APV Focus Group Drug Regulatory Affairs

International Association For Pharmaceutical Technology

Newsletter, Issue 3/2007

Editorial

The APV Focus Group Drug Regulatory Affairs considers itself to be a forum for an open scientific discussion of any issues relevant from a regulatory point of view within the field of marketing authorisation and pharmacovigilance of medicinal products. In this context we would like to inform you about current developments and draw your attention to APV events in a newsletter which will be issued on an irregular basis for the time being. Interested readers are welcome to provide proposals as to which topics the Focus Group should address and/or comment on. Please send your suggestions to the e-mail address of the Focus Group. Of course any kind of feedback and proposals concerning the contents of the newsletter and events organised by the Focus Group will also be appreciated.

Upcoming Revision of the Variations Regulations

In an "Issue Paper" entitled "Better Regulation of Pharmaceuticals: Towards a simpler, clearer and more flexible framework on variations" published in October 2006, the European Commission has announced its intention to revise the Variations Regulations. This document describes first ideas of the Commission on decreasing the administrative hurdles for post-authorisation changes and life-cycle management. The 5 key items outlined include an extension of the EU variations regulations to nationally authorised products, which so far fall within the responsibility of the national legislation of the Member States (key item 1). However, this change will require a different legal procedure, the so-called co-decision procedure, and thus will take more time than the other changes which can be implemented via the comitology procedure. Key item 2 proposes measures to enable and facilitate implementation of the new concepts described in the ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q 10 (Pharmaceutical Quality Systems). However, as has already been outlined in the various comments, the first proposal provided in this section does not fully embrace the ICH philosophy as it would still require annual reporting of changes performed within an approved design space – ICH Q8 clearly states that movements within the design space are not considered changes. Following the adopted ICH philosophy, this would consequently not require any notification to the regulatory authorities. Key item 3 foresees the introduction of a new "do and tell" procedure for administrative changes not requiring assessment and approval by regulatory bodies - most wanted by the pharmaceutical industry. Key item 4, the possibility for a single evaluation of common changes, intends to reduce administrative hurdles by repeated submissions of identical notifications and thus at the same time the work-load of authorities. Key item 6 proposes the use of the type IB procedure by default. Thus, any changes not specifically outlined in the future annexes would be handled as Type IB and no longer as Type II changes. In addition to these five key items, a number of other improvements are suggested in the document, e.g. a reclassification of certain Type IB changes to Type IA changes and a reclassification of certain Type II changes for biologicals.
Based on the comments received on above named "Issue Paper", the Commission has published a proposal for the revision of the variations regulations on their website (http://ec.europa.eu/enterprise/pharmaceuticals/varreg/index.htm <<draftRegulation-NR-2007-10-24.pdf>> <<Consultation paper-NR-2007-10-24.pdf>>) on October 24, 2007 for public consultations. Comments are requested until January 4, 2008. Given the significant impact any change in the variations regulations will have on both pharmaceutical industry and regulatory authorities, the APV focus group DRA intends to organise a meeting on the reivision of the variations regulations in order to provide a platform for an open and scientific discussion on the issues at stake. We will keep you informed!!

Generics: Bioequivalence and Biowaiver – Current Status and Current Developments in the EU

For the marketing authorisation of a generic medicinal product human in-vivo bioequivalence studies to prove interchangeability with the originator are known to be man-

datory. Depending on the different galenic and biopharmaceutical complexity of the combination of API, pharmaceutical form and strength one or several bioequivalence studies may be required.

The currently valid „Note for Guidance on the Investigation of Bioavailability and Bioequivalence"(CPMP/EWP/QWP/1401/98) has defined since July 2001 basic requirements for studies in humans (particularly bioequivalence studies) on the investigation of generics with a systemic effect in Europe with respect to their necessity, design, conduct, evaluation and reporting.

However, over the past few years practice has shown during many MRP and DCP procedures that frequently the Guideline (NfG) is differently interpreted by Member States. True myriads of delayed (or totally blocked) marketing authorisations of generics have been (and still are) the consequence with corresponding impacts on companies and national health markets.

In order to bring about an improved trans-European consensus, the EMEA Efficacy Working Party proposed a comprehensive revision of the currently valid NfG on 24th May 2007 and compiled a corresponding Concept Paper ((EMEA/CHMP/EWP/200943/2007). Parameters required to be revised as well as new aspects are proposed therein, e. g.:

- Discontinuation of the concept of „essential similarity" for generics with the „Review 2004" (amended Directive 2001/83/EC)
- Conditions for the choice of design
- Choice of analytes (metabolites, enantioselectivity)
- Assessment of Cmax in bioequivalence studies
- Broader acceptance limits for 90% CI
- Handling of outliers
- Standardised food intake
- Selection of strength(s) to be measured
- Proportionality concept

Modern developments in bioanalytics as well as experience with the Biopharmaceutics Classification System (BCS) are to be significantly taken into account.

It is recommended to compile a new CHMP Draft Note for Guidance within the next 12 months and submit to consultation with the objective to pass the revised Guideline within further 12 months.
In parallel the EWP has published a „Concept Paper on BCS-based Biowaiver (EMEA/CHMP/EWP/213035/2007).

In an interdisciplinary manner the BCS concept (Biopharmaceutics Classification System) links biopharmaceutics (pharmacokinetics) and pharmaceutical quality to an economically interesting concept of evidence. It enables waiving specific human in-vivo bioequivalence studies provided that closely defined prerequisites are fulfilled (multidimensional interaction of substance and pharmaceutical form parameters and attributes of the biological system).
Since its introduction by the FDA in the nineties, this concept has continuously been advanced scientifically. Essentially the BCS classifies a pharmaceutical form according to its solubility of API, intestinal permeability and in-vitro dissolution behaviour, i. e. those parameters determining the speed and extent of oral absorption (bioavailability) of immediate-release pharmaceutical forms.

The BCS concept can be used quite profitably within both, the development of medicinal products and the so-called „life cycle management"; in comparison to human in-vivo bioequivalence studies 80 % of the costs can be saved.

Some marketing authorisation procedures and variations have already been successfully performed using BCS-based biowaivers.

The Concept Paper of the EWP intends to dedicate a specific annex to the BCS concept in the revised „Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98), addressing in more detail those aspects that have so far only been regulated to a minor extent. This would for instance be the entirety of parameters to be fulfilled by the drug substance and its pharmaceutical form and how the applicant has to prove this in detail.

For the consultation period of this Concept Paper the following schedule is planned: CHMP Draft Annex within 6 months, public consultation 6 months, afterwards finalisation within 3 months.

From an industrial point of view, particularly also from the point of view of generic manufacturers, any measure to harmonise and standardise requirements for marketing authorisations in Europe are greatly appreciated, as is this initiative.

Common eCTD Standards in Europe – A snap-shot

In 2002 the first guidance on the generation of an eCTD (electronic Common Technical Document) including a specification for the data structure and the single documents (i.e. DDD, XML-backbone, Document type definition [DTD], leaf document properties) was published. Throughout the years this guidance document has been revised and amended, reflecting the content of the questionnaires received from the users (pharmaceutical industry and national competent authorities (NCAs)). Considering that eCTD specification agreed upon after discussion at ICH only covers Modules 2 to 5, the relevant European working party additionally released a specification for Module 1 to be used in Europe. To provide for the necessary flexibility this specification allows including both, the documents commonly required and the documents to be submitted in order to comply with specific national requirements.

Currently electronic dossiers (Modules 1 to 5) generated in compliance with the eCTD specification (version 3.2) and the specification for the European Module 1 (version 1.2.1) can be employed applying for marketing authorisations via different regulatory procedures (centralised, decentralised, national) and during the life cycle of the drug product for variations and renewal procedures. Electronic documentations compiled in compliance with these specifications should be importable into the NCA's internal databases without any difficulty for review by the assessors.

The Heads of Agencies agreed in their meeting held in Reykjavik in February 2005 that from 2009 on eCTD submissions should be possible in all Member States and that additional provision of any hard (paper) copies should be dispensable in these cases, i.e. from this point in time the 30 NCAs in the European Union, Iceland, Norway and Liechtenstein should be in a position to process eCTD submissions generated in line with the current specifications.

At the moment – i.e. somewhat more than one year prior to the target date - only two Agencies (in Belgium and the UK) are prepared to accept electronic submissions without requiring any additional hard copies.

Four other Agencies (AT, DE, NL, PT) have published guidance documents on the submission of (almost) "paper free" electronic documentations (these guidance documents set out requirements for non-eCTD e-submission (NEES) considered as a transition step to "real" eCTD applications) and the vast majority of NCAs still considers the provision of additional hard copies inevitable.

Both, the adaptation of an eCTD following specific national provisions and the compilation of additional hard copies present an additional (logistic) workload for the companies. Furthermore, the storage of the hard copies requires expensive archive resources at the authorities' sites. Such waste of resources is irritating, considering that specifications for the generation of the documents and for electronic transmission have existed for several years and pharmaceutical industry wishes to submit documents in e-format only.

Companies have also had to realise that the NCAs not only have somewhat divergent approaches with regard to the specification for electronic dossiers (NEES or eCTD) but that there is also no common validation tool in use by the NCAs for controlling incoming NEES or eCTD. As a consequence companies submitting electronic applications have had to realise that eCTD submissions classified "valid" by an internally used control tool working in line with the specifications and by a number of NCAs may be rejected as "invalid" by other NCAs.

Both, the different requirements applied by the NCAs for electronic dossiers and the fact that no common validation tool is employed, are counterproductive to the efficient use of electronic submissions. To overcome current problems in the near future a "roadmap" for the implementation of the standards and systems required for proces-

sing real eCTD applications should be agreed upon on a European level and in this context a guidance document should be published to harmonise the different already existing national requirements for electronic submissions.

Import of IMPs from Third Countries
The import of medicinal products intended for clinical trials (Investigational Medicinal Products = IMP) is subject to less strict import requirements. State controls in third countries by EU authorities are not provided for.
Nevertheless an on-site inspection cannot be ruled out; the authority responsible for approving the clinical trials (regulatory authority) has the possibility of inspecting the criteria and background of the documents submitted on site.

Section 72 (German Drug Law): Import Authorisation
(1) A party wishing to bring medicinal products within the meaning of Section 2 subsection1 or sub-section 2 No. 1, … on a commercial or professional basis into the purview of the present Act from countries which are not Member States of the European Communities or other States Parties to the Agreement on the European Economic Area for the purpose of supplying others or for further processing, shall require an authorisation by the competent authority. …

Hence the import of IMPs requires an import authorisation.

Section 72a (German Drug Law): Certificates
(1) The importer may only introduce medicinal products within the meaning of Section 2 sub-sections 1 and 2 Nos. 1, 1a, 2 and 4 which are not intended for clinical trials on human beings, … from countries which are not Member States of the European Union or other States Parties to the Agreement on the European Economic Area into the purview of the present Act, if …

According to the requirements of the respective EU Directive no GMP certificate issued by an EU regulatory authority is required for the introduction into the EU!

Section 9 (GCP Ordinance)
Authorisation by the Competent Authority
For preparing its decision the Competent Authority can inspect the information contained in the application according to Section 42, sub-section 2, sentence 1 and 2 of the German Drug Law or changed according to Section 10, subsection 1 at the trial site, the manufacturing site of the investigational medicinal products, any laboratory used for analyses in the clinical trials, the sponsor's premises or other premises. For this purpose authorised agents of the competent Federal Central Office in consultation with the competent authorities can visit the premises and offices during normal business hours, inspect documents and demand transcriptions or copies therefrom as well as information as long as no individual-related data are contained therein.

Die GCP Ordinance enables the authority responsible for authorising the clinical trial to conduct on-site inspections. Hence third country inspections are also possible.

AMWHV (German Ordinance for Manufacturers of Medicinal Products and Active Substances)
Section 17 (AMWHV) Marketing and Import
(1) Medicinal products, blood products and other blood components as well as products of human origin, which were manufactured and tested within the purview of the German Drug Law, may only be put on the market provided that they were released in compliance with Section 16.

This clarifies that the responsibility for quality entirely lies with the Qualified Person (QP). The manufacturer's assessment includes a qualification.
Investigational medicinal products do not have to be tested within the EU. The type and extent of testing, however, is not restricted; these investigations may also be performed by the manufacturer abroad, for whose appropriate assessment of his compliance the importer's QP is responsible…

(4) If investigational products, which were manufactured in a country which is not a Member State of the European Union or a different State Party to the Agreement on the European Economic Area and for which an authorisation of marketing in the country of origin is available, to be used as comparator products in a clinical trial, the Qualified Person in accordance with Section 14 of the German Drug Law is responsible

for every production batch to have been subjected to all of the required tests in order to confirm the quality of the medicinal products in compliance with the information notified concerning the clinical trials in which they are to be used. Sentence 1 shall also apply if no documents are available to the Qualified Person according to Section 14 of the German Drug Law that confirm that every production batch has been manufactured in conditions at least equivalent to the standards of Good Manufacturing Practice laid down by the Union.

With regard to the authorisation for marketing, in cases of doubt, it must be proved that an authorisation for marketing is not required in the country concerned.
Generally speaking it is clarified that the principle that all necessary tests must be conducted also applies to IMPs. This responsibility lies with the QP performing the release. The exception that this testing does not have to be performed within the EU applies – as opposed to the release!

Section 16
Release for Marketing
(1) Release of a batch for marketing can be performed by the Qualified Person according to Section 14 of the German Drug Law, who is familiar with the product and the methods used for its manufacturing and testing…
…
(5) In the cases described in sub-section 4, the Qualified Person according to Section 14 of the German Drug Law must assure herself/himself through personal notice or through confirmation by other sufficiently qualified and appropriate persons that the manufacturer is capable of manufacturing and testing in compliance with GMP and in accordance with the manufacturing and test method. Manufacturing in a country which is not a Member State of the European Union or State Party to the Agreement on the European Economic Area must provably be performed in conditions at least equivalent to the GMP standards laid down by the European Union. The manufacturer must be authorised according to national regulations to perform the respective activities.…

Again this is a clear statement that the Qualified Person is responsible for a qualified assessment of whether manufacturing and testing comply with European Standards. With respect to the authorisation for manufacturing and testing the same as mentioned above applies: in case of doubt it must be proved that such an authorisation (permission, approval) is not required in the country concerned.

This short illustration is to make clear that for clinical trial medication, too, all aspects of drug safety during manufacturing and testing must be observed and that the responsibility for this lies with the Qualified Person.
Only the „official" inspection of the manufacturer abroad by an EU authority and the associated GMP certificate do not apply. However, many a Qualified Person will only reluctantly dispense with a GMP certificate.