Pharmacovigilance Referrals - Changes in line with the new Pharmacovigilance Legislation 2010 / 2012

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

Beate Stadler

aus Münster

Bonn 2013

Betreuer und 1. Referent: Dr. Axel Thiele

2. Referent: Prof. Dr. Barbara Sickmüller

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AR	Assessment Report
CAP	Centralised approved MP
CHMP	Committee for MPs for Human Use
CMD(h)	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CP	Centralised Procedure
CoRapp	Co-Rapporteur
EC	European Commission
EMA	European Medicines EMA
EU	European Union
DCP	Decentralised Procedure
GVP	Good Vigilance Practices
HMA	Heads of Medicines EMA
LoOI	List of Outstanding Issues
LoQ	List of Questions
MP	Medicinal Product
MS	Member State
MRP	Mutual Recognition Procedure
NAP	National Approved Product
NCA	National Competent Authority
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAES	Post-authorisation Efficacy Study
PASS	Post-authorisation Safety Study
PhVWP	Pharmacovigilance Working Party
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RA	Rapid Alert
Rapp	Rapporteur
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

1. INTRODUCTION

While the development of medicinal products (MPs) leads to major improvement in the treatment and control of diseases all medicines have the potential to cause side effects. At the beginning of the process they occur whilst extensive testing takes place in clinical trials. The way in which MPs will act in a minority of patients in the population is often unforeseeable and cannot be accurately measured in a small number of subjects.

The full safety profile of medicines can only be known at later stages once they have entered the market and have reached wide clinical use.

Collecting and managing these data on the safety of medicines and taking action to reduce the risks is called pharmacovigilance.

Regardless of its initial authorisation (i.e. centralised or national authorisation including authorisation via decentralised or mutual recognition procedure) an MP is subject to surveillance by the competent authorities as well as by the marketing authorisation holder (MAH). Adverse drug reactions (ADRs) can be collected by spontaneous reporting, intensive monitoring and database studies.

Regulatory agencies and pharmaceutical companies both are obliged to ensure that emerging safety information is reported and appropriate action is taken to safeguard public health. The two keystones of legislation that underpin pharmacovigilance activities in the European Union (EU) are Regulation 726/2004/EC and Directive 2001/83/EC as amended.

Since 2004 a number of weaknesses of the pharmacovigilance legislation have been revealed. Examples for this are the withdrawal of rofecoxib in 2004 or the suspension of the marketing authorisation of rosiglitazone after a great deal of discussion about its cardiovascular safety (1). The European Commission (EC) declared that the former legislation was too complicated without clear rules of responsibilities (2). In the course of the changing EU market a need for an improvement of the pharmacovigilance system became obvious.

In December 2010 a new European Pharmacovigilance legislation (Directive 2010/84/EC (3) and Regulation 1235/2010/EC) (4) was passed and came into

effect in July 2012. Further amendments to the EUs pharmacovigilance legislation have recently been adopted in the form of a Directive and a Regulation.

The new pharmacovigilance legislation in 2010/2012 has made substantial changes with regard to existing pharmacovigilance requirements, e.g. more post-authorisation safety and efficacy studies, a new Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (EMA) and a broader reporting of side-effects by patients.

A further part of these changes applies to the pharmacovigilance referrals ("safety referrals") that will be further described in this thesis.

In the case of issues identified by the MAH or the competent authorities the EU legislation offers an arbitration mechanism, called referral that is used to resolve disagreements and to address concerns.

Whenever a referral is invoked, a scientific evaluation of the matter is performed by the relevant committees (PRAC/CHMP/CMD(h)).

Referral procedures that are based on the evaluation of data resulting from pharmacovigilance activities are the following:

- Article 107i of Directive 2001/83/EC ("Urgent Union Procedure")
- Article 31 of Directive 2001/83/EC ("Union Interest Referral")
- Article 20 of Regulation 726/2004/EC
- Article 5(3) of Regulation 726/2004/EC

In the course of the new legislation the number of safety referrals was reduced from five to four. Although most of the changes apply to Art. 107i and Art. 31 for the sake of completeness the Art. 20 and Art. 5(3) referrals will be described in this context as well.

The present master thesis is intended to identify the main changes of the pharmacovigilance referrals in line with the new legislation taking into account the historical development, the different impacts and the outlook for the future.

2. LEGAL FRAMEWORK

Regulations

Regulation 726/2004/EC

- lays down Community procedures for the authorisation and supervision of MPs for human and veterinary use and establishes the EMA

Regulation 1235/2010/EC

- came into force on 1 January 2011
- amends, as regards pharmacovigilance of MPs for human use Regulation 726/2004/EC and Regulation 1394/2007/EC on advanced therapy MPs
- applies to CPs and advanced therapy products
- provisions apply as of 2 July 2012

Regulation 1027/2012/EC

- became operative on 14 November 2012
- amends, as regards pharmacovigilance, Regulation 726/2004/EC and 1394/2007/EC
- provisions apply as of 5 June 2013

Directives

Directive 2001/83/EC

- Relates to MPs for human use

Directive 2010/84/EC

- came into effect on 20 January 2011
- amends, as regards pharmacovigilance, Directive 2001/83/EC
- provisions apply as of 21 July 2011

Directive 2012/26/EC

- came into force 16 November 2012
- amends, as regards pharmacovigilance, Directive 2001/83/EC
- applies to MRP/DCP/national products

- provisions apply as of 28 October 2013

Commission Implementing Regulation 520/2012

- adopted on 19 June 2012 with an implementation date of 10 July 2012
- completes Regulation 1235/2010/EC and Directive 2010/84/EC by providing more technical details and transition periods until 10 January 2013.

3. RELEVANT SCIENTIFIC COMMITTEES AND GROUPS

3.1 PRAC

The assessment and monitoring of all pharmacovigilance related issues are carried out by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC is part of the EMA and replaced the Pharmacovigilance Working Party (PhVWP) when Directive 2010/84/EC and Regulation 1235/2010/EC entered into force. Details of the PRAC´s main tasks are described in "*The establishment and functioning of the Pharmacovigilance Risk Assessment Committee*" (5). Thus, the PRAC takes on the task of assessing, minimising and communicating the risk of adverse reactions. Furthermore it is responsible for the structure of post-authorisation safety studies (PASS) and pharmacovigilance audits.

Relevant for this thesis the PRAC carries out the assessment on the pharmacovigilance related referrals in accordance with Art. 107i and Art. 31 of Directive 2001/83/EC and with Art. 20 and Art. 5(3) (only upon request) of Regulation 726/2004/EC. At the end of the assessment the final recommendation is forwarded to the CHMP, the CMD(h), EMA secretariat, Management Board and EC, if applicable.

Composition (6)

- One chair and one vice chair, elected by serving PRAC members;
- One member and an alternate nominated by each of the 27 MSs (additionally for Iceland and Norway respectively);
- Six independent scientific experts nominated by the EC;
- One member and an alternate nominated by the EC after consultation of the European Parliament to represent both healthcare professionals and patient organisations.

3.2 CHMP

As described in “CHMP – Rules of Procedure” (7) the Committee for Medicinal Products for Human Use (CHMP) is the EMA´s scientific committee responsible for elaborating the EMA´s opinions on applications submitted for centralised MAs and on all issues regarding MPs for human use. For centralised procedures the CHMP´s main role is not only the initial assessment but also the post-authorisation activities such as variations and renewals.

In case of disagreement between MS that can not be resolved at the CMD(h) level the CHMP arbitrates concerning the MA of a specific MP. With regard to pharmacovigilance referrals the CHMP gives the final opinion after having reviewed the PRAC recommendation in cases where at least one centrally authorised MP is involved.

Composition (8)

- One chair, elected by serving CHMP members;
- One member and an alternate nominated by each of the 27 MSs (additionally for Iceland and Norway respectively);
- Up to five co-opted members nominated by the MS or the EMA to provide additional expertise in a particular scientific field.

3.3 CMD(h)

As laid down in Art. 27(1) of Directive 2001/83/EC the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) is responsible for “*the examination of any question relating to marketing authorisation of a medicinal product in two or more Member States in accordance with the mutual recognition procedure or the decentralised procedure*”.

In case of disagreements between the MS the CMD(h) seeks to resolve all issues before a referral has to be triggered by one or more MSs. According to Art. 30 of Directive 2001/83/EC the CMD(h) should promote a harmonisation of the SmPCs of specified MPs.

With regard to the new pharmacovigilance legislation the CMD(h) receives and considers the PRAC recommendation in cases where only non-centrally authorised products are involved.

Composition (9)

- One chair and one vice chair, elected by serving CMD(h) members;
- One member and an alternate nominated by each of the 27 MSs (additionally for Iceland, Norway and Liechtenstein respectively);
- If necessary external experts

4. HISTORICAL DEVELOPMENT

In 2004 the pharmacovigilance legislation was amended in form of the so-called "2001 Review" (Directive 2004/27/EC (10)) although the concrete changes with regard to the pharmacovigilance system were rather insignificant. A systematic revision of the existing regulations was still missing. The potential of simplification and clarification of the amendments for example by using information technologies was not exhausted. But above all: Each year approximately 200,000 people in the EU died as the consequence of adverse drug reactions (ADRs). One reason for this was the lacking speediness of EU reactions in case of drug safety alerts that implicated a high risk for patient safety (11). In the view of the EC the post-marketing evaluation of the benefit risk profiles was not as efficient as it should have been. Furthermore patients should have been given the information on the risks they needed.

In the beginning of 2006 the EC initiated a process of public consultation that was divided into two steps. First the EC invited all stakeholders including patients and consumers in its "*Assessment of the Community System of Pharmacovigilance*" (2) to express their point of view on the existing pharmacovigilance system. The main focus was laid on the manner of cooperation between the different parties monitoring adverse drug reactions (ADRs) (12).

Between the end of 2007 and the beginning of 2008, as part of the second step of the consultation process the EC asked the stakeholders for concrete proposals for changing the legislation ("*Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance").*

The analysis of the whole process showed that there was a strong need for improving the legal framework. In detail the following topics were addressed (13):

- Robust and fast decision-making on safety issues
- Strengthening of the role of risk-management planning
- Simplification of ADR reporting (including patient reporting)
- Strengthening of medicine safety, transparency and communication
- Improvement in quality of non-interventional safety studies

The existing legislation offered the following pharmacovigilance referrals:

Art. 31, 36 and 107 of Directive 2001/83/EU and Art. 5(3) and 20 of Regulation 726/2004/EC.

During the consultation process the referral procedure was confirmed as an instrument to address concerns. In detail the stakeholders expressed the following wishes:

- More transparency and clearness as the companies would like to be informed more explicitly about the referral procedures their products are involved in.
- The procedure should be carried out faster.
- The CMD(h) should play an important role in the decision-making process.
- The overall decision after the referral procedure should be legally binding throughout the EU (no divergent decisions of the MSs).
- The implementation of public hearings by consumers and healthcare professionals should be supported.

As a result of this consultation process the European Parliament and the Council adopted two legislative proposals (Directive and Regulation) as part of the so-called “pharmaceutical package” on 10 December 2008 (14) (15).

Regarding the rationalisation of the decision-making in the EU there was a strong demand for “an automatic pharmacovigilance referral procedure with non-discretional referral triggers placed on the Member States” (11). In this context the EC started an implementation process of the new Article 107 procedure and invited the stakeholders to comment on the “Guideline concerning Recommendation on Pharmacovigilance Urgent Measures” (16) in January 2009.

In December 2010, the EU Regulation 726/2004/EC was amended by Regulation 1235/2010/EC while the EU Directive 2001/83/EC was updated by Directive 2010/84/EC. All comments and recommendations were taken into consideration at the end of this legislative process.

Since then patients of all MSs can report suspected side-effects directly to the NCA for transparency reasons. Furthermore the EMA has started to publish the agendas, minutes, assessments and recommendations from the PRAC (including CMD(h) position and CHMP opinion) whilst the pharmacovigilance part of the

CMD(h) minutes is published on the CMD(h) website. Where it is considered necessary the public is able to play a part in the work of the EMA, e.g.in the form of public hearings. Further changes of the new pharmacovigilance legislation that are not mentioned in this thesis apply to the Risk Management Plan (RMP), Periodic-Safety-Update-Report (PSUR) and Post-Authorisation-Safety-Studies (PASS) / Post-Authorisation-Efficacy-Studies (PAES).

The old legislation offered the Art. 36(1) referral of Directive 2001/83/EC ("Follow up referral"), that was used to resolve any post-harmonisation divergencies that might have arisen between MSs. In cases where it was necessary to protect public health this referral could be triggered by a MS in case variation, suspension or withdrawal of a MA was considered. In most cases it was initiated for reasons of union interest or safety issues.

As this scope might overlap with the content of Art. 31 or Art. 107 it was deleted in order to tighten the process of referrals. The details of the changes related to the pharmacovigilance referrals will be described in the following chapters.

In 2012 a further amendment of the pharmacovigilance legislation became necessary since the so-called "Mediator case" raised people´s awareness of emerging safety issues.

Mediator (active substance: benfluorex), an MP patented and manufactured by the French pharmaceutical company Servier had been marketed in France between 1976 and 2009. It was also approved in other European countries like Italy and Spain. Benfluorex is an anorectic and hypolipidemic substance that was indicated as an adjuvant antidiabetic. Similar to the structurally related fenfluramine that had been withdrawn from the market in 1997 benfluorex was suspected of causing heart valve disease and pulmonary hypertension. In 1998 the French NCA ordered an additional monitoring program for benfluorex. As a result the indications were restricted in 2007. In Spain, the MAH took the MP off from the market in 2003 for commercial reasons but did not have it checked. Only at the end of 2009, years after having been pulled in Spain and Italy the EMA recommended the withdrawal of all MPs containing benfluorex in the EU. All in all it took more than 10 years from the first warning within the French NCA to the prohibition. It was estimated that 500 – 2000 deaths could be linked to the use of Mediator (17).

In this connection the EC had taken a closer look into the new pharmacovigilance legislation (“stress test” (18)) and identified further weak points. Therefore in December 2012, with regard to pharmacovigilance, the legislation was amended by the adoption of Directive 2012/26/EC and Regulation 1027/2012/EC.

Changes are the following (19):

- Notification by the MAH and NCA is required when a MP ceases to be placed on the market
- Any company that voluntarily withdraws or decides not to renew a medicine's MA will have to declare whether that decision was due to safety concerns. Thus, it is avoided that pharmaceutical companies can plead commercial reasons for the withdrawal (affects Art. 23a, 107i and 123 (2) of Directive 2012/26/EC and Art. 13 and 14b of Regulation 1027/2012/EC).
- The Urgent Union Procedure (Art. 107i) is further specified (automatic access in certain circumstances, cf. Chapter 5).
- Clarification of the rules regarding the Art. 31 and the Art. 107i procedure (cf. Chapter 5).
- The list of medicines subject to additional monitoring will be extended, and will include all MPs subject to a PASS or other conditions. These products will have to carry a black symbol as described in the Commission Implementing Regulation 198/2013/EC adopted on 7 March 2013.

In order to support the implementation of the new pharmacovigilance legislation the EMA is currently establishing new clear standards in the form of the “Good Vigilance Practices – GVP”. These GVP modules will replace Volume 9A of, "The rules governing MPs in the European Union - Pharmacovigilance". Most of the 16 modules are already finalised, but it is not intended to cover the pharmacovigilance referrals in one module.

5. TYPES OF REFERRALS (PROCESS AND EXAMPLES)

5.1 Art. 107i ("Urgent Union Procedure")

The old Art. 107 referral that was in use since 2005 was described rather briefly (10). Where an MS, after having evaluated pharmacovigilance data, considered that an MA should be suspended or revoked this type of referral was triggered mandatorily. In case of variations to the MA, this referral procedure was solely initiated when urgent action was considered necessary.

According to the new legislation (Directive 2010/84/EC) (3) the Art. 107i referral procedure called "Urgent Union Procedure" is described extensively and in much more detail.

After evaluation of data resulting from pharmacovigilance activities the Art 107i referral can apply to situations in which NCA/EC considers that swift action across the EU is necessary. This measure can be taken in at least one of the following situations (Art 107i(1) of Directive 2001/83/EC):

Criteria:

a) when it considers suspending or revoking an MA;

b) when it considers prohibiting the supply of an MP;

c) when it considers refusing the renewal of an MA;

d) when it is informed by the MAH, that on the basis of safety concerns, he has interrupted the placing on the market of an MP or has taken action to have an MA withdrawn, or that he intends to do so or has not applied for the renewal of an MA;

e) when it considers that a new contraindication, a reduction in the recommended dose, or a restriction to the indications is necessary.

General guidance on this new pharmacovigilance referral is laid down in "*Questions & answers on practical implementation of Urgent Union Procedure*" (20).

This guidance does not yet reflect the changes that apply to the recently adopted Directive 2012/26/EC which still has to be implemented into national law until 28 October 2013.

In accordance with Directive 2010/84/EC, amending Directive 2001/83/EC, there is no automatic assessment designed for safety issues in case one MS considers to suspend, revoke or refuse the renewal of the MA but does not consider that urgent action is required. The way the French NCA and the EMA handled the "Mediator case" showed that the Art. 107i Procedure should automatically be triggered if a MS withdraws a MP from the market. This aspect has been taken into consideration in Directive 2012/26/EC.

In future, the Urgent Union Procedure is to be initiated automatically in statutorily required cases (amended Art. 107i (1) of Directive 2001/83/EC):

The wording of the first paragraph of Art. 107i has been changed as follows:

"*A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the procedure provided for in this section by informing the other Member States, the Agency and the Commissions where….".*

Therefore the phrase *"when urgent action is considered necessary"* and the criterion "e" (see above) as initial conditions have been deleted. The criterion "e" (considering of including a new contraindication, reducing the recommended dosage or restriction to an indication) shall only be triggered in urgent cases (Art. 107i(1a) of Directive 2001/83/EC). Otherwise the Art. 31 of Directive 2001/83/EC (see section 5.2) shall apply.

Irrespective of the criteria that trigger such an Art. 107i procedure the procedural steps are as follows:

5.1.1 Process

1. Verification

Further to the assessment of data resulting from pharmacovigilance activities the MS should inform the other stakeholders before any regulatory action is taken. This should be done on the following working day at the latest.

Whenever applicable the so-called Rapid Alert (RA) System should be used. This system has been established since 1991 and is run by the CA of the MS in order to facilitate early exchange of information.

Subsequently an official notification should be circulated by the initiator including the description of the safety concern and the regulatory action to be initiated.

In this phase all available scientific information should be provided.

2. Notification

Once the notification has been circulated the EMA checks whether

a) the safety concerns also apply to other products, even to a range of products or a therapeutic class

b) the MP in question is also authorised in other MSs.

c) all criteria for an Urgent Union Procedure are fulfilled.

If the MP is only approved in one MS, this is the initiator for keeping the procedure on a national level. On the other hand, the scope is extended to include all concerned products, after the EMA has identified safety concerns relating to more than one MP.

After having checked the above-mentioned criteria the justification is released in the course of the next PRAC meeting. The MAH will be informed about the initiation of the procedure by the EMA or the MS.

Temporary measures such as suspension of the MA or prohibition of the MP at national level can be implemented immediately by the MS, while the procedure is ongoing. This information should be circulated to the MS, the EMA and to the EC on the next working day (Art 107i (2) of Directive 2001/83/EC).

Even the EC may request the MS to take immediate provisional measures in case no MP authorised via the CP is involved. If CAPs are affected the EC by itself may implement temporary measures.

3. Initiation step

For the next PRAC meeting the safety issue in question is put on the agenda and is discussed on basis of the circulated notification and the present scientific data.

The following questions will be addressed:

- Who will take over the PRAC Rapporteurship?
  Generally the trigger MS takes over the role of the PRAC CoRapp. The PRAC Rapporteur´s part is open to all other MSs taking their expertise into account.
- Are temporary measures needed?
  On the recommendation of the PRAC the EC may take actions at any time of the procedure (Art 107i(3)of Directive 2001/83/EC).
- Does the List of Questions (LoQ) cover everything? Are supplemental information or data necessary?
  Here it should be considered if further data from the concerned MAHs, Public, Healthcare Professionals is needed. According to Art. 107j(2) of Directive 2001/83/EC all of these parties have the same right to submit information relevant to the procedure.
- Should the MAH be given the opportunity for a public or a non-public hearing?
  Depending on the degree of urgency the PRAC should discuss whether a public consultation may be held at this step of the procedure. Generally a public hearing can be operated here, during the PRAC assessment in the opinion-making phase and for transparency reasons at the end of the procedure to explain the final recommendation. This is a major change compared to the old legislation where this issue was handled confidentially between the company and the authority.
  In agreement with the PRAC the hearing can also be held in a non-public manner if confidential data is connected with this issue
- Is an Oral explanation a useful option?
  An Oral explanation is possible at any time of the assessment phase and can be carried out upon request of the PRAC or the MAH. Even in the CHMP/CMD(h) step (see below) it might be possible in some cases.

As a result of the first PRAC plenary meeting the EMA publishes an official notification on the EMA´s website.

Furthermore the following documents are provided by the EMA:

- the preliminary list of all concerned MPs, MAHs and active substances
- the list of questions including the adopted timetable
- the results of the first PRAC meeting in addition to the press release
- if applicable the recommendation on momentarily provisions
- if applicable information about the date of the public hearing.

At the same time the concerned MAHs are informed by the EMA that the Art. 107i referral procedure has been initiated.

On national level the CAs should update their website accordingly.

Before starting the assessment phase all involved parties have the opportunity to submit relevant data with a time period of not more than 20 days.

4. Assessment step

The procedure has a total 90-day timeframe. The first 60 days are assigned for PRAC review and 30 days for the CHMP/CMD(h) decision.

Importantly, no clockstop is intended, nor is there an option for a re-examination procedure for MAHs.

The assessment step starts on the last day of the 2nd PRAC meeting following the receipt of the notification. The appointed PRAC Rapporteurs perform their assessment on the presented data before they circulate the preliminary assessment report (AR) by Day 20.

During the following PRAC plenary meeting, it is further discussed whether additional data is required or a hearing by the MAH or other stakeholders would be beneficial for a final recommendation. A consultation of the scientific advisory group (SAG) or other expert groups would also be feasible at this stage of the procedure (also at any other stage).

If further data is expected the next step of the procedure can be shifted, a new timetable should be circulated by the EMA.

Otherwise all PRAC members, the CHMP members (if CAPs are involved) and CMD(h) members with a leading role send their comments on the preliminary AR by Day 35.

By Day 45 the PRAC Rapporteurs circulate the updated version of the assessment report reflecting all comments to the EMA, all PRAC members and the concerned CHMP/CMD(h) members.

For transparency reasons the EMA forwards the ARs to the concerned MAHs.

On Day 60 the PRAC assessment step closes with the final recommendation.

The Art. 107i procedure timetable in short form:

Day	PRAC Assessment steps
1	Start on the last day of the 2nd PRAC meeting following the receipt of the notification
20	PRAC Rapporteur(s) circulate the preliminary assessment report(s)
25	PRAC adopts a draft recommendation based on the preliminary AR. Supplemental data, temporary measures, public hearing or oral explanation needed?
35	Comments by PRAC members, CHMP Rapporteur´s member (CAPs involved), CMD(h) member with leading role
45	PRAC Rapporteur(s) circulate an updated AR reflecting all comments and additional data received
50	Comments by PRAC members, CHMP Rapporteur´s member (CAPs involved), CMD(h) member with leading role
60	PRAC recommendation
Day	**CHMP / CMD(h) assessment steps**
	On Wednesday after the PRAC meeting: PRAC sends the recommendation to the CHMP / CMD(h) for adoption
(61)	Decision on next CHMP / CMD(h) meeting when recommendation is adopted immediately or within the next 30 days

61	When 30 days are required: Start is the last day of the CHMP / CMD(h) meeting
80	CHMP Rapporteur or CMD(h) member with leading role send their written comments on the PRAC recommendation
90	CHMP opinion and CMD(h) position are adopted.

Source: *Questions & answers on practical implementation of Urgent Union Procedure (Article 107i of Directive 2001/83/EC)* (20)

5. Content of the PRAC recommendation

The proposed PRAC recommendation must obtain the majority for decision. According to Art 107j(3) of Directive 2001/83/EC the recommendation should lead to the following results:

- Authorisation should be suspended, revoked or not renewed
- Variation of the MA is necessary such as changes in the Product Information, i.e. new contraindications, restriction of indications, reduction in dose or restriction in the availability of the MP.
- No further action required
- Data should be further evaluated by the MAH
- MAH should perform a post-authorisation safety study (PASS)
- Measures to reduce risk on the part of MAH or MS

6. CHMP/CMD(h) decision

On Wednesday of the following week the PRAC adopted recommendation and assessment report are forwarded to the CHMP in case at least one CAP is affected or to the CMD(h) in case no CAP is affected.

Opinion of CHMP

If the CHMP does not agree with the proposed recommendation directly on the following Monday (first day of the CHMP plenary week) a new 30 days time-frame will start:

On Day 20 the CHMP Rapporteurs give a written statement including a reader´s guidance. If necessary, an additional oral explanation is given.
On Day 30 the CHMP should give an opinion on the maintenance, variation, suspension, revocation or non-renewal of the MA(s) concerned (Art 107k(3) of Directive 2001/83/EC) by majority.

If the decision deviates from the recommendation, an equivalent representation of the reasons should be provided.

In any case the following documents should be included:

- Final assessment report and recommendation
  In case of a recommended suspension, revocation or non-renewal of the MAs the scientific results and requirements (including timelines for implementation)
- In case of an upcoming variation: revised PI for the CAPs and an annex for all national MAs containing the new safety warnings and risk minimisation measures in the concerned sections of the PI (including timelines for implementation)
- If applicable the disagreement between the CHMP members

For CAPs the usual way of closing the procedure is the EC decision. Thus, at the end the MAH(s), the EMA and the CA(s) receive the final decision by the EC.

According to Art. 107k(a) of Directive 2001/83/EC the EC shall address the final decision for national MA(s) to the CA(s) of the MS. The CA(s) for their part ensure the national implementation within 30 days unless otherwise specified.

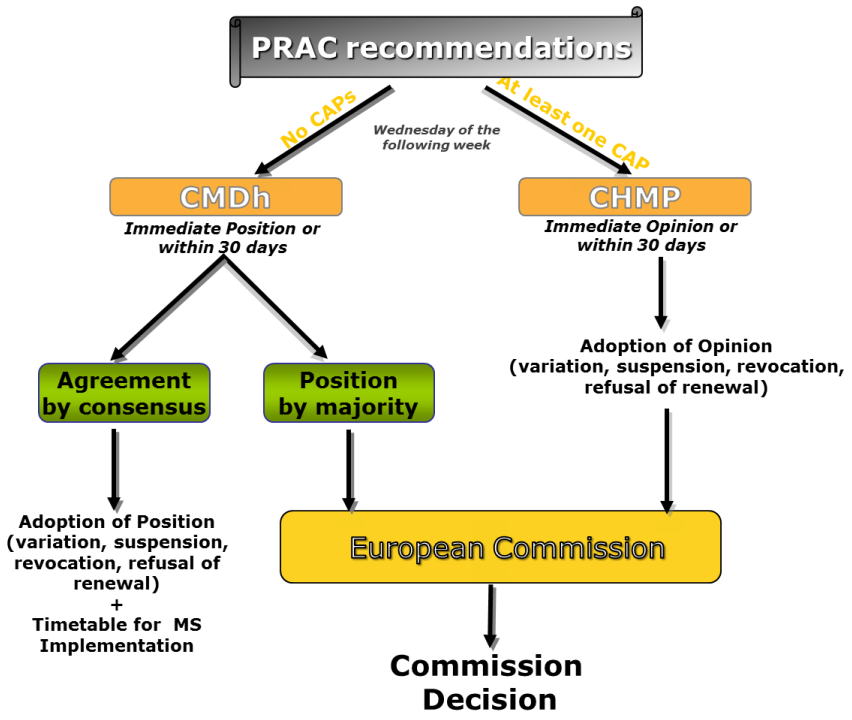
Position of CMD(h),

Analogous to the CHMP opinion the CMD(h) agrees either immediately on the final recommendation for only national approved MPs (including those authorised through the MR- and DC procedure) or within the next 30 days. In such a case the CMD(h) members with the leading role give their written statement by Day 20 before a consensus or a decision by majority is reached by Day 30.

In case of a consensus, the position is sent directly to the MAH(s) and CA(s). According to the agreed action the CA attends to its duty and implements the adopted measures.

In case of a CMD(h) position reached only by majority vote and not by consensus the position in addition to its accordant documents and annexes is sent to the EC for a legally binding decision.

Figure 1. Overview of the process for adoption of CHMP Opinion / CMD(h) Position



Source: *Questions & answers on practical implementation of Urgent Union Procedure (Article 107i of Directive 2001/83/EC)* (20)

5.1.2. Example

Tetrazepam-containing medicines EMEA/H/A-107i/1352

In January 2013 the EMA started an Art. 107i procedure. For the first time after implementation of the new pharmacovigilance legislation in July 2012 the PRAC made use of this instrument. It deals with tetrazepam-containing medicines. Tetrazepam is an active substance that belongs to the group of the so-called

benzodiazepines and is authorised nationally in 12 MS. It is indicated for the treatment of painful muscle spasm mainly in patients with rheumatological diseases.

A review of data based on the evaluation of the French National pharmacovigilance database was performed by the French medicines agency. It revealed that serious side effects affecting the skin arose at a higher rate compared to other benzodiazepines. In detail, serious concerns regarding the risk of Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome were raised (6).

France concluded that the overall risks appeared unacceptable and proposed suspension of the MA.

In case of a possible suspension an Art. 107i procedure is obligatory. Therefore upon France´s request, the EMA initiated an Art. 107i procedure in order to review all available data on the safety of tetrazepam-containing medicines with regard to cutaneous toxicity.

As described in the chapters above this review is assessed by the PRAC. After having published an official notification on 20 December 2012 (21) this safety issue was discussed at the PRAC plenary meeting in January 2013 and the Urgent Union Procedure was started with the following timetable (22):

Procedural step	Date
Notification	20 December 2012
Start of the procedure (PRAC)	January 2013 PRAC
List of questions	10 January 2013
Submission of responses	04 February 2013
Start of assessment (Day 0)	11 February 2013
PRAC Rapp AR(s) circulated to PRAC and to CMD(h) (Day 20)	03 March 2013
Comments (Day 35)	17 March 2013

Updated PRAC Rapp AR(s) circulated to PRAC and to CMD(h) (Day 45)	28 March 2013
PRAC recommendation (Day 60)	11 April 2013

By 10 January 2013 two LoQs that were discussed in the PRAC meeting were published on the EMA website. One was to be addressed by the MAHs including questions about the current status of the MAs and all reported cases regarding cutaneous reactions. The other LoQ was addressed to healthcare professionals, patients´ organisations or the general public. In the course of a referral procedure it was the first time that the EMA invited all stakeholders to submit data by 4 February 2013.

Data were submitted by the European registry of severe cutaneous adverse reactions to drugs (RegiSCAR database), by two patients and by different MAHs (23).

Belgium assumed the rapporteurship while France as the initiating MS acted as the CoRapporteur.

After having reviewed and discussed all relevant data on the risk of skin reactions with tetrazepam (post-marketing data in the EU and the published literature, and the available information on efficacy in licensed indications) the PRAC gave its recommendation by Day 60. Herein the PRAC concluded that tetrazepam in comparison with other benzodiazepines is associated with an increased risk of serious cutaneous adverse reactions. The clinical efficacy on the other hand showed no significant superiority against the comparators.

Risk minimisation measures such as an restricted indication or the option of a patient alert card were not considered effective enough to reduce the risks. As a result the PRAC concluded that the benefit no longer outweighs the risks and therefore recommended the suspension of the MAs for all MPs containing tetrazepam.

13 PRAC members did not agree with this recommendation and were of the opinion that the benefit/risk balance remains positive so that the MAs could be maintained.

As all MPs containing tetrazepam were authorised nationally (including authorisation via the MRP or DCP) in this case and no CAP is involved the CMD(h) gave its position to the final PRAC recommendation.

At the CMD(h) meeting in April 2013, the majority of the members endorsed the PRAC recommendation and adopted a final position that the MAs should be suspended throughout the EU.

As the CMD(h) position was not given by consensus in accordance with Art. 107k of Directive 2001/83/EC the CMD(h) position was sent to the EC, which took a legally binding decision on 29 May 2013.

5.2 Art. 31 ("Union Interest Referral")

A referral under Article 31 of Directive 2001/83/EC, as amended comes into operation whenever the interests of the union are involved. Generally the issues can relate to the quality, efficacy or pharmacovigilance of MPs. In accordance with the new legislation the matter will be referred to the PRAC in cases where the Art. 31 referral results from the evaluation of data relating to pharmacovigilance (Art. 107j(2) of Directive 2001/83/EC). Where the quality and/or efficacy of an authorised MP are affected the matter will be referred to the CHMP. This thesis deals exclusively with the Pharmacovigilance referrals.

Concerning the old pharmacovigilance legislation general guidance on Art. 31 referrals was laid down in Chapter 3 of Volume 2A of the Notice to Applicants (NtA) (24). Until now the only published guidance document on the Art. 31 pharmacovigilance referral is the common "*EMA questions and answers on referrals*" (25).In contrast to the Art. 107i referral procedure the Art. 31 pharmacovigilance referral cannot only be triggered by the MSs or the EC but by the MAH as well. Just as the Art. 107i procedure, Art. 31 is carried out for only one MP, a range of MPs or a therapeutic class independent of the type of approval (national authorisation including authorisation via the MRP or DCP and centrally authorisation). Therefore the new legislation extended the scope for the CAPs. If a range of MPs or a therapeutic class are affected the EMA may restrict the scope

on certain parts (e.g. pregnancy and lactation) of the MA (Art. 31(2) Directive 2001/83/EC, as amended).

Since Directive 2010/84/EC failed to clarify the rules regarding Art. 31 and Art. 107i procedures, Directive 2012/26/EC which must be implemented into national law in October 2013 gives further clearity on this matter:

According to Directive 2010/84/EC the Art. 31 procedure is to be used where no urgent action is considered necessary in all cases listed in Art. 107i (a-e). The Directive 2012/26/EC changed this criterion into: „*However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107k shall apply.';* Therefore the urgency of the matter is only a relevant decision criterion for the case, when it is considered that a new contraindication, a reduction in the recommended dose, or a restriction to the indication is necessary. Furthermore in accordance with Art. 31(3)(new) the safeguard clause from the old Art. 36(1) referral has been included so that in urgent cases, one MS can suspend the MA and prohibit the use of the MP at any stage of the procedure. It raises the question how and when there is the possibility for switching the legal basis to the Art. 107i procedure when one MS considers that the suspension of the MP on a EU wide level is necessary.
In cases where exclusively centrally authorised products are concerned the Art. 20 procedure of Regulation 726/2004/EC (see section 5.3) is the legal basis although it follows the process of the Union Interest Referral.

For transparency reasons the notification together with the list of concerned MPs and/or active substances and the summary of the PRAC plenary meeting are published on the EMA website.

5.2.1. Process

The new pharmacovigilance legislation stipulates that the PRAC is involved where the Art. 31 referral is invoked due to the data relating to pharmacovigilance.

The procedural steps are laid down in Art. 32, 33 and 34 of Directive 2001/83/EC. Similar to the Art. 107i procedure the Art. 31 referral has a 60-day time-frame. However, in this procedure a clock-stop can be included if necessary for the

preparation and submissions of responses (written and/or oral explanations). Thus, the time-frame can be extended to 120 days.

First, the MS, EC or the MAH(s) send an official notification of the referral to the PRAC and the EMA secretariat (Day 0). At the first PRAC plenary meeting after receipt of this notification the concerned safety issue is discussed. The PRAC adopts the LoQ in addition to the appointment of the PRAC Rapporteurs and decides whether an oral explanation or a public hearing is to be held (Day 1).

If triggered by the MS or the EC, the MAH gives responses to the LoQ within the following period of the clock-stop. The clock is restarted on Day 2 when the MAH has sent the responses. The appointed PRAC Rapporteur(s) have 20 days to circulate the assessment report to the involved parties (PRAC, CHMP concerned Rapporteur(s) or CMD(h) member(s) with leading roles if applicable). If the MAH is the initiator of this procedure there is no LoQ and no clock stop since the MAH submits the relevant data in the form of a report by Day 20.

After the concerned parties have given their statement within the following five days (Day 25) the next discussion at the PRAC meeting follows adopting the PRAC recommendation or the PRAC List of outstanding Issues that have to be answered writing or in a hearing. At this step a second clock-stop may follow before the clock is restarted on Day 31. If applicable, the MAH presents his data once again before the PRAC gives the final recommendation on Day 60.

The Art. 31 procedure timetable in short form:

Day	PRAC Assessment steps
0	Referral notification is sent to the PRAC/EMA secretariat
1	1st PRAC meeting following the receipt of the notification, 1st discussion on the questions (public hearing?, oral explanation?) Appointment of PRAC Rapporteur(s) Adoption of the PRAC LoQ
Clock-stop	

2 (restart)	Submission of MAH(s) responses to PRAC LoQ
20	PRAC Rapporteur(s) circulate the preliminary report on the MAH´s responses
25	Comments by PRAC members, CHMP Rapporteur´s member (CAPs involved), CMD(h) member with leading role
30	2nd Discussion at PRAC Adoption of PRAC recommendation or LoOI (public/non public hearing? oral explanation?)
Clock stop	
31 (restart)	If applicable submission of written responses and/or at the time of oral explanations
60	PRAC recommendation

Content of the PRAC recommendation

As described in Art. 32(4) of Directive 2001/83/EC the PRAC gives its recommendation on Day 60 with the following outcome:

- From the pharmacovigilance point of view the MA can be maintained under specific conditions or
- The Product Information should be corrected.
- The MA should be suspended, changed or revoked.
- The MAH should conduct further evaluation of data
- The MAH should conduct a PASS
- The MAH or MSs should implement risk minimisation measures.

CHMP/CMD(h) decision

The final PRAC recommendation is forwarded to the CHMP or CMD(h) respectively and is followed by the next procedural step as for the Urgent Union Procedure (Art. 107i) within the next 30 days.

In contrast to the Art. 107i and Art. 20 referrals a re-examination procedure in accordance with Art. 32(4) of Directive 2001/83/EC is still possible for this type of referral. Thus, within 15 days after receipt of the opinion the MAH should request a re-examination of the opinion followed by a 60-day- period to address the detailed grounds for the request to the EMA. In this case new Rapporteurs will be appointed.

5.2.2 Example

Diclofenac-containing medicines EMEA/H/A-31/1344

In October 2012 an Art. 31 procedure was started at the request of the United Kingdom concerning MPs containing diclofenac.

Diclofenac is an active substance belonging to the group of non-selective Non-Steroidal Anti-Inflammatory Drug (NSAID) which blocks the effects of both cyclo-oxygenase (COX) enzymes, known as COX-1 and COX-2. As a widely used type of medicine indicated to reduce pain and inflammation diclofenac has been in focus for its cardiovascular risk for many years as this is known from the selective COX-2 inhibitors (“coxibs”).

In 2006 the CHMP already concluded that in high-dose regimen and long-term treatment the risk of thrombotic events could not be excluded (26). As a result warnings about the risk of thrombotic events were included in the PI for all NSAIDs.

In October 2012 it was concluded in the context of the scientific review carried out by the CHMP (under Art. 5(3) of Regulation 726/2004/EC) that “*the accumulating evidence shows remarkable consistency in the reported results for diclofenac, which appears to be associated with thrombotic risks similar to those of coxibs*” (26). This review was based on additional studies and additional data from the EC that was available since 2006.

In the UK´s opinion, the warnings already included in the PI were insufficient and should be further expanded based on the evidence currently available. As diclofenac is a widely-used MP the “union interest” is given.

Regarding the classification into Art. 107i or Art. 31 referral (urgent or non-urgent) the UK was of the opinion that there was no need for an urgent action since the scientific data was not new and already published. Please notice that at this time the Directive 2012/26/EC amending Directive 2001/83/EC did not yet apply. For this reason, UK requested an Art. 31 referral for products containing diclofenac for systemic use.

Consequently the PRAC adopted a list of questions in the October 2012 plenary meeting addressed to the numerous MAHs in order to get adequately responses.

For details of the time-table please refer to the table shown below.

Procedural step	Date
Notification (Day 0)	17 October 2012
Start of the procedure (PRAC)	November 2012 PRAC
List of questions (Day 1)	31 October 2012
Clock stop	
Submission of responses (Day 2)	7 January 2013
Re-start of the procedure	11 February 2013
PRAC Rapp/CoRapp AR(s) circulated to PRAC and to CMD(h)	8 April 2013
Comments (Day 25)	22 April 2013
Updated PRAC Rapp/CoRapp AR(s) circulated to PRAC and to CMD(h) (Day 35)	2 May 2013
PRAC LoOI (Day 60)	16 May 2013
Submission of responses in writing	27 May 2013
PRAC Joint Rapp/CoRapp AR circulated to PRAC and to CMD(h)	3 June 2013
Comments	5 June 2013
Re-start of the procedure	11 June 2013
PRAC recommendation to CMD(h)	June 2013

In its recommendation on 13 June 2013 the PRAC stated that diclofenac for systemic use at high doses (150 mg daily) has similar cardiovascular risks as selective COX-2 inhibitors. Although the benefit/risk balance is still positive special risk minimisation measures effecting the heart and circulation should be implemented.

Since diclofenac is authorised only nationally in the EU the final recommendation was forwarded to the CMD(h) for a final position. Hence, in June 2013 the CMD(h) has confirmed by majority the PRAC´s recommendation on new safety advice for MPs containing diclofenac. The legally binding decision of the EC after the CMD(h) position by majority is still pending at the time of this thesis.

5.3 Art. 20

The Art. 20 of the Regulation 726/2004/EC applies to centrally authorised products (CAP) and allows the EC to request the Opinion of the EMA (Art. 20(2)). It comes into operation either for manufacturer and quality issues or for pharmacovigilance aspects. As this thesis deals exclusively with pharmacovigilance issues only the pharmacovigilance aspect will be discussed in this context.

5.3.1 Process

a) Art. 20(8) EC 726/2004:
The Art. 20(8) applies when solely CAPs (at least one) are affected. Procedures under Art. 31 and Art. 107i of Directive 2001/83/EC shall be used in case reasons for triggering an Art. 20 are based on the evaluation of pharmacovigilance data. Although in those cases the process and procedural steps of Art. 31 or Art. 107 of Directive 2001/83/EC are applied the Art. 20 remains the legal basis.

By means of the new Regulation 1027/2012/EC which provisions apply as of 5 June 2013 the paragraph 8 of Art. 20 has been changed as follows: The opinion of the EMA shall be adopted by the CHMP taking the recommendation of the PRAC into consideration.

b) Art. 20(9) EC 726/2004:
In cases where CAPs are involved in addition to nationally approved MPs the procedure follows the process of the union procedures laid down in Art. 31 and Art. 107i of Directive 2001/83/EC, as amended (see above).

Analogous to the Urgent Union Procedure no re-examination is intended for the Art. 20 referral.

5.3.2 Example

Tredaptive EMEA/H/C/889/A20/37
Pelzont EMEA/H/C/903/A20/38
Trevaclyn EMEA/H/C/897/A20/38

Tredaptive, Pelzont and Trevaclyn (active substances nicotinic acid and laropiprant) are identical MPs that were authorised via the CP on 3 July 2008. They are indicated in the treatment of adults with dyslipidaemia, particularly combined mixed dyslipidaemia and primary hypercholesterolaemia (27). In December 2012 the Art. 20(8) referral of Tredaptive / Pelzont / Trevaclyn was triggered after a large, long-term study called HPS2-THRIVE revealed that the combination of nicotinic acid / laropiprant with a statin did not reduce the risk of major vascular events. Furthermore, a higher frequency of non-fatal ADRs was observed.

On 21 December 2012 the PRAC started the review. As the PRAC considered that urgent action is required it followed the procedural steps of Art. 107i of Directive 2001/83/EC. Please notice that at this time the provisions of Regulation 1027/2012/EC amending Regulation 726/2004/EC did not yet apply.

The following timetable was adopted (27):

Procedural step	Date
Notification (Day 0)	19 December 2012
List of questions (Day 1)	20 December 2012
Submission of responses (Day 2)	27 December 2012
PRAC Rapp AR(s) circulated to PRAC and to CMD(h) (Day 20)	4 January 2013
PRAC recommendation (adopted)	January 2013
PRAC recommendation to CHMP	11 January 2013
CHMP opinion	January 2013 CHMP

In its recommendation dated 10 January 2013 the PRAC stated that the benefit/risk balance has become unfavourable and proposed suspending the MAs. As the CHMP in its January meeting confirmed this recommendation the CHMP opinion was sent to the EC which adopted the legally binding decision on 22 March 2013. A few weeks later (10 April 2013) the EC confirmed the withdrawal by the request of the MAH.

5.4 Art. 5(3)

5.4.1 Process

In accordance with Art. 5(3) of Regulation 726/2004/EC this procedure applies when the Executive Director of the EMA or of the EC asks the CHMP for an opinion on a scientific issue with regard to the evaluation of MPs. In some cases it will be applied to the request from a MS or where there is a disagreement in the assessment of MPs through a MRP. This procedure where in certain circumstances MAHs are also involved concludes with a “CHMP Scientific Opinion” that will be publicly available on the EMA website. If necessary the CHMP will advise the PRAC to give a recommendation on a specific matter, but no

further decision by the EC is provided for. The procedural steps do not follow by a fixed timetable.

5.4.2 Example

Octagam EMEA/H/A-5(3)/1309

Octagam is a human normal immunoglobulin for intravenous administration that is indicated to strengthen the body´s immune system in immunodeficient patients. As a result of a review under Art. 107 of Directive 2001/83/EC the MA of Octagam was suspended on 4 October 2010 following an increase in reports of thromboembolic reactions (28). In the mean time the unexpected presence of a pro-coagulant, factor XIa was identified to have caused these reactions. Therefore, the MAH has introduced several preventive measures like improving the manufacturing process. After a review in April 2011 the CHMP concluded under Art. 31 of Directive 2001/83/EC that Octagam can be placed back on the market.

Since Octagam is a plasma-derived product, the MAH wanted to rework the still existing batches. However, these batches were not produced corresponding to the improved manufacturing process. According to the relevant Good Manufacturing Practice guidelines, reworked batches should be specifically evaluated and tested.

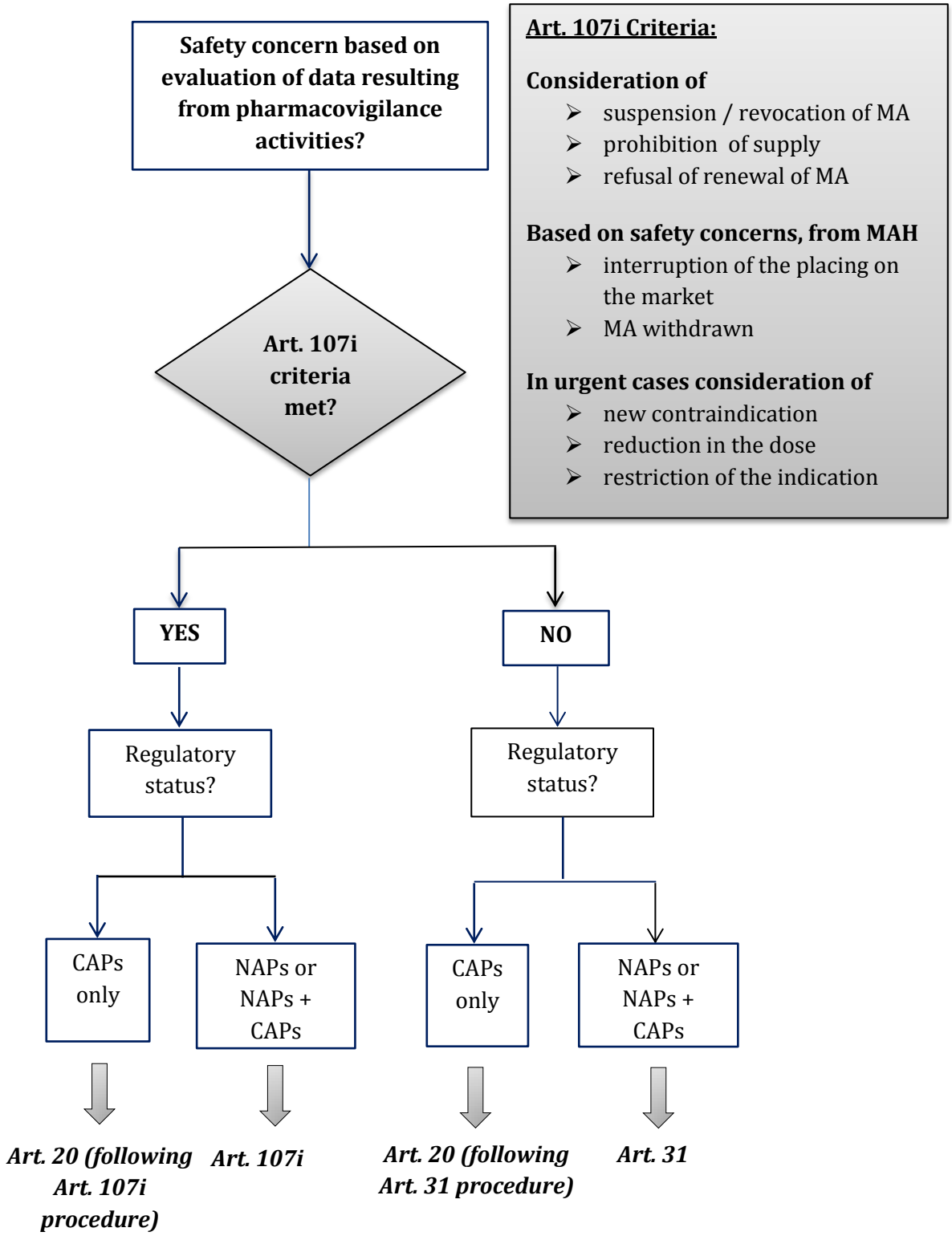
As the proposed re-processing procedure was rather complex and could apply for other immunoglobulin products as well, the German Paul-Ehrlich-Institut (PEI) requested the CHMP on 19 July 2011 to come to an opinion under Art. 5(3) of Regulation 726/2004/EC (29). The aim of this scientific opinion was to achieve a harmonised view on the reworking of Octagam batches.

After having assessed the quality as well as, preclinical and clinical aspects, the CHMP concluded that all in all the quality of the reworked Octagam was acceptable. However, further stability and clinical data together with more pharmacovigilance monitoring were considered necessary.

6. Decision tree

A proposal for a decision tree for the pharmacovigilance referrals is provided below. This chart is intended to streamline the major points of ramifications and is based on the latest amendment to Directive 2001/83/EC (by Directive 2012/26/EC) and to Regulation 726/2004/EC (by Regulation 1027/2012/EC)

Figure 2. Decision tree for pharmacovigilance referrals in line with Dir. 2012/26/EC (amending Dir. 2001/83/EC) and Reg. 1027/2012/EC (amending Reg. 726/2004/EC)



7. Procedural steps after the CHMP opinion / CMD(h) position

7.1 Translation process

As part of the Commission's decision-making process, a linguistic review of the Product Information is carried out once the CHMP opinion or the CMD(h) position is adopted. Useful information on this subject is available in the "*Practical information on translations for referrals and community procedures (human)*", published by the EMA on 14 November 2012 (30). Thus, on Day 5 after opinion / position the translations of the adopted Annex I (list of products) and Annex III (SmPC, labelling and package leaflet text) have to be sent electronically to the MSs and to the EMA´s secretary. Due to the short timelines and due to the fact that the Product Information has to be translated into each official EU language (21 + Norway and Iceland, if applicable), it is highly recommended that the MAHs be prepared for this process well in advance.

By Day 19 the MSs send linguistic comments on the PI to the MSs which have to be accepted by Day 22 after opinion / position.

By Day 27 the EMA forwards the final Annexes to the EC for the following 22-day Standing Committee consultation. Once the EC decision is adopted it is publically available in the Community register.

In case of a CMD(h) agreement by consensus, the EMA sends the final copies to the NCAs and publishes them on the its website.

7.2 National implementation

7.2.1 National implementation after EC decision

Following completion of a pharmacovigilance referral and adoption of the binding EC decision, the MSs must implement any measures on the MA (e.g. revocation or variation) within 30 days following its notification unless otherwise specified (Art. 34(3) of Directive 2001/83/EC as amended). If a variation of the Product Information is necessary, the MAH is obliged to submit a Type IA_{IN} variation within 10 days in case the MPs cover the defined scope of the Commission Decision (31).

7.2.2 National implementation after CMD(h) position by consensus in Germany

When an Art. 31 or Art. 107i pharmacovigilance referral is adopted by a CMD(h) position reached by consensus, no further EC decision follows. In case the Product Information is amended as a result of risk minimisation measures it is the obligation of the MAH to submit a Type IB variation within 60 days. The reason for this is described in Section 11a(d) of the Arzneimittelgesetz (= AMG, German Medicinal Products Act) in connection with Art. 23 (3) of Directive 2001/83/EC and Art. 26 of Regulation 726/2004/EC. Therefore, the MAH is obliged to update the German “Fachinformation” (corresponds with the SmPC) in the light of scientific knowledge. In accordance with Section 30(3)1 AMG, the MAH is entitled to be heard in case of variations to the MA unless there are exigent circumstances. This fact has been implemented in Section 30(3)2 of the AMG (latest amendment: “*Zweites Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 19.10.2012*“, Bundesgesetzblatt I S. 2192(31). Thus, there is no possibility for the MAHs to invoke an official hearing in cases of CMD(h) positions agreed by consensus.

Furthermore, the MAH should stay abreast of current developments by referring to the European medicines web-portal which makes assessment reports, recommendations and other information publicly available (cf. Art. 11f of the Commission Implementing Regulation 520/2012/EC). (32)

8. FEES

The EC impact analysis estimated that a minimum of € 237 million per year could be saved by means of the new Pharmacovigilance legislation (15) (14).

Nonetheless for conducting of the new pharmacovigilance activities, especially for the PRAC the EMA needs money that will be retrieved from the pharmaceutical industry. The legal basis for this is laid down in the changed Art. 67(4) of Regulation 726/2004/EC.

In June 2012 the EC released a “Concept paper on the introduction of fees to be charged by the European Medicines EMA for pharmacovigilance” (33) to which the stakeholders were invited to reply.

Since as of now the EMA is involved in pharmacovigilance activities of nationally approved MP (including MRP/DCP) the fees will apply to all MPs. For an EU-wide assessment of a PSUR or for the assessment of each final study report of a PASS the EC has proposed new fees of €80,300.

For an assessment of pharmacovigilance referrals the fees shall range from €80,300 to a maximum of €267,400 depending on the complexity. The maximum amount would be due if the workload is comparable to the assessment of an initial MA.

Additionally a pharmacovigilance service fee of a maximum of €1,000 per year per MP is payable. For small and medium-sized enterprises a reduced fee is suggested and, for micro-enterprises a remission.

The responses to the public consultation were published on 30 November 2012 (34). Most of the stakeholders did not agree with the high amount of fees especially against the background that the new legislation should reduce the costs.

With regard to the pharmacovigilance referrals the respondents did not understand the maximum fee (€267,400) and argued that a full benefit/risk assessment is much broader than the assessment of a referral. They said that it should be taken into consideration that a referral may be followed by a Type II variation that is also subject to a fee.

The EC decision on this is still pending. Currently, the pharmaceutical companies have no other option than to wait and see which costs are in store for them.

9. CONCLUSION AND OUTLOOK

The new pharmacovigilance legislation affects the way post-marketing surveillance is carried out. The new legal framework is based on two pillars: the first one is related to the process that has to be well structured and defined where the involved parties know their roles, responsibilities and obligations. The second one is related to the collecting and managing of safety relevant data which is essential for a proper identification of potential risks and a potential regulatory action.

The new legislation clarifies the scope of Art. 31, Art. 20 and Art. 107: In accordance with the first amendment of Directive 2001/83/EC (Directive 2010/84/EC) the Art. 107i only applies in cases where urgent action is considered necessary. Otherwise Art. 31 or Art. 20 (only for CAPs) have to be executed.. The latest amendment to Art. 107i (by Directive 2012/26/EC) provides an automatic assessment including an EU safety evaluation and possible EU-wide withdrawal of the MP in certain circumstances. One example for this procedure is when an MS withdraws a product or a company decides not to renew the MA for safety reasons. Hence, the new legislation introduces the Art. 107i referral as a standard procedure in case of pharmacovigilance issues.

In the past, pharmacovigilance referrals took too much time until they resulted in a binding decision. As this procedure does not provide for a clock-stop there is the chance to take regulatory action as quickly as possible in case of serious safety issues. The safety expertise that underpins this procedure comes from the PRAC that plays a key role in the pharmacovigilance assessments - not only for the referrals. This committee ensures that appropriate regulatory action is taken in a timely manner. Concentrating all the expertise for an evaluation at one central body helps to ensure a consistently high level of assessment. Once a recommendation is given, the CHMP or the CMD(h) have the task of adopting the decision/opinion. Thus, the role of the CMD(h) has additionally been strengthened as well. If the CMD(h) opinion is made by consensus no further EC decision will follow.

Now the EMA – via PRAC - has a stronger role in direct involvement in pharmacovigilance issues that are related to NAPs.

The deletion of Art. 36(1) cuts out a duplicative and confusing procedure and clarifies the demarcation to Art. 31 and Art.107.

Another important development is the increasing involvement of patients and patient organisations. While in the past the patient´s reporting of ADRs to the reporting systems was allowed in some MSs (e.g. the United Kingdom and the Netherlands) the EC now permits this individual reporting on an EU wide level. Furthermore a public hearing has become possible during the Art. 107i procedure as well as the participation of patient organisations in the PRAC.

From the regulatory perspective the pharmacovigilance system has taken a great step forward. However, it has not yet been proven if these changes contribute to a better drug surveillance and thus to an increase in drug safety.

Obtaining information about the drug´s safety at an early stage in a timely manner is essential for the future. The role of the patients is currently changing. Nowadays patients are highly informed about the disease and want to play an active role in their medical treatment. Therefore the growing involvement of patients in the reporting of ADRs can help to ensure that the information gathered leads to more communication and to a broader and more accurate assessment.

The pharmacovigilance referrals are an instrument for taking regulatory action needed to protect public health, e.g. by changing the PI or revoking the MA. The future pharmacovigilance system has to identify new safety issues without delay. Especially the new Urgent Union Procedure can help to put this into practice. Examples like the “Mediator case” show that apparently scandals are necessary to force governments to an adequate reaction. In addition it shows that there is a need for an automatic and swift procedure quite independent of the initial route of authorisation and presence on the market.

The automatic updating of the list of MPs, the obligation to inform the competent authorities of as to why a MA has been withdrawn and the automatic initiation of Art. 107i procedure can be appropriate measures to improve the surveillance of MP safety. From the viewpoint of the pharmaceutical industry the new information and transparency requirements that are imposed on the MAHs are not exorbitant and can help the EMA and the NCAs to detect risks in MPs more easily.

On the other hand it remains to be seen if at the time of initiation it is really obvious whether the Art. 31 or Art. 107i should be triggered. Is it distinguishable at the beginning of the process whether the procedure will end with the introduction of a new contraindication or with the suspension from the market after all? How it is possible to switch the legal basis from one referral procedure to the other?

Since the implementation of the new legislation no public hearing has been taken place. It is very questionable how the EMA wants to handle such an event where probably a few hundred people are involved.

In accordance with Art. 1(11) of Directive 2001/83/EC as amended the definition of “adverse reaction” has been changed. The reference to “under normal conditions of use” has been deleted so that a favourable benefit/risk balance can possibly be overturned. As a consequence regulatory action by triggering a pharmacovigilance referral can now be taken even if the safety issues are concerned outside the terms of the authorisation, e.g. misuse, overdose or off-label use (35). Due to the higher sensitivity to urgent issues and to more ADR reporting the number of safety referral may further increase.

For the EMA the implementation of the new legislation is a challenge. As a result of the improved transparency a large number of documents and requests have to be handled. Especially the automatism of initiating the Urgent Union Procedure will raise an enhanced need for personnel and finances at the EMA.
In its “Road map to 2015” that was published on 26 January 2011 (36) the EMA underlined its strong desire and motivation to strengthen the post-authorisation phase.

However, not only from the regulatory point of view but rather from the scientific perspective the frequency of adverse drug reactions can be reduced. At the time a physician has to decide which MP is the most appropriate one for a patient he/she has to ask himself/herself the following questions: is this patient vulnerable to the ADR connected with the MP? Is it possible to avoid this ADR by choosing an alternative drug? In most cases the physicians do not have an answer to these questions. The relatively new field of pharmacogenetics could give useful information on the responder rate of the given MP and the prediction rate of special ADRs. (37)

The pharmacovigilance legislation especially the further amendment in 2012, is still rather new. More practical experience and more time will show whether hospitalisations and the severe cases of ADRs decrease and whether the new legislation is really able to fill the gaps in European drug safety monitoring systems.

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

Weilerswist,

Unterschrift