European Commission,
DG Enterprise & Industry, Unit F2 'Pharmaceuticals'
Mr. Nicolas Rossignol
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Eschweiler, December 21, 2007
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Draft Commission Regulation concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products of 24. October 2007

Dear Mr. Rossignol, dear Sirs,

I refer to the above draft regulation and would like to contribute to the discussion of the draft.
I refer in particular to those aspects of the proposed new variations regulations which relate to variations caused by changes to the primary packaging materials and which impact our company as a premier manufacturer of medicinal product immediate packaging materials.

Introduction

(…….) West Pharmaceutical Services is the world leading manufacturer of elastomeric closures for containers for aqueous parenteral preparations, powders and freeze-dried powders with more than twenty manufacturing sites in Europe, Asia-Pacific, and in South- and North America.
We manufacture our closures from a variety of predefined chemicals, following written manufacturing SOP's and we ensure formulation consistency throughout the entire world with FDA-DMF filing of our formulations and with cross-checking our various manufacturing locations.
We apply Good Manufacturing Practices which also ensure that our products meet the same specification and performance criteria irrespective where in the world these products have been manufactured.
(…….)

Problem Statement

We are recently experiencing situations where changes to the qualitative and quantitative composition of immediate packaging materials are caused by decisions of the manufacturers of the raw materials we use.

(.……..)

The number of such kind of supplier decisions is being anticipated to significantly increase in the future due to the ongoing globalization of the market as well as due to the upcoming additional requirements to the chemicals manufacturers due to the REACH regulations of the European Community.

(.….) (Recently, the) discontinuation of one raw material has affected about twenty of our elastomeric formulations used for the manufacturing of closures for more than fifty different medicinal products. For these medicinal products our customers have been granted marketing authorizations from different countries' agencies so that this change is affecting a multiple of fifty authorizations.

The current and the proposed variations regulations require this kind of change to be individually handled for each and every marketing authorization involved. And as these authorizations have been granted individually and based on either national, or mutual recognition/decentralized, or centralized procedures the reviews of these variations applications will be multiple.
This does not only lead to a multiple of applications to the agencies but also to a broad redundancy of validation efforts for the applicants as well as for us as the manufacturer of the closures.

Being fully aware of the necessity to verify the compatibility of a medicinal product together with its immediate packaging material we would like to suggest a procedure that allows a kind of grouping of these variations or at least facilitating the change:

Proposal:

If a medicinal product is sterile or a biologic changes to the qualitative and quantitative composition of immediate packaging materials are classified type II variations.

Where a change to the composition of an immediate packaging material at the same time concerns

- many medicinal product marketing authorizations
- been granted to different holders and/or by different agencies

a worksharing procedure applying a risk based approach should be considered (e.g. under the governance of the CMD(h)) and aiming to:

- collect a set of analytical data on the change that can jointly be referred to by all variation applicants
- allow reclassifying the resulting/subsequent variation applications type IB,
- or if indicated by the nature of the change, type IA_{IN}

The manufacturer of the packaging component should agree upon the protocol with the work sharing project rapporteur, validate the change and submit a technical dossier for assessment to the work sharing project rapporteur.

The dossier should typically include but is not limited to

1. a brief description of the change from the approved to the proposed material composition(s)
2. the protocol(s) applied for the investigation

3. a comparison of the chemical, physical, functional and biological specifications of the approved and the proposed material composition(s), including compliance with all applicable pharmacopoeial requirements
4. comparison of the potential extractables from both the approved and the proposed material composition(s) showing no significant differences and supporting the assumption that an adverse effect to the medicinal product is most unlikely
5. a conclusion of the above validation from the supplier's perspective and experience showing that the approved and the proposed material composition are equivalent

Applying the timelines as for a variation type II the work sharing project rapporteur should assess the documentation and provide an assessment report including a statement on the potential risk related to the efficacy, quality, purity and strength of the medicinal products and defining the documentary requirements for the subsequent variation applications.
The report should be addressed to the agencies of the concerned member states.
The concerned member states should review the assessment and state either their agreement or request additional information from the manufacturer.

If an agreement on the assessment has been achieved the final statement should be given to the attention of the manufacturer for being made available to all marketing authorization holders/variation applicants concerned.
When then applying for variations the applicants should submit the

- assessment report from the work sharing project rapporteur

if classified a type IB variation:

- confirmation that the relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months' stability data are at the disposal of the applicant
- commitment that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action) are observed or assumed
- Certificate of Analysis of the batch(es) of the immediate packaging material being used for the stability studies

If classified a type IA_{IN} variation

- confirmation that the relevant stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches
- commitment that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action) are observed or assumed
- Certificate of Analysis of the batch(es) of the immediate packaging material being used for the stability studies

If an agreement on the assessment statements cannot be achieved the variation applications should be handled as type II variation.

(…..)

With my best regards

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