not comply with obligations in connection with marketing authorizations that are granted under the centralized procedure. The Commission has issued 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.

[9] 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 Court of First Instance of 26 November 2002.

Finally, the revision of the legislation 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 for 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, also 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 or regulatory data exclusivity, which provides protection against the approval of generic copies.[10] A similar provision applies to new indications that are developed for already well known substances (ibidem).[11]

3.1.2. Legislation and Guidance Texts

The current Community pharmaceutical Legislation mainly consists of the following pieces of legislation (only human medicines):[12]

- 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;

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

[11] 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 as from 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).

[12] We did not list the amending directives or Regulations but indicated when the law has been subject to amendment.

- 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 (currently subject to amendment, for draft see: http://dg3.eudra.org/F2/pharmacos/docs/Doc2005/04_05/com2005_0106en01.pdf);

- 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 NtA) and by the European Medicines Agency (EMEA).

These texts are accessible on the web site of the Pharmaceutical Unit of the Commission (http://dg3.eudra.org/F2/eudralex/vol-2/home.htm) and of the EMEA (http://www.emea.eu.int/index/indexh1.htm; mainly under "Guidance documents").

3.1.3. Institutions Involved in the Decision[13] Making Process

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**

[13] 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 competent body 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 Agency (EMEA)**

The European Medicines 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 itself, as an administrative body without comprehensive competences, only has limited possibilities of issuing decisions on its own but relies on the Commission transposing its scientific opinions into final administrative decisions. However, the EMEA can refuse the validation of an application for marketing authorization or for variation of a marketing authorization, or to grant a product List B status14. It also can issue fee decisions, including fee waivers, ask for further pharmacovigilance data, appoint 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.

- **Specialized Committees within the EMEA**

[14] Medicines, falling within the scope of List B of the Annex to Regulation 2309/93, can optionally be approved under the centralized procedure. In future, the Annex will only list the requirements when a product must be applied for in the centralized procedure, while the criteria for optional inclusion will be contained in Art. 3 of Regulation 726/2004.

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

The main committees are:

- The CHMP, the Committee for Medicinal Products for Human Use (ex CPMP), which is responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use.

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

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

- The abovementioned committees can form own standing and temporary working parties. Furthermore, the committees are to establish a standing working party for providing scientific advice to undertakings. 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.

- **Coordination Group of National Regulators (formerly the Mutual Recognition Facilitation Group)**

The Coordination Group of National Regulators is involved in the decentralized procedures and acts as a mediating committee between Member States in case of dissent concerning marketing authorization applications. The Coordination Group's primary task is to achieve agreement between Member States to avoid an arbitration procedure. The Coordination Group as an official legal body has only recently been introduced by Art. 27 of Directive 2004/27 amending the Human Use Directive. Its predecessor, the informal Mutual Recognition Facilitation Group (MRFG), however, has served this purpose on an informal basis already from the beginning of the new authorization regime in 1995 to facilitate 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 is an instrument to involve the Member States in the procedure. The Standing Committee's involvement generally isin writing. However, under specific circumstances, meetings may be required. The Commission may issue its draft decision in case of consent with the Standing Committee, otherwise the Council of Ministers has to be involved in the decision making process. The NtA, Volume 2A, Chapter 6, lists the Standing Committee's involvement for the following situations:

- New application;

- Application in accordance with annex II to Commission regulation (EC) No 1085/2003 (line extension);

- Annual reassessment;
- Renewal of the marketing authorization;
- Variation type II with changes in the annexes of the Community marketing authorization;
- Community referral;
- Centralized suspension;
- Centralized withdrawal.

Further details on its procedures can be found on its revised Rules of Procedure, which have recently been published and contain detailed information about the organization of the Committee's meetings, its preparing its decision, etc. (Rules of Procedure for the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products, published 09/14/2005; http://dg3.eudra.org/F2/pharmacos/docs/Doc2005/09_05/Post%20Stand%20Cttee%20clean%20version%20-%20%20RoP%20Standing%20Cttees%202005%85.pdf).

3.1.4. Types of Decisions

The key decisions in the pharmaceutical sector relate to (i) the granting or 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 for a marketing authorization when regulators consider specific measures are needed (often in light of pharmacovigilance data that suggest a different benefit-

risk ratio for the product). The latter two categories of course often overlap when companies take the initiative to restrict the approval.

Most of the decisions are taken by the European Commission, after consultation of the Standing Committee under a so-called comitology procedure (the latter allows the Standing Committee to object to a draft Commission decision and have the issue decided by the Council of Ministers, but to our knowledge this has not yet occurred for adjudications in the pharmaceutical sector. They are typically taken on the basis of a scientific or technical assessment by the CHMP, within the EMEA.

Sometimes, preliminary decisions are taken by the EMEA and if they are negative do not result in a Commission decision. Typical examples are the denial of List B status for a medicine, or refusals to validate applications.

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

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

Decisions on the granting or refusal of marketing authorizations are taken on the Commission level on basis of an scientific opinion of the CHMP (or other relevant Committee). While, generally, the Commission will adopt a decision in accordance with the opinion of the CHMP, the Court of First Instance is currently dealing with a Commission refusal to grant a marketing authorization although the CHMP had issued a positive opinion on the medicine (*Case T-15/04, Sandoz GmbH vs. Commission of the European Union*, concerning the medicine OMNITROP.). An application could also be refused without the file reaching the stage of a Commission decision. The NtA, for instance, 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 the completeness and should be completed within ten working days. In case of a negative validation, the application is refused as being invalid.

It is also possible that an application under the centralized procedure is not accepted because the product does not fall under one of the categories of products that can be centrally approved. This can in particular be an issue for products for which the applicant has the option to go centrally. This is the case for, for instance, products that are produced with new manufacturing techniques that "*in the opinion of the Agency, demonstrate a significant technical advance*"[15] and, under the new centralized procedure, for products that "*constitute a significant therapeutic, scientific or technical innovation" or when a centralized marketing authorization is 'in the interest of patients*."[16]

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 NtA, Volume 2, Chapter 4, Centralized Procedure, contains further information on this part of the procedure.

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

b) Application for a variation to a centralized marketing authorization

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

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

Subject to the type of variation, as further defined in Art. 3 of Regulation No. 1085/2003, the application requirements and the procedure for evaluating the admissibility of a variation to a marketing authorization differ. While minor variations Type IA only require a notification procedure and receive an acknowledgement of validity by the Agency, if the legal prerequisites are fulfilled, Type IB variations are subject to a more detailed review of the proposed variation by the Agency and the applicant may be required to amend its application according to the proposal of the Agency otherwise the application would be rejected. Type II variations are always reviewed by the competent Committee (CHMP or CVMP) and may be subject to an arbitration procedure in case of disagreement between the applicant and the Committee. Finally, variations as defined in Annex II of the Regulation are treated as extension applications and require a complete authorization procedure.

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

Examples for variation procedures, which lead to judicial review before the Court of First Instance are:

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

  The EMEA denied to validate a Type I (Minor) Variation applied for under Regulation 542/95 (the predecessor of Regulation 1085/2003), with which the applicant wanted to ad product names to its centrally approved product in order to be able to use different names in several member states, and to have a different layout of the package in one country. The Agency took the - in the final judgment rejected -

view that a centrally approved product could only be marketed in the Community under one name and with an identical package layout throughout the Community.

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

  The EMEA refused a Type I Variation to a marketing authorization concerning the change of the name of one of the three pharmaceutical forms covered by the marketing authorization. A judgment has not been issued so far.

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

  In this case, no formal variation procedure was subject to the application, which was denied by the Commission. It, however, dealt with changes to the information displayed on the outer package of a centrally approved medicine. The applicant, a company promoting and distributing the centrally approved product in Italy, wanted to include its logo in the so-called "blue box", where country specific information, such as the naming of local representatives, can be displayed. the EMEA, taking a critical view, referred the matter to the Commission, where it was discussed in the pharmaceutical Committee with the Member States. While the inclusion of the logo of the marketing authorization holder on the package was not objected, the inclusion of the logo of the distributor on the box was and the Commission issued a negative decision.

c) Imposed variation, suspension or withdrawal of the marketing authorization

Marketing authorizations are subject to permanent review and therefore, decisions may be taken concerning the suspension or withdrawal of a marketing authorization after the re-assessment of a medicine, based on new data as obtained by pharmacovigilance measures or notification obligations imposed on the marketing authorization holder. Such decisions occur on both centralized and decentralized level and, despite the procedural differences in achieving such a decision, the substantial criteria for the decision are identical. While suspensions are appropriate in cases of uncertainty, withdrawals are the result of 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. While the medicine can stay on the market, variations are generally a consequence of safety issues and may result in amended SmPCs, including new warnings, limitations of indications, etc. All measures are the result of an investigation in the products safety or efficacy status.

d) Arbitration under the decentralized procedure

If marketing authorizations are not subject to the centralized rules as set out in Regulation 2309/93 (in future Regulation 726/2004), pharmaceutical rules provide for a mechanism of arbitration to assure that decisions about marketing authorizations (or subsequent decisions) are harmonized on Member State level in order to provide for the free movement of goods in the Common market. The arbitration procedure, as laid down in Article 32 of Directive 2001/83 as amended provides for a review of the application by the CHMP, including the right to be heard by the Committee and finally leading to a decision on Commission level, which has to be transposed into national decisions by the affected Member States. However, an arbitration procedure is only required if the Member States themselves cannot on their own or after having involved the coordination group reach an agreement about the application.

e) Specific Community referrals

Community pharmaceutical law provides for different types of Community referrals, which comprise

- Article 29 of Directive 2001/83/EC as amended ("Mutual Recognition referral");
- Article 30 of Directive 2001/83/EC as amended ("Divergent decision referral");
- Article 31 of Directive 2001/83/EC as amended ("Community interest referral");
- Articles 35, 36 and 37 of Directive 2001/83/EC as amended ("Follow-up referrals").

Medicines included in such referrals may be subject to investigative actions, followed by decisions on the Community level. In the past, for the application of the referral procedures, it was highly dependent on whether the medicines had already been subject to harmonization measures during their authorization procedure or mutual recognition procedures carried out later. This also limited the competence of the Commission to issue binding decisions. Concerning the Art. 31 referral (community interest referral) of the Human Use Directive, the European Court of First Instance ruled in its Anorectics judgment that decisions taken on Commission level after community referral and concerning products which had not undergone harmonization yet are not binding to the Member States as the law only allows for the Committee to issue an opinion but not for the Commission to take a final and binding decision addressing the Member States. However, after the latest revision of the Community rules in 2004, the Commission is now legally entitled to also take binding decisions in such procedures.

f) Fee decisions

Fees for EMEA services are laid down in Council Regulation No. 297/95/EC as amended (currently subject to amendment again, for details see draft: http://dg3.eudra.org/F2/pharmacos/docs/Doc2005/04_05/com2005_0106en01.pdf). Fee decisions are taken by the Agency itself through the Executive Director, who also has the competence to decide on fee waivers. Fee waivers 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 payable.

g) Penalty decisions (under the draft Penalties Regulation)

Penalty decisions are taken by the Commission to sanction infringements of the pharmaceutical rules of the marketing authorization holder of a centrally approved product. Such decision can be taken on Commission level after the Agency on its own or on the Commission's or Member States' initiative has conducted an investigation into the alleged infringement and drafted a report on the investigation.

h) 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 of the life cycle of a medicinal product to assess the risk-benefit balance of the product and hence be able to supervise marketed medicines sufficiently (Art. 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 Agency has to publish the assessment report supplemented by the reasons in favour of granting an authorization at the same time as the

marketing authorization is issued. Confidential information must not be made available. To ensure the latter, the applicant will receive a draft EPAR in advance and has to indicate, the information that he considers confidential.

Decision to put information on the Internet -- For transparency reasons Art. 80 of Regulation No. 726/2004 entitles the EMEA to provide non-confidential information to the public of regulatory, scientific or technical information concerning the authorization or supervision of medicinal products in accordance with specific rules of procedure. 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 for document access 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 the agency and is further implemented by rules set up by the EMEA's Management Board. Access can generally be granted after application, subject to restrictions mentioned in the Regulation. Negative decisions can be challenged. For further details, see below, section on "Access to Commission documents."

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

1. the decision on a marketing authorization under the centralized procedure.
2. the decision on the application for a variation to a centralized marketing authorization.
3. the decision issued after an community interest referral based on Article 31 of Directive 2001/83 as amended.
4. the 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 (marketing authorization decision) typically starts with an application. The others typically start at the initiative of the regulators, possible after a complaint (for penalties) or when concerns are raised by third parties.

This section only describes marketing authorization applications under the centralized procedure.

4.1.1. Dossier Requirements

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

- name,
- composition,
- manufacturing method,
- therapeutic indications and contraindications as well as adverse reactions,
- pharmaceutical form,
- dose,
- route of administration,
- precautionary and safety measures,

- descriptions of control methods,
- results of pharmaceutical, preclinical and clinical trials,
- SPC,
- packaging materials,
- etc.

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 the information required by Art. 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 contains detailed information about the CTDs content and presentation and should therefore be consulted to ensure compliance with the requirements. In addition, the "NtA Volume 2B" "Presentation and content of the dossier" and particularly the document on "Incorporating the Common Technical Document (CTD) (June 2004)" (http://dg3.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 a Drug Master File (DMF) for an active ingredient exists, the applicant must ensure that the Drug Master File 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, i.e. for generic medicines, or applications for biosimilar products, which are follow-on products of biological medicines the dossier requirements are modified. Applications for generic medicines, for example, are exempted from the requirement to provide pre-clinical and clinical studies (Art. 10 (1) Directive 2001/83/EC as amended). For biosimilar products, which have been comprised by legislation recently, specific requirements are set out in the Directive's Annex. As a general rule, follow-on products in the biological medicines section require the provision of more comprehensive data to allow for a valid risk-assessment. The products being of a big variety and highly-specific, the exact requirements will be set out product-specific in implementation guidelines. The EMEA to date has already issued guidance on the study and data requirements for biosimilars (to be found under the "Guidance document" Section ("Biosimilar Products") of the Human Medicines EMEA web site). Currently, the Court of First Instance is handling a marketing authorization

refusal for a biosimilar product (Omnitrop), which was issued by the Commission although the CPMP had issued a positive opinion.[17]

4.1.2. Forms to be filed

Application forms for the different procedures are available on the Internet and can be found under the following link: http://dg3.eudra.org/F2/eudralex/vol-2/home.htm.

4.1.3. Submission to the EMEA

Applications in the centralized procedure need to be send to the EMEA. The address is

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

The dossier is to be delivered to the following address:

EMEA Loading Dock; Ontario Way; Canary Wharf; London E 14 4HB; United Kingdom.[18]

The Application can also be submitted electronically. The EMEA has set up a Q&A document, dealing with the formal and substantial parts to be dealt with until submission (http://www.emea.eu.int/htms/human/presub/list.htm), which also contains information about electronic submission, as well as information about the number of copies, timing aspects, etc.

Applications in the decentralized procedures have to be submitted to the Member States Authorities in Charge for the issuing of marketing authorizations. The NtA, Volume 2, Chapter

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[17] The Omnitrop authorization is not only subject to judicial review in Europe but Sandoz is also sueing the FDA for failing to adopt a decision about the application filed in 2003 (see SCRIP 16 September 2005, page 15).

[18] The NtA, 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.

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" web site (http://heads.medagencies.org/) by clicking on the relevant country name. 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 "NtA, Volume 2A Chapter 2 Mutual Recognition". In addition, the local procedures in the Member States become crucial.

4.1.4. Notifications about filing for application

The EMEA requests a pre-filing announcement at least six months in advance when a company intends to lodge an application to organize the workload of the members of their committees and to allow for an efficient and fast 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 web site. Therefore, pending applications are from that time on made public. In the Ferriprox case, Dr. Olivieri notified the CPMP shortly after the first opinion had been made public and it is therefore likely that she found out about the application and its positive assessment in that way.

It is worthwhile mentioning that the applicant, who wants to submit an application for the optional centralized procedure (List B product, in future Art. 3 of Regulation 726/2004) should indicate this in its letter of intention to submit and comprise the following information into the letter as to allow the Agency to evaluate the product's eligibility for the centralized procedure:

- *"a draft Summary of Product Characteristics (SPC);*
- *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 of preferably maximum 2 pages stating why the product should qualify for the granting of 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;*
- *in case of 'generic' or 'bio-similar' applications, details of the proposed Originator and Reference product;*
- *if appropriate, a statement on the appropriateness of the granting of a Marketing Authorization under exceptional circumstances;*
- *if appropriate, information on scientific advice received in accordance with Article 51(j) of Council Regulation (EEC) No 2309/93, as amended;*
- *a statement as to whether orphan designation is granted / pending for the medicinal product;*
- *a proposed classification for the supply of the medicinal product;*

- *if appropriate, their intention to present a Active Substance Master file (previously known as a European Drug Master file) for active ingredients;*

- *any preference regarding Rapporteurships (preferably three to four names amongst CHMP members, alternates or co-opted members, from three to four different EU Members States, Norway or Iceland);*

- *proposed invented name(s). Up to three invented names per marketing authorization application can be proposed for consideration. However, the applicant is advised to indicate his preference, if any, so that the acceptability of any back-up invented name can be considered without loss of time;*

- *general statement to inform that the product falls under the scope of the Directive 2001/18/EC on the deliberate release into the environment of genetically modified organism (GMO), if relevant;*

- *the details of proposed manufacturing and batch release arrangements of finished product and active substance manufacturing;*

- *any intention to request for total or partial fee exemptions;*

- *a specification of any regulatory issues or difficulties already identified which may require clarification or detailed consideration (e.g. multiple application, dossier content, single invented name…).*"[19]

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

4.1.5. 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."*

An applicant can ask for a pre-filing meeting to discuss legal and procedural steps and to prepare for the evaluation of its application to be organized (such as discussing preferences for Rapporteurs, appointment of "project managers" within the EMEA, etc.). 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 also helps the applicant lodge an application, which is in accordance with the legal requirements and which can thus be validated speedily.

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 web site. The "NtA, 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 (NtA - 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 may be well in advance of an actual application. 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.

4.1.6. Time limits for consideration[20]

Time limits for the consideration of an application are clearly indicated in the relevant laws. The procedure of evaluating a centralized marketing authorization application is divided in the scientific evaluation, which finally leads to the adoption of an opinion by the Committee in charge, such as the CHMP for human medicines, and the issuing of the final decision on Commission level.21 Therefore, we will describe the time limits for each part separately.

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

The procedure begins after the Rapporteur and Co-Rapporteur confirm that they have received a dossier. The evaluation procedure should be completed and an opinion issued within 210 days.

Within the first month of the procedure, members of the CHMP must confirm that they have received requested documents. If confirmation fails, there may be a clock-stop in the evaluation procedure until confirmation is received.

The Commission has provided tables, which describe the time structure of the evaluation and decision making process. We will discuss this further in point 4.7, Conduct of the Investigation.

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

[21] Time limits can be different dependent on the decision in question. The marketing authorization application under the Regulation only serves as a typical example.

4.1.7. Forms of denial of application

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

Furthermore, an application would be denied if the medicine does not fulfill the authorization criteria, such as safety, efficacy and quality. Generally, the CHMP will have issued a negative opinion and the Commission will then accordingly adopt a negative decision. However, the Commission could supersede the CHMP opinion and refuse an application despite a positive opinion of the CHMP (see OMNITROP case).

4.2. Applications—investigatory phase:

The project manager is in charge for the organization of the whole 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 the filing, he has to coordinate the validation, the assessment by the Rapporteurs as well as the CHMP participation and involvement of scientific advisory groups and experts, etc. He must make sure that the time frames are kept and that necessary steps are proceeded at the foreseen points in time.

With the validation of an application the CHMP checks whether the application is complete and suffices the formal legal requirements. Following this, comes the crucial part of the application procedure, which is the substantial evaluation of the application, to check whether the medicine fulfills the criteria of safety, efficacy and quality and can therefore be authorized.

The CHMP will appoint a Rapporteur and Co-Rapporteur for the assessment of the application. They have to evaluate the application on basis of the dossier and provide the CHMP with a

preliminary assessment. The CHMP can request scientific advisory committees to provide scientific input on basis of the assessment of the Rapporteur and/or Co-Rapporteur, which then has to be reflected in the CHMPs assessment of the application.

The preliminary assessment is discussed within the Committee and will normally lead to the drafting of a list of questions and a recommendation to be 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.*"

- The applicant has up to 6 months to answer the CHMP questions and provide additional information. During this time, the clock for the evaluation of the application is stopped. The applicant can liaise with the project manager, the Rapporteur and Co-rapporteur in order to clarify issues concerning the questions and the further processing of the application (it can also withdraw the application with a view to re-lodging it at a later stage). In addition to written answers, the applicant can also provide for oral explanations concerning the questions raised. In that case, it has to apply for it if it did not receive an invitation to orally explain the issues by the CHMP itself.

On basis of the response, both Rapporteurs will draft a joint response and provide it to the CHMP and the EMEA, which then may comment on it. The applicant will also receive it for

information purposes. The CHMP may at that point decide to request oral explanations from the applicant and therefore, stop the clock again. If not, the final draft of the SPC, package leaflet, etc. is provided and finally, at day 210 the latest the CHMP opinion together with the assessment report is issued on basis of scientific consensus. If no consensus ca be reached, the majority vote will prevail and the diverging opinions have to be reflected in the assessment report.

In case of an unfavorable opinion; or if the CHMP requires the SPC to be changed; or the labeling and / or package leaflet is not in accordance with the legal requirements; or if the authorization can only be granted subject to conditions; 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. In these cases, the applicant may request in writing (within 15 days after the receipt of the opinion) that the opinion is 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 CHMP opinion together with the assessment report will then be provided to the Member States, the applicant and Commission for the adoption of a decision (see below).

4.3. Complaints—pre-complaint phase:

4.3.1. Variation of a centrally approved product

If the marketing authorization holder of a centrally approved product wants to submit an application for a variation, it is strongly advised to inform the EMEA and (Co-) Rapporteur of all upcoming Post-Authorization submissions for the following 6-12 months, in order to allow optimal planning, identification of procedural issues and handling of overlapping applications. Details about the variation procedure and its handling are provided for in the NtA, Volume 2A, Chapter 5 and on EMEA web site http://www.emea.eu.int/htms/human/postguidance/index.htm. contains further information in form of a Question & Answer document, comprising the different types of Variations. The EMEA has also adopted SOPs for Variation procedures.

4.3.2. Community Referrals

In case of Community Referrals, such as the Community Interest Referral based on Art. 31 of Directive 2001/83, before the actual referral is lodged, the Commission advises in its NtA, Volume 2A, Chapter 3 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 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 regulatory and procedural issues connected with the intended referral. With this pre-submission coordination the conduct of the actual referral procedure shall be streamlined and prepared.

4.3.3. Draft Penalties Regulation Art. 7 (2) and (3)

Before a decision to initiate an infringement procedure is taken by the Agency, the draft Penalties Regulation foresees to request information from the marketing authorization holder concerning the alleged infringement. Thus, the target of such a complaint procedure gets the chance to provide a statement with regard to the allegations before he is confronted with a formal investigation procedure.

In addition, the Agency has to notify in writing its decision to start an infringement procedure. The notification is addressed to the marketing authorization holder and the concerned Member States and needs to include the allegations and relevant facts for the substantiation 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 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 lodging an application or by the introduction of an urgent safety restriction either on initiative of the marketing authorization holder or the Commission. An urgent safety restriction is an interim change to product information concerning particularly one or more of the following items in the summary of product characteristics, the indications, posology, contra-indications, warnings, target species and withdrawal periods due to new information having a bearing on the safe use of the medicinal product. The urgent safety restriction may be imposed by the marketing authorization holder or

by the competent authorities and it needs to be followed by an according application for a variation to formally implement the urgent measure to 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 not only reflected in the right to ask the marketing authorization holder for data to be able to assess whether the risk-benefit-balance of a product remains positive (Art. 16 Regulation 726/2004) but also by the installation of a pharmacovigilance system, which imposes information/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 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, etc.

With new information, the risk-benefit-assessment may clearly become negative with the consequence of a marketing authorization withdrawal, but there are much more possibilities to keep the risk-benefit assessment positive, such as the changing of information (warnings, contraindications, etc) or to limit the indications, etc. While the urgent safety restriction allows to implement the measure quickly to protect public health, the variation procedure then formally implements the measure and provides for a scientific assessment of the situation and the variation.

b) Community Referral Art. 31 Directive 2001/83

The Community Interest Referral can be triggered by the Member States, the Commission, the applicant or the Marketing authorization holder of the concerned medicinal product in cases

where the Community interest is at stake. The Community interest has a very broad meaning and covers not only public health issues but also internal market issues or consumer protection tasks. However, the Community interest must be demonstrated by the referrer.

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

c) Penalties Regulation

The Agency can initiate an infringement procedure on its own initiative; on initiative of a Member States competent authority, or on initiative of the Commission (Article 7 (1) of the draft Regulation). The Commission must always be informed. In addition, the agency shall request information about the allegations from the marketing authorization holder. For further details on the scope of the Penalties Regulation see the part on "Enforcement action".

4.4.2. Are there checks on the investigation process? Any requirements that probable cause be established before investigations take place or 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 Code of conduct provides for measures of good administrative behaviour, which apply to the EMEA's conduct of the investigation. However, these provisions are of a more general nature and do not provide for specific checks on the investigation process in case of

procedures. In addition, the EMEA has developed SOPs on the handling of variation procedures within the centralized marketing authorization context.

- 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 web site.

b) Community Referral (Art. 31)

The Referral procedures generally require to clearly identify the issues and questions that are referred to the CHMP. In case of an Art. 31 referral, the referrer must establish that Community interest is involved. However, there are no further checks or protective measures that will limit or control investigative measures by the Agency.

c) Draft Penalties Regulation

The Draft Penalties Regulation requires the Agency to disclose information about the alleged infringements together with any evidence present that could found the allegations when it notifies the marketing authorization holder, the Commission and other authorities. This requirement to provide the factual basis for the infringement procedure ensures that procedures

cannot be initiated without any facts to support them and it can therefore be regarded as a protective mechanism. However, there are no such requirements as prior approval, etc.

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

A third party may provide scientific input during the evaluation of an application, or, at a later stage, during pharmacovigiliance, where the safety of a marketed product is questioned. However, third parties do not have any legal basis for interfering evaluation procedures. The Court of First Instance, in the Ferriprox judgment clarified that third parties do not have any rights to participate in an application procedure other than ensuring that their scientific input is assessed. It held:

> *"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."*[22]

The main purpose of marketing authorization application or re-assessment procedures in the pharmaceutical licensing context is to safeguard public health but not to protect competitors. Therefore, the procedural relevance of third party involvement is very limited. In cases, where

[22] No. 91 of the Findings of the Court of First Instance in its Judgment of 18 December 2003 - T-326/99.

generic approvals are at stake, this may be different, as the generic applicant may want to refer to data of the marketing authorization holder for the original medicine, who then has a significant interest in protecting his data from being used for the review of the generic application. This has not yet become crucial though on EMEA level.

4.5. Personnel and committees:

4.5.1. Staff during application/investigation

a) EMEA

As far as centralized applications for human medicines are concerned, the CHMP (Art. 61 Regulation 726/2004) is leading the evaluation of human medicines on the EMEA side. A list of the CHMP members with contact details and information on their scientific profile can be found on the EMEA web site (http://www.emea.eu.int/htms/general/contacts/CHMP.html).

The requirements for the composition of the CHMP are laid down in Art. 61 of Regulation 726/2004. The members are appointed for a prolongable period of three years by the Member States after consultation of the EMEA's management board. They have to be chosen due to their experience in the evaluation of medicines and they represent the national authorities. They, however, do are bound by the requirements of public health and do not serve as points of influence for the interests of national authorities. The CHMP comprise the maximum of five additional members appointed on basis of their scientific qualification. The CHMP has set up its own rules of procedure as required by the regulation.

For the evaluation of a medicine, a project manager has to be appointed in the pre-application phase and in addition, 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 Ro-Rapporteur.

Furthermore, the CHMP may involve additional groups or experts in the evaluation of a product, dependent on the medicine to be reviewed. Generally, the following bodies can be 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.

The Member States provide the EMEA a list with experts, which due to their knowledge could participate in the ad-hoc working groups and the scientific advisory groups.

For specific medicines, the following committees play a crucial role in the evaluation procedure:23

- COMP (Committee on Orphan Medicinal Products);
- HMPC (Herbal Medicinal Products Committee);
- In the future, a Committee on Advanced Therapies (CAT), likely to be subordinated to the CHMP, may be involved in evaluation procedures concerning advanced

[23] The draft paediatrics regulation (…) also foresees the installation of a specific paediatric committee, which would comprise specific knowledge in the paediatric sector and therefore be involved in the evaluation procedure of paediatric data, which in future under specific conditions may have to be submitted with new marketing authorization applications.

therapy products (for details see the Draft Regulation on Advanced Therapy Products).

EMEA staff generally needs to comply with its Code of Conduct (http://www.emea.eu.int/pdfs/general/admin/Conduct/647003en.pdf).

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

The Coordination Group in future will be an official part of the decentralized procedures with the task of reaching agreement between Member States in case of dissenting opinions concerning marketing authorization applications or variation applications and to avoid a formal arbitration procedure. The Coordination group has been introduced in 2004, when the pharmaceutical law underwent a major revision. Art. 27 of Directive 2001/83 as amended provides for its legal basis. The group shall consist of one representative per Member State appointed for a renewable period for 3 years. The EMEA provides the Secretariat of the Group, which needs to set up its rules of procedure.

Creating an official body for the mentioned task has resulted from experience with the coordination groups informal predecessor, the so-called "Mutual Recognition Facilitation Group" (MRFG), which was established by the Member states in March 1995. In its own description, the MRFG states on its homepage:

> *"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."

The Coordination Groups tasks will lie within the decentralized procedures concerning marketing authorizations, variations and suspensions, etc.

c) Commission

The DG Enterprise's Unit F2 deals with Pharmaceuticals. The Acting Head of the Unit is Nils Behrndt. The Unit is structured in five subgroups comprising

- Legal, economic and horizontal affairs, which includes decision-making procedures, pediatrics, penalties and orphan regulation, pharmacovigilance, enlargement, borderline products, etc. The group consists of Ms Irene Sacristan-Sanchez, Ms.Claire Joan Scharf-Kröner, Mr. -Erik Helstad, Ms. Sandrine Planisi Llobera and Fanny Deneyer.

- Decision making process, which includes marketing authorizations, designation of orphan medicine status, etc. The group consists of Ms. Melanie Cailleret, Ms. Rosa Galvano, Ms. Monika Jaros-Lanquetot, Ms. Maryse Robert, Ms. Brigitte Schauterden and Mr. Aurelien Perez.

- Medicinal products for human use, which includes the decision making process for human medicines; coordination with the different bodies involved in the authorization process, clinical trials, NtA, pharmaceutical law review, etc. The group consists of Ms. Birka Lehmann, Mr. Peter Arlett, Ms Marie-Claire Dubrunfaut, Mr. Nicolas Rossignol, Ms. Elena Prats and Ms. Nadia Boukhenfouf.

- Veterinary medicinal products, which includes NtA, pharmaceutical law review, Maximum Residue Limits, GMP, etc. The group consists of Ms. Karin Krauss, Ms. Anne Gautrais, Ms. Sabine Azor, and Ms. Erika Maffessoni.

- Telematics, which includes the EUDRA system, IT standardization, Pharmacos web sites. Mr. Rochus de Raat deals with Telematics.

For details: http://dg3.eudra.org/F2/commit/profile.htm.

d) Standing Committee on medicinal products for human use

The Standing Committee on medicinal products for human use is involved in the decision making process on Commission level, which is reflected in Art. 121 Directive 2004/27 and Art. 87 of Regulation No. 726/2004. 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). However, it is an external committee and not a body within the Commission. It has its own

"Rules of Procedure for the Standing Committee on Medicinal Products for Human Use and the Standing Committee on Veterinary Medicinal Products."

Its members are not individually appointed by Member States.

> *"The Standing Committee is chaired by the Commission representative, although this person does not take part in voting. Member states representatives' votes are weighted as described in Article 205, paragraph 2 of the Treaty. The Committee makes its decision by a qualified majority (62 out of 87). A written procedure for the Standing Committee opinion is expressly provided for by Regulation (EEC) No 2309/93 (now Regulation 726/2004) The special provisions necessary for this written procedure were set out in Commission Regulation (EC) No 1662/95 laying down certain detailed arrangements for implementing the Community decisions making procedures. The draft decision is forwarded to the Committee members (in their own language) by electronic telecommunication. Member states have 22 (before 30) days from dispatch to advise whether they approve the draft, reject it, or abstain. Any member state failing to respond within the time is deemed to have approved the draft."*[24]

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

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

[24] NtA, Volume 2A, Chapter 6.

The CHMP can involve standing or temporary working groups to provide scientific advice if required in the evaluation of an individual product. The decision to involve them is upon the CHMP, that is generally in charge of the scientific evaluation of a medicine. Details of their involvement are laid down in the CHMP's rules on procedure, which must provide for details on the appointment of members of such groups and their involvement in an evaluation.

Regulation No. 141/2000 on orphan medicines established the COMP (Committee on Orphan Medicinal Products), which is in charge for the evaluation of applications for orphan drug designation but it also has a major function in advising the Commission on the development of a policy strategy concerning orphan medicines, assistance in the drafting of guidelines or assistance in international negotiations on orphan medicines, etc. (Article 4 of Regulation 141/2000).

The Scientific Committee on Medicinal Products and Medical Devices is not involved in the evaluation of a medicine but deals with Scientific and technical questions relating to Community legislation concerning medicines for human and veterinary use, without prejudice to the specific competences given to the CHMP in the context of the evaluation of medicines. Scientific and technical questions relating to Community legislation concern medicinal materials and equipment.

Directive 78/25/EC installed a Committee dealing for the adaptation to technical progress of the Directives on the elimination of technical barriers to trade in the sector of colouring matters which may be added to medicinal products, which 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 Comitology procedures are laid down in Commission Decision 1999/468/EC and are relevant for the pharmaceutical decision making process. The body involved in the Comitology procedure other than the Commission and Council is the Standing Committee, as already introduced above. The relevant procedures are the Management Procedure (Art. 4 of the Decision) in case of central procedures and the Regulatory Procedure (Art. 5 of the Decision) in case of the decentral procedures. The Comitology process provides the Member States agencies the possibility to take influence in the decision making process as they can issue written remarks to the draft decision of the Commission and they also ask for a oral hearing in the Standing Committee (for details see above "Standing Committee for Medicines for Human Use"). While the Comitology process is therefore 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, to our knowledge the Comitology procedure has never become crucial in the adoption of decisions in the pharmaceutical sector.

4.6. Notice:

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

a) Variation of a Centrally Approved Product

In case of the Commission ordering urgent safety restrictions, no complaint will precede the actual ordering of the urgent safety restrictions.

b) Referral

In case of referrals, no formal complaint is foreseen in pharmaceutical legislation. The affected applicant / marketing authorization holder has to be notified about the starting of a referral (see below).

c) Penalties Regulation

In the case of investigating infringements due to the draft Penalties Regulation, according to Article 7 of the Draft Penalties Regulation, the target must be notified in writing, when the Agency takes the decision to start an infringement procedure against it. Together with this notice the Agency shall require the termination of the alleged infringement.

4.6.2. What are the requirements of 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 Member States or the Commission start a referral procedure, the applicant or marketing authorization holder must be informed about the referral and the questions identified by the referrer.

b) Draft Penalties Regulation

As already stated above, the target must be notified in writing, when the Agency takes the decision to start an infringement procedure against the target. In the notification, the Agency must disclose the details of the allegations against the marketing authorization holder and any element of fact and law, on which such allegations are founded. In addition, the notification

must comprise the information that penalty payments may be imposed together with a request to terminate the infringement.

If the Agency states an infringement and therefore involves the Commission, the marketing authorization holder again, has to be notified in writing. The Commission will therefore issue a statement of objections. Together with the allegations, the evidence shall be disclosed in the notification and the possibility of imposing fines or penalty payments together with an request to stop the infringement shall comprise the notification.

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 measures taken. Article 26 of Regulation 726/2004 provides for the possibility to provide the information on pharmacovivigilance issues to the general public.

In addition, the EMEA web site 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

Pharmaceutical rules provide for detailed rules on time limits for the conduct of the scientific evaluation on the EMEA level and the Commission’s decision making process. The time frames

provided there are mandatory and may only be extended in specific circumstances when the law provides for it, such as when the CHMP in assessing a central application applies for a prolongation of the time to review the dossier according to Article 6 (3) of Regulation 726/2004.

The different procedures have different time frames, dependent on the scope of the review, the complexity of the issues involved and, in case of pharmacovigilance measures, the urgency of an issue. To provide some illustration on the timing of an investigation, the typical evaluation and decision making structure for a central marketing authorization application as well as for a Community referral are displayed below.

The NtA, Volume 2A Chapter 4, page 15p. describes the structure for central marketing authorizations as follows:

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 Web site (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 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 is 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 NtA, Volume 2A, Chapter 6. The following table displays the decision making structure and its time frame. However, following the replacement of the original Regulation 2309/93 by Regulation 726/2004, the time frame for the Commissions' drafting a decision is limited to 15 days and Member States will only have 22 instead of 28 days for the written procedure. After the receipt of the input of the Standing Committee the Commission generally has to adopt a decision within 15 days if the Counsel need not be involved in the decision making process (due to a dissenting opinion from the Standing Committee).

EMEA opinion

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Around 30 days	***Reception by the European Commission services of the appropriate documentation*** - Documentation checking - Generation of the draft Commission decision - Interservices consultation (around 10 days)
30 days	***Written Procedure (30 days according to Regulation (EEC) No 2309/93)*** - Draft Commission decision with the annexes sent in the 11 Community linguistic versions to the member states and marketing authorisation holder
Around 30 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 authorisation holder) to the "Secretariat Général" - Signature of the Director General of DG Enterprise (DG ENTR) on behalf of the Commissioner : subdelegation procedure
	Notification phase - Notification by paper copy to the marketing authorisation holder of the final Commission decision with the annexes in the authentic language only for decisions concerning centralised marketing authorisation - Notification for referral procedure : the decisions with annexes are notified to the Permanent Representatives who are in charge of their transmission to the National Authorities - Sending of the final Commission decision with Annexes in the 11 Community linguistic versions to the member states, EMEA, marketing authorisation holder and EFTA by electronic way (Eudrasafe)

For Community Referrals time limits are displayed in the NtA, 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 0	Notification of a referral to the CPMP
Day 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 2)	First CPMP meeting after submission of responses (including 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

Day 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.
Day 55	Comments from CPMP members on the (Co-) Rapporteur(s) assessment report(s) plus draft SPC (if applicable).
Day 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
Day 90	Adoption of the CPMP opinion with annexes, if applicable as provided in Article 32 of Directive 2001/83/EC as amended

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

Day 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. Instruments / techniques of investigation to discover the facts

The EMEA and the Commission have different measures of investigating issues. We will in the following section provide an overview on the information sources available to the EMEA and Commission. Generally, it must be borne in mind that the supervision of the pharmaceutical sector as far as manufacturing, importing, distribution, advertising, etc. is concerned lies within the competence of the Member States, which do have measures of investigation, such as plant controls comprising access to plants, comprehensive rights to ask for information, documents, etc, and to take samples. Such measures may be relevant for authorization procedures as well as referral procedures and, more general, for pharmacovigilance measures. However, these powers,

being exercised on Member State level, will not be comprised by the following description of the main sources of information.

a) Central Marketing Authorization Application

Application Form

The main information measure in the application procedure is the application itself and particularly the dossier on the medicine, which needs to be evaluated to check whether the requirements for issuing a marketing authorization as set out in Article 12 of Regulation 726/2004 (safety, efficacy and quality of the medicine) are met. In addition, the CHMP may ask the applicant to supplement the provided documents, which it may do in writing or with oral explanations.

List of Questions

Furthermore, the CHMP will normally produce a list with questions to the application after the initial Rapporteur and Co-rapporteur assessment of the application. The applicant may answer these questions in writing and, if need be, also in an oral hearing before the CHMP. While the applicant prepares for the answers, there will be a clock stop for the evaluation of the medicine, which should not be longer than 6 months.

Laboratory Check of Medicines

The CHMP can also request that a laboratory checks the medicine, its starting materials, intermediate products or other compounds in order to assure the validity of the control methods applied in the manufacture of the product (Art. 7 b of the Regulation).

GMP-Inspection

If it is necessary for the evaluation of the medicine, the Committee will ask for an GMP inspection of the manufacturing plant. Information about the manufacturer or importer may also be obtained from Member States upon written request by the CHMP.

Scientific Committees

The CHMP is also entitled to ask pecific 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 Committee's rules of procedure (Art. 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 available to the marketing authorization holder and the Agency through pharmacovigilance measures (for further details see below, 4.7.2. (c)). However, the variation procedure itself is started by a notification (Type IA) or application (Type IB or Type II) for variation by the marketing authorization holder. The Notification procedure for minor variations Type IA requires the applicant to submit (i) all necessary documents including those amended as result of the variation, and (ii) the relevant fee; the Notification Procedure for minor variations Type IB requires to submit (i) all necessary documents demonstrating that the conditions laid down in Annex I (of the Variation Regulation) for the requested variation are met, including all documents amended as a result of the variation and (ii) the fee to be paid. In case of a Type II Variation, the applicant is required to submit (i) the relevant particulars and supporting

documents, (ii) supporting data relating to the variation applied for, (iii) all documents amended as a result of the application; (iv) an addendum or update of existing expert reports/overviews/ summaries to take account of the variation applied for, and (v) the fee to be paid. These documents to be submitted to the Agency give an overview of the information sources the Agency uses when considering the notification or application. However, a Type II Variation, which comprises an CHMP opinion, may use further sources of information and may also 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 (Section 6 (7) Regulation 1085/2003).

c) Community Referral Art. 31 Directive 2001/83

Information from the Referrer

The referrer must provide the Committee with all available information relating to the matter in question. The question limits the review conducted by the Agency.

The review of a marketing authorization has to take everything into account that is of importance to evaluate the validity of an existing authorization and to check whether amendments, or the suspension or withdrawal are necessary. The following sources (see also NtA, Volume 9 Pharmacovigilance - Medicinal Products for Human Use and Veterinary Medicinal Products) are of major importance for the gathering of information about the safety, efficacy and quality of a marketed product:

Periodic Safety Update Reports (PSURs)

The marketing authorization holder is obliged to provide periodic reports about the safety of its product to the Agency and the Member States either on request or after specific time periods clarified in the law (Article 104 of the Human Use Directive), dependent on how long the product is already marketed. PSURs need to include a scientific risk-benefit-assessment.

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

The Agency can frequently ask the marketing authorization holder to supply it with data that allow the checking that the risk-benefit assessment remains positive.

Notifications of adverse events

The marketing authorization holder must provide for an adverse event reporting to the Member States and the Agency, dependent on the event involved (expected or unexpected serious events, within the Community or in third countries). The details about reporting and its presentation are laid down in the NtA on Pharmacovigilance (Volume 9).

Information generated through pharmacovigilance system

Member States are obliged to install a functioning pharmacovigilance system and to ensure information exchange with other Member States and the Agency. Pharmacovigilance systems had been in place in individual Member States before and involved specific reporting schemes from health care professionals or pharmacovigilance centers for the collection of reports. Today's system provides for harmonized institutional requirements in the Member States, electronic data exchange and a European Database for Pharmacovigilance information. These sources of obtaining information about medicines are important for signal generation concerning drug risks and may be further used in the re-assessment of a medicine.

Scientific Material, Studies

In addition, new scientific material, publications of studies in specialized journals, new studies conducted by the company or competitors may provide information that requires the re-assessment of the authorization of the medicine.[25]

Expert Advice

The CHMP may call for expert advice on specific questions. In that case the Committee must specify the questions to be answered by the expert.

Written and Oral Explanations

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

Information from third parties

The Committee may request information from third parties, who may provide information on the issue. Third parties may also, on their own initiative, approach the Agency and supplement information about a medicine. In the Ferriprox case the Court of First Instance held that the Agency needs to take all information into account that concerns the evaluation of a medicine since it is bound by the purpose to serve public health.

Other information available

[25] See NtA, Volume 9, Pharmacovigilance, page 88.

The NtA, 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.*"

In addition, it may well be kept in mind that the Member States authorities are to supervise pharmaceutical companies and manufacturers and have the power to inspect plants, ask for records, require the cooperation of companies and the staff, may take samples, etc.

d) Draft Penalties Regulation

The Agency 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 Art. 7 b of Regulation 726/2004; the cooperation of national competent authorities (such as request for inspections, conduct of supervisory measures).

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

4.8. Rights and duties of target

4.8.1. Privileges? Attorney-client? Self-incrimination? Work product? Pharmaceutical Law does not provide for any specifics, which 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 plenty of obligations to cooperate with the authorities. As already described earlier, the marketing authorization holder must provide PSURs, notify adverse events and provide data needed for the risk-benefit assessment of a medicine if requested by the agency. In addition, obligations to cooperate with national authorities responsible for the supervision of the manufacturing, distribution, etc. of medicines are imposed on the marketing authorization holder (and other entities, which conduct specific activities). The different procedures provide for the authorities, particularly the CHMP, to request further information, inspections, etc., which the marketing authorization holder needs to comply with.

b) Draft Penalties Regulation

The draft regulation explicitly includes a cooperation requirement of the marketing authorization holder towards the Agency and the Commission during the investigation procedure (Art. 16 (2)).

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

a) Community Referral Art. 32 (3) of Directive 2001/83

The CHMP may call upon any other person, who can provide information to the issue. However, the law does not foresee any specific notification requirements towards the applicant or marketing authorization holder.

b) Penalties Regulation

In the draft Penalties Regulation, the Commission may hear any legal or individual person, who can provide information on the alleged infringement. Again, the draft does not foresee a specific obligation to notify the target if the Commission questions such 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 may provide information about its product and new scientific data to the Agency at any time, since he is obliged to cooperate with the Agency (and other national bodies) and has notification obligations. In the context of an ongoing investigation, the main possibility to raise issues is in written or oral explanations or in specific hearings. The EMEA's Code of Conduct contains a specific provision concerning hearings (also see below) and the right to make statements, which reads:

> *"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 possibility to present written or oral explanations on the issue. If after the issuing of an opinion, the applicant or marketing authorization holder will appeal the opinion, he may do so and provide written explanations to the appeal.

c) Penalties Regulation

The draft Regulation provides for oral or written explanations for the marketing authorization holder as far as the first stage of the investigation, the Agency procedure, is affected (Art. 8 of the draft regulation). The Commission, on the second stage, has to provide the possibility to written explanations and / or an oral hearing to its statement of objection (Art. 11 of the draft regulation). In addition, the target may raise issues, when asked for information by the Commission (Art. 12 of the draft regulation). Article 16 of the draft regulation enshrines the rights of participation of the target and allows it to submit any documents, books or records, or copies, etc.

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

No, there are no specific defenses against investigation foreseen in the pharmaceutical legislation since investigations are triggered for public health reasons. However, the EMEA's code of conduct, which is an implementation of good administrational behavior, lays down some principles that have to be respected by the agents when carrying out an assessment of a medicine. The code of conduct particularly 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 subject to Regulation No. 1049/2001 on public access to documents of the European Parliament, the Council and the Commission. This regulation aims

at transparency and supporting the participation of Community citizens in decision-making in order to achieve broader legitimacy, efficiency and responsibility of the administration towards the citizens. The regulation provides for the details on the right to access, restrictions to access, such as protection of public interest, business secrets, or to ensure the proper completion of a decision-making process, as well as rules for classifying documents etc., application and reconsideration procedures and the exercise of the right to access (copies, electronic access, etc.). If the documents relate from third parties or Member States, the Commission has to involve them in order to decide about the granting of access (Art. 4 of the Regulation). The bodies are required to install an administrative procedure to grant access to its documents (documents that it produced or that are in its possession) and to lay down the rules on access in their rules of procedure. In addition, the bodies shall install document registers for the (electronic) access to documents. The Commission has adjusted its rules of procedure (http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_345/l_34520011229en00940098.pdf) to comply with the rights to access and does have different registers with documents available (such as the document register, the comitology document register (http://europa.eu.int/documents/comm/index_en.htm) and, particularly for the pharmaceutical sector the "Community register of medicinal products", http://dg3.eudra.org/F2/register/index.htm). For detailed information on access to documents also see the Commission page: 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 decision through the mentioned register, which comprises marketing authorization approvals, refusals, variation decisions, withdrawals, suspensions, decisions in the decentralized procedures, etc. However, documents may only be accessed if they do not contain confidential information. It is

worthwhile mentioning that no document is excluded a priori from the right to access, including classified documents. The "Access to European Commission Documents - A Citizen's guide" states that also internal documents can be requested. Those are documents which are either not finalized or which are not intended for publication. The Guide lists preparatory documents on Commission decisions and policy initiatives, such as preliminary drafts, interim reports, draft legislative proposals or decisions; explanatory documents, correspondence between the Commission and Member States, the public and companies as examples.

b) Commission: Access to the files by directly involved parties

The draft Commission decision will be made available to the applicant or marketing authorization holder at the same time as it is send to the Member States and therefore access is granted automatically. However, access to the written remarks of the Standing Committee is not explicitly granted in the law and could be restricted on the grounds that the document is for internal use and no decision on the issue has been taken yet (See Art. 4 (3) of the regulation on access.) In addition, if several marketing authorization holders are concerned, confidentiality issues amongst them may arise and therefore, the information disclosed to the different companies may have to be separated.

As mentioned above, internal documents are not excluded form being accessed and therefore, an involved party can access such documents on basis of the rules on access if no restriction applies in the individual case.

Penalties Regulation Art. 16 (3)

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

c) EMEA: Access to files by directly involved parties

Rapporteur reports

The initial assessment report is made available to the applicant. The EMEA will send this report to it regardless it being a preliminary conclusion only and only serves information purposes.

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)

The joint report will also be provided to the applicant, again with the disclaimer that it serves information purposes only.

Final opinion and assessment report

These documents will be send to the applicant as well within 15 days after the adoption.

Access to reports when more than one company is involved

Access to reports can be problematic, when, for instance in a class review, reports refer to different medicines as commercial secrets of the single companies may be included. In such cases, access must also be restricted between the different companies since there is no legal

ground to disclose information to competitors only because they are subject to the same review procedure. In practice, it appeared in the Cisapride review (Art. 31 referral) that rapporteur's assessment reports were restricted to access by those companies only that, for instance, had answered the "CPMP lists of Outstanding Issues" due to confidentiality reasons.

Penalties Regulation Art. 16 (3)

See above, point (b).

d) EMEA: Access to the files by third parties

EPAR

The EPAR is published by the EMEA on its web site and publicly available. However, the EPAR does not contain material that is commercially confidential (Art. 13 (3) Regulation 726/2004).

Before an EPAR is published, the applicant may comment on what he considers to be confidential. The project manager will then prepare a draft EPAR, which must be decided upon by the CPMP.

Access to documents in general

The "Rules on the Implementation of Council Regulation (EC) No 1647/2003 on Access to EMEA Documents" provides for the details on getting access to EMEA documents. The rules were adopted in 2004 by the Management Board of the Agency.

It grants access to documents that are produced by the Agency or that it has received or has in its possession unless access is restricted. Among the reasons, why access is refused, is the

protection of commercial interests of a natural or legal person, including intellectual property, etc. (Art. 3 of the Rules) or if disclosure would seriously undermine the decision-making process. If documents originate from a third party, the Agency must consider, whether access has to be refused on basis of Article 3. In case of inclarity, the third party shall be consulted to determine whether any exception from access applies.

In addition, Art. 57 of Regulation 726/2004 provides different instruments of disseminating information to or accessing of information by the general public, such as publicly available databases on adverse events, pharmacovigilance information to the public, etc.

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 involved parties

As mentioned above, involved parties will be made available the Commission documents such as the draft and the final Commission decision automatically and therefore no application is necessary.

b) Access to Commission documents by third parties

Details about access to documents is found in the Rules of procedure of the Commission as amended to implement the Regulation on access to documents (http://europa.eu.int/eur-lex/pri/en/oj/dat/2001/l_345/l_34520011229en00940098.pdf). The Secretariat-General is dealing with access requests.

Access to documents requires a written application (mail, e-mail, fax). The applicant does not have to provide reasons but it must identify the document referred to precisely. The Commission may help with the identification of the document.

Generally, an application has to be processed immediately (within 15 days) and an acknowledgement of receipt about the application will be sent to the applicant. If access is granted, it can be exercised in different ways such as providing copies, electronic access, access where the document is stored, etc. If access is refused, the applicant must be given reasons for it and be informed about the possibilities to have the application reconsidered by the Commission (confirmatory application). The procedure is the same as for the initial application. If access is denied again, the body must inform about the possibilities of appealing the decision before the European Court of First Instance. If the document originates from third parties, they must be consulted before access can be granted and objections have to be taken into account.

c) Access to EMEA documents by involved parties

EMEA documents such as the Rapporteur and Co-Rapporteur report, the draft assessment report, etc. will be sent to an applicant or marketing authorization holder directly without any requirement to apply for it.

d) Access to EMEA documents by third parties

Third parties may lodge an application asking for access to documents in writing (also electronic form) to the Executive Director precisely identifying the document. The procedure within the EMEA is basically the same as described above for the Commission. However, if access is denied the second time, the applicant may also involve the European Ombudsman. 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).

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

Pharmaceutical law does not provide for any specific rules to grant third parties access to documents that affect a party of a procedure. The general rules of access to Commission's or EMEA's files (see above) apply and provide access to certain extent. However, access to documents is subject to restrictions. Concerning Commission documents, Art. 4 of Regulation 1049/2001 allows to refuse access if disclosure would undermine the protection of public interests, or privacy and the integrity of the individual, or commercial interests of natural or legal persons, including intellectual property; court proceedings and legal advice; or the purpose of inspections, investigations and audits unless there is an overriding interest in the disclosure. In addition, access may be restricted when internal documents are concerned that relate to a matter, on which a decision has not been taken yet. If the document origins from a third party, the party must, in addition, be consulted before a positive decision about access is taken.

Competitors may therefore not have access to Commission's files that are containing commercial secrets of its competitor and even if commercial secrets are not involved, the Commission may turn down an application because a decision has not yet been taken.

The EMEA rules on access to documents contain rules that are alike and may therefore restrict competitor's access to documents in the same way for documents relating to an ongoing or a completed procedure. The EMEA's code of conduct also comprises some general rules on information requests and requests for access to documents that read:

"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 but does not contain confidential material. In addition, the Agency may provide information to the public, such as the refusal to grant a marketing authorization together with its reasons (Art. 12 (3) of Regulation 726/2004), or pharmacovigilance information (Art. 26 of the Regulation). Art. 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 EMEAs transparency strategy is further detailed on http://www.emea.eu.int/htms/human/postguidance/q91.htm.

[How about people representing the public interest? Isn't the public interest represented by the agency when it acts in public health interest? [First discuss "interveners" (rare!): Olivier not successful in getting reports in Apotex (- but later in CFI a bit); Where do we have information?

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

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 mentioned exemptions only apply to parts of the document, the rest of it must be disclosed.

Since the EMEA's rules on access to documents contain the same restrictions, the information should apply analogously to its documents.

Penalties regulation - restrictions of access (Art. 17 (2))

The draft regulation restricts the target's right to access documents relating to the infringement procedure if the documents or material is deemed to be confidential with regard to third parties or to the Agency, Commission or national competent authority.

4.9.5. Consequences if Commission fails to provide access to information?

If the Commission or the EMEA fail to provide information, the applicant may invoke the Court of First Instance (Art. 8 of Regulation 1049/2001). If the EMEA refuses access, the applicant may also lodge a complaint with the European Ombudsman.

4.10. Settlement or compromise:

An applicant for a marketing authorization, who faces a denial of its application, or a marketing authorization holder, whose product is subject to review and whose marketing authorization may be suspended or withdrawn may avoid such negative outcome by agreeing on changes to the marketing authorization application or the issued marketing authorization. As far as safety is concerned, amendments concerning the indication of the product, as well as contraindications, special warnings and precautions, etc. may balance such concerns an 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."[26]

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

The Commission and the Agency do not only fulfill executive functions, such as assessing medicines and taking decisions concerning marketing authorization but also play a crucial role in legislation itself, and its administrative implementation on a more general level through Guidance documents, such as the Notice to applicants or the CHMP guidelines.

Concerning legislation, the Commission plays a crucial part in leading background research for legislation, asking for reports on specific issues to prepare legislative proposals, consultation with the public and evaluating statements of the public concerning proposals, and in drafting such proposals for legislation. Current examples are the Advanced Therapies Regulation, the Paediatrics Regulation and the Penalties Regulation (for details on the proposals as well as the different steps towards legislation see http://dg3.eudra.org/F2/home.html), which are on their way in the legislative procedure, through parliament discussions and readings.

Other than the aforementioned legislation, guidance documents, such as the Commission's Notice for Applicants, the GMP Guidance documents and EMEA Guidelines both in Volume 3 and on the EMEA web site, are not binding to the applicant / marketing authorization holder but they are, nevertheless, of major importance for the practical implementation of the legislation. They assist in the preparation of research intended to be used in applications as well as

[26] NtA, Volume 2A, Chapter 3.

applications itself and provide detailed procedural guidance for the various situations covered by Community law.

The Notice to Applicants, as a Commission guidance to the procedures and requirements of authorization in the pharmaceutical context has its legal basis in Article 6 Regulation 2309/93 (in future Art. 6 of Regulation 726/2004). Concerning Good manufacturing practices, Directive 2001/83 as amended requires the Commission to publish GMP guidelines and - in future - to also include guidance on GMP for active substances used as starting materials (Art. 47) as well as guidelines on the form and content of manufacturing authorizations, the content of inspection reports and the GMP certificate. The law further requires to issue guidelines on the definition of a potential serious risk to public health (Art. 29 (2) Human Use Directive as amended).

As an example for the legal basis of EMEA guidance documents may serve Directive 2003/63 amending the Human Use Directive and requiring in Part II point 4 for data requirements for similar biological products that "*[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.*" The already mentioned EMEA guidelines on biosimilar products are based on this provision.

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 guidance at the moment. Updates are recently being published or will be published soon. However, the new guidance has not been available for the production of this sectoral report yet.

To provide an example from outside the human medicines sector, the CFI case T-13/99 Pfizer Animal Health SA versus the Council of the European Union dealt with an application for

annulment of a Council Regulation concerning the withdrawal of the authorization of certain antibiotics as additives in feedingstuffs. This authorization procedure, while it is de facto a Commission decision, requires the inclusion of a substance into a list contained in the relevant regulation containing additives that can be used in feedingstuffs. Technically speaking, the inclusion in legislation makes this legislation as it is more generalized , while it is, however,de facto an administrative decision. As stated earlier, this concerns veterinary medicines and is not at all typical for the human medicines sector.

Also quickly discuss Capoten case and Merck: applying new policy ("clean indication" in SmPC) before guidelines are adopted -- but is different issue.

6. Hearing phase

6.1. Rights to an administrative hearing

(The following comprises points 6.1.1 to 6.1.7, without distinguishing the points. We refrained from this for consistency and readability reasons)

The different procedures allow for the applicant / target of a procedure to give written or oral explanation to the bodies involved in the evaluation of medicines. For the centralized marketing authorization procedure, the variation procedure, community referrals or the infringement procedure under the future Penalties Regulation the law contains explicit provisions about the applicant / marketing authorization holder to be heard during the procedure. However, these "hearings" form part of the investigation process and are conducted together with the scientific evaluation of a medicine.

6.1.1. centralized marketing authorization procedure

Generally, the marketing authorization application already gives the applicant a comprehensive possibility and obligation to disclose information about the medicine (for details see Art. 6 (1) of the Regulation in connection with Art. 8 of Directive 2001/83 and 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 for further information by supplementing the provided documents. This situation is reflected in the description of the time limits (see above), as in this case, at day 120, there may be a clock stop, if further information is requested. The applicant may as a reply provide written and oral explanation. This "hearing" takes place, while the application is still under consideration within the CHMP. The NtA, Volume 2A, Chapter 3 states about the conduct of such an explanation:

> *"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, independent of the aforementioned supplementation request, ask for an oral hearing to provide explanations. The CPMP has also issued a guidance paper on the conduct of hearings, which contains specific and practical information about carrying out such hearings, as well as a schematic overview of the different steps and pictures of the hearing facilities. Applicants, who are subject to a hearing, should prepare for the hearing in accordance with these recommendations.[27]

Article 9 (2) 726/2004

If the CHMP opinion is negative or not entirely positive, the applicant may within 15 days after the receipt ot the opinion, notify the Agency that he requests a re-evaluation of the opinion. He has to supplement this request within 60 days (after receipt of opinion) with a comprehensive reasoning. The re-assessment may, again, include an oral explanation if required to clarify the issues that were raised in the appeal.

Art. 20 (2) 726/2004

In case, a centrally approved product is under review, the marketing authorization holder should be given the possibility to provide oral or written explanation concerning the questions raised.

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

Art. 8 (2), 11, 16 Penalties Regulation

The draft Penalties Regulation grants the marketing authorization holder the right to be heard by the Agency during the investigation procedure to present its defence. In addition, the draft Regulation also foresees a right for the marketing authorization holder to request an oral hearing in its written explanations on the Commission's statement of objections. This hearing may involve hearing third persons if the marketing authorization holder requests this to support its written explanations. The hearing will be conducted by the Commission on its premises and is not made public.

6.1.2. decentralized procedure (referral procedures)

Art. 32 (3) of Directive

In the referral procedures, the applicant or marketing authorization holder, generally, can give written or oral explanations to the CHMP. However, this right to an oral hearing, so far, was limited to referrals due to Art. 29, 30, 35, 36 and 37, while in case of Art. 31 referrals the right to a hearing was not mandatory, as the opinion did not found basis for a binding Commission decision but was merely a recommendation. Still, in those cases, the applicant or marketing authorization holder might have been requested to provide oral or written explanations. The NtA, Volume 2A, Chapter 3 as a general approach recommends to provide for hearings even if they were not legally mandatory. 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.*"

Art. 32 (4) of Directive

In case of an unfavorable opinion, the marketing authorization holder can request a re-examination, the requirements are the same as described above.

6.1.3. General Comments on third party information

As a general rule, the CHMP may request information from third parties if it considers it necessary to carry out the scientific evaluation of the medicine. This is legally reflected in Art. 32 (3) of Directive 2001/83 or in Art. 12 of the draft Penalties Regulation. It was, however, also confirmed in the Ferriprox case, when the court held that the Commission indeed 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's code of conduct states that information from third parties may at every stage of the procedure be taken into account.

6.2. Hearing officer

6.2.1.

Oral explanations are before the CHMP, the EMEA's scientific committee. There is no specific hearing officer appointed and no specific training given to the persons conducting the hearing.

6.2.2. […] Not relevant

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

a) Conflicts of interests

EMEA

Regulation 726/2004 (like the predecessor 2309/93) provides for rules on how to handle conflicts of interest. Article 63 requires that Members of the administrative body, the Committees, Rapporteurs and experts must not have any financial interests in the pharmaceutical industry, which could impart their neutrality. They are obliged to act in public interest and in order to ensure this they need to disclose information about their financial interest annually. The Agency includes direct or indirect interests that may relate to the pharmaceutical industry in a register, which is publicly available on request. It can, however, only be accessed in the premises of the Agency. In addition, members of administrative bodies, or of the Committees or Rapporteurs

and experts need to clarify any interests they may have concerning the topics of individual meetings.

The Agency's Code of Conduct contains further provisions in this respect putting the requirements and procedure in precise terms as

> *"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 requires the agents to be impartial and independent (Art. 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 pharmaceutical industry and links with other

industries relevant to the nature of the work. It also provides for details on the procedure of declaring interests and its evaluation, as well as forms for the declaration of interests.

In addition, the EMEA has issued a "EMEA policy on the handling of conflicts of interests for EMEA scientific committees members and experts" (EMEA/H/5475/04/Final) further detailing its handling of conflicts of interests and specifically the criteria and procedure for assessing risk levels when interests are involved. Dependent on this assessment, it will be determined if and to what extent a person can participate in a procedure (such as the drafting of general guidelines, or the scientific assessment of a medicine either as a member of the CHMP or a working group or acting as rapporteur, etc.). The EMEA has a special body, the "Declaration of Interests Assessment Group" (DIAG) to deal with these assessment and determination. The EMEA policy contains in-depth information about the procedure and the substantial criteria to determine risk levels and to decide upon participation accordingly.

Commission code of Conduct

b) […] Not .relevant

c) […] N.r.

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 as mentioned above, Art 61 of Regulation 726/2004 prohibits the Member States to influence the work of the Agency and its Committees by giving orders to the national representatives, which could conflict with their duties and tasks within the Agency. In addition, it requires the opinion to be science based. In

general, the EMEA has the task to provide scientific input and not to take political decisions. Art. 61 (6) and (7) read as follows:

> *"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."*

In judicial review, the Courts have stressed that decisions in the pharmaceutical sector have to 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 Court of First Instance, for example, 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)."

In the ECJ case *Pierrel SpA et al. versus Ministero della Sanità, C- 83/92* the court held that a national provision that terminated the validity of an authorization that the holder did not actively use for placing the product on the market was not compliant with Community legislation (However, the new rules will contain a so-called sunset-clause). In that case, the applicant challenged decisions of the Italian Ministry of Health declaring some of its authorizations invalid on basis of the specific Italian provisions. The Ministry of health was forced to declare the authorizations invalid as the national rules asked for it. This may serve as an example of legislative pressure put on the decision makers, which at that time was considered not being in line with Community law as it added a condition for the ceasing of a marketing authorization not reflected in Community law and therefore also putting an obstacle to the internal market..

6.3. Conduct of the hearing

(comprises whole section 6.3.1 to 6.3.11)

As indicated earlier, the applicant or marketing authorization holder has different possibilities of providing input in the investigation and assessment procedure. Dependent on the procedure concerned, the way of providing input will vary. As stated above, explanation can be provided in writing or in oral hearings. As to the initiation, procedure and practical requirements the NtA, 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 for the way, oral hearings will be conducted within the Agency.

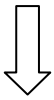
The CPMP guideline on the conduct of a hearing (http://www.emea.eu.int/pdfs/human/regaffair/239001en.pdf) details the hearing as follows:

STEP 1 (Day 180)

List of Outstanding issues adopted by CPMP

Applicant requires clock-stop

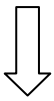
(30 days as default, 60 or 90 days to be agreed at CPMP level)



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

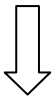
Step IV

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)

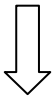
Revised CPMP AR

Draft CPMP Opinion

Draft SMOP

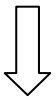
Day +5

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



Day +10

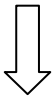
EMEA PTL provides Rapporteur/Co-Rapporteur with revised draft CPMP AR, draft CPMP opinion and SMOP for final comments



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 Penalties Regulation

However, as far as hearings at he Commission are concerned, the draft Regulation on Penalties requires the hearing to be held at the Commission's premises and by the persons appointed for that purpose by the Commission. The hearing will not be public and the marketing authorization holder may propose that other persons, who may corroborate any aspects of the provided written comments, should be heard. However, in order to avoid procedures from being blocked by

asking for a lot of persons testifying, the request has to be within reasonable limit and may only relate to the written comments the marketing authorization holder has provided.

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

The CHMP as the body that scientifically evaluates a medicine and that also conducts the hearing of an applicant will provide for an opinion on a marketing authorization and for the assessment report for the medicine together with a draft summary of the product characteristics (SPC); 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 text. The decision itself is, however, drafted by the Commission, which will also attach the abovementioned documents attached to the CHMP opinion. Generally, the decision will be taken by the Commission. In the special case of disagreement between the Commission and the Standing Committee on the Commission's draft decision, the Council would become the body competent to take the decision (see Comitology procedure above). If the Standing Committee rises new questions concerning the safety, efficacy or quality of the product, the Commission may also stop the decision making process and refer the issue back to the CHMP for further evaluation. A prominent example for the latter is the Ferriprox case, where the Commission after having obtained the new data from Dr. Olivieri decided to refer the application

back to the CHMP. Another example for the Commission deciding to send the opinion back to the CHMP and not to proceed with the decision making procedure is the OMNITROP-case. In that case, the Commission disagreed with the CHMP's finding on the "essential similarity" of the products concerned (biological products). Currently, Sandoz is challenging this decision in the Court of First Instance, 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; (...)"*

Generally, the Commission will only issue one decision. However, in cases of the review of a whole product class comprising different substances and different products, the Commission may issue several decisions even if they are in content the same or similar. The decisions in the Anorectics cases may serve as an example, where the Commission issued more than one decision (Clobenzorex, Fenproporex, Fenbutrazate, Propylhexedrine; Mazindol, Mefenorex, Norpseudoephedrine, Phendimetrazine, and Phenmetrazine (Commission Decision C(2000)608); Amfepramone (C(2000)453); and Phentermine (C(2000)452). The addressee of the decision is notified in paper copy about the Commission's decision.

However, before a decision is lodged, different bodies may be involved in the decision-making process and may issue opinions or decisions, which affect the final decision. The Pharos case concerning an application for inclusion of a substance into Annex II of the MRL (Maximum Residue Limit) Regulation 2377/90 (Pharos versus Commission of the European Union, T-105/96, 17 February 1998 for declaration that the Commission unlawfully failed to pursue the

procedure of inclusion of a substance into Annex II of the MRL Regulation) may serve as an example for the different bodies involved in issuing the final decision. These involved bodies were the Commission for validation of the application and for the decision, the CVMP, the veterinary aequivalent of the CHMP for the scientific evaluation of the application, the Committee for the Adaption to Technical Progress of the Directives on Veterinary Medicinal Products for an opinion on the draft measures of the Commission and, in case of disagreement between the Commission and the Adaption Committee, the Council as the body finally deciding over the proposal.

Pharos T-105/96 decision - there were one or two more instances) . Isn't that more or less the same as in the "normal decision procedure"?

Note: for judicial review Commission now accepts that it can be sued before CFI.]Haven't included this yet as it did not really fit somewhere.

EMEA decision

As described earlier, the EMEA's part is mainly in the scientific evaluation of medicines and in the drafting of an opinion, which is the basis for the final Commission decision. However, some decisions are taken by the EMEA. We have already mentioned that fee decisions, for instance, are issued by the EMEA's Executive Director itself. In addition, the decision to start an infringement procedure under the Penalties Regulation will be taken by the Agency as well although it is not competent to issue the final penalties decision but only carries out the factual investigation.

In case of a centralized variation procedure concerning minor variations Type IA the Agency upon its own decides about the validity of such a notification and informs the marketing authorization holder accordingly. Therefore, the Commission is not participating in this decision.

Also, the decision as to whether a product is eligible for the optional centralized review (so far Part B of the Annex, in future Art. 3 of Regulation 726/2004) is taken on the level of the Agency.

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 for an application is highly dependent on the correct selection of the 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?

7.2.1. Art. 81 Regulation 726/2004 Substantiation obligation

Generally, Art. 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 of the decision in detail, particularly, when applications are denied or authorizations withdrawn or restricted, the requirement to state the reasons for the decision becomes more crucial than in cases where the decision is in favour ouf the addressee.

7.2.2. Statement of reasons in the CHMP opinion

The CHMP is obliged to provide for reasons underlying its conclusions as stated in the opinion. In addition, the assessment report must be made available to the applicant (Art. 9 Regulation No. 726/2004 and Art. 32 (5) of Directive 2001/83). The EMEA's code of conduct in general, asks 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.*"[28]

It further comprises a provision, which requires the public agent to ensure the lawfulness of its actions:

"Article 4 - Lawfulness

[28] 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."[29]

7.2.3. Special substantiation obligations for Commission in cases of different opinion to EMEA

If the Commission wants to deviate from the CHMP opinion in its final decision, the law explicitly requires a detailed explanation of the reasons for the differences. However, the law does treat this as an exceptional case and clearly imposes a strict requirement to provide for explanation. The NtA clearly states that the deviation from the EMEA opinion is an exceptional case but that the Commission must generally be allowed to deviate from the decision provided 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.*"

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

A recent prominent example is the Commission's refusal to grant a marketing authorization for the medicine Omnitrop as it did not accept the CPMP's conclusion that the medicine was essentially similar to the reference product (*Case T-15/04, Sandoz GmbH vs. Commission of the European Union*, concerning the medicine OMNITROP).

7.2.4. Substantiation requirements in Penalties Regulation

The draft Penalties Regulation also contains an explicit requirement to state reasons in Article 14 and it be provided in writing to the marketing authorization holder.

7.3. Dialogue requirement

Is there a duty of care imposed on decision maker 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 their authorization as laid down in law. Therefore, the decision maker must, of course, take into account all relevant information provided by the parties. However, in case of appealing an CHMP opinion, the review is limited to data that has already been available in the original review (Art. 62 (1) of Regulation 726/2004).

7.4. Is there a reasonableness requirement imposed on discretionary decisions?

The EMEA's code of conduct requires to act in accordance with the principle of proportionality. Art. 6 of the 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 may become relevant in the case of fee decisions or fee waivers. However, EMEA opinions concerning the evaluation of a medicine are not discretionary. While in situations of uncertainty the outcome of an assessment may well be positive or negative dependent on the risk-approach of the Committee rendering the opinion, such opinion is however not discretionary but has to comply with public health protection.

7.5. What remedies are available to the Commission?

As discussed in earlier passages, the Commission may withdraw or suspend marketing authorizations if public health requires so, or may issue penalties in cases of infringements of pharmaceutical law and of obligations resulting from the marketing authorization or to make the marketing authorization holder comply with the measures of inquiry (Article 8 of the Penalties Regulation) imposed by the Agency.

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

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

7.6.1. 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 web site (http://dg3.eudra.org/F2/register/index.htm). The web site grants access to all decisions relating to a specific product and including the Annexes to the decisions, which comprise the CHMP assessment reports, the SPC, specific conditions for the marketing authorization as well as labeling and package leaflet in all languages. In case of a refusal to grant a marketing authorization, the decision is annexed only by the CHMP report and the statement of reasons for the refusal. Art. 12 (3) of Regulation 726/2004 explicitly requires to make the information about the refusal to grant an authorization and its reasons publicly available. Art. 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. In addition, Art. 13 (3) obliges the Agency to publish the assessment report and the reasons for the opinion in favour of granting a marketing authorization. This publicly available document, which does not contain confidential information, is called European Public Assessment Report (EPAR).

The EMEA web site (http://www.emea.eu.int/index/indexh1.htm) also contains a register with the EPAR of authorized products, which comprises information about the procedural steps taken before the marketing authorization was issued as well as a listing of the steps taken later. In addition, the site also provides for access to product safety announcements and for public statements of the EMEA concerning suspensions or withdrawals issued by the Commission. However, the Commission decisions concerning the products are not provided for on this site.

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

7.6.2. Decisions concerning referrals

Decisions resulting from referral procedures are also available on the Commission page (http://dg3.eudra.org/F2/register/index.htm) their content is dependent on the specifics of the decision but they will, generally, consist of the decision itself and annexed documents concerning the findings of the CHMP and including SPCs, etc. Again, for medicines the whole history of decisions is displayed and can be publicly accessed.

The EMEA web site (http://www.emea.eu.int/index/indexh1.htm) also contains a listing of products that were subject to referrals providing for background information on the referral as well as the Annexes to the marketing authorizations (SPC, labeling and package leaflet, etc.)

7.6.3. Penalties Regulation

The Commission decision to ask for ending an infringement and to impose fines on a marketing authorization holder is to be published in accordance with Article 84 (3) of Regulation 726/2004 (Art. 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 taking the decision.

7.7. Process resulting in a rule instead decision

[Not relevant?]

8. Administrative reconsideration

8.1. Reconsideration of the Commission's decision?

The following case may serve as an example of an administrative reconsideration. On 9 September 2002 the Commission issued a decision following an Article 30 Directive 2001/83 procedure, with which it ordered the Member States to amend the listed marketing authorizations to produce a harmonized summary of product characteristics for the medicine Capoten and associated names. This decision was contested in the Court of First Instance but the proceeding was stopped as the Commission revoked its prior decision on 11 June 2003 conceding that

> *"(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."*

There is, however, no general rule in pharmaceutical law that the Commission has to reconsider its decision.

As far as access to documents is concerned, the law provides for reconsideration of administrative decisions on both Commission and EMEA level. 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 partly or fully denied on initial application (Art. 6 and 7 of the Rules).

8.2. Administrative appeal:

Administrative appeals other than the described contesting of the opinions of the CHMP within the procedure of issuing a marketing authorization, for instance, are not provided for in European pharmaceutical law. The Commission decision itself and the EMEA opinion can only be challenged before the Courts but not in a procedure on administrative level.

9. Enforcement actions

The enforcement of pharmaceutical law and of compliance with the conditions of the marketing authorization by the marketing authorization holder is mainly executed on Member State level. This is reflected in Art. 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 therefore generally not directly involved in such enforcement actions. Both may, however, get involved, either to adopt regulatory measures concerning the marketing authorization itself or - in future - to issue penalties for the infringement of obligations by the marketing authorization holder.

As already mentioned above, when Member States notify the CHMP and the Commission according to Article 20 of Regulation 726/2004/EC that manufacturers or importers do not fulfilll their obligations anymore or when Member States or the Commission itself consider that measures provided for in Chapter IX and XI of Directive 2001/83 should be adopted, the CHMP on Commission request has to issue an opinion, which serves as a basis for preliminary and final decisions of the Commission concerning the referred issue. The CHMP and the Commission may be involved accordingly in decentralized procedures on basis of Article 36 or Article 107 (pharmacovigilance measures), if a Member State considers it appropriate to suspend, withdraw

or amend an existing marketing authorization. In this case, the CHMP has to assess the issue and provide for an opinion on the intended measure. In such cases, the Member States and the Commission can order preliminary measures to safeguard public health.

In future, the draft Penalties Regulation will provide for a special enforcement measure for the Commission for centrally approved products. If infringement with specific requirements of the pharmaceutical rules occur, the Commission can order a Company to pay Penalties. It is foreseen that the following infringements lead to the Commission's competence of issuing penalties:

> *"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 issuing penalties concerning centrally approved products as proposed will be very broad. In addition, the Commission's competence to issue penalties does not hinder the Member States from enforcing infringements themselves and it could therefore come to parallel enforcement of the same infringements. To avoid this, the draft Regulation foresees communication obligations and a coordination mechanism between the Member States, the Agency and the Commission.

The Commission may impose two types of penalties onto the infringer: fines (lump sums) for the infringement of obligations connected to the marketing authorization and periodic pennalties for the enforcement of measures of inquiry and of decisions finding the existence of an infringement.

The draft Penalties Regulation foresees a two-step procedure for the imposing of penalties:

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

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

The Explanatory memorandum to the draft 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

Lawyers advising companies in the pharmaceutical sector should follow the following considerations in order to keep away regulatory problems from its clients:

Pharmaceutical law is guided by the general principle of public health. This principle is the overarching principle relevant for the implementation of pharmaceutical measures. The Court of First Instance, in its Anorectics ruling stressed this principle:

> *"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. "

Therefore, in providing advice, lawyers should also put the principle of public health first.

Companies must ensure the safety of their product. This not only applies to the marketing application phase but is equally relevant after the marketing of the product starts. The authorities may not only request follow-up information on the product to allow for a continued risk-benefit assessment of the product but 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 with this demonstrates reliability and credibility, which will build confidence on the regulators part.

Responding to regulators questions in an honest and frank way as well as open cooperation with them on issues raised, will create an environment, which allows for a smooth life-cycle management of a medicine together with the regulators.

However, in order to also keep companies interests, they should stress the importance of procedure and insist on their rights within the procedure in order to be provided with an fair assessment of its medicines.

11. Related Questions

[to be added]

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?

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?

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

11.4. Is there a principle of res judicata?

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?

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

11.7. Are hearings or other proceedings open to the public?

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

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)

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 if they feel that an administrative decision has not been properly performed.

However, the Capoten case, in which the Commission has withdrawn its decision after the company lodged a claim with the Court of First Instance, shows that there may be remedies outside judicial review. However, specific complaint procedures investigating maladministration are not explicitly foreseen in the pharmaceutical rules. But the Codes of Conduct of both, the EMEA and the Commission require these bodies to be in line with good administrative behaviour. The Commission's Code of conduct also provides for a complaint procedure to investigate in an alleged misadministration (based on the Code of Conduct). Details of the Code together with practical information on its "enforcement" can be found on the following web site: http://europa.eu.int/comm/secretariat_general/code/index_en.htm.

Other than that, an applicant or marketing authorization holder may, in principle, start a new procedure at any time.

[indirect attempt to challenge via national procedure: see the French Organon - Genevrier case, unsuccessful.] Sorry, I could not read it, as it is in French.

12.2. Ombudsman

The European Ombudsman plays a crucial role in the context of Access to documents (see above), it however, is not involved as far as Commission documents are concerned. In the pharmaceutical sector it has to our knowledge not played a crucial role in any administrative procedure.

12.3. Quashing evidence

[to be checked]

12.4. Damages

Claiming damages for not having authorized a medicine or having delayed the authorization of a medicine, or for having suspended or withdrawn an authorization, which then has caused losses in the return of a company, is in theory an option for a company. However, successful claims concerning damages on EC level are rare in general and have not yet been lodged concerning human pharmaceuticals. The general substantive requirements for lodging a claim for damages are dependent on the nature of the act. In liability for Acts of Community bodies there is a distinction between discretionary and non-discretionary acts.

In case of discretionary acts, liability on basis of Art. 288 of the EC Treaty is dependent on the requirement that

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

- that the violation has caused damages.

The margin of discretion is decisive for the application of the requirement of a sufficiently serious violation.

In case of non-discretionary acts a claimant needs to show

- the existence of illegality,
- causation, and
- damage.

However, in the Pharos case (see above) claims for damages concerning the failure to include a substance into Annex II of the MRL Regulation in a timely manner failed because the court could not find that the Commission acted illegally.

The details of liability, which concern general European Law and does not have any specifics in the pharmaceutical sector, may not be further discussed in this section.