

Public Assessment Report

Scientific discussion

Change in qualitative and quantitative composition of rubber stoppers of West Pharmaceutical Services

EU – Work Sharing Procedure

Manufacturer: West Pharmaceutical Services

Final
21 July 2008

This module reflects the scientific discussion for the approval of change in the qualitative and quantitative composition of rubber stoppers of West Pharmaceutical Services. The procedure was finalised at 9th of June 2008. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This variation notification has been submitted by West Pharmaceutical Services for processing via the EU Work Sharing Procedure coordinated by CMD(h). The work sharing was initiated as a request by the EMEA at the April 2007 CMD(h) meeting, and the proposed procedure was agreed at the July CMD(h) meeting. The Norwegian Medicines Agency accepted to be the Rapporteur in this procedure. The proposed change is to replace the discontinued rubber elastomer component – polyisobutylene (PIB) by halogenated butyl rubber, which is already the major rubber component of the elastomers.

The proposed change is not related to any specific marketing authorisation. The rubber is used for the manufacture of vial- and plunger stoppers that form a part of the immediate packaging material to a wide range of drug products. A large number of equivalent variation applications are expected as a consequence of the present change. Based on the review of the data, the Rapporteur considers that the variation notification submitted within the work sharing procedure for the change in qualitative and quantitative composition of rubber stoppers is recommendable.

II. QUALITY ASPECTS

II.1 Introduction

The supply of the rubber component polyisobutylene (PIB) will be discontinued. Therefore, the affected rubber formulations manufactured by West have to be changed. The discontinuation of one of these formulations has been decided so that total 23 formulations are actually concerned. The proposed change is to replace the PIB by halogenated butyl rubber, which is already the major rubber component of the elastomers. PIB has been included in the rubber formulations as a binder/ carrier for e.g. colorants in rubber pre-mixes previously used in the rubber manufacture. PIB is not involved in the chemical cross-linking of the rubber. Although no longer necessary for processing purposes, the inclusion of PIB has been continued to keep the rubber compositions unaltered. Two classes of rubber formulations are affected by the change. These are mainly composed of chlorobutyl rubber (CIIR) or bromobutyl rubber (BIIR), respectively. Replacing PIB with CIIR or BIIR, respectively, slightly increases the degree of unsaturation in the rubber mixture, possibly resulting in an increased number of cross-links by vulcanisation of the rubber. Thus, the material could appear harder than before the change. The change does not involve the inclusion of any new component. Any toxicological concerns, such as an increase in extractables or leachables would therefore only be related to any stabilising effect exerted by the PIB.

A total of 23 rubber formulations are affected by the proposed change. The composition of each of the formulations has not been presented, but they all consist mainly of CIIR, BIIR, polyisoprene (IR), butyl rubber (IIR), PIB and cure systems. It was explained by the applicant that any significant change in rubber characteristics or functionality would be similar among the different formulations. A reduced test regimen was therefore applied to evaluate the consequences of the change. Representative formulations were selected for evaluation of the change.

II.2 Analytical Results

In addition to the EP 3.2.9 requirements for rubber closures, the following characteristics were determined for the original and the modified rubber formulations, respectively: UV reference (EP 2.2.25), moisture vapour transmission, biological reactivity of extract (USP), O₂ transmission, residual moisture, physical characteristics (hardness, specific gravity), standard rubber tests (compression set, tensile strength, 300 % modulus, elongation), swelling (cotton seed oil, mineral oil, isopropanol, water, trichloroethylene), and extractables (water, isopropanol, methylene chloride). No significant change was observed in any of the characteristics following the change.

The adsorption of solutes to the rubber has not been addressed by the manufacturer, and is not included in the test regimen. This issue is highly relevant for certain classes of drug product, such as peptides, biological drug products and poorly soluble drug substances.

It is however confirmed that measures taken to minimise adsorption, such as fluorocarbon coating, are not affected by the formulation change. Although not investigated it is declared that any change in rubber stability due to the formulation change is unlikely. The manufacturer refers to long experience with a wide range of rubber compositions.

II.3 Summary of Quality Related Aspects

The rubber manufacturer has demonstrated that the performance of rubber products as sold is not adversely affected by the change in rubber formulations. However, marketing authorisation holders should consider investigating drug product specific compatibility with the reformulated rubber, but also should consider that the deletion of one component will not have the same effect as the addition of a component would have.

III. NON-CLINICAL ASPECTS

Saline and oil extracts of both the original and the reformulated formulation have been tested in single dose local and systemic toxicity studies, and in *in vitro* cytotoxicity assays. Those two of the rubber formulations were investigated which represent the greatest quantitative change. An extractables screening study was performed on the original and the reformulated formulation. The samples were extracted with water, isopropanol, and methylene chloride, respectively, and each extract was analyzed by HPLC/PDA/MS, GC/MS, ICP and IC techniques.

Following intracutaneous injection into rabbits, there were no tissue reactions from the saline extracts, while very slight erythema was observed from both the test and the blank corn oil extracts. No signs of toxicity were observed following intravenous or intraperitoneal injections in mice. *In vitro* cytotoxic reactions were only observed in the positive control group. The Applicant concludes that there are no significant differences in extractables between the M-formula and the control samples.

IV. CLINICAL ASPECTS

N/A

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The questions raised by the Norwegian Medicines Agency in the preliminary assessment report was addressed by the Applicant, and the final assessment report concludes that the variation notification submitted within the work sharing procedure for the change in qualitative and quantitative composition of rubber stoppers is recommendable.

This evaluation will be followed by subsequent product specific variation applications by Marketing Authorisations Holders.

The CMD have agreed on the following proposal for variation procedures in this case:

A Type I no.29 variation would be followed for chemical medicinal products approved via MRP.

For products not fulfilling the conditions of a Type I no.29 variation, i.e. sterile and biological products, a Type II variation would be followed with a shorter timetable (30 days). All the other conditions and documentation requirements of Type I no. 29 should be fulfilled.

If the Marketing Authorisation Holder considers the Type II variation application for a specific product to require additional product specific data, they will provide so. Then an additional evaluation will have to be done at the National Competent Authority and the fast 30 day procedure may not be applicable.

Companies with variations affected multiple biological products should consider to seek EMEA for scientific advice regarding the data package required.

Applicants are asked to refer to this work sharing in the subsequent variation applications
