Referral procedures – Overview, analysis and outlook

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Dr. Angelika Hönlinger
aus Ludwigsburg

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Betreuerin und 1. Referentin:	Prof. Birka Lehmann
2. Referentin	Dr. Christine Mayer-Nicolai

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Abbreviations

bid	twice daily
CA	Competent Authorities
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CP	Centralised Procedure
CPMP	Committee for Proprietary Medicinal Products for Human Use
DCP	Decentralised Procedure
EEA	European Economic Area
EMEA	European Medicines Agency
EC	European Commission
EU	European Union
EWP	Efficacy Working Party
HCMP	Committee for Herbal Medicinal Products
LoQ	List of Questions
LoI	List of Outstanding Issues
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
MRI	Magnetic Resonance Imaging
MRP	Mutual Recognition Procedure
MS	Member State
NtA	Notice to Applicants
PL	Package Leaflet
PRAAC	Pharmacovigilance Risk Assessment Advisory Committee
SmPC	Summary of Product Characteristics
UTI	Urinary Tract Infections

1 Introduction

A medicinal product can only be placed on the market in the European Union (EU) when a marketing authorisation (MA) has been issued. There are different types of procedures leading to MAs: national authorisation, Community authorisation via centralised procedure (CP), mutual recognition (MRP) and decentralised procedure (DCP).

A MA can either be granted by the competent authority of a particular Member State (or an European Economic Area (EEA) country) for its own territory only (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community at the same time (Community authorisation) under the CP.

In cases where national authorisations are requested for the same medicinal product in more than one Member State (MS) and the Marketing Authorisation Holder (MAH) had already received a marketing authorisation in a MS, the applicant/MAH can submit an application in the MS concerned using the procedure of mutual recognition. The MSs concerned should then recognise the MA already granted by the reference MS and authorise the marketing of the product on their national territory (Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended).

If no MA has been granted in the Community, the applicant can also make use of a DCP and submit an application in all the MSs where he intends to obtain a MA at the same time, and choose one of them as reference MS. Based on the assessment report prepared by the reference MS and any comments made by the concerned MS, marketing authorisation should be granted in accordance with the decision taken by the reference MS and concerned MSs in this DCP (Directive 2001/83/EC, as amended).

With the exception of the CP, leading to a Community authorisation of the same prescribing information (Summary of Product Characteristics (SmPC), labelling, package leaflet), other authorisation procedures could potentially lead to differences in the prescribing information due to divergent decisions taken by some MSs. This could have an impact on the free movement of goods, i.e. medicinal products, within the EU, if for example a medicinal product is approved in different indications in several MSs.

There are several legal means and procedures that involved parties (i.e. MSs, applicant/MAH, the European Commission) have through a referral to address such heterogeneity of MAs and resulting prescribing information following authorisation (via national procedure or MRP) or prior to authorisation (via MRP or DCP), in order to achieve harmonisation of such information.

A referral is an European procedure that allows to address any concerns related to a medicinal product via an arbitration mechanism leading to an EU-wide, binding decision. The overall purpose of the referral procedure is to reach and maintain harmonisation as well as to safeguard public health in the EU/EEA.

There are a number of reasons as to why a referral procedure may be started, ranging from concerns over the safety of a class of medicinal products to unresolvable different opinions amongst MS on the use of an individual medicinal product in a certain indication. Referrals

may be started by the European Commission (EC), any MS and by the applicant/MAH, respectively, depending on the category/legal basis of the referral.

The Community pharmaceutical legislation (Directive 2001/83/EC, as amended) sets the legal basis for referrals. It provides for a binding Community arbitration mechanism, based on a number of different legal grounds (see section 2 of this thesis). Independent of the applicable legal basis, the matter is referred to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) for a scientific evaluation. Following the CHMP's opinion, the European Commission issues a single decision, binding to all MSs. (IDRAC14891 - Marketing Authorisation Procedures - European Community Referral/ Arbitration; Notice to Applicants (NtA), Chapter 3).

This thesis is intended to give an overview of the referral procedure and different referral types. It then provides and analyses examples of the various types to determine how well the referrals work and what their impact on the different involved stakeholders is. Finally, it considers the proposed pharmacovigilance amendment of the Directive 2001/83/EC as regards to the respective articles on referrals.

2 Legal basis

Referral procedures may be initiated based on one of the following articles of Directive 2001/83/EC, as amended (see also Question 3 - EMEA Questions & Answers on referrals; IDRAC 14891 - Marketing Authorisation Procedures - European Community Referral/ arbitration; NtA Chapter 3):

- Article 29(4) of Directive 2001/83/EC – "Mutual Recognition and Decentralised referral"
- Article 30 of Directive 2001/83/EC – "Divergent decision referral"
- Article 31 of Directive 2001/83/EC – "Community interest referral"
- Articles 35, 36(1) and 37 of Directive 2001/83/EC – "Follow-up referrals"
- Article 107 of Directive 2001/83/EC – "Unilateral action by MSs in urgent cases"
- Articles 5(11), 6(12) or 6(13) of the "Variation Regulation" (EC) 1084/2003 (by reference to Article 35(2) of Directive 2001/83/EC)
    - Article 5(11) applies to Type IB variations and can be initiated by the MSs concerned by a MRP or by MAH
    - Article 6(12) applies to Type II variations and can be initiated by the MSs concerned by MRP
    - Article 6(13) applies to Type II variations and can be initiated by the MAH

The referral procedure itself is described in Articles 32, 33 and 34 of Directive 2001/83/EC, as amended (see section 4 of this thesis).

In general, medicinal products authorised through the Centralised Procedure according to Regulation (EC) No 726/2004 cannot be included in referral procedures. However, this regulation includes two articles that can be used as basis for initiating a referral procedure, i.e. Articles 5(3) and 20. Article 5(3) indicates that "*At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Human Use shall also draw up an opinion on any scientific matter concerning the evaluation*

of medicinal products for human use. The Committee shall take due account of any requests by Member States for an opinion.". Examples for products that were evaluated under Article 5(3) can be found on the EMEA website (Opinions on any scientific matters). A procedure under Article 20 of the Regulation could be triggered by the EC in parallel for products of the same active substance or therapeutic class that are part of a review under an Article 31(2) referral (Question 4 - EMEA Questions & Answers on referrals). For centrally authorised products, referrals will therefore not occur due to inconsistent national SmPCs but there are circumstances where a review of the safety data is required.

For herbal medicinal products, there is also Community legislation (Directive 2001/83/EC, Articles 16c(1)(c) and 16c(4)) by which certain matters may be referred by MSs to the Committee for Herbal Medicinal Products (HCMP) of the EMEA, which for these products does not lead to a binding Community procedure (NtA Chapter 3).

This work will focus on referrals for medicinal products based on Directive 2001/83/EC, as amended only. Referrals based on Regulation (EC) 1084/2003, Regulation (EC) No 726/2004, exconcertation procedures (i.e. Article 37) and referrals for herbal medicinal products will not be further covered but may be mentioned where deemed appropriate.

3 Referral categories

Referrals falling under the scope of Directive 2001/83/EC, as amended, can be initiated by a MS, Applicant, MAH or the EC. The specifics of the different referral categories and the fact as to who can initiate which kind of referral are described in Table 1 below.

Table 1 Types of referrals

Legal basis	Reference name	Who can initiate such referral	What types of products are affected	Purpose
Article 29(4) of Directive 2001/83/EC	Mutual Recognition and Decentralised referral	During MRP/DCP, concerned MSs in procedure	Specific medicinal product (MP) for which MAA is applied for within MRP/DCP	Harmonisation - based on concern raised on grounds of potential serious risk to public health.
Article 30 of Directive 2001/83/EC	Divergent decision referral	Any MS, EC, Applicant/MAH	Specific MPs for which divergent decisions have been adopted in MSs [Article 30(1)], and products placed on list of products [Article 30(2)], respectively.	Harmonisation – divergent decisions by MSs concerning authorisation, suspension or withdrawal
Article 31 of Directive 2001/83/EC	Community interest referral	Any MS, EC, Applicant/MAH	Both applications and authorised MPs in some or all MSs (national and mutually recognized products). Article 31(1) includes only specific MP Article 31(2) includes all MPs containing same active substance or all MPs belonging to same therapeutic class (including different active substances)	Harmonisation – where interest of Community is involved, i.e. interests of public health in the Community e.g. concerns relating to quality, efficacy, and/or safety of a MP or new pharmacovigilance information.
Articles 35, 36 and 37 of Directive 2001/83/EC	Follow-up referrals	Any MS, EC or MAH (depending on the applicable article)	Article 35 for products where a type IB or type II variation is refused. For Article 36 only MRP products can be included. Article 37 for products authorised before 1 January 1995 (“ex-concertation products”).	To resolve post-authorisation divergences between MSs. Triggered by MS or EC when it is considered that a variation, suspension or withdrawal of a harmonised MA is necessary to protect public health. Triggered by MSs or MAH in frame of follow-up procedure for MPs which have been granted a MA via MRP or which have been subject to complete harmonisation in frame of referral procedure.
Article 107 of Directive 2001/83/EC	Unilateral action by MSs in urgent cases	MSs	Specific MP	To protect public health

3.1 Article 29(4) of Directive 2001/83/EC ("Mutual Recognition and Decentralised referral")

An Article 29(4) referral is also called "Mutual Recognition and Decentralised referral" and can be initiated only during a MRP/DCP, i.e. pre-authorisation, when the full dossier is being assessed, to resolve disagreement between the concerned MSs. This referral category relates only to a specific medicinal product, for which a MAA is applied for (Question 4 - EMEA Questions & Answers on referrals).

Article 29(1) of Directive 2001/83/EC, as amended, states that "*If, within the period laid down in Article 28(4)* (**Note:** the period as described in Article 28(4) means that MSs have 90 days to approve the Assessment Report, SmPC, labelling and package leaflet following positive evaluation by the reference MS)*, a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be forthwith referred to the coordination group."* [**Note**: the "coordination group" refers to the Coordination group for Mutual recognition and Decentralised procedure for human medicinal products, CMD(h). This group consists of one representative per MS. The group is responsible for the smooth functioning and positive outcomes of MRPs and DCPs. One of their tasks is to consider disagreement raised by a MS and to bring the MSs together for a further discussion to resolve such issues (NtA Chapter 2)].

If the MSs involved in a MRP or DCP fail to reach an agreement on the assessment report on the full dossier (i.e. Modules 2-5), SmPC, labelling and package leaflet within 60 days in the CMD(h) procedure [see NtA Chapter 2 section 5; Directive 2001/83/EC, as amended, Article 29(3)], then a referral according to Article 29(4) is triggered to the EMEA/CHMP based on the grounds of potential serious risk to public health raised by one or more MSs (for a definition of potential serious risk to public health please see "Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC, as amended — March 2006 (2006/C 133/05)"). Such concern is the only reason for an Article 29 referral to be initiated.

Following the referral to the CHMP and based on its opinion followed by the EC Decision, the outcome of the referral is a fully harmonised product with a harmonised SmPC, labelling and package leaflet that has to be implemented within the MSs involved in the MRP/DCP.

There might be situations where a product is already approved in some MSs (e.g. the reference MS) before the potential serious risk to public health concern was raised. According to Article 29(6) "*Member States that have approved the assessment report, the draft summary of product characteristics and the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 32. In that event, the authorisation granted shall be without prejudice to the outcome of that procedure.*" Therefore, in these MSs, the product can become available on the local market. However, depending on the outcome of the referral procedure, the prescribing information has to be harmonised and implemented nationally in line with the EC decision without submission of an additional variation by the

applicant/MAH, as the Regulation (EC) 1084/2003 is not applicable in this case (CMDh/101/2001/Rev4). NtA Chapter 7 in its Section 6 describes the required national procedure that the applicant will have to follow for each individual EU/EEA country after the EC Decision on a referral. If the EC decision is to withdraw the medicinal product in the EU, then the product has to be withdrawn in all MSs where the product was approved and already on the market.

3.2 Article 30 of Directive 2001/83/EC ("Divergent decision referral")

In general, Article 30 referrals can be triggered if divergent decisions on the authorisation, suspension or revocation of a particular medicinal product have been taken by two or more MSs and a need for their harmonisation has been identified by a MS, the EC, an applicant or the MAH. A serious risk to public health concern is not a necessary criterion. In such case, a referral should be made under Article 31.

Article 30 includes two paragraphs [30(1) and 30(2)] that differentiate between divergent decisions on a specific medicinal product and products identified on a list for harmonisation, respectively:

An Article 30(1) referral may be initiated when divergent decisions have been adopted by MSs concerning the authorisation, suspension or withdrawal of a particular medicinal product and there is a need to harmonise across the EU, e.g. where such medicinal product has been authorised in two or more MSs and the authorisations diverge in particular concerning the product information (e.g. different indications, contraindications or posology). It may be triggered by the EC, a MS, a MAH or an Applicant (Question 2- EMEA Questions & Answers on referrals).

According to Directive 2001/83/EC, Article 30(2), "*In order to promote harmonisation of authorisations for medicinal products authorised in the Community, Member States shall, each year, forward to the coordination group a list of medicinal products for which a harmonised summary of product characteristics should be drawn up. The coordination group shall lay down a list taking into account the proposals from all Member States and shall forward this list to the Commission.* Therefore, a referral under Article 30(2) may be initiated for the reason of divergent decisions when the medicinal product is on the list laid down for harmonisation yearly by the CMD(h), following endorsement by the EC (Question 2 - EMEA Questions & Answers on referrals; NtA Chapter 3).

Depending on the grounds of the referral, an assessment of e.g. only the clinical section could be initiated. As an outcome of the referral, the relevant clinical sections of the prescribing information, i.e. indication, contraindications etc. would be harmonised but different dosage strengths or pharmaceutical forms might still be authorised in different MSs. Therefore only partial harmonisation of the medicinal product would have been achieved in such a case.

3.3 Article 31 of Directive 2001/83/EC ("Community interest referral")

An Article 31 referral may be initiated by the MSs, the EC or the applicant/MAH in specific cases where the interest of the Community is affected. The expression 'Community interest' has a broad meaning but it refers in this case particularly to the interest of the public health in the Community, for example following concerns related to the quality, efficacy and/or safety

of a medicinal product or new pharmacovigilance information, that became available (Question 2 - EMEA Questions & Answers on referrals).

Depending on the scope, the referral can relate to a specific medicinal product only [Article 31(1)], or to a class/range of medicinal products (all medicinal products containing the same active substance or to all medicinal products belonging to a specific therapeutic class (including different active substances) [Article 31(2)] (Question 2 - EMEA Questions & Answers on referrals). Article 31(2) further states that the procedure could be limited to certain specific parts of the authorisation, e.g. only information related to clinical data but not quality data. Therefore, similar to Article 30, Article 31 referrals most likely lead to partial harmonisation of the product if only e.g. the clinical data are assessed.

If a class of medicinal products is assessed in an Article 31(2) referral, including centrally authorised medicinal products, then these products are not part of the referral procedure itself but could be handled if necessary via a procedure according to Article 20 of Regulation (EC) No 726/2004 triggered by the EC (section 2 of this thesis; NtA Chapter 3).

3.4 Articles 35, 36 and 37 of Directive 2001/83/EC ("Follow-up referrals")

Article 35, 36 and 37 of Directive 2001/83/EC, as amended, relate to changes of a marketing authorisation.

These referrals may be triggered by MSs or the MAH in the context of follow-up procedures (i.e. variations) for medicinal products, which have been granted a MA via MRP or DCP or which have been subject to complete harmonisation in the framework of a previous referral procedure (Question 2- EMEA Questions & Answers on referrals; NtA Chapter 3).

Article 35 provides for an Article 5(11), 6(12) or 6(13) referral (of the "Variation" Regulation (EC) 1084/2003) (IDRAC 14891). Article 5(11) applies to Type IB variations and can be initiated by the MSs concerned by a MRP or by the MAH. Article 6(12) applies to Type II variations and can be initiated by the MSs concerned by the MRP. Article 6(13) applies to Type II variations and can be initiated by the MAH. Article 35 will not be further covered in this work.

An Article 36(1) referral may be initiated to resolve any post-harmonisation divergences that may arise between MSs. It can be triggered by a MS when it is considered that a variation, suspension or withdrawal of a harmonised MA (e.g. harmonised under a prior Article 31 procedure) is necessary for the protection of public health (Question 2- EMEA Questions & Answers on referrals). It is mainly initiated in cases of Community interest and for safety related reasons (IDRAC 14891).

Article 37 provides for referrals with respect to exconcertation products previously authorised under Article 4 of Directive 87/22/EEC (IDRAC 14891), i.e. for products authorised before 1 January 1995. This article will not be further covered in this work.

3.5 Article 107 of Directive 2001/83/EC ("Unilateral action by MSs in urgent cases")

When concerns about a medicinal product have an European-wide dimension (i.e. the product is authorised in more than one Member State) or are of Community interest, divergences between the MSs on the need to vary, suspend or revoke the marketing authorisation need to be taken up and resolved at the European level, using the referral mechanisms. In principle, unilateral national action by one MS is regarded as being not appropriate in the EU. However, there might be the need for unilateral measures by MSs. Therefore, Article 107(2) of Directive 2001/83/EC, as amended, does recognise the need for such unilateral measures where, in exceptional cases, urgent action is essential to protect public health (from e.g. availability of new pharmacovigilance data) and until a definitive action is adopted on the European level.

In accordance with Article 36 (2) of Directive 2001/83/EC, as amended, in these specific cases, the Member States may temporarily adopt national measures suspending the marketing and use of a medicinal product. If this action is taken, the Member State needs to inform the EMEA, the EC and the other MSs no later than the following working day.

The CHMP will then prepare an opinion to address the issue and the EC may request the MSs where the product is authorised to take temporary measures immediately, while waiting for the adoption of final measures by the EC (NtA Chapter 3).

4 Procedural steps

The procedures and timelines applicable to referrals are laid down in Articles 32 to 34 of Directive 2001/83/EC, as amended, and are further described in the Notice to Applicants Chapter 3 and the EMEA Questions & Answers on referrals. A referral ends with a scientific opinion given by the CHMP (Article 32) and is then forwarded to the EC, who issues a decision, binding within the EU (Articles 33 and 34). The different steps are further described below.

4.1 Documentation

Referral procedures can be initiated by different parties. When a MS, applicant, MAH or the EC decides to initiate a referral, a notification form is sent to the CHMP/EMEA Secretariat, clearly identifying its legal basis, the product(s) concerned and a detailed explanation of the issue(s) referred (EMEA Questions & Answers on referrals).

4.1.1 Referrals triggered by a MS or the EC (under Articles 29(4), 30, 31, and 36)

In case a MS triggers a referral procedure, it should submit all available information (i.e. dossier, assessment report, SmPC, labelling, PL) on the product to the CHMP. The specific concerns on a medicinal product are already available from the previous assessment procedure and would be clearly outlined based on the concerns raised. Therefore, these types of referrals start based on the available information with the immediate adoption of a List of Questions (LoQ) provided by the CHMP to be answered by the applicant/MAH (see Table 2).

The applicant/MAH needs to provide the answers and relevant the documentation to the CHMP in the following structure:

Part I

- Introduction, written summary answering all questions, conclusion, proposed SmPC / labelling / package leaflet
- Table listing all studies referred to in the answers with further information on each study

Part II

- Supportive documentation (protocols, study reports, literature, risk management plan) organised by quality, pre-clinical data, clinical pharmacology, clinical efficacy and safety and post-marketing experience, if available.

4.1.2 Referrals triggered by a MAH/Applicant (under Articles 30 and 31)

In case of a referral is being initiated by an applicant/MAH, all relevant information including expert reports/overview documents, which, if needed, have to be updated to include data supporting the reasons for referral, should be forwarded to the CHMP members, the CAs of the MSs and the EMEA (NtA Chapter 3). Only then the assessment can be started and the CHMP will issue their List of Questions on Day 30 of the procedure (see Table 3).

4.2 Rapporteur appointment

Following the receipt of information on a referral procedure, the CHMP appoints a Rapporteur/Co-Rapporteur on a case-by-case basis. In cases of a 'Community/class referral' [Article 31(2)], affecting several products, one lead Rapporteur and more than one Co-Rapporteur may be appointed (EMEA/124066/2005). In addition to the (Co)Rapporteurs, the CHMP may also appoint individual experts to advise the Committee on specific questions (Article 32(2) of Directive 2001/83/EC, as amended; NtA Chapter 3).

4.3 Grouping of applicants/MAHs

An applicant/MAH can be represented by another party. In that case, a "Letter of representation" needs to be provided to EMEA. Applicants/MAHs can also group themselves for the purpose of the referral procedure in order to provide a single consolidated answer and/or oral clarifications of the questions raised by CHMP. In such case the EMEA requests that a group representative be designated (Question 7 - EMEA Questions & Answers on referrals).

4.4 Fees

Fees have to be paid only for referral procedures under Article 30(1) and 31 initiated by the applicant or MAH. The fee is 58.000 Euros per referral procedure. The fee is independent of the number of MAs/applications and number of pharmaceutical forms, dosages or pack sizes held by a specific applicant/MAH.

In cases where more than one applicant/MAH is involved, they can either group themselves or participate individually. For applicants/MAHs, who are grouping, a fee of 58.000 Euros needs to be paid per group (Question 6 - EMEA Questions & Answers on referrals).

4.5 Timetable and clock stop

According to Article 32(1) of Directive 2001/83/EC, as amended, the CHMP should issue a reasoned opinion within 60 days of the date of the start of the referral following its notification. For Article 30 and 31 referrals, this period may be extended by the CHMP by up to 90 days (total of 150 days) taking into account the views of the applicants or the MAHs concerned.

The CHMP may suspend the time limit of 60/150 days (clock-stop) in order to allow the applicant(s)/MAH(s) to prepare the responses to CHMP LoQ, List of Outstanding Issues (LoI) or an oral explanation (NtA Chapter 3). This is laid down in Article 32(3) of Directive 2001/83/EC, as amended, as follows: "*before issuing its opinion, the Committee shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations within a time limit which it shall specify*".

The time given to the applicant/MAH to answer the CHMP LoQ/LoI is defined on a case-by-case basis by the CHMP. In general, both periods should not exceed 3 months. In exceptional cases and when duly justified, the applicant/MAH can request for an extension of three further months to answer the questions raised. When several MAHs are involved in a referral procedure and when the CHMP has accepted an extension based on the request of one of the MAHs, the timetable for the whole procedure for all MAHs will be extended. The CHMP can also decide to have a shorter timetable, depending on the nature of the issue raised in the referral (Question 8 - EMEA Questions & Answers on referrals).

The applicable timetable for referral procedures distinguishes between referrals triggered by a MS or the EC and referrals triggered by an applicant/MAH (NtA Chapter 3). Tables 2 and 3 give an overview of these timetables. The reason for such difference is that if a referral is triggered by a MS or the EC, all documentation including assessment reports, SmPC, labelling and package leaflet are already available and have been reviewed previously, whereas in the case when an MAH triggers a referral procedure all documents needed for review will be included in the referral dossier and review has to be initiated thereafter.

The number of clock-stops also differs between referrals triggered by a MS or the EC and referrals triggered by an applicant/MAH: there are two clock-stops in case the referral is triggered by a MS or the EC and one clock-stop only if the referral is triggered by the applicant/MAH.

Table 2 Timetable for referrals under Article 29(4), 30, 31 or 36(1) triggered by a MS or the EC (according to NtA Chapter 3)

Timepoint	Procedural step
Day 0	Notification of a referral to the CHMP/EMEA Secretariat
Day 1	1st CHMP meeting following notification of referral. CHMP discusses question(s) referred during the plenary meeting. (Co)Rapporteurs appointment/confirmation, as applicable.
	Adoption of CHMP List of Question (LoQ) to be addressed by the

Timepoint	Procedural step
	applicant/MAH and of the timetable.
Clock stop	MAH to answer CHMP LoQ
Clock start (Day 2)	Clock restarts following provision of responses (if applicable including English SmPC, labelling, PL)
	Adoption of CHMP timetable for rest of procedure.
Day 20	(Co)Rapporteur(s) circulate their draft Assessment Report(s) on the written responses from the applicant(s)/MAH(s) if applicable, together with the draft SmPC / labelling / PL.
Day 25	Comments from CHMP members on the Assessment Report(s) and draft SmPC / labelling / PL.
Day 30	Discussion at the CHMP.
	Adoption of the CHMP opinion, or Adoption of a CHMP LoI to be answered in writing and/or in oral explanation.
Clock stop	Clock stop for the applicant(s)/MAH(s) if needed for preparation and submission of written answers and/or an oral explanation.
Clock restart	If applicable in case submission of written responses and/or at the time of the oral explanation.
Day 60	Adoption of the CHMP opinion.

Table 3 Timetable for referrals under Article 30 and 31 (according to NtA Chapter 3) triggered by the applicant(s)/MAH(s)

Timepoint	Procedural step
Day 0	Notification of a referral to the CHMP/EMEA Secretariat
Day 1	CHMP meeting following notification of referral. Prerequisite: relevant documentation has been submitted by the applicant/MAH in advance of the start of the procedure. CHMP discusses question(s) referred during the plenary meeting. (Co)Rapporteurs appointment/confirmation.
	Adoption of timetable.
Day 20	(Co)Rapporteur(s) circulate their Assessment Report(s) on the written responses from the applicant(s)/MAH(s) if applicable, together with comments on the proposed SmPC / labelling / PL.
Day 25	Comments from CHMP members on the Assessment Report(s) and draft SmPC / labelling / PL.
Day 30	Discussion at the CHMP.
	Adoption of the CHMP opinion, or Adoption of a CHMP LoQ to be answered in writing and/or in oral explanation.
Clock stop	Clock stop for the applicant(s)/MAH(s) if needed for preparation and submission of oral explanations.
Clock restart	If applicable, following submission of written explanations and/or at the time of the oral explanation.
Day 60	Adoption of the CHMP opinion.

4.6 Withdrawal of an MAA and stopping of a referral procedure

According to the NtA Chapter 3, "*an application for a marketing authorisation may be withdrawn by the applicant at any time during the MRP/DCP. However, once a potential serious risk to public health has been raised in accordance with Article 29(1) of Directive*

2001/83/EC, to be dealt with by the CMD(h), and if failed, by the CHMP in an arbitration procedure, the opinion of the CMD(h) and of the CHMP will be given unless all applications and existing marketing authorisations for the product are withdrawn" for a product reviewed via an MRP or for a product during the assessment step II of a DCP. Therefore, once an Article 29(4) referral procedure is triggered based on a potential serious risk to public health concern of a MS during an ongoing review procedure of a MRP or DCP, a withdrawal of the application will not stop a referral procedure being triggered. The referral can only be stopped if the applicant/MAH withdraws the application in all EU/EEA MSs.

Article 30, 31, 36(1) and 107 referral procedures can only be stopped if the MAH withdraws the concerned MA from all EU/EEA markets.

4.7 CHMP opinion and re-examination

In general, the CHMP opinion on a referral procedure can recommend the granting or non-granting of a MA, variation, suspension or withdrawal of a MA.

4.7.1 CHMP opinion outcomes

There might be different implications of the opinion for the applicant(s)/MAH(s) (Article 32(4) of Directive 2001/83/EC, as amended). Besides the granting of a MA, the opinion could include situations where the CHMP finds that:

- the application does not satisfy the criteria for authorisation; or
- the SmPC/labeling/package leaflet proposed by the applicant/MAH in accordance with Article 11 of Directive 2001/83/EC should be amended, or
- the authorisation should be granted subject to certain conditions, in view of conditions considered essential for the safe and effective use of the medicinal product including pharmacovigilance, or
- the MA should be suspended, varied or revoked.

4.7.2 Re-examination

The further steps are also described in Article 32(4): *"Within 15 days of the receipt of the opinion, the applicant(s)/MAH(s) may notify the EMEA in writing of his/their intention to request a re-examination of the opinion. In that case he/they forward the detailed grounds for the request to the EMEA within 60 days after receipt of the opinion"*.

Within 60 days from receipt of the detailed grounds for the request, the CHMP shall re-examine its opinion (in accordance with the fourth paragraph of Article 62(1) of Regulation (EC) No 726/2004). In order to do so, it will appoint a new Rapporteur and, where necessary a new Co-rapporteur, different from those appointed for the initial opinion. The (Co-) Rapporteur(s) is/are responsible for making an assessment of the detailed grounds for re-examination (see also NtA Chapter 3). Within 60 days from the receipt of the detailed grounds for re-examination, the CHMP will re-consider its opinion. If deemed necessary, an oral explanation can be held within this 60 days timeframe. No clock-stops apply to this procedure (Regulation (EC) No 726/2004 Article 9(2); NtA Chapter 4).

4.7.3 Final CHMP opinion

Within 15 days after adoption of the CHMP opinion, the EMEA shall forward the final opinion to the EC and the applicant(s) or MAH(s) together with an assessment report including the reasons for its conclusions (Article 32(5) of Directive 2001/83/EC). In case of a re-examination, the conclusions will be part of the evaluation and therefore integrated into the final assessment report (NtA Chapter 3).

In case of a positive opinion of granting, maintaining or varying a marketing authorisation for the medicinal product concerned, in accordance with Article 32(5) of Directive 2001/83/EC, as amended, the following documents are annexed to the opinion (Question 21 - EMEA Questions & Answers on referrals):

- Opinion page:
  stating the legal basis for the referral, the scope and the CHMP recommendation
- Annex I:
  List of invented names, Applicant(s)/MAH(s), strengths, pharmaceutical forms and route of administration
- Annex II:
  Scientific conclusions (on efficacy, safety and/or quality) and grounds for the granting/amending the Product Information/the suspension/the withdrawal of the MAs
- Annex III:
  English SmPC, labelling, patient leaflet if CHMP recommends to grant MA or to vary the terms of the MA
- Annex IV:
  Conditions of the MA affecting the authorisation considered essential for the safe and effective use of the medicinal product including any actions related to pharmacovigilance, and any conditions or restrictions with regard to the safe and effective use of the medicinal product.

In cases where only parts of the SmPC and the corresponding parts of the labelling and package leaflet are harmonised (i.e. Article 29, Article 31(2) or follow-up referrals) only these will be annexed to the opinion. Where no amendments to the SmPC, labelling or package leaflet are foreseen, a statement will be included in the annex for clarity.

If an opinion is given recommending the suspension or revocation of the MA(s) for the medicinal product concerned, the ‘scientific conclusions and grounds for suspension or revocation of the marketing authorisation’ are added to the opinion, as well as any condition for the lifting of the suspension.

In the case where conditions and restrictions regarding the safe and effective use of a MP [foreseen in Article 32(4)(c) and (5)(b) and (c) of Directive 2001/83/EC] are provided, the authorisation should be granted subject to certain conditions, including pharmacovigilance or other recommended conditions or restrictions with regard to the safe and effective use of the medicinal product. The opinion/assessment report of the CHMP should then include justification for the conditions proposed, i.e. timelines to be kept and details of the reports, including the details for the pharmacovigilance (as described in e.g. a risk management plan) reports to be presented to guarantee a sufficient follow-up of the MA.

4.8 Commission Decision and follow up

After the receipt of the final CHMP opinion, the European Commission starts the Community decision-making procedure. Following receipt of an opinion, the EC prepares a draft decision. The EC is assisted by the Standing Committee on Medicinal Products for Human Use (the "Standing Committee"). The Commission will then take a final decision after the end of the Standing Committee phase (for more details, please refer to NtA Chapter 6).

4.8.1 Actions to be taken by the MSs following a referral

Following the completion of a referral procedure and according to Article 34(3) of Directive 2001/83/EC, as amended, the adoption of the binding EC Decision, which is addressed to all MSs, the concerned MSs and the reference MS must either grant or revoke the MA, or vary its terms as necessary to comply with the decision within 30 days of its notification (NtA Chapter 3; CMDh/101/2001/Rev4). For Article 30 and 31 referrals NtA Chapter 7, Section 6 needs to be followed for national implementation. The national competent authorities have to implement any conditions imposed on the MA and to perform necessary subsequent assessments (NtA Chapter 3). They are also required to inform the Commission and the Agency of the measures taken.

In the MSs, who are not directly concerned by a referral procedure, no immediate action is necessary. However, all involved MSs need to take appropriate actions, based on the outcome of the referral procedure, in case of future regulatory activities, e.g. an application for a MA in a particular MS.

4.8.2 Subsequent applications occurring after finalisation of the referral

If subsequent applications for a specific medicinal product, which has been the subject to a referral, are submitted, the harmonisation achieved following the referral must be used as basis (NtA Chapter 3). Following Article 29, 30 and 31 referrals, subsequent applications for the same medicinal product must be submitted through the MRP or DCP (even if the product had been approved previously via national procedures) and must be mutually recognized in accordance with the relevant EC decisions. However, a new referral could be triggered with respect to a new potential serious risk to public health at any time. In accordance with Articles 8(3)(l) and 18 of Directive 2001/83/EC, as amended, the MRP will also apply if the same company, or a company from the same group of companies, applies for a separate marketing authorisation for the product, regardless of whether the product has been the subject of full harmonisation.

In addition, with regard to the Article 30 and Article 31 referrals there are some particularities that are described below (NtA Chapter 3):

- Where the referral leads to harmonisation of e.g. nationally authorised products, the MRP has to be followed afterwards, in order to maintain the achieved harmonisation.
- Where the procedure is limited to certain specific parts of the authorisation, the obligation to follow a MRP only applies if the MAs were granted initially by the DCP or MRP. In this case, the MAs granted through "purely" national procedures stay national. Nevertheless, it is the responsibility of the marketing authorisation holder and the Member State to keep the level of harmonisation reached by the referral procedure.

- In case of an Article 31(2) referral, there may be a large number of products involved. In this case, different reference Member States can be chosen for different medicinal products but the harmonisation should be maintained.
- In the case of Article 30 or Article 31 referrals and where there is no reference MS (i.e. in case of national approvals), the applicant(s)/MAH(s) must choose the reference MS for the follow up of the procedure.

5 Examples of referral procedures

The EMEA website on referrals provides a list of referral opinions that were completed to date. An overview of referral procedures that had a CHMP opinion during 2007 to 2008 is given in Annex 1. For each type of referral (Articles 29, 30, 31, 36(1) and 107) an example is included in this section to illustrate outcomes of the applicable procedure.

5.1 Example of Article 29(4) referral – Ciprofloxacin

Ciprofloxacin is an antibiotic belonging to the quinolone family. The MAH of the "original product" is Bayer. Currently approved indications of Ciprofloxacin Bayer are in adults for the treatment of lower respiratory tract infections due to Gram-negative bacteria, chronic suppurative otitis media, acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria, urinary tract infections, gonococcal uretritis and cervicitis, epididymo-orchitis including cases due to *Neisseria gonorrhoeae*, pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*, infections of the gastro-intestinal tract (e.g. travellers' diarrhoea), intra-abdominal infections, infections of the skin and soft tissue caused by Gram-negative bacteria, malignant external otitis, infections of the bones and joints, treatment of infections in neutropenic patients, prophylaxis of infections in neutropenic patients, prophylaxis of invasive infections due to *Neisseria meningitides*, and inhalation anthrax (post-exposure prophylaxis and curative treatment). In children, the following indications are approved: broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*, complicated urinary tract infections and pyelonephritis, and inhalation anthrax (post-exposure prophylaxis and curative treatment).

The following oral and intravenous formulations are currently approved and marketed in different EU countries:

- Immediate release film-coated tablets: 100 mg, 250 mg, 500 mg, 750 mg
- Granules and solvent for oral suspension: 250 mg/5 ml, 500 mg/5 ml
- Solution for infusion (glass bottles and flexibags): 100 mg/50 ml, 200 mg/100 ml and 400 mg/200 ml
- Modified release film-coated tablets: 500 mg, 1000 mg.
- Sachets: 250mg, 500mg

In 2005, three generic applications were filed with the reference medicinal product Ciprofloxacin Bayer. The generic applications filed were: Ciprofloxacin Kabi, Ciprofloxacin Hikma, and Ciprofloxacin Nycomed. These applications were submitted only for a 200mg/100ml solution for infusion of ciprofloxacin. The authorised indications differed for the three generic applications:

- For Ciprofloxacin Kabi and Ciprofloxacin Hikma, the following indications were approved: complicated urinary tract infections, infections of the lower respiratory tract including pneumonia caused by aerobic gram-negative bacteria, complicated skin and soft tissue infections, and osteomyelitis. Furthermore, Ciprofloxacin Kabi may also be administered in the treatment of acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* in children and adolescents aged 5-17 years with cystic fibrosis.
- For Ciprofloxacin Nycomed, there are more indications approved. They were: pneumonia caused by aerobe gram-negative bacteria, complicated urinary tract infections, prostatitis, bacterial enteritis, skin and soft tissue infections by gram-negative bacteria, osteomyelitis, intra-abdominal infections, and infections in immune-suppressed patients.

Interestingly, there were three Article 29(4) referrals for these generic products (ciprofloxacin 200 mg/100ml solution for infusion) conducted almost simultaneously during 2006 to 2008 initiated by different reference MS (EMEA/CHMP/515890/2006; EMEA/CHMP/75066/2007; EMEA/CHMP/350278/2007). All three referral procedures were started between November 2005 and January 2006, based on the request of the reference MS of each procedure. For all three generic applications, the posology for treatment of urinary tract infections was the basis of the Article 29(4) referral procedure (the recommended dose in urinary tract infections (UTI) and the maximum adult daily dose). The approved posology of Ciprofloxacin Bayer for the treatment of UTI is 400 mg twice to three times a day. From the available information, it seems like the generic applicants proposed a treatment regimen of 100 mg twice daily and 200-400 mg twice or three times daily treatment regimen in relation to complicated and uncomplicated upper and lower urinary tract infections. Of note is that the 100 mg twice daily and the 200 mg twice or three times daily was not approved for Ciprofloxacin Bayer.

The same Rapporteur (Dr Ian Hudson from the United Kingdom) and Co-Rapporteur (Dr Bengt Ljungberg from Sweden) were appointed for the assessment of the three generic products.

Ciprofloxacin Kabi

Ciprofloxacin Kabi 2 mg/ml solution for infusion was approved by the Netherlands (acting as reference MS during the MRP) in September 2005. Following approval by the reference MS, a MRP was initiated by Kabi in December 2005. Concerned MSs were Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Greece, Spain, Finland, Hungary, Italy, Poland, Portugal, Sweden, Slovak Republic and the United Kingdom.

The referral procedure started in June 2006 with the adoption of the list of questions by the CHMP. The MAH was requested to submit:

- Clinical data and discuss the benefit/risk of the proposed dose in UTI, in particular both the 100 mg twice daily (bid) dose and the 200-400 mg bid dose from a safety and efficacy point of view.
- Clinical data and discussion of the risk/benefit of the maximum adult daily dose, i.e. whether it should be 400 mg bid or 400 mg three times daily.

The CHMP agreed to support the recommended posology, based on the review of published clinical studies from the mid 1990's to 2006 provided by the MAH. They also concluded that the data presented provide adequate justification, both from an efficacy and safety viewpoint,

for the dosing regimen of 200-400 mg ciprofloxacin twice daily for the treatment of complicated UTI. In addition, the data had demonstrated a favorable risk/benefit profile for the proposed dose 400 mg i.v. three times daily as a maximum dose.

Therefore, the posology in the agreed SmPC for treatment of adults is 200-400 mg ciprofloxacin twice daily. The administration of 100 mg twice daily was not approved. In case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. The maximum dose is 1200 mg.

During their November 2006 meeting, the CHMP adopted a positive opinion, which was converted into a EC Decision in January 2007.

Ciprofloxacin Hikma

Ciprofloxacin Hikma 2 mg/ml solution for infusion was approved by the Netherlands (acting as reference MS during the MRP) in April 2005. A MRP was initiated in January 2006. Concerned MSs were Austria, Germany, Ireland, Italy, and United Kingdom. The referral procedure was started in July 2006 with the adoption of the list of questions by the CHMP. The points that Hikma had to address during the referral procedure were identical to the ones for Ciprofloxacin Kabi, i.e. the recommended dose in UTI and the maximum adult daily dose. The applicant also provide published data to support their proposed posology. The CHMP gave a positive opinion during their January 2007 meeting, which was converted into an EC Decision in July 2007. The approved posology is: for treatment of adults is 200-400 mg ciprofloxacin twice daily. In case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. The maximum dose is 1200 mg.

Ciprofloxacin Nycomed

Ciprofloxacin Nycomed 2 mg/ml solution for infusion was approved by the reference MS (United Kingdom) in March 2005. A MRP was initiated in November 2005 in the concerned MSs Denmark, Finland, Norway and Sweden. The referral procedure started in June 2006. The basis for the referral to the CHMP was again the proposed dosage regimen for UTI.

A positive opinion was adopted by the CHMP in November 2006. In June 2007, the CHMP adopted a revised opinion in order to focus and facilitate the translations of the specific amendments in the SmPC, which was further reconsidered in October 2007. The final CHMP opinion was then finally converted into a decision by the European Commission in January 2008. The approved posology is again: for treatment of adults is 200-400 mg ciprofloxacin twice daily. In case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. The maximum dose is 1200 mg.

Of note is that the reference medicinal product Ciprofloxacin from Bayer (EMEA/CHMP/384874/2008) was also referred to the CHMP, however on the basis of Article 30 to harmonise the nationally authorised SmPCs, labelling and package leaflet with respect to the indications, posology, contra-indications and special warnings and precautions for use, based on a request from France. It belonged to the list of products identified in 2007 for SmPC harmonisation. The referral procedure was started in July 2007, well after finalisation of the referrals under Article 29(4) for the generic ciprofloxacins. The CHMP gave their positive opinion in July 2008 with an EC Decision in October 2008. This procedure

led to the withdrawal of some indications, some revisions in the posology section and other sections of the SmPC. It is interesting to see that for the solution for injection to be used in urinary tract infections, 400 mg twice to three times a day are the approved dosages, which is not totally in line with the generic products approved in this indication.

For all three generic products, harmonisation of the SmPC was achieved with regard to the posology for treatment of UTI not only in the MSs that were part of the MRP, but also across all three products. The time needed for the referral procedure varied significantly: From the start of the procedure to the EC Decision the procedure took 7 months for Ciprofloxacin Kabi, 12 months for Ciprofloxacin Hikma and 18 months for Ciprofloxacin Nycomed. The reason for this huge difference in timelines are not obvious from the available information but might have been due to the different clock-stop time needed by the companies to address the list of questions. A further reason for the long review timelines of Ciprofloxacin Nycomed could be that this company had applied for more indications as compared to the other two companies.

5.2 Example of Article 30 referral – Risperdal

Risperdal (INN risperidone) and associated names is an antipsychotic, indicated for the treatment of schizophrenia, manic episodes associated with bipolar disorders, persistent aggression in patients with moderate to severe Alzheimer's dementia and treatment of persistent aggression in conduct disorder in children. Risperdal was originally approved via national procedures in different MSs.

Risperdal was included in the list of products identified in 2007 for SmPC harmonisation by the EC and was referred to the EMEA/CHMP in July 2007 under Article 30(2) of Directive 2001/83/EC, as amended. The purpose was to harmonise the nationally authorised SmPCs, labelling and package leaflets as there were divergences in the SmPCs approved across MSs, with respect to the indications, posology and method of administration, contra-indications, special warnings and precautions for use and interaction with other medicinal products and other forms of interaction. The referral included Risperdal and associated names for oral use and Risperdal Consta and associated names for intramuscular use, both from the MAH Janssen-Cilag.

The procedure started in September 2007. The MAH provided supplementary information in January 2008 and April 2008. The CHMP gave a positive opinion in July 2008 and recommended the harmonisation of the SmPC, labelling and package leaflet. The EC decision was issued in October 2008.

Based on the scientific conclusions available from this referral procedure (EMEA/CHMP/384877/2008), it seems like the CHMP has done an overall assessment of available data in the different indications including posology and any potential interactions. They recommended various changes for the SmPC. It also seems like the MAH was given the opportunity to propose harmonised language for the SmPC, labelling and package leaflet, which was then assessed by the CHMP. Following this assessment, several SmPC changes were recommended and implemented by the MAH:

<u>Schizophrenia:</u>

- Physicians are to individualise treatment and use the lowest efficacious dose for each patient.

- Data in elderly patients were limited but a lower starting dose with a more conservative dose titration than in younger adults is recommended.

Manic episodes associated with bipolar disorders:

- Based on safety and efficacy data, the starting dose was to be restricted to 2 mg for the first day in bipolar mania.
- Submitted efficacy data demonstrated that over the recommended dose range 1 to 6 mg/day, some patients could effectively be treated at doses in the lower end of this dose range.
- Due to low number of elderly patients available, the CHMP did not consider it justified to treat elderly with bipolar mania with the posology recommended in adults and concluded that the upper limit of the dosage was to be restricted.
- Based on assessment of data submitted in the treatment of mild forms of mania, the CHMP recommended to restrict the indication to the treatment of patients with moderate to severe manic episodes associated with bipolar disorders only.

Severe aggression in Alzheimer's Dementia:

- The CHMP decided to restrict the duration of the short-term therapy to 6 weeks due to safety considerations.
- The rating scales regarding the qualification of "severe aggression" were not practical in the clinical settings. The most important clinical criteria to be met before treatment initiation is that the aggression places the person or carer at risk of harm. Therefore, the indication section needed to be amended.
- The efficacy in Alzheimer's dementia was similar compared to efficacy in vascular/mixed dementias and patients with severe aggression in vascular/mixed dementias are to be excluded from treatment with the product because of safety concerns. Therefore, the indication section was limited to Alzheimer's dementia only and several warning statements were included in the SmPC regarding the magnitude of the risk of cerebrovascular adverse events in patients with vascular/mixed dementias.
- The CHMP was of the opinion that the current weight of evidence support a favorable benefit/risk ratio in this restricted patient population indication of persistent aggression in Alzheimer's dementia for short-term treatment only (6 weeks) and with all restrictions and conditions as indicated in the SmPC.

Severe aggression in children/adolescents with conduct disorder

- The safety profile in children/adolescents was assessed, in particular any evidence of regression in sexual maturation. Based on this assessment, the CHMP was of the opinion that while regression of sexual maturation was not supported, the SmPC stated that "the effects of long-term treatment on sexual maturation and height have not been adequately studied" and as a consequence, the sentence "Treatment with risperdone for up to 1 year showed not adverse effects on sexual maturation" in section 4.4 (Special warnings and precautions for use) was to be deleted.
- Based on the assessment of the "Relapse Prevention Study", treatment should be restricted to short-term treatment (6 weeks instead of 12 weeks) as the safety profile in children/adolescents appeared to be worse than in adults.

- The controlled trials were predominantly conducted in children with borderline IQ or mental retardation. Therefore, according to the safety profile in children, the indication should not have been expanded to children and adolescents with normal IQ, since due to structural differences between the brains of children and adolescents with normal IQ and those with mental retardation, it could not be assumed that the response to antipsychotic medication would be the same in the two populations.
- The efficacy in children and adolescents with autistic disorders was also discussed with the consequence that this patient population was to be excluded in the proposed indication.

Other changes to the SmPC:

- For section 4.2 (Posology and method of adminstration): Risperdone was not to be recommended for use in children/adolescents under 18 years of age with schizophrenia or with bipolar mania, due to lack of systemic efficacy/safety and clinical data for this age group.
- For section 4.4 (Special warnings and precautions for use): Revised wording for hyperprolactinaemia and statement on the risk in elderly patients with dementia treated concomitantly with furosemide and risperidone. In addition, a number of revisions in the subsection on children and adolescents were needed.
- For section 4.5 (Interaction with other medicinal products and other forms of interaction): Harmonisation of wording on interactions with other medicinal products and food.
- For section 4.8 (Undesirable effects): The text was completely revised, taking into account new adverse events and revisions of the groupings of terms of adverse events.

The CHMP made an overall assessment of available data relevant to the grounds of the referral, i.e. the indications, posology, special warnings and precautions for use, interactions and undesirable effects. Based on this assessment and the implementation of major revisions of the relevant sections in the SmPC, labelling, package leaflet, the CHMP was of the opinion that harmonisation of product information was achieved. The MAH had agreed to commit to certain conditions of Marketing Authorisation, i.e. to collect long-term data for the evaluation of long-term safety of risperidone in children and adolescents with conduct disorder in terms of potential effects on growth (height and weight), mental development and sexual maturation. The MAH also agreed to make a proposal as to how it would be possible to assess effects on cognitive development.

Overall, this referral procedure led to major revisions of key sections of the product information, applicable to all related products and further pharmacovigilance actions had to be implemented, but harmonised only the prescribing information of the reviewed sections in the countries where the product is approved. The quality sections were not part of the harmonisation and there are still different pharmaceutical forms and dosage strengths available in different MSs. The procedure took 13 months from initiation to EC decision. One could imagine that there were quite long clock-stops, possibly due to the overall assessment and the need to provide all available data. Most likely, the MAH did not plan for this resource intensive harmonisation activity and needed time to pull together the resources and available documentation to support this procedure.

5.3 Example of Article 31 referral – Agreal (veralipride)

Veralipride 100 mg hard capsules was registered since 1979 for the treatment of vasomotor symptoms (hot flushes) associated with menopause. Veralipride is a neuroleptic and works by blocking the activity of the neurotransmitter dopamine (EMEA/299468/2007).

The product was originally nationally authorised in 6 MSs: Belgium, France, Italy, Luxembourg, Portugal and in Spain (EMEA/CHMP/432352/2007).

Following reports of serious side effects affecting the nervous system, the Spanish Health Authority reviewed the safety and effectiveness of the product and concluded that its benefits did not outweigh its risks. Therefore, the Spanish HA withdrew the MA in June 2005. This led to a number of regulatory actions in other countries where the product was authorised, including changes to the product information in order to reduce the risk of patients developing side effects (EMEA/299468/2007, CHMP/309507/2007).

Following this withdrawal in Spain, the regulatory actions and the notification of the EC, the EC referred the matter to the EMEA/CHMP under Article 31 of Directive 2001/83/EC in September 2006, who then started the referral procedure. Written explanations were provided by the MAH in January 2007. An oral explanation was held in June 2007. In July 2007, the CHMP recommended the withdrawal of the MA for all medicinal products containing veralipride based on a negative benefit/risk profile. The final opinion was then converted into a decision by the EC in October 2007 (EMEA/CHMP/432352/2007, EMEA/299468/2007, CHMP/309507/2007), after more than 2 years of the initial withdrawal in Spain in June 2005.

For their assessment, the CHMP reviewed all available information on safety and efficacy of veralipride. The review of efficacy included mainly 11 studies that involved 600 women, in which veralipride was compared to placebo and two studies in approximately 100 women where it was compared to conjugated oestrogens. In addition, other small studies were assessed. Based on these data, the CHMP concluded that the data submitted showed only limited effect of veralipride in the treatment of vasomotor symptoms associated with menopause. Due to methodological shortcomings and the too short duration of the trials, the effect size could not have been accurately quantified to allow a proper assessment of efficacy.

For the safety assessment, the 27-year post-marketing experience provided a long-term safety profile that was reviewed by the CHMP. The following events were of concern:

- Neurological adverse events (extrapyramidal symptoms and tardive dyskinesia) had been reported and were considered to present a real concern due to their potential seriousness and irreversibility. Tardive dyskinesia was not predictable and could develop even following discontinuation of treatment. In order to address these safety concerns, the MAH had proposed a change to the SmPC to limit the maximal treatment duration to 3 months. However, there was a concern that tardive dyskinesias had also been reported within the first 3 months of treatment.
- There had also been reports on depression and anxiety mostly occurring beyond 3 months of treatment but it was concluded that the role of veralipride on these events was not always clear.
- Other concerns regarding the safety profile included events related with the blockage of the dopamine receptor, especially hyperprolactinemia. Although veralipride was contraindicated in patients with prolactin-dependent tumors, the effect of

hyperprolactinemia in women with a history of breast cancer was not elucidated. The MAH proposed an intermittent treatment of 20 days, followed by a 10 day period of non-treatment. However the CHMP was not convinced that this measure would have had any effect on the adverse event pattern.

- Although QT-prolongation is a known class-effect of dopamine-antagonists, the data did not show any such effect. No studies had been performed to evaluate any potential effect on the QT interval. This was regarded as insufficient to conclude that QT-prolongation would not occur with veralipride.

In order to address these findings, the MAH had proposed several changes to the SmPC to limit the risks:

- Restriction of treatment duration to 3 months and monthly examination to limit the psychiatric and neurological adverse events.
- Introduction of contraindications in patients with Parkinson's disease, or in combination with other neuroleptics and dopaminergic agonists.
- Introduction of warnings regarding class effects of neuroleptic medicines and withdrawal symptoms such as anxiety and depressive syndrome.
- Recommendation of medical breast monitoring and intermittent schedule to reduce the risk of hyperprolactinemia, aimed to improve 'breast safety'.

At the end of this lengthy procedure, the CHMP was of the opinion that the restriction to limit the use to 3 months in combination with monthly medical neurological examinations and breast monitoring as well as the proposed warnings and contraindications were not adequate to limit the risk of all adverse effects reported, especially as some side effects could also occur when therapy was stopped. Therefore, based on the action taken by one EU MS and the assessment of all available data, the CHMP concluded that the benefit/risk balance was negative under normal conditions of use and recommended the withdrawal of the MA in all MSs, a recommendation which was followed by the EC in their decision.

5.4 Example of Article 36(1) referral – Gadograf / Gardovist

Only one referral procedure falling under the scope of Article 36(1) was ongoing during 2007 and 2008. The product reviewed during the referral was Gadograf/Gadovist. It contains gadobutrol, a neutral macrocyclic gadolinium complex with contrast-enhancing properties, used for magnetic resonance imaging (MRI). Gadograf-based contrast agents are frequently administered prior to contrast-enhanced dynamic liver MRI to improve detection and classification of focal liver lesions.

Gadograf/Gadovist was approved in January 2000 in Germany and in June 2000 via MRP in the EU and Norway for "contrast enhancement in cranial and spinal magnetic resonance imaging" (EMEA/508212/2007). There was a label extension in November 2003 to include the indication "contrast-enhanced magnetic resonance angiography".

In June 2005, a MRP was started for a type II variation to add the indication *"contrast enhanced MRI of other body regions: liver, kidney"* and posology and method of administration/dosage: *"CE-MRI of other body regions: The recommended dose for adults is*

0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution".

The MRP was finalised in May 2006 with the approval of the proposed indication and inclusion of the imaging study results into the SmPC/labelling/PL. After the approval, the Spanish Health Authority raised a major objection related to the wording of the indication. The reason was that the approved indication neither reflected the population studied in the two pivotal studies nor the clinical context for which Gadograf/Gardovist had demonstrated to have the same diagnostic accuracy than its comparator. Therefore, the Spanish Health Authority initiated a referral to the CHMP.

The referral procedure was started in May 2006 with the adoption of a list of questions. The CHMP made several proposals for revision of the SmPC. In addition, the applicant was asked to address the following issues:

- The current indication did neither reflect the studied patient population in the two pivotal studies nor the clinical context for which the product had demonstrated to have the same diagnostic accuracy than its comparator. As only patients with high suspicion or evidence of having a focal disease of liver of kidney obtained by other diagnostic tests or histopathology were included in the pivotal studies, the indication had to reflect the studied population.
- The requested indication was not to be approved for paediatric population since there were no efficacy and safety data available. This information needed to be included in the SmPC/PL.
- The MAH was requested to provide information on clinical utility of the product for the requested indication according to the Points to Consider on the evaluation of diagnostic agents.

The MAH provided the responses to the questions in September 2006 and additional supplementary information in November 2006. Also, the MAH agreed to the proposed changes of the SmPC by the CHMP. The indication section was updated to read *"Contrast enhanced MRI of liver and kidney in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant"*. The posology section was updated to read *"Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety."* Therefore, the prescribing information now includes only the population studied, which is in line with the concerns initially raised by the Spanish Health Authority. Based on these changes to the SmPC and the additional data provided, the CHMP adopted a positive opinion. The EC decided on this case in April 2007.

All in all, following a thorough assessment, the procedure took 11 months to complete and led to the amendment of the prescribing information originally approved via a type II variation.

5.5 Example of Article 107 referral – lumiracoxib-containing medicinal products

Lumiracoxib was a non-steroidal anti-inflammatory drug (NSAID) belonging to the group of selective cyclooxygenase-2 inhibitors (COX-2), indicated for symptomatic relief in the treatment of osteoarthritis of the knee and hip. Other COX-2 inhibitors that were approved at some stage included celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib. They had

been introduced in medical practice for treatment of patients with chronic inflammatory degenerative diseases such as rheumatoid arthritis and osteoarthritis.

Medicinal products containing 100 mg lumiracoxib were authorised in the United Kingdom in 2003 and were authorised in a number of EU Member States via mutual recognition. They were available under the invented names Frexocel, Hirzia, Prexige and Stellige as film-coated tablets for oral administration (EMEA/CHMP/579301/2007).

In September 2004, the MAH of rofecoxib informed the EMEA that new clinical trial data for rofecoxib had revealed a risk of thrombotic cardiovascular events. These data resulted in the worldwide withdrawal of rofecoxib (Vioxx®) from the market on 30 September 2004 by the MAH and raised questions regarding the cardiovascular safety of other COX-2 inhibitors (EMEA/CHMP/324332/2005).

Further to discussions at the CHMP in October 2004, the EC recommended that this public health issue on all aspects of cardiovascular safety including thrombotic events and cardio-renal events should be the subject of Community referrals under Article 31 of Directive 2001/83/EC, as amended, regarding decentrally authorised products containing celecoxib, etoricoxib and lumiracoxib and subject to a review procedure under Article 18 of Council Regulation (EEC) No 2309/93, as amended, regarding the centrally authorised products containing celecoxib (Onsenal®), parecoxib (Dynastat®/Rayzon®) and valdecoxib (Bextra®/Valdyn®). These review procedures were started in November 2004 with a request for comprehensive cardiovascular safety information for these products.

In April 2005, the United States Food and Drug Administration and the EMEA requested Pfizer to voluntarily withdraw Bextra (valdecoxib) from the market. Pfizer agreed to suspend sales and marketing of Bextra worldwide pending further discussions on the unfavorable risk versus benefit due to data on serious skin reactions.

Pfizer presented data on serious skin reactions for valdecoxib during a hearing. Therefore, in April 2005 further to a request from the EC, the CHMP broadened the scope of the procedure under Article 31 of Directive 2001/83/EC, as amended, to include the assessment of serious skin reactions in the ongoing class review in addition to the cardiovascular safety aspects.

The MAH of lumiracoxib provided written explanations in January and May 2005. Upon consideration of all available data, the CHMP adopted an opinion for lumiracoxib in June 2005, recommending the maintenance of the MA for lumiracoxib containing medicinal products. The EC adopted their opinion based on this opinion in November 2005.

In August 2007, the product information of lumiracoxib-containing medicinal products was updated to minimise any potential risk with contraindications for patients with potential liver problems and advice to doctors that they should frequently monitor patients treated with lumiracoxib for liver reactions.

On 9 November 2007, the United Kingdom Competent Authority (Medicines and Healthcare products Regulatory Agency, MHRA) issued a Rapid Alert informing the Member States, the EMEA and the EC in accordance with Article 107 of Directive 2001/83/EC, as amended, of their intention to suspend the MAs for lumiracoxib containing medicinal products in its territory. In its assessment the MHRA concluded that lumiracoxib at the 100 mg dose was associated with an increased risk of hepatotoxicity.

On 15 November 2007, an Europe-wide review of the safety of lumiracoxib-containing medicines was started following assessment of reports of serious liver injury by the United Kingdom. The CHMP was asked to give a scientific opinion on whether the marketing authorisations for lumiracoxib should be withdrawn, suspended or changed across the EU.

On 19 November 2007 the United Kingdom suspended the marketing authorisation of this medicinal product. Similar regulatory action was taken in Germany, Cyprus and Belgium. The liver safety of lumiracoxib had been monitored continuously since its launch in 2005.

The CHMP considered that the proposed measures to reduce the risk for liver reactions (contraindications for patients with potential liver problems, restriction of pack size to 2 weeks of treatment, the implementation of a treatment registry, and a long-term epidemiological cohort study) could not assure adequate patient safety, and were not considered realistic, given the approved clinical indication. Consequently, the CHMP recommended the withdrawal of the marketing authorisations in December 2007, only one month after the MHRA had issued their Rapid Alert, leading to the Article 107 referral.

It seems like an Article 107 referral can be a very quick procedure with an outcome within about 1 month. However, in the example provided, the Article 107 referral was preceded by an Article 31 referral, initiated in 2004 for COX-2 inhibitors, based on cardiovascular findings. The Article 31 referral took 13 months to EC decision. Therefore, previous assessment and harmonisation steps already took place to further ensure the safety of the patients. It could well be that the new safety findings regarding potential liver problems added to the earlier identified concerns, which were still regarded manageable based on available data and through the prescribing information, and finally, led to withdrawal due to overall major concerns.

6 Discussion

The referral procedure based on Directive 2001/83/EC, as amended, is applicable within the European Union to resolve disagreement and to address serious concerns related to medicinal products during a MRP/DCP and also for marketed products by an additional independent scientific assessment via the CHMP. Further to the opinion adopted by the CHMP the EC decides on the particular case. The EC decision is binding to all MSs. Therefore, the general purpose of the referral procedure is to reach and maintain harmonisation and thus free trade, as well as to safeguard public health in the EU/EEA.

How well does this procedure work and what is its impact?

6.1 Article 29(4)

If the MSs involved in an assessment of a new medicinal product via MRP/DCP fail to reach an agreement on the assessment report of a complete dossier, SmPC, labelling and package leaflet within 60 days in the CMD(h) procedure based on a potential serious risk to public health concern raised by one or more MSs (see section 3.1 of this thesis), a referral according to Article 29(4) is triggered by the reference MS. Therefore, Article 29(4) provides for a mechanism to resolve disagreement between MSs by the CHMP, not resolvable at the CMD(h), followed by a binding EC decision, and to reach full harmonisation of the SmPC, labelling and package leaflet based on a complete dossier (i.e. all Modules) within the

reference and concerned MSs prior to authorisation and thus avoiding disparities with the EU/EEA.

Article 29(4) referrals are initiated based on a potential serious risk to public health concern of a concerned MS prior to authorisation. Therefore, once such a referral procedure has been started, the authorisation of the particular medicinal product will be delayed in all concerned MSs until the referral procedure has been finalised (unless the applicant withdraws the application in all EU/EEA MSs). The company could however market the product in the reference MS but would have to change the prescribing information or even withdraw the product from the market, depending on the outcome of the referral procedure.

The examples described in section 5.1 of this thesis demonstrate that the posology for urinary tract infection for the three generic products reviewed in an Article 29(4) referral procedure was agreed to by the MSs involved and was harmonised even amongst the products. Therefore, the referral process worked well in this case. It was interesting to note that for the generic products the posology allows for additional daily doses when compared to the reference medicinal product: For the generic products, the approved posology for treatment of adults is 200-400 mg ciprofloxacin twice daily and in case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. For the reference medicinal product it is 400 mg twice to three times a day. It remains unclear why the posology for UTI was not adjusted across the EU for all ciprofloxacins as part of the referral procedures, especially as the originator product was part of an Article 30 referral.

Since the implementation of Directive 2001/83/EC, there were a total of 51 referrals under Article 29(4) basically all initiated by a MS. Of those, 32 were generic products (63%) (EMEA website on referrals, accessed on 27 July 2009). For the concerned MSs involved in a MRP or DCP, the Article 29(4) referral procedure provides a tool to raise their concerns even if the reference MS issued a favorable opinion and allowed the authorisation of the product in its territory. It is then followed by an additional, independent thorough assessment by the CHMP, which could give the MS, who had raised the concern, more comfort with the product as their particular issue will be specifically reviewed. In the examples of Ciprofloxacin, provided in section 5.1, the outcome was that the lowest dose proposed (100 mg) was not regarded as being acceptable on the European level although the reference MS had already allowed the placing of the product on their territory with the lowest dose.

For the authorisation of generic products, bioequivalence studies need to be conduct as part of the development, to waive full clinical development. For some of the generic products included in an Article 29(4) referral procedure (see Annex 1), the concern was that bioequivalence was not proven. Bioequivalence data are the only clinical data provided in the dossier, supporting the generic approach. Therefore, if bioequivalence is not shown, the whole comparability of the generic product to the reference medicinal product can be put into question and is certainly a good reason for a MS to raise a potential serious risk to public health concern, if the originator is supposed to be substituted by a less expensive generic in their territory.

Another reason for the high number of generic products involved in an Article 29(4) referral could be that medicinal products used as reference for generic applications can have different prescribing information approved in different MSs, e.g. different indications, posologies, pharmaceutical forms etc. For generic companies such differences have an impact on the

dossier and the prescribing information to be referred to, as for a DCP they in principle would use the smallest common denominator for these sections of the prescribing information to gain fast market access. If a generic company decides to expand the smallest common denominator to other indications or posologies approved for the originator product in some but not all MSs, then it can easily be imagined that this could lead to an Article 29(4) referral from a MS not having a certain indication approved due to concerns related to a potential serious risk to public health concern. As an outcome of the referral, the generic company may either have to restrict the prescribing information based on the smallest common denominator or in best case, could have the possibility to expand their prescribing information to indications not approved for the originator in a particular MS. Therefore, an Article 29(4) referral could be of advantage to generic companies, when they can have a broader prescribing information approved in more MSs as compared to the originator product, as shown in the examples presented in section 5.1, and can have an expanded market share.

In the examples provided in section 5.1 the EC Decision for the generic products with revised SmPCs, labelling and package leaflets took between 7 and 18 months from initiation. The average timelines from initiation of the referral procedure to EC decision in the examples given for Article 29(4) referrals in Annex 1 was 8.7 months (4-18 months). It seems like there were very lengthy clock-stops needed during the 60 days active review time procedure (see section 4.5) to provide the required data and to finally bring the products to the markets. However two basic principles of Directive 2001/83/EC, as amended, were fulfilled, i.e. to safeguard public health and to avoid differences in the prescribing information at the time of authorisation that would hinder the free trade between MSs in the EU.

6.2 Article 30(1) and (2)

Article 30(1) provides for a mechanism to resolve divergent decisions taken during the authorisation, suspension or withdrawal of a particular medicinal product. Article 30(2) is applicable to products laid down on a list of products to be harmonised by the CMD(h) following endorsement by the EC.

For the medicinal products for which a referral procedure according to Articles 30(1) or 30(2) have been performed during 2007 and 2008, this procedure was initiated for nine products by the EC, for three products by a MS and for four products by a MAH (see Annex 1).

In the example given in section 5.2, the product was added to the list of products to be harmonised by the EC, i.e. falling under the scope of Article 30(2). It took 13 months from the initiation of the referral procedure to its finalization. These timelines are in line with the average of the Article 30 referral procedures during 2007 and 2008, which was 14 months from initiation to EC Decision (see Annex 1). These lengthy clock stops are due to the time needed by the MAH to address the questions raised.

When the grounds for Article 30 referrals are reviewed, as provided in section 5.2 and Annex 1, it becomes obvious that the main drivers for referrals are related to the indication, posology, method of administration, contraindications, and special warnings and precautions for use sections of the product information, i.e., mainly related to clinical concerns. Therefore, as an outcome of an Article 30 referral, the clinical sections of the SmPC, labelling and package leaflet are harmonised but the sections related to e.g. quality are not. This was also the case for Risperdal, described in section 5.2. Different pharmaceutical forms and dosage strengths

are still available in different MSs. In the examples reviewed in Annex 1, there was no case where the pre-clinical information raised a concern and it is highly unlikely that different pre-clinical information is included in the approved prescribing information and dossiers in different MSs. The reason could be that as such development is performed at an early stage and once all necessary data available, there will hardly ever be any further pre-clinical development. As a consequence of a referral under Article 30, only partial harmonisation of a particular medicinal product is achieved (i.e. Modules 4 and 5 and relevant prescribing information). If full harmonisation is wished, the MAH would have to first generate a harmonised dossier considering all aspects, e.g. whether different pharmaceutical forms or dosage strengths are available in various MSs. Then a harmonised dossier, including an updated Module 3 (e.g. for specific pharmaceutical forms and dosage strengths) would have to be generated, and in a second step, full harmonisation could be achieved by applying for a variation of the MA.

Overall, since 2002, forty Article 30 referrals have been completed (EMEA website on referrals). There were five with a publication date in 2002, four in 2003, seven in 2004, one in 2005, five in 2006, one in 2007, twelve in 2008 and five in 2009 (up to 27 July 2009) The number was relatively low following implementation of the amendment of Directive 2001/83/EC and has drastically increased during the last years. The initiation of an Article 30 referral can occur with different motivations as it can be initiated by either the MAH, a MS or the EC and the trigger for starting such referral varies:

For a MAH, a reason for harmonisation could be to facilitate activities around any planned variations to the MA so that only one dossier instead of several dossiers would have to be updated and maintained. Another reason could be found in Article 36(3) of the Paediatrics Regulation (EC) No 1901/2006 as the reward of a six months extension of the Supplementary Protection Certificate only applies when a product falling under the scope of Directive 2001/83/EC is approved in all MSs. Therefore, following the harmonisation of a particular product, a MAH could more easily apply for approval of the product in the MSs where so far no MA was available and then in a second step request the paediatric reward following completion of the paediatric studies according to an agreed Paediatric Investigational Plan (and no complete waiver was granted for the product).

For the MSs and EC, a harmonised product information for an originator product expected to be used as reference medicinal product for generic applications, could facilitate the review and approval of future generic products with identical prescribing information to the reference medicinal product. In addition, generics with identical prescribing information to their reference medicinal product will have a positive impact on the Health Insurance System by reducing costs and therefore, MSs could benefit from early availability of generic products. One could therefore even speculate that possibly originator products are placed on the list of products to be harmonised based on anticipated patent expiry time. This could be one potential reason for the increase of the number of article 30 referrals, including blockbusters like Cozaar® and Diovan®.

In summary, Article 30 referrals can lead to partial harmonisation. Further actions are required to achieve full harmonisation. As a first step it is expected that harmonisation is reached, mainly on clinical sections of the prescribing information. Therefore, follow up steps will be needed in order to further harmonise the product. Following complete harmonisation,

the MAH has the advantage to have only a single dossier to update and maintain. Additionally, a harmonised product dossier can form the basis to apply for approval in all MSs, and once completed and approval has been achieved, will fulfill one condition to get a reward (6-month extension of the Supplementary Protection Certificate) based on paediatric development. For generic companies, the harmonised prescribing information of the reference medicinal product can facilitate any further generic applications to allow generic companies to apply for similar product information as for the originator without any constrains in e.g. the indication section. As a consequence, following approval of generic products, they can be more easily used by Health Insurance Systems to substitute for original medicinal products because the only obvious difference between the medicinal products would then be the price. Therefore, one could assume that another purpose for the referrals falling under the scope of Article 30 might be linked to economical reasons to achieve cost containment in the EU MSs.

6.3 Article 31

An Article 31 referral provides for a mechanism to raise any concerns (i.e. quality, efficacy/safety or pharmacovigilance activities) that could affect the Community interest, i.e. interest of the public health in the Community. Whereas Article 31(1) relates to a specific medicinal product, an Article 31(2) referral can be started for a whole class of medicinal products.

The example given in section 5.3 is related to the benefit/risk of a particular product. It was started based on a concern raised by a single MS and led to an EU-wide action, i.e. withdrawal. It took 13 months from the start of the referral procedure to the EC Decision and it took more than two years from the initial withdrawal of the product in one MS to the EC Decision binding to all MSs. The examples listed in Annex 1 support this information: For all the products that went through an Article 31 referral during 2007 and 2008, it took more than 1 year from the start to the EC Decision. Therefore, a referral using this Article 31 procedure is quite lengthy, in particular considering the fact that the reason for the referral is a specific health concern regarded to have an EU wide impact. One of the reasons for the long duration could be that such referral procedure would be initiated without having planned for it both at the Health Authorities but also at the pharmaceutical companies level. Data collection, analysis and preparing adequate responses to address any concerns usually take time. Therefore, the turn around time of any possible questions could be longer than expected. It appears likely that the safety concern is regarded as not being serious, and thus not warranting immediate action but rather further analysis and observation.

From the list of Article 31 referrals given in Annex 1 it seems like one product fell under the scope of Article 31(2) – a class referral. As such class referral affects several pharmaceutical companies, they would have to collaborate quite closely, which could be difficult due to the coordination needed and due to any conflicts of interest. Also, as a class of products could be affected, Article 31(2) stipulates that such a procedure could be limited to certain specific parts of the authorisation, and therefore only partial harmonisation would be reached for e.g. a particular indication or safety concern but the remaining SmPC, labelling, package leaflet of the products would still be different.

Upon review of the reasons for referrals under Article 31 in Annex 1, it becomes clear that in basically all cases, the referral was linked to available safety information, which impacted on

the prescribing information. Therefore, like an Article 30 referral, an Article 31 referral leads to partial harmonisation, i.e. the clinical information only.

Both Articles 31 and 107 address safety concerns of European-wide interest to protect public health. In the latter case, one MS can take unilateral action and the matter will in any case be ultimately discussed at the CHMP, as for Article 31. One could wonder whether the applicability of the two Articles depend on the safety concern, which could be regarded as serious or less serious.

In the "Proposal for a Directive of the European Parliament and of the council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use" published in December 2008 by the EC, it is foreseen to amend Article 31(1). The first subparagraph of this article should be replaced by the following: "*The Member States or the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary.*" And the following subparagraph is inserted: "*However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107l shall apply.*" In the proposal for amendment of Directive 2001/83/EC, the criteria for a MS to initiate an Article 107i-l referral procedure are fulfilled when:

a. it considers suspending or revoking of a marketing authorisation;

b. it considers prohibiting the supply of a medicinal product;

c. it considers refusing the renewal of a marketing authorisation;

d. it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or withdrawn a marketing authorisation, or that he intends to do so;

e. it considers that new contraindications, a reduction in the recommended dose, or a restriction to the indications is necessary;

f. it has conducted a pharmacovigilance inspection and found serious deficiencies.

In the proposed procedure laid down in Article 107i-l (that will apply instead of the currently applicable Article 107 procedure) it is described that a new Committee, the "Pharmacovigilance Risk Assessment Advisory Committee" (PRAAC) is to be established to assess the safety matter. This Committee is intended to be part of the EMEA and should play a key role in the pharmacovigilance assessments in the Community, by providing support both to the CHMP and the CMD(h). In addition, there is the possibility that public hearings may be considered. Therefore, the assessments made by the CHMP will be supported by the PRAAC.

This new proposal to amend Directive 2001/83/EC should help to further clarify the scope of Article 31 and Article 107.

6.4 Article 36(1)

An Article 36(1) referral provides for a mechanism to resolve any post-harmonisation divergences that may arise between MSs. It can be triggered by a MS when it considers that a

variation, suspension or withdrawal of a harmonised Marketing Authorisation is necessary for the protection of public health.

In the example provided in section 5.4, it was interesting to see that the referral procedure was started immediately after completion of the MRP for a type II variation to expand the indication of the medicinal product, by one national competent authority based on the approved indication wording. One would have thought that such concern would have been considered during the MRP rather than directly following approval of the type II variation. The referral procedure took 11 months from initiation to EC Decision. It is not obvious from the information available for Gadograf/Gadovist, why the national competent authority acted in such way, however it seems like this Article 36(1) provides a last resort for MSs in case of disagreement to sort out issues following post-approval changes.

Upon review of the Article 36(1) referral procedures during 2007 and 2008, such referrals are rarely used. There was only one referral procedure completed within this period. On the EMEA website on referrals a total of four Article 36(1) referrals are listed with three of them published in 2002. It is not clear why this number is so low in comparison to the other referral procedures. Possibly, the referral to the CMD(h) and a resolution of any concerns of a MS at this instance prior to the referral to the CHMP could be a reason for the low number. In the "Proposal for a Directive of the European Parliament and of the council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use" published in December 2008 the following subparagraph is proposed to be added to Article 36(1): "*However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107l shall apply*" [see section 6.3 for the criteria listed in Article 107i(1)]. This amendment should help to clarify the scope of the different referral procedures.

6.5 Article 107

Article 107 of Directive 2001/83/EC, as amended, provides for a fast mechanism to react to serious concerns related to the protection of public health from a medicinal product and to obtain an EU wide resolution on such concern within a very short time frame. This article also allows individual MSs to even take unilateral measures to e.g. suspend a product from the market. However, this action will always be followed by an European-wide decision following CHMP review.

To date, there were only six Article 107 referrals conducted, five in 2007 and one in 2008 (see Annex 1). Based on available data, it can be concluded that for the products that were assessed via an Article 107 referral, safety signals were already detected earlier. In the case of lumiracoxib, cardiac concerns had been identified. For other products e.g. available literature data showed a certain signal, which upon follow up proved to be correct and indeed raised a safety concern. Based on these available safety findings, it is useful to have a legal basis available for very fast action from start to opinion date to protect public health in the EU in certain cases. Reviewing the outcome of the procedures in Annex 1, all products were suspended from the market, except for one. In the one case where the medicinal product was not suspended from the market further pharmacovigilance actions were required to be taken by the MAH.

The “Proposal for a Directive of the European Parliament and of the council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use” published in December 2008 provides in Article 107i-l much more guidance on this type of referral, e.g. criteria when a referral can be started, responsibilities of review, timelines and transparency throughout the discussion, including involvement of the public (see also section 6.4). In addition, the scope of Article 107 referrals is clarified further and is even expanded to include products approved via the Centralised Procedure, falling within the scope of Regulation (EC) 726/2004.

7 Conclusions and outlook

Directive 2001/83/EC, as amended, lays down the Community code relating to medicinal products for human use and as stated in its introduction, supports the Treaty establishing the European Community. The aim is to govern the production, distribution and use of medicinal products and to safeguard public health [Directive 2001/83/EC, as amended (2)]. The Directive also is regarded as representing an important step towards achievement of the objective of the free movement of medicinal products in the EU [Directive 2001/83/EC, as amended (14)].

Further to the review of the available articles related to referral procedures within Directive 2001/83/EC, as amended, and some examples, it can be concluded that a procedure has been put in place in the EU/EEA that is used successfully to resolve any disagreement between MSs, applicants/MAHs, and the EC and to address any serious public health concerns about a particular product or a class of products prior to authorisation or post-authorisation. This is achieved by an independent scientific evaluation of available data by the CHMP, followed by an EC Decision, binding to all MSs. As an outcome of a referral procedure, the prescribing information is either harmonised by amending it to include e.g. more safety information, or the product is suspended or revoked. Therefore, these referral procedures support the basis of Directive 2001/83/EC to safeguard public health and to ensure free trade in the EU.

The available referral categories can lead to partial or full harmonisation of the prescribing information. Only an Article 29(4) referral will lead directly to full harmonisation of a medicinal product. The reason is that a full dossier including the quality, non-clinical and clinical information is being assessed in a MRP/DCP and the EC Decision is binding for all MSs. In case of partial harmonisation of the clinical information only (mainly under Article 30 and 31), it could be advisable to MAHs to harmonise their dossiers following completion of the referral in order to keep a harmonised product dossier including the quality information for any future changes. Full harmonisation can have some advantages to the MAH, i.e. only one dossier to maintain but also, if applicable, the possibility to apply for a six months extension of the Supplementary Protection Certificate following completion of a Paediatric Investigational Plan (and no complete waiver was granted for the product), provided that the product is approved in all MSs. For Health Authorities, having had the possibility to raise any potential concern they might have had, harmonisation could then help to reduce turnaround time as only one dossier would have to be reviewed in case of any post-marketing changes. For generic companies, harmonisation of an originator product information could help to apply for an approval of a generic product in all MSs that have the product approved, as reference can then be made to one originator product with the same prescribing information

across the EU rather than submitting different applications with different product information in different MSs. Availability of generic products with the same prescribing information as for an originator product can be of benefit to the Health Insurance System in the different MSs as reimbursement costs could be reduced by substitution of originator products with generics with identical prescribing information. Following the identification of a serious concern by a MS and following a referral procedure and harmonisation of the prescribing information, physicians and patients could feel more reassured that a medicinal product they are prescribing or get prescribed has gone through a thorough assessment within the responsible bodies in the EU and still has a positive benefit/risk assessment.

Considering the duration of the referral procedures conducted during 2007 and 2008 (see Annex 1) it can be concluded that referral procedures are overall very lengthy procedures. In principle, without clock-stops, a referral procedure would be finished basically within 60 days of its initiation (section 4.5; NtA Chapter 3). In most cases, the procedure took more than one year to complete. A reason for these lengthy clock stops could be due to the long time an applicant/MAH needs to gather the required information to address the questions raised. In particular if the referral is initiated by a MS or the EC, the MAH might be caught by surprise without having planned for addressing these concerns. It could also be speculated that in particular for Article 30 and 31 procedures, as they apply to approved products, which could have been approved a long time ago without the need for excessive information, it might be difficult to provide the required information and additional information would have to be collected through other means e.g. literature searches. When there is a class referral, e.g. under Article 31, affecting more than one company, any agreement that the affected companies would need to achieve has an impact on the timelines. This could be due to a conflict of interests between the companies, which needs to be sorted out during the referral. Such lengthy processes are in particular a concern if the referral relates to a public health risk but in that case most likely, the safety concern is regarded as being less serious, otherwise there would be the possibility for an Article 107 procedure.

In contrast to the long referral procedure for products that were reviewed under Article 31 for any concerns related to public health, the “unilateral action by MSs in urgent cases” mechanism under Article 107 provides an efficient way for individual MSs for fast action, being addressed in a second step at the European level to review any serious concern affecting the public health. The availability of Article 31 (Community interest referrals) and Article 107 could lead to some confusion as both can be applied in case of public health concern. This issue will most likely be addressed by the proposed revision by the EC of Directive 2001/83/EC (Proposal for a Directive of the European Parliament and of the council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use). It clarifies the scope of Articles 31 and 107 and provides much more guidance on criteria when a referral can be started, responsibilities of review, timelines and transparency throughout the discussion, including involvement of the public. In addition, it also clarifies the scope of Article 36(1) versus Article 107 referrals. Based on this revision regarding the referral categories and their scope, one could question whether all referral articles as currently included in Directive 2001/83/EC are needed. Time will tell how useful the distinction between the different referral categories is and based on the frequencies of their use, further amendments may be issued, to provide further clarification or even revoke a particular article.

8 Executive Summary

Directive 2001/83/EC and its amendments have set the legal basis and the process for referral procedures within the European Community to resolve disagreement between MSs prior to authorisation and for authorised products. Referrals can be initiated to address any concerns related to medicinal products at the European level. Reasons for a referral can range from concerns over the safety of an approved class of medicinal product to different opinions among Member States on the use of a medicinal product in a certain indication during the review and approval process. The overall aim of a referral is to safeguard public health and to allow free movement and trade of medicinal products in the EU.

Referrals can be initiated by different bodies and organisations within the Community: the EC, any MS or the MAH/applicant, depending on the particular reason for a referral. Any product falling under the scope of a referral will be referred to the CHMP for a scientific evaluation, providing the MSs and the MAH/applicant with the possibility to support their case by relevant information. The CHMP issues an opinion based on their scientific assessment. The final decision is taken by the European Commission and is binding to all MSs in the Community and needs to be implemented at the national level. It can lead to a variation, revocation or suspension of a medicinal product.

Directive 2001/83/EC, as amended, provides for several different referral options. The initiator and the purpose of the referrals differ:

- Article 29(4) – "Mutual Recognition and Decentralised referral" – initiated by MS based on any potential serious risk to public health identified during a MRP/DCP.
- Article 30 – "Divergent decision referral" – initiated by any MS, EC, applicant/MAH on divergent decisions taken by MSs concerning authorisation, suspension or withdrawal of a medicinal product. Article 30 includes cases where a medicinal product is placed on a list of products to be harmonised, following a request by the EC for harmonisation.
- Article 31 – "Community interest referral" – initiate by any MS, EC, applicant/MAH in cases where the interest (public health) of the Community might be affected.
- Article 36(1) – "Follow-up referrals" – initiated by any MS or EC to resolve any post-authorisation divergences to protect public health following e.g. a variation.
- Article 107 – "Unilateral action by MSs in urgent cases" – initiated by any MS to protect public health, followed by an assessment by the CHMP on an European level.

A referral can lead to full or partial harmonisation of the prescribing information (SmPC / labelling / package leaflet). In most cases, referrals consider the clinical information of a product and therefore could affect the indication, posology, contraindication and special warnings and precautions for use sections of the prescribing information of a particular product. Following the completion of a referral procedure, further action by the MAH/applicant could be required to harmonise the complete dossier (e.g. the quality information). In the case of Article 29(4) referrals, where a new medicinal product is being assessed prior to its authorisation and based on a complete dossier, full harmonisation will be achieved in the reference and concerned MSs taking part in the MRP/DCP, followed by

national implementation of the EC Decision in all respective MSs that were part of the procedure.

Harmonisation can have different advantages to the involved stakeholders. The MAH needs to maintain only a single dossier. In addition, based on a harmonised product, the MAH could relatively easily apply for an authorisation of a product in all EU MSs, if not previously done, to fulfill the prerequisite to apply for a 6-month extension of the Supplementary Protection Certificate following completion of a Paediatric Investigational Plan. MSs Competent Authorities have the possibility to raise any potential concern to public health in their territory with a follow-up action on an EU-wide level to ensure the same prescribing information is applicable within the whole EU. In addition, harmonisation could also help to reduce turnaround time as only one dossier would have to be reviewed in case of any post-marketing changes. For generic companies, harmonisation of an originator product information is of benefit as they could apply for an approval in all MSs where a particular product is authorised, as reference can then be made to one originator product with the same prescribing information across the EU. Availability of generic products with the same prescribing information as for an originator product can be of benefit to the Health Insurance System in the different MSs as reimbursement costs could be reduced by substitution of an originator medicinal product by a generic product with identical prescribing information to the originator product but lower price.

In general, referral procedures have a 60-day active review time but due to clock-stops can be a lengthy process. They frequently take more than one year from initiation to completion. There is however one exception, which relates to Article 107 referrals, where urgent action based on critical safety findings, is required. In these cases, the CHMP opinion can be adopted even within one month only, but usually safety measure had been initiated already at earlier times, even before the initiation of such a procedure.

A proposal for an amendment of the pharmacovigilance parts of Directive 2001/83/EC is currently being prepared by the European Commission to further differentiate the use of Article 31, 36(1) and 107 referrals. This could provide further clarification on their differentiation and applicability. This proposal includes the establishment of a new Committee, the “Pharmacovigilance Risk Assessment Advisory Committee” (PRAAC) at the EMEA to be established to assess the safety matter, falling under the scope of the (revised) Article 107. It should play a key role in the pharmacovigilance assessments in the Community, by providing support both to the CHMP and the CMD(h). In addition, there is the possibility that public hearings may be considered. Therefore, the assessments made by the CHMP will be supported by the PRAAC. It will be interesting to observe the changes to the current referral system following the finalisation of this amendment of Directive 2001/83/EC.

9 References

CHMP/309507/2007 Verlipride, Annex I, List of invented names, pharmaceutical forms, strengths of the medicinal products, routes of administration and marketing authorisation holders in the member states, Annex II Scientific conclusions and grounds for withdrawal of the marketing authorisation presented by the EMEA

CMDh/101/2001/Rev4 Recommendation for Mutual Recognition Procedure after finalisation of a referral procedure with positive decision by the EC, Revision 4, May 2009

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67)

EMEA/124066/2005; CHMP Rapporteur/Co-Rapporteur appointment: Principles, objective criteria and methodology.

EMEA website on referrals; http://www.emea.europa.eu/htms/human/referral/referral.htm, accessed 27 July 2009

EMEA Questions & Answers on referrals http://www.emea.europa.eu/htms/human/referral/q_a/list.htm, accessed 27 July 2009

EMEA/CHMP/324332/2005 Committee for Medicinal Products for Human Use (CPMP) Opinion following an Article 31 Referral for all medicinal products containing celecoxib, etoricoxib, lumiracoxib, parecoxib, and valdecoxib

EMEA/CHMP/515890/2006 Opinion following an Article 29(4) referral for Ciprofloxacin Kabi and associated names

EMEA/CHMP/75066/2007 Opinion following an Article 29(4) referral for Ciprofloxacin Hikma and associated names

EMEA/CHMP/350278/2007 Opinion following an Article 29(4) referral for Ciprofloxacin Nycomed and associated names

EMEA/CHMP/384874/2008 Opinion following an Article 30 referral for Ciprofloxacin Bayer and associated names

EMEA/CHMP/384877/2008 Opinion following an Article 30 referral for Risperdal and associated names

EMEA/299468/2007 Questions and answers on the recommendation to withdraw the Marketing Authorisation of veralipride

EMEA/CHMP/432352/2007 Opinion following an Article 31 referral for Agreal and associated names

EMEA/508212/2007 Opinion following an Article 36(1) referral for Gadograf/Gadovist

EMEA/CHMP/579301/2007 Press release, European Medicines Agency recommends withdrawal of the marketing authorisation for lumiracoxib-containing medicines

IDRAC14891 – Marketing Authorisation Procedures – European Community Referral / Arbitration

IDRAC 21042 – Referral opinions

Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC - March 2006 (2006/C 133/05)

Notice to Applicants (NtA), Volume 2A, Procedures for marketing authorisation, Chapter 2, Mutual Recognition, February 2007, ENTR/F2/ SM(2007)

Notice to Applicants (NtA), Volume 2A, Procedures for marketing authorisation, Chapter 3, Community referral procedures, September 2007, ENTR/F2/SM D(2007)

Notice to Applicants (NtA), Volume 2A, Procedures for marketing authorisation, Chapter 4, Centralised Procedure, April 2006, ENTR/F2/BL D(2006)

Notice to Applicants (NtA), Volume 2A, Procedures for marketing authorisation, Chapter 6, Decision making procedure for the adoption of Commission Decisions, November 2005, F2/BL D(2005)

Notice to Applicants (NtA), Volume 2A, Procedures for marketing authorisation, Chapter 7, General information, revision July 2008

Proposal for a Directive of the European Parliament and of the council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, Commission of the European Union, COM(2008) 665 final, 2008/0260 (COD) from 10 December 2008

Opinions on any scientific matters, EMEA website: http://www.emea.europa.eu/htms/human/opiniongen/list.htm

Regulation (EC) 1084/2003 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State

Regulation (EC) No 726/2004 of the European Parliament and of the council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Regulation (EC) No 1901/2006 of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

10 Annex

Annex 1

Table 4 Referral procedures during 2007/ 2008, including CHMP opinions adopted during this period (EMEA website on referrals)

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
ARTICLE 29								
Bleomycin Pharma-chemie	Bleomycine	EMEA/CHMP /191900/2009	MS	Concerns on a particular indication which had been deleted from the authorised indications for all bleomycin-containing products in the MS because the balance of benefit/risk for bleomycin in these indications was considered negative	20-Nov-08	18-Dec-08	Benefits outweigh its risks, and therefore MA should be granted in all concerned MS.	12-Mar-09
Sanohex	Salbutamol	EMEA/CHMP /662198/2008	MSs	Not enough data showing equivalence to reference medicine. Concerns on how to store product	19-Mar-08	18-Dec-2008	Products are bioequivalent and that the benefit-risk ratio is positive.	12-Mar-09
Sabumalin	Salbutamol	EMEA/CHMP /661652/2008	MSs	Not enough data showing equivalence to reference medicine. Concerns how to store product	19-Mar-08	18-Dec-2008	Products are bioequivalent and that the benefit-risk ratio is positive.	12-Mar-09
Uman Big	Human hepatitis B immuno-globulins	EMEA/CHMP /661396/2008	MSs	Concerns over insufficiency of clinical data submitted to establish efficacy. Absence of product specific safety data or post-marketing safety data	31-Oct-08	18-Dec-08	• Post marketing safety data submitted are adequate to establish positive safety profile, • Efficacy profile is satisfactory for indications applied for in SmPC, • benefit/risk is positive.	6-Mar-09

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
Implanon	etonogestrel	EMEA/124262/2009	MSs	During renewal concerns regarding the side and data on effectiveness in obese women.	6-Oct-08	20-Nov-08	Benefits outweigh its risks, and therefore the renewal of the marketing authorisation for Implanon should be granted with conditions.	6-Feb-09
Lisonorm and associated names	(lisinopril / amlodipine)	EMEA/CHMP/633842/2008	MSs	Proof of bioequivalence. Lack of wide therapeutic experience.	21-Feb-08	24-Jul-08	Benefit/risk ratio is favorable SmPC/labelling/PL to be amended	12-Nov-08
Activelle and associated names	Estradiol and norethisterone acetate	EMEA/CHMP/496102/2008	MSs	Significant differences identified with regard to clinical safety	19-Mar-08	26-Jun-08	Benefit/risk is favorable SmPC/labelling/PL to be amended	11-Sep-08
Rapinyl and associated names	Fentanyl citrate	EMEA/CHMP/495857/2008	MSs	Need for further clinical efficacy and safety data Lack of PK data	18-Oct-07	26-Jun-08	Benefit/risk is favorable SmPC/labelling/PL to be amended	11-Sep-08
Oracea and associated names	Doxycycline monohydrate	EMEA/CHMP/428671/2008	MSs	Lack of sufficient safety and efficacy evidence Emergence of bacterial resistance Insufficient demonstration of positive benefit/risk ratio	20-Sep-07	24-Apr-08	Objections should not prevent granting of MA SmPC/labelling/PL to be amended	22-Jul-08
Alvesco and associated names	Ciclesonide	EMEA/CHMP/151554/2008	MSs	Significant difference with currently approved posology for control of exacerbations in severe asthma. Data did not support authorisation of specific daily doses.	15-Nov-07	19-Mar-08	Benefit/risk is favorable SmPC/labelling/PL to be amended MAH to commit to obtaining scientific advice in relation to exploring suitable study design and executing such study to provide further information on higher doses	11-Jul-08

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
							of product in control of severe asthma.	
Menitorix	*Haemo-philius influenzae* type b polysaccha-ride conjugated to tetanus toxoid and *neisseria meningitidis* serogroup C polysaccha-ride conjugated to tetatnus toxoid	EMEA/CHMP /180097/2008	MSs	No immunological correlates of protection of vaccine and additional data requirements in infants and toddlers.	26-Apr-07	15-Nov-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	1-Apr-2008
Cipro-floxacin Nycomed	Ciprofloxa-cin	EMEA/CHMP /350278	MSs	Significant differences with regard to approved posology (proposed dosage regimen was considered too low)	1-Jun-06	16-Nov-06 Revised opinion on 21-Jun-07 Revised opinion in Oct-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	18-Jan-08
Bicaluplex	Bicalut-amide	EMEA/43369 1/2007	MSs	Significant differences with regard to benefit/risk ratio regarding two indications	26-Apr-07	20-Sep-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	22-Nov-07

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
Xeomin	Clostridium botulinum neurotoxin type A	EMEA/CHMP/	MSs	Concerns on posology, repeated administration and safety profile in two Phase III studies.	26-Apr-07	19-Jul-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	24-Oct-07
Fentanyl-Ratiopharm 25/50/75/100 µg/h Matrix-pflaster	Fentanyl	EMEA/338591/2007	MSs	Significant differences with regard to indication, posology, contraindications and demonstration of bioequivalence	24-Jan-07	19-Jul-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	23-Oct-07
Fentanyl-Ratiopharm 25/50/75/100 µg/h TTS	Fentanyl	EMEA/331678/2007	MSs	Significant differences with regard to indication, posology, contraindications and demonstration of bioequivalence	24-Jan-07	19-Jul-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	23-Oct-07
Lanso-prazole	Lansopra-zole	EMEA/283378/2007	MSs	Bioequivalence was proven in fasting state but not under fed conditions	14-Dec-06	21-Jun-07	Benefit/risk is favorable SmPC/labelling/PL are valid final versions and do not need to be amended.	18-Sep-07
Cefuro-ximaxetil	Cefuroxime (as axetil)	EMEA/CHMP/248862/2007	MSs	Significant differences with regard to safety and efficacy of proposed indication	18-Oct-06	26-Apr-07	Objection raised by MS was agreed to and SmPC/ labelling/Pl should be amended. Existing MAs should be varied accordingly.	22-Aug-07
Ciprofloxa-cin Hikma	Ciprofloxa-cin	EMEA/CHMP/75066/2007	MSs	Significant differences with regard to posology and request for additional information in the SmPC	27-Jul-06	24-Jan-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	11-Jul-07
Vantas	Histrelin acetate	EMEA/CHMP/247760/2007	MSs	Efficacy was not demonstrated in comparison to other approved,	7-Mar-07	24-May-07	Benefit/risk is favorable SmPC/labelling/PL to be	30-Jul-07

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
				effective treatments and safety was not adequately demonstrated.			amended	
Alendronate Hexal	Alendronic acid (as sodium alendronate trihydrate)	EMEA/CHMP /75285/2007	MSs	Significant difference with regard to indication	27-Jul-06	24-Jan-07	Benefit/risk is favorable SmPC/labelling/PL to be amended	13-Apr-07
Cipro-floxacin Kabi	Ciprofloxa-cin	EMEA/CHMP /515890/2006	MSs	Significant difference with regard to posology	28-Jun-06	16-Nov-06	Benefit/risk is favorable SmPC/labelling/PL to be amended	24-Jan-07
ARTICLE 30								
Tritace	Ramipril	EMEA/665249/2008	EC	Identified as needing harmonisation by CMD(h)	24-Jan-08	18-Dec-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	6-Mar-09
Triatzide	Ramipril and hydrochloro-thiazide	EMEA/665250/2008	EC	Identified as needing harmonisation by CMD(h)	24-Jan-08	18-Dec-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	6-Mar-09
Diovan	valsartan	EMEA/CHMP /137577/2009	EC	Identified as needing harmonisation by CMD(h)	24-Apr-08	20-Nov-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	16-Feb-09
Efexor depot	-	EMEA/CHMP /384876/2008	EC	List of products identified in 2007 for SmPC harmonisation Divergences in SmPC regarding way of treatment of several indications	24-May-07	24-Jul-08 and revision on 25-Sep-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended	28-Nov-08
Efexor and	Venlafaxine	EMEA/CMP/	EC	List of products identified in 2007	24-May-07	24-Jul-08	Proposal for harmonisation	28-Nov-08

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
associated names		348875/2008		for SmPC harmonisation Divergences in SmPC regarding way of treatment of several indications		and revision on 25-Sep-08	was acceptable and SmPC/labelling/PL should be amended.	
Risperdal and associated names	Risperidone	EMEA/CHMP /384877/2008	EC	List of products identified in 2007 for SmPC harmonisation Divergences in SmPC regarding indications, posology, method of administration, contraindications, special warnings and precautions for use, and precautions for use and interactions	20-Sep-07	24-Jul-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	7-Oct-08
Ciprofloxa-cin Bayer and associated names	Ciprofloxa-cin	EMEA/CHMP /384874/2008	MS	Divergences in SmPC regarding indications, posology, contraindications, special warnings and precautions for use.	19-Jul-07	24-Jul-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	7-Oct-08
Risperdal Consta and associated names	Risperidone	EMEA/CHMP /384879/2008	EC	List of products identified in 2007 for SmPC harmonisation Divergences in SmPC regarding indications, posology, method of administration, contraindications, special warnings and precautions for use, and interactions	20-Sep-07	24-Jul-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	7-Oct-08
Zyrtec and associated names	Cetirizine	EMEA/CHMP /541853/2008	EC	List of products identified in 2007 for SmPC harmonisation Divergences in SmPC regarding indications, posology, contraindications, special warnings and precautions for use.	18-Oct-07	30-May-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	6-Oct-08

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
Remeron and associated names	Mirtazapine	EMEA/CHMP /500252/2008	MAH	To harmonise nationally authorised SmPCs, labelling, PL Divergences in SmPC including quality aspects with respect to treatment of major depressive episodes.	15-Nov-07	26-Jun-08	Proposal for harmonisation including quality aspects was acceptable and SmPC/labelling/PL should be amended.	15-Sep-08
Gemzar	Gemcita-bine	EMEA/CHMP /512295/2008	EC	List of products identified for SmPC harmonisation Divergences in SmPC including quality aspects mainly regarding indications, posology, contraindications, special warnings and precautions for use.	21-Jun-07	26-Jun-08	Proposal for harmonisation including quality aspects was acceptable.	23-Sep-08
Cozaar Comp and associated names	Losartan + hydrochloro-thiazide	EMEA/CHMP /494914/2008	MS	Divergences in SmPC with respect to several indications	22-Mar-07	24-Apr-08	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	3-Sep-08
Cozaar and associated names	Losartan	EMEA/CHMP /494721/2008	MS	Divergences in SmPC with respect to several indications	22-Mar-07	24-Apr-08	Proposal for harmonisation was acceptable; SmPC/ labelling/PL to be amended.	3-Sep-08
Lamictal	Lamotrigine	EMEA/21211 4/2008	MAH	Divergences in SmPC including quality aspects with respect to several indications	29-Mar-07	24-Apr-08	Proposal for harmonisation including quality aspects was acceptable and SmPC/labelling/PL should be amended.	23-Jul-08
Singulair and associated names	Montelukast	EMEA/CHMP /411086/2008	MAH	Divergences in SmPC including quality aspects with respect to several indications	20-Sep-07	24-Apr-08	Proposal for harmonisation including quality aspects was acceptable and SmPC/labelling/PL should be amended.	11-Jul-08

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
Xefo	Lornoxicam	EMEA/144030/2007	MAH	Divergences in SmPC with respect to several indications	2-Jun-06	22-Feb-07	Proposal for harmonisation was acceptable and SmPC/labelling/PL should be amended.	29-May-07
ARTICLE 31								
Arcoxia	Etonicoxib-containing medicinal products	EMEA/329177/2008	MS	During assessment of type II variation for additional indication, concerns were raised over safety of medicine when used at this dose for long periods.	20-Sep-07	26-Jun-08	Benefits outweigh risks	9-Sep-08
Norfloxacin	Norfloxacin	EMEA/378867/2008	MS	During the assessment of renewal an agency questioned effectiveness of oral formulations for complicated pyelonephritis, in comparison with other fluoroquinolones. Request to carry out assessment of benefit-risk balance of oral formulations of all norfloxacin-containing medicines for complicated pyelonephritis.	20-Sep-07	24-Jul-08	Benefits of oral formulations of norfloxacin do not outweigh their risks for complicated pyelonephritis. Recommendation that this indication should be removed.	19-Nov-08
N/A Class referral	Ergot derivatives	EMEA/CHMP/319054/2008	MS	Review of risk of fibrosis in long term use, particularly cardiac fibrosis The development of symptoms of fibrosis has been known as a side effect of ergot-derived dopamine agonists. However, two studies published in scientific journals using echocardiography have shown that fibrosis of the heart	N/A	N/A	The MA for ergot-derived dopamine agonists should be maintained, but changes to the prescribing information for the medicines should be introduced to reduce the risk of fibrosis. The CHMP also concluded that the risk of fibrosis, including fibrosis of the heart valves, does not	N/A

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
				valves can begin to develop well before symptoms start to appear. This suggested that cardiac fibrosis may be more common than previously thought.			appear to be the same for all five medicines in the class. In addition, certain changes should be made in the prescribing information of the different products in the class, however depending on the product.	
Feldene	Piroxicam	EMEA/380917/2007	EC	Request by EC to further review safety data of some non-selective of NSAIDs including piroxicam based on limited epidemiological data and spontaneous adverse drug reaction data providing signal of increased risk of gastrointestinal and skin reactions.	21-Sep-06	21-Jun-07	Benefit/risk balance positive in certain indications (treatment of symptomatic relief of osteoarthritis, rheumatoid arthritis or ankylosing spondylitis) but negative in others (treatment of acute conditions). Indications had to be revoked and certain restrictions on use, contraindications and warnings had to be added.	7-Sep-07
Agreal	Veralipride	EMEA/CHMP/432352/2007	EC	Withdrawal of product from one market due to reports of serious side effects affecting nervous system	21-Sep-06	19-Jul-07	Benefit/risk provide is negative and product needs to be withdrawn.	1-Oct-07
Casodex	Bicalut-amide 150 mg	EMEA/378451/2007	MS	Review of benefit/risk profile	27-Jul-06	24-May-07	Benefit/risk profile remains favorable. Recommendation to maintain or granting as appropriate the MA with amendments to relevant sections of SmPC. Restriction of indication.	3-Sep-07

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
							Potential association of medicinal product and heart failure cannot be ruled out. Therefore need for further study as part of risk management plan	
ARTICLE 36(1)								
Gadograf / Gardovist	Gadobutrol	EMEA/508212/2007	MS	Insufficient data for evaluation regarding additional indication intended to be added to the SmPC/PL through type II variation	May 06	14-Dec-06	Indication was granted by CHMP with addition of information to SmPC/PL.	13-Apr-07
ARTICLE 107								
Avalox/Avelox	Moxifloxacine	EMEA/380454/2008	MS	Following a review of the safety, including eight cases of liver problems that led to the patients' death benefit-risk balance.	Jun-08	24-Jul-08	Warnings in product information to be strengthened to include information on liver problems, heart problems in women and older patients and diarrhoea.	N/A
Aulin, Nimed	Nimesulide-containing medicinal products	EMEA/432604/2007	MS	Reports of serious side effects affecting the liver.	May-07	21-Sep-07	Data did not support suspension. All packs containing more than 30 doses (tablets or sachets) to be removed from market. Nimesulide should not be used at same time as other medicines that can also cause liver damage or in patients whose liver is already damaged. Further surveillance	N/A

Invented name	INN	Reference	Body initiating referral	Grounds for referral	Start of procedure	Opinion date	Outcome	EC Decision Date
							measures and studies to investigate risk of liver injury in patients taking nimesulide, and letter to healthcare professionals to increase awareness of correct way of use of nimesulide.	
Silomat	Clobutrinol-containing medicinal products	EMEA/480863/2007	MS	Suspension by national Health Authority	Sep-07	Oct-07	Use of clobutinol is associated with risk of prolongation of 'QT interval': Benefits do not outweigh risks. Recommendation of withdrawal of MAs.	N/A
Somadril	Carisoprodol-containing medicinal products	EMEA/520463/2007	MS	Suspension by national Health Authority	N/A	15-Nov-07	Risks outweigh benefit and product should be suspended.	N/A
Trasylol	Aprotinin-containing medicinal products	EMEA/533599/07	MS	Suspension by national Health Authority	N/A	21-Nov-07	Risks outweigh benefit and product should be suspended	N/A
Prexige	Lumaricoxib-containing medicinal products	EMEA/CHMP/32166/2005 – Article 31 referral and EMEA/579301/2007 – Article 107 referral	MS	Suspension by national Health Authority	15-Nov-07	13-Dec-07	Risks outweigh benefit and product should be suspended	N/A

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Lörrach, den

Unterschrift: