Annex 1

Towards Harmonised Birth Dates of Medicinal Products in the EU[1]
revision 1, adopted by HMA through written procedure on 17 October 2005

This document was originally adopted by the Heads of Medicines Agencies (human) under the title **"Towards Harmonised Active Substance Birth Dates"** on 13 September 2004. It was felt necessary to update the document for several reasons:

- The Commission has expressed the view that the project is aimed to harmonise the PSUR submission schedules of medicinal products containing the same active substance, rather than to harmonise birth dates of active substances for which it is difficult to find a legal basis. Therefore the term "harmonised substance birth date" has been replaced with "harmonised birth date of medicinal products containing the same active substance" or simply "harmonised birth date";
- To take into account that Review 2001 has changed the 5-yearly PSURs into 3-yearly PSURs;
- To take into account that in the revised Vol. 9 "PSUR cycle" has been replaced with "PSUR submission schedule";
- To improve the text where this has been subject to questions for clarification.

The aim of the revised document has not changed.

1. Introduction

The submission schedule for PSURs of an authorised medicinal product is triggered by the so called birth date of the product concerned. Each product has a birth date determined by the authorisation date of the product. The International birth date (IBD) is the date when the product was first authorised and the EU birth date is the date it was first was authorised in the EU (these may be the same date). In order to meet regulatory requirements in individual member states, in practice, PSUR submission is usually based upon national birth dates. However, when a product has different national birth dates in different member states it will have different PSUR submission schedules. In the Mutual Recognition procedure the Renewal dates and PSUR submissions are harmonised by the RMS. However, there are still many nationally authorised products where this is not the case which makes it difficult to share the workload of PSUR assessment among the Member States. The European Risk Management Strategy Facilitation Group of the HMA has proposed that the PSUR assessment workload for national as well as mutually recognised authorisations may be shared. The procedure is described in the Paper 'Principles for PSUR Work Sharing' from the Joint MRFG/PhVWP Working Group and the project is now in the pilot phase.

Furthermore, it is not efficient for pharmaceutical companies to have different PSUR submission schedules for the same product in the different EU member states. Although Volume 9 of "The rules governing medicinal products in the EU" points to the possibility of applying for a change in the birth date in order to achieve the same birth date in the whole EU this facility has not been widely used by the industry. In addition, generic products have their own PSUR submission schedules and therefore it is not easy to keep the safety information in the SPCs of innovator products and generics in line with each other.

[1] This document is not applicable to centrally authorised products

In summary it can be said that:

- All pharmaceutical companies are faced with different PSUR submission schedules for many of their nationally approved products in the EU Member States. This results in unnecessary duplication of work and may have a negative effect on the quality of reports.
- All national competent authorities are faced with the problem that it is difficult to share PSUR assessment activities among the Member States because of different birth dates for the same product in the different Member States.
- Innovator products and generics usually have different birth dates which make it difficult to maintain similar safety information in the SPCs of similar products.

2. The principle of harmonised birth dates (HBD's)

The difficulties described above could be reduced substantially if all medicinal products containing the same active substance had the same birth date throughout the whole EU, i.e. HBD. If this could be achieved the production of PSURs by industry and the assessment of PSURs by competent authorities would become much more efficient.

3. Advantages of HBD's for industry

What the innovative industry will gain is that they will have to prepare only one PSUR (for the product or product range) once in three years time, to be used throughout the whole EU. What the generic industry will gain is also a reduction in the number of PSUR submissions and the opportunity to prepare PSURs together, for instance as a consortium, and hence share the workload.

4.1 New line extensions and HBD's

The PSUR submission schedule of a new line extension should be agreed as a condition for the granting of the marketing authorisation (Article 104(6) of Directive 2001/83/EC). The PSUR submission schedule for a new line extension will usually be identical to the one already in place for the authorised products containing the same active substance. However, there may be valid reasons for amending the PSUR schedule for the line extension, at least initially. For example, approval of a new route of administration may require that 6-monthly or yearly PSURs are submitted for a period after authorisation with subsequent phasing in of the PSUR submission schedule with that of the other products. This will have to be decided on a case by case basis.

4.2 New generics and HBD's

The PSUR submission schedule of new generics should be agreed as a condition for the granting of the marketing authorisation (Article 104(6) of Directive 2001/83/EC). The PSUR submission schedule will usually be identical to the one already in place for the related innovator product(s). In the case of specific safety concerns, it may be more appropriate to start with PSUR submissions at a higher frequency, but this should be decided on a case by case basis, for example, in circumstances of:

- An active substance which is a different salt/ester complex/derivate (with the same therapeutic moiety)
- The presence of an excipient without an established safety profile
- A specific risk management plan in place for the corresponding innovator product requiring specific monitoring.

Phasing in of the PSUR submissions with that of the other products containing the same active substance may be achieved through an early renewal of the marketing authorisation. So, the first PSUR of a new generic would normally cover a period of up to three years depending on the HBD of the other products containing the same active substance. The second PSUR would then cover a period of three years.

5. Assignment of HBD's

The introduction of HBD's would mean that for the vast majority of products the current PSUR submission schedule has to be amended. If the initiative to change the birth date of an MRP product is taken by the MAH, under current legislation, a Type II variation procedure has to be followed. However, the situation where the initiative is taken by the competent authorities falls outside the scope of the EU legislation regardless of the registration procedure followed for the product concerned. If both the MAH and competent authorities can agree a HBD (which would require an amendment of the current PSUR submission schedule in some member states) the change is a simple administrative change which has no implication for public health. A prerequisite is that the period covered by a PSUR will never be longer than three (five) years, and all member states should accept PSURs covering a period shorter than three (five) years as an interim measure.

5.1 Procedure for the assignment of HBD's

A possible procedure for the assignment of HBD's is the following:
A Joint Action Group of representatives of the MRFG, PhVWP and industry associations will ask the headquarters of the pharmaceutical companies to come forward with proposals for HBD's for their innovative products. (Definition of innovative product: medicinal product containing a certain active substance for which the company is the first MAH in the EU.) The MAHs are free to take into account birth dates already applicable outside the EU and to propose an international birth date. Normally the proposals for HBD's will be accepted as such. Fixed combination products should preferably have the same birth date as the HBD of one of the related single substance products.

EFPIA have been found willing to take on the secretariat for sending out the request to company members of their association and to collect the proposed HBD's. The Joint Action Group will produce a list for Member States endorsement comprising the names of active substances and HBD's of the relevant products. The list will be published on the HMA website and included in the CTS system (MRP database). The HBD's should be used for the relevant generic products as well.

5.2 Scope

Initially the work should focus on chemical synthetic substances, for the time being not including herbals, homeopathics and certain biologicals such as vaccines and blood products.
At this stage also older products are not included: products authorised in the EU before December 1976, the date at which Directive 75/318/EC came into force, are not in the project for the time being.