Response regarding PCIM/1101 – Public Consultation on Implementing Measures for Pharmacovigilance

1. Introduction

1.1. Who is ECHAMP?

Homeopathic and anthroposophic medicinal products cover a broad portfolio of effective, safe and high quality medicines derived mostly from natural substances.

ECHAMP stands for European Coalition on Homeopathic and Anthroposophic Medicinal Products. ECHAMP is a European Economic Interest Grouping (EEIG) of companies active in the production and distribution of those products. Our members mainly are SMEs and we are registered in the transparency register of the Commission and the Parliament with the user number: 48260423804-68.

ECHAMP represents the majority of the manufacturers of Europe's homeopathic and anthroposophic pharmaceutical industry with at the moment 51 member companies. Our niche in figures amounted in the year 2010 to 1009 million Euros in turnover, 8,000 employees and more than 110 million active users throughout the EU Member States.

We endorse the rights of patients and consumers to have easy and comprehensive access to homeopathic and anthroposophic medicinal products which meet the highest standards of quality, safety and effectiveness.

1.2. Where is our specific concern in respect of this consultation?

It is the aim and the obligation of our industry to watch over the quality and the safety of the medicinal products that we produce. Pharmacovigilance is an indispensable tool related to public health and patient safety and it has to be a main priority in an unchallenged way. Homeopathic and anthroposophic medicinal products generally have a highly positive risk profile: Compared to the overall burden of adverse drug reactions in conventional pharmaceutical industry, the occurrence of adverse drug reactions in our field is extremely rare.

In addition, we would like to stress that, in homeopathy and anthroposophic medicine, the range of essential remedies is considerably larger than in other fields of the pharmaceutical industry. Indeed, due to the strongly individualised character of their therapeutic approaches, homeopathy and anthroposophic medicine need a large range of starting materials (in the range of thousands) and of specific medicinal products. A large number of them have a low to very low turnover. ***This leads to the consequence that our member companies maintain an amount of authorisation applications from several hundreds to more than thousand***. ***In terms of finished medicinal products the figures can cover up to 400.000 different finished products per company*** (refer to 1.3).

Therefore, it is of an extreme economic importance for homeopathic and anthroposophic industry, which consists mainly of SMEs, that the regulatory and administrative burden linked to Pharmacovigilance should be rationale, efficient and proportionate to the very low risk profile i. e. it should stay restricted to a minimum while of course guaranteeing the quality and the safety of the products. It goes without saying that the relevant fees should be fair, too.

So, a rigid, clear and efficient system of pharmacovigilance, which is not overloaded by purely administrative measures without added value to patient safety, is needed for homeopathic and anthroposophic pharmaceutical industry in Europe.

1.3. In which legal background is the consultation on concept paper to be seen?

Placing on the Market:

We consider helpful to give an introduction into about the specific conditions of placing on the market on homeopathic medicinal products. These specific rules are linked to the very specific pharmaceutical characteristics of homeopathic medicinal products as such. And these conditions are ***highly relevant to a specific aspect of implementing pharmacovigilance rules into practice, namely the "databases"***.

Today, homeopathic medicinal products are marketed in the EU Member States based on national authorisation procedures. They can be based on simplified registrations according to Art. 14 of Directive 2001/83/EC or marketing authorisation based on Art. 16.2 of the Directive 2001/83/EC. Or the marketing is based on so-called "grandfather rules" in accordance with Art. 13 of the same Directive.

As pointed out above, ***the order of magnitude of files to be maintained per authorisation holder can easily meet the figure of 500 or 1.000 or more***, while the turnover gained per file is low to very low.

Due to the special characteristics of homeopathy, the principle of producing several potencies and also dosage forms from one starting material, one single registration number may cover a magnitude of finished products. These are derived from the different types of dilution used in homeopathy (decimal, centesimal, quintesimal and Korsakov) and the different degrees of dilution. These degrees of dilutions may exist in different administration forms. This results in a fast multiplication of the number of finished products per application. Legally this principle is implemented in Art. 15 of the Directive 2001/83/EC: According to this article an application (in accordance to Art. 14) may cover a series of medicinal products from the same starting material. ***As a conclusion, a series of finished products may be authorised per registration file and registration number.***

Although the provision regarding the series of medicinal products per application explicitly is found with respect the Art. 14 procedures only, this principle also applies to other ways of placing on the market as for example the medicinal products, which are on the markets due to national "grandfather rules" in accordance with Art. 13.

***In fact a company may place on the markets an amount of medicinal products in terms of finished medicinal products in the order of magnitude of thousands to hundred thousands*.**

There are other legal rules specific to homeopathic medicinal products in the Directive 2001/83/EC: With respect to labelling and package leaflet for the applications according to article 14, they are laid down in article 69 of the Directive. An explicit requirement for a package leaflet does not exist. In view of the very specific catalogue of content for labelling and, if applicable, package leaflet the necessity and possible content of an SPC is not clear from a European legal point of view. So far, this point is left open by the EU legislator and Member States seem to handle the requirement of an SPC for the simplified registration applications in different ways. In addition, the Member States provisions for homeopathic medicinal products as granted according to article 13 of the Directive with respect to package leaflet and SPC are heterogeneous.

Some pharmacovigilance aspects:

In this section we consider helpful to give an introduction on the specific legal provisions regarding Pharmacovigilance as far as they refer to homeopathic medicinal products. This is relevant for the understanding of implications for the Eudravigilance database.

For the simplified registrations according to Art. 14 of Directive 2001/83/EC Chapter IX of the Directive does not apply (refer to article 16.3 of the Directive) on a European base. *However, certain Member States require some aspects of chapter IX for Art. 14 products like for example reporting of adverse drug reactions. In the same way the national rules for medicinal products authorised according to Art. 13 are different. Some Member States require reporting of adverse drug reactions.* ***This means, that although not relevant from a perspective of the EU Directive, for different national legal reasons, adverse drug reaction reporting has to be managed for these kinds of products, where one registration file covers many medicinal finished products*** (see above).

In addition, Chapter IX legally applies to medicinal products placed on the market based according to Art. 16.2 of the Directive.

For all categories of products where the European legislator or certain Member States foresee reporting of adverse drug reactions, the provisions of Art. 107 of Directive 2001/83/EC as amended by Directive 2010/84/EU will apply. This includes reporting of suspected serious adverse reactions within 15 days and suspected non serious adverse reactions within 90 days to the database according to Art. 24 of Regulation (EU) No726/2004.

The "European Database"

In this section we consider helpful to shortly analyse the legal situation with respect to the "databases" to be organised by the EMA. ***For our industry, the issue of the "databases" seems to become the utmost important aspect linked to the implementation of pharmacovigilance measures with respect to our specific medicinal product category*.** Respectively the functioning of the "databases" linked to our medicinal product categories as well as the need to keep realistic scenarios for the maintenance of these databases is of highest relevance.

According to Art. 24 of Regulation (EU) No 726/2004 the EMA shall set up a database and data processing network, namely "the *Eudravigilance database*". For this, *the EMA* shall collaborate with the *Member States* and the *Commission*. This is the "database" to take up "information on suspected adverse reactions in human beings arising from use of the medicinal products" (art. 24(1) second subparagraph). The "Eudravigilance database" is not determined to be made public.

In addition to the "*Eudravigilance database*", provisions for "a second database" are to be found in Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010: Art. 57(2) requires that "*marketing authorisation holders* shall, by 2 July 2012 at the latest, electronically submit to the Agency information *on all medicinal products for human use authorised or registered in the Union,* using the format referred to in point (a)" (subparagraph 2). This "d*atabase on medicinal products*" "shall include the summaries of products characteristics, the patient or user package leaflet and the information shown on the labelling" (art. 57(2) first subparagraph) and "where appropriate, …data on clinical trials currently being carried out or already completed" (art. 57(2) 3rd subparagraph). The content of this "database" is determined to be made accessible to the general public.

Confusion is generated by the Legal Notice (EMA/505633/2011) with respect to the differentiation between the "*Eudravigilance Database*" in responsibility of *EMA*, *Member States* and *Commission* (where marketing authorisation holders just are responsible for the reporting of adverse drug reactions) on the one hand, and the "*medicinal products database*" where the m*arketing authorisation holders* are responsible for data input, on the other hand.

Formally, the Legal Notice refers to the requirements for the electronic submission of information on medicinal products for human use authorised or registered in the Union as provided for in Article 57(2), second sub-paragraph of Regulation (EC) No 726/2004. However, in addition to the legally defined data of the Summary of Products Characteristics, Labelling and Package Leaflet, a huge catalogue of additional data is requested from the marketing authorisation holder respectively registration holder. We do not see any legal base for (1) asking for these data in the context of this database nor (2) for making these data public.

This leads us to the suspicion that the contents of both "databases" of different responsibilities - as legally provided - is somehow mixed.

Therefore, it is essential to distinguish between the sets of data to require for each database because of the different legal starting points concerning homeopathic medicinal products. In addition, as we will show below, the "medicinal product data base" should be based on registrations, in order to keep the database functioning. On the other hand, reporting of adverse drug reactions into Eudravigilance, as far as applicable, is connected with adverse drug reactions linked to specific individual finished products; however, the administration of an information background (eventually a metadata background) again should be based on registrations in particular on "stocks" or "series of potencies" *(see 1.3).*

2. Comments

We will leave the comments relevant to all pharmaceutical applicants and to the general associations of pharmaceutical industry, which are not specifically focused on homeopathic medicinal products. By our reaction on the present consultation we intend to direct your attention to different aspects which are particularly relevant from the perspective of European homeopathic and anthroposophic pharmaceutical industry.

2.1. Comments beyond the consultation items

Apart from the concrete items asked for consultation the issue of the European "database" touches some needs which are highly crucial to our industry due to the specific characteristics of our products. As the database is linked to the implementation of measures in order to harmonise the performance of the pharmacovigilance activities as provided for in Directive 2001/83/EC and Regulation (EC) No 726/2004, we consider necessary to address related issues in the frame of the present consultation.

Both databases, the "Eudravigilance database" as well as the "medicinal products database", are relevant to our industry. Due to the different type of information legally foreseen to be put in as well as due to the different legal background, we consider necessary to distinguish with respect to homeopathic medicinal products.

We express our need to touch the administrative conditions not only for the "Eudravigilance database" but also for the "medicinal product database" from the perspective of our category of products in the frame of the current consultation; this is mainly motivated by the fact that the Legal Notice (EMA/505633/2011) requires data for the "medicinal product database" which we would expect more related to the "Eudravigilance database".

Considering the "medicinal products data base"
According to Art. 57(2) of Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010

➔ *marketing authorisation holders* shall, by 2 July 2012 at the latest, electronically submit to the Agency information on all medicinal products for human use authorised or *registered* in the Union (art. 57(2) subparagraph 2).

- **It is indispensable for registered homeopathic medicinal products that the format of the data sets is flexible enough to allow information to be put in based on the "unit" of a "stock" respectively of a "series of medicinal products" (instead of expressing it in the "unit" of individual finished products). The unit would be for example the application, respectively the registration or authorisation.**

Reasons:

Insisting on a finished product related format just would make it impossible for manufacturers of registered homeopathic medicinal products to use the database. Respectively, without knowing the technical solutions behind the database, we are afraid that a finished product related format would overload the capacity of the database.

This is due to the fact, that one of the specific characteristics of homeopathic pharmacy is the huge amount of finished products resulting from one starting material. For example, some of the ECHAMP member companies do offer more than 400.000 finished products based on around 1.500 different starting materials (for more explanations refer to 1.2 and 1.3).
The principle of communicating based on units of "series of medicinal products" is recognised by the EU legislator as well as by the EU Member States agencies at different places:

* Art. 15 of Dir 2001/83/EC: "An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks. The following documents shall be included with the application….:- scientific name of other name given in a pharmacopoeia of the homeopathic stock or stocks, together wit a statement of the various routes of administrations, pharmaceutical forms and degree of dilution to be registered;"

* The way of data presentation in an independent specific application form for homeopathic medicinal products in the Notice to Applicants: "Homeopathic stock(s) and *potenc(ies)"* (that means several finished products*)* are presented in one application form.
http://ec.europa.eu/health/files/eudralex/vol-2/b/applicformhomeo_2005_12_en.pdf

* CMD(h) advice with respect to the number of application forms for registrations of homeopathic medicinal products in a MRP of DcP of homeopathic medicinal products: The Member States agreed that only one application form per homeopathic stock for the same pharmaceutical form is needed in the case of several dilutions of a homeopathic stock http://www.hma.eu/214.html.

- **The time frame between publishing format and technical requirements and deadline for data input has to be proportionate with respect to the amount of applications per manufacturer being SMEs**

Reasons:
* Our member companies mainly are SMEs (refer to 1.1)
* The number of applications per manufacturer in our field may cover an order of magnitude between several hundreds to more than thousand with a low to very low turnover per finished product (refer to 1.2 and 1.3)

- **The administrative burden for the maintenance of the database has to be proportionate. This means, that the set of metadata of the database to be maintained over the life cycle of the products has to be limited to the data which are essential for the purpose of the exercise "information to the general public"**.

Reasons:
* Our member companies mainly are SMEs (refer to 1.1)
* The number of applications per manufacturer in our field may cover an order of magnitude between several hundreds to more than thousand with a low to very low turnover per finished product (refer to 1.2 and 1.3).
* Active substances for homeopathic medicinal products are generic. The manufacturing processes as well as the quality testing criteria are published in the European Pharmacopoeia respectively in official national or pharmacopoeias. Therefore there is absolutely no need, to require product specific data on homeopathic substances from all companies.

- **The set of information requested has to be limited to the definitions given by article 57(2). So far, we do not see the legal base for the set of additional data required by Legal Notice (EMA/505633/2011) section 3 point i) to xiv).**

Reasons:
As above, this is again an indispensible necessity for reasons of proportionality. The administrative burden for this particular industry are unnecessarily high in relation to the aim for which this measure is applied, i. e. to properly inform the general public about registered or authorised homeopathic medicinal products and their generic character (see above).

The requirement of additional data is legally even more critical for the category of homeopathic medicinal products, registered according to article 14 of Dir 2001/83/EC, as chapter IX of the Directive does not apply to this type of products. However, art. 57 of the Regulation above does apply. Refer to the explanations given under 1.3.

- **The technical requirements for the data entry and the format of the data sets has to be flexible enough to consider, that certain information as package leaflet or summary of product characteristics may not exist for all medicinal products.**

Reasons
Refer to the explanations given under 1.3 on the products registered under the regime of Art. 14 (simplified registration) or Art. 13 (national "grandfather rules").

Considering the "Eurdravigilance data base"
According to Article 24 of Regulation (EC) No 726/2004

➔ "Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 … information on all serious suspected adverse reaction….., shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions…" (Art. 107 (3) of Dir. 2001/83/EC)

➔ "In order to harmonise the performance of the pharmacovigilance activities… the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in ….(c) the use of internally agreed terminology, formats and standards for the performance of pharmacovigilance activities; …. (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and marketing authorisation holder; " (Art. 108 of Directive 2001/83/EC).

The same needs and criteria as given above for the database according to Article 57 of Regulation (EC) No 726/2004 also apply to this database:

Especially with respect to the following issues:

- **Adverse drug reactions, as a matter of principle, are related to defined finished products. However, for the same reasons as given above, it is necessary to be able to link this finished product related information to a set of metadata, which is based on the "unit" of a "stock" respectively a "series of medicinal products" (instead of expressing it in the "unit" of individual finished products)**
- **The administrative burden for the maintenance of the database**
- **Flexibility of technical requirements and data sets for niche products with own criteria**

Our member companies have a need to technically stay able to report adverse drug reactions linked to simplified registrations for partially national reasons. However, for reasons of proportionality the set of metadata to be asked for must be limited to the absolutely minimum essential for the purpose of the exercise "pharmacovigilance".

2.2. Comments regarding the consultation items

Consultation items no. 11 and no. 12

ECHAMP and its member companies are too small in order to have own capacity to enable to track the standardisation processes behind the respective ISO norms (refer to 1.1).

However, we clearly are aware that ISO is an international standard. In consideration of the international standardisation process behind such norms we doubt and are afraid if certain specific necessities for the declaration of product category niches as homeopathic medicinal products with all their particularities will be considered.

Therefore we call the EU Commission

- **To take due care of the specific needs of niches of product categories which usually are marketed by the SME of the EU**
- **To mandate the delegates of the EU in the relevant ISO committees to consider certain specific terminology needs of homeopathic medicinal products**
- **To instruct the EMA to establish a database where sufficient flexibility is provided if certain terminologies will not be suitable to certain types of products.**

Reasons:
This is a matter of specificity of the product category as well as a matter of proportionality.