APV Focus Group Drug Regulatory Affairs

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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.

Your Focus Group Members

Revision of the Variations Regulations – Do You Know All The Details Yet?

On June 10 2008, the two Standing Committees have adopted the first part of the revised variations regulations – a flagship project on the Commissions's "Better Regulation of Pharmaceutials" agenda. This piece of legislation, which has been elaborated following the "Comitology Procedure", puts the proposals for a reduction of administrative hurdles in the context of a product's life-cycle management that had been published in the Commission's October 2006 issue paper into practice (see version 3/2007 of this newsletter). Namely, it creates the legislative framework to allow industry to benefit from the potential regulatory flexibility linked to the submission and approval of a design space, in line with the three latest ICH quality guidelines Q 8, Q9 and Q 10. It follows the expressed wish of industry to introduce a "do-and-tell"- procedure for minor variations which now will be able to be notified in an annual report. The revised regulation foresees different options for a single evaluation of common changes, e.g. identical changes to a number of medicinal products of the same marketing authorisation holder, and formalises work-sharing between member states. Another severe item of criticism in the current legislation, the definition of any change not explicitly defined as being categorised as a type II variation by default has also been remedied in the revised variation regulation.

Following adoption by the Standing Committees, the document has now been transferred to the European Council and Parliament for scrutiny until September 13, 2008. Should Council and Parliament not raise any objections due to a perceived violation of the subsidiarity principle, it is expected that the regulation will be formally adopted by the Commission in the fourth quarter of 2008. In order to allow for sufficient time for implementation, the new rules will only apply one year after entry into force.

Now, while the revised regulation addresses industry's main concerns in principle, there are still a number of crucial details that need to be addressed. Examples are further details on the operation of work-sharing, but first and foremost a clearer and better definition of the classification of changes which will be covered in additional guidance documents. Last but not least, the second part of the revision of the variations regulati-

ons, namely the application of the system established for the "European" procedures to nationally authorised products, is still underway. Due to the different nature of this document, this exercise needs to follow the "co-decision" procedure. A first version has been adopted by the Commission in March 2008 and is presently being discussed under the French presidency of the European Council.

Given the enormous impact the revised variations regulations will have on both industry and regulators, it is vital for all those involved to keep themselves updated on the status and details of the legislation. The APV focus group "Drug Regulatory Affairs" is holding a conference dedicated to the revision of the variations regulations in Brussels, September 16/17 2008. This conference, jointly organised with EFPIA and EGA, offers the unique opportunity to meet and discuss the implications of the details of the legislation. In addition to presentations on the state of play, parallel repeated work-shops will be held the outcome of which will be reflected in the trade associations' comments on further guidance documents. Don't miss this unique opportunity to actively contribute to the further process!

FContamination with mesilate esters and related compounds

Evaluating applications for marketing authorisation [MA] of drug products containing low molecular weight sulfonic acids that may form alkyl esters in the presence of lower alcohols some regulatory authorities required already in recent years provision of data demonstrating that the processes established prohibits the formation of these esters or – if this should not be the case - provides for their essentially complete removal.

Review of the Ph. Eur. monographs reveals that all current monographs on active substances in the form mesilates (10) and diisetionates (3) already include a section 'Production' requiring evaluation of the formation of alkyl mesilates and – as far as applicable - validation of the production method to demonstrate that alkyl mesilates are not detectable. The discussion on the need for limits on methyl, ethyl and isopropyl mesilate esters in active substances presented as mesilates final resulting in the amendment of the relevant monographs had been initiated by the EDQM in 2000 requesting the readers of Pharmeuropa to provide their opinion on the need for a test and limit in the light of their experience with mesilate salts (cf. "Enquire alkyl mesilate impurities in mesilate salts" in Pharmeuropa 12.1. An resulted in the amendment of the above mentioned monographs in 2003 - 2005. However, as of today such provision is missing in the monographs on the besilates (amlodipine, atracurium) and the tosilate (sultamicillin) salts.

In January and February 2008 the EMEA (EMEA/44714/2008) and the CMDh (EMEA/CMDh/98694/2008) issued letters addressed to the marketing authorisation holders [MAH] for medicinal products containing active substances in the form of mesilates, (di)isetionates, tosilates or besilates requiring for these products a risk assessment concerning the potential occurrence of alkyl or aryl sulfonic acid ester contaminations.

The wording in this letters is identical except for the fact that the EMEA request for MAs issued by the EU Commission provision of confirmation that the risk analysis has been carried out as well as information on the outcome by 30 April 2008 whereas - considering its legal status - the CMDh requests the MAHs concerned to provide the same upon request from any Competent Authority. Thus, considering that the EMEA has set a period of about 3 months (the EMEA letter dates 24 January 2008) for the conduct of the risk assessment and the identification of corrective measures, if required, it cannot be excluded that other Competent Authority requiring such information for medicinal products will shorten such period referring to the fact that all MAHs have

been expected to take the necessary measures after publication of the CMDh letter on 27 February 2008. In consequence Competent Authorities might expect to obtain a risk analysis for the products effected from each MA on rather short term notice.

In this context it is of note that the Swissmedic required the MAH for medical products containing drug substances in the form of mesilates, besilates and tosilates already in essentially identical letters issued in October 2007 to provide such risk assessment by 30 April 2008. Comparing the provisions published in the EU and in Switzerland it turns out that the Swissmedic does not explicitly refer to diisetionates and refrains from requiring information on the risk potentially related to use of alcohols during the cleaning procedures.

The request for this risk analysis has been triggered by the results of preclinical studies with certain mesilate esters that revealed that their DNA alkylation action can induce mutagenic, carcinogenic and teratogenic effects. As it is not unreasonable to suspect that similar toxic effects may exist for other alkyl esters of other low molecular weight sulfonic acids the range of drug substances to be covered by a risk analysis was widened to cover also besilates, tosilates and diisetionate salts.

With regard to the limits acceptable for alkyl or aryl sulfonic acid esters the EMEA/CMDh letters as well as the letters issued by the Swissmedic refer to the EMEA guideline 'Limits for Genotoxic Impurities (EMEA/CHMP/QWP/251334/2006)' and explicitly indicate that in the absence of toxicological data the threshold of toxicological concern (TTC) for genotoxic impurities (1.5 µg/day) should be used. From a formal point of view this provision differs from the Ph. Eur approach requiring that "alkyl mesilates are not detectable". However, considering that the Ph. Eur. monographs have been published prior to the adoption of the above mentioned CHMP guideline in June 2006, it is justified to consider the compendial provision superseded, i.e. amounts of alkyl sulfonic acid esters below the limit stipulated applying the provisions of the above cited Note for Guidance do not compromise Ph. Eur compliance.

From deficiency letters issued it is evident that assessing applications for MAs a number of EU authorities routinely requests the risk assessment described in the EMEA/CMDh letters for months. This requires the applicant to demonstrate e.g. adherence to the TTC based limits for any ester potentially present due to the use of lower alcohols during the manufacture of the drug substance or the drug product. For the drug product this does not only apply for alcohols used e.g. during granulation but also in cases where an alcoholic solution is used applying the film coating on a tablet core containing a low molecular weight sulfonic acid.

Considering that the quantification of alkyl or aryl sulfonic acid ester contamination in the ppm range in particular in the drug product requires development and validation of sensitive methods the time and efforts required to complying with the provisions of the EMEA/CMDh letters for the individual products should not be underestimated.

Revised CHMP Guideline on the Investigation of Bioequivalence published for comments

In May 2007, a "Recommendation on the need for revision of the CHMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)" had been published for comments, outlining the reasons why EU regulators felt the guidance provided was outdated and not any longer sufficient to avoid different interpretation of Member States, thus creating problems mainly in Mutual Recognition and Decentralised Procedures. In this recommendation, it was

highlighted that firstly, the present guideline was no longer in line with the pharmaceutical legislation following the new amendment of Directive 2001/83/EC. Furthermore, it had been identified that bioavailability and bioequivalence, both covered in the guideline, needed specific attention due to divergent requirements.

Following discussions in both CHMP's Efficacy Working Party (EWP) and Quality Working Party (QWP), CHMP now adopted the draft revised guideline for release for consultation. Major changes in the guideline text compared to the current version relate to the following aspects:
provision of specific recommendations on bioavailability studies, including definition of requirements on exploratory and confirmatory bioavailability and bioequivalence studies in separate sections
updating of current recommendations regarding, amongst others, the changed concept of essential similarity as introduced in the pharmaceutical legislation, selection of the study design, analytes to be measured and to be taken into account in the assessment of bioequivalence, dissolution test conditions. Proportionality of compositions
incorporation of topics currently covered by the recent Question and Answer document published on the EMEA website, e.g. as regards assessment of Cmax in bioequivalence studies, potential extension of acceptace ranges of bioequivalence limits (90% Cis)
potential revisions to BCS concepts and biowaiver requirements

In line with the changed EMEA naming policy on guidelines, the draft document is now entitled "Guideline on the Investigation of Bioequivalence" and is published on the guideline section of the EMEA website (http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf) for comments until 31 January 2009. Given the impact of the revised document on the development of both innovator and generic products, APV's focus groups "Biopharmaceutics and Pharmacokinetics" and "Drug Regulatory Affairs" intend to organise a seminar which will offer the opportunity to discuss the changed requirements in depth. Please watch the APV website for further details.