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Reflection paper on the use of starting materials and intermediates collected from different sources in the manufacturing of biological medicinal products

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1. Introduction

In the European pharmaceutical legislation, requirements are outlined for particulars and documents that should accompany an application for marketing authorisation of a biological medicinal product. All information, which is relevant to the evaluation of the medicinal product concerned, shall be included in the application. This includes also information related to the starting and raw materials used in the manufacture of a medicinal product.

In view of the general definition of what a biological medicinal product is in Annex 1 to Directive 2001/83/EC, knowledge of the manufacturing process and its control is needed for the characterisation and determination of the quality for a biological medicinal product.[i] For biological medicinal products the interpretation of European legislation thus adheres to the principle of "one process = one product" as a general paradigm, i.e. the product is process specific.

It thus becomes relevant to clearly define where the manufacturing process starts and particularly whether starting materials from various sources are used. In 2007 the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh) clarified the regulatory status as "biological medicinal product" for a group of medicinal substances derived from biological sources such as heparins, gonadotrophins and urokinase.[ii] Historically, for such products a certain level of flexibility may have been allowed in sourcing and initial processing steps. This applies also to products from non-recombinant origin that are considered as biological active substances/biological medicinal products in the current legislation (e.g. allergens).

This position statement addresses to which extent any variability in the early manufacturing steps for certain biological products would be acceptable.

2. Problem statement

The marketing authorisation dossier should include information that adequately describes the manufacturing process and process controls. Information on quality and control of all starting materials and process reagents used in the manufacture of a drug substance should be provided. For drug substances derived from biological starting materials special attention is drawn to clearance and control of adventitious agents and an appropriate safety evaluation of a medicinal product derived from it is requested.

The requirement that the MAH should have full access to Drug Substance manufacturing data implies that all manufacturing steps and manufacturing sites have to be covered in the marketing authorisation dossier. In particular, this causes complexity for products undergoing multi-source processes. Examples of such products are heparins (including Low Molecular Weight Heparins), urine derived products like gonadotropins and urokinases, and plasma derived medicinal products.

For these products, variability in sourcing and/or initial manufacturing steps has traditionally been allowed in contrast to the well characterised biotechnological products of recombinant origin for which the declared manufacturing process starts from a unique and well identified cell bank system. Such variability is triggered by the high demand for the starting material and consequential manufacturing and market logistics. For some products such as heparins there is an increasing difficulty on finding

[i] Directive 2001/83/EC, Annex 1 Active substance 3.2.1.1.b General information and information related to the starting and raw materials

[ii] CMDh Guidance for applicants on biologicals [available at http://www.hma.eu/215.html] and http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Compilation_Biological_Active_Substance_non-recombinant_origin.pdf.

starting materials suppliers in the EU and there is a need for manufacturers/MAHs to source outside the EU (e.g. China). As manufacturers inevitably need to have several suppliers, flexibility of sourcing in the biological substances of non-recombinant origin may be needed to ensure product supply.

The multi-step manufacturing processes of biological substances have also caused differences in the definition of 'starting materials' for the drug substance manufacturing by both regulators and industry. Consequently, this resulted in differences in the level of detail for the early manufacturing steps presented in the marketing authorization dossier. This document clarifies the definition of starting materials for specific groups of biologicals and it presents CHMP's current position on the use of variant processes in the early manufacturing stages of these products.

3. Scope

This position statement addresses to what extent any variability may be acceptable in the early manufacturing steps for biological medicinal products which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin[iii] and for which flexibility of sourcing in the biological starting materials may be needed to ensure product supply. This document also clarifies the definition of starting materials for these products. A number of major examples are given which illustrate the concept of accepting process variability. The principles outlined in this document could be applied to other biological medicinal products for which flexibility of sourcing in the biological starting materials may be needed, e.g. porcine pancreas for insulin and pancreatin, and allergens. Advanced Therapy Medicinal Products (ATMP) are excluded from the scope of this document.

4. Discussion

The particulars and documents accompanying an application for marketing authorisation pursuant to Articles 8 and 10(1) shall be presented in accordance with the requirements set out in Annex I of Directive 2001/83/EC and shall follow the guidance published by the European Commission in The rules governing medicinal products in the European Community, Volume 2B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD).

4.1 Starting materials and process intermediates

According to Dir. 2001/83/EC, for biological medicinal products, "*starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).*"

Within the context of this document, a process intermediate is defined as a substance produced during steps of the processing of the drug substance that undergoes further molecular change or purification before it becomes the drug substance.

Any other substances such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. used in the manufacturing or extraction of the active substance, but from which this active substance is not directly derived are defined as raw materials; therefore, these materials are outside the scope of this guidance document.

[iii] Volume 4 Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 2: Manufacture of Biological Medicinal Products for Human Use

Following the CMDh recommendations and in accordance with the requirements set out in Annex I of Dir. 2001/83/EC, it is not possible to use the Active Substance Master File (ASMF) procedure[iv] and existing CEPs cannot replace the relevant data in Module 3.[v] The main reason is that the MAH should have full access to the Drug Substance manufacturing data to take full responsibility for the medicinal product, all of its intermediate products and starting materials. Consequently, this data should be part of the marketing authorisation dossier for new and existing marketing authorisations.

Examples of three major classes of biological medicinal products are given below.

Heparins

Heparin and derivatives fulfil the regulatory definition of 'biological substance' given by Directive 2001/83/EC: the substance is of biological origin and, due to its complexity, a combination of physico-chemical-biological testing together with testing and control of the manufacturing process is needed for its characterisation and determination of quality.

Therefore, according to Dir. 2001/83/EC, porcine mucosa is defined as the starting material for any heparin or LMWH from porcine origin. Different process intermediates may exist and be qualified for use in the manufacture of LMWH, such as resin bound heparin, partly purified crude heparin or heparin sodium/calcium LMMH. However, these process intermediates shall not be considered as starting materials according to Directive 2001/83.

Module 3 of the marketing authorization dossier should cover the whole manufacturing process starting from the sourcing of the mucosa. Aspects with potential impact on product quality and safety needs to be presented in sufficient detail e.g. species and country of origin, traceability from slaughterhouses/abattoirs, confirmation that the animals used are fit for human consumption etc.

Urine derived products

As for the heparins, urine derived products (e.g. urokinases, gonadotrophins) fulfil the definition of 'biological substance'. Human urine should be defined as the starting material for urine derived medicinal products. Different process intermediates may exist. For example, (resin) adsorbed urokinase, urokinase paste, semi-purified urokinase have been described as process intermediates for medicinal products containing urokinase as the active substance. For the contents of module 3 sufficient detail should be provided to enable a full assessment of the manufacturing steps to be made.

Plasma derived products

The legal basis for EU minimum standards for the quality and safety of the starting material for plasma-derived medicinal products have been established along with the pharmaceutical legislation and specific provisions have been laid down in the pharmaceutical Directive 2001/83/EC as amended. The starting material for fractionation is plasma (pool) which is obtained from either recovered or source human plasma.

According to the recently revised guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010), an intermediate plasma fraction (intermediate) is a partially fractionated starting material which must undergo further manufacturing steps before it becomes a bulk product or final product. Intermediates, commonly used for further processing into a final product, are fractions recovered from the process for the manufacturing of clotting factors (e.g. cryopaste) or

[iv] CMDh Guidance for applicants on biologicals [available at http://www.hma.eu/215.html]

[v] Report from the CMDh meeting held on 16-18 November 2009 [available at http://www.hma.eu/259.html], CHMP Monthly report November 2009 [available at http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2009/12/WC500016941.pdf], and guideline on ASMF : CPMP/QWP/227/02 Rev2 [available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002811.pdf]

from the manufacturing process of immunoglobulins or albumin (e.g. fractions II, III, IV, V), and may be prepared and stored by the product manufacturer or obtained from another supplier, a contract manufacturer.

The collection and control of starting materials for the manufacturing of an intermediate plasma fraction are important factors in the assurance of its quality. Information up to and including the manufacturing of the plasma pool should be provided in the Plasma Master File or in the dossier following the Guideline on the Scientific Data Requirements for a Plasma Master File (EMEA/CHMP/BWP/3794/03). This information and information on the manufacture of the intermediate from the plasma pool should be provided to the manufacturer of the finished product.

For plasma-derived medicinal products, a variant of an established process may be employed if it concerns an intermediate plasma fraction.

4.2 Variant manufacturing processes

When defining tissues, fluids such as urine or plasma as the starting material of the manufacturing process it is acknowledged that some flexibility within the ”one process = one product” paradigm might be needed for the very early drug substance manufacturing steps. Indeed, for the above mentioned examples, large volumes or quantities of starting materials (urine, porcine mucosa, human plasma) have to be collected and pre-treated before initiating the final drug substance manufacturing steps which will result in drug substance with the desired quality. These first steps of collection, testing and pre-treatment of the starting material may be carried out by different suppliers who could apply different processes to obtain an “early intermediate”.

The approach of an “early intermediate”, derived from the same starting material but using variant manufacturing processes should however be well defined and its quality control and qualification a key step in the manufacturing process of the drug substance.

If multiple processes are used in the early stages, the MAH should justify the use of intermediate(s) manufactured by variant processes.

Full information about the manufacturing process, starting from the sourcing of the starting material (e.g. mucosa, urine, human plasma) should be given for each intermediate. Relevant Quality Attributes for each intermediate (e.g. purity profile, biological activity) should characterise the manufacturing process and should be defined by the manufacturer of the drug substance. Any differences among variant processes, e.g. additional purification/extraction step, process conditions, intermediates, materials and equipment, should be listed and justified for each intermediate. Provided that the intermediate from variant processes is sufficiently characterised, and that the final steps of the manufacturing process of the drug substance is robust enough (and validated) to obtain a comparable drug substance irrespective of the initial process steps or intermediate used, the application of variant processes in early drug substance manufacturing steps is acceptable for the type of products that are within the scope of this document.

Thus, if a manufacturer decides to use starting materials or intermediates from different sources and / or a different manufacturing process for the early production steps it should be shown that comparable products are consistently obtained in terms of relevant quality attributes irrespective of the process applied.

Comparability should also be demonstrated taking into account the principles laid down in guidance [(Note for Guidance for Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)]. Discernable differences in quality attributes should be discussed and justified in terms of product quality (e.g. product heterogeneity) as well as safety (including virus

safety) and efficacy of the finished product. The extent of the studies necessary to demonstrate comparability will depend on (1) the complexity of the biological drug substance for example the quality attributes of heparin are well defined but those of urokinase are less well defined, and (2) how early in the production process a different intermediate is introduced. Any storage periods for intermediates should be set and justified by stability data.

Additional measures are taken for plasma-derived products as regards to risk of transmission of infectious agents, in accordance with the guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).

GMP measures (e.g. contract between supplier and manufacturer of medicinal product, audit system) should be adequate to ensure an appropriate control while allowing sourcing of starting materials or early intermediate biological products in different locations from third countries. Reference is made to Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 2: Manufacture of Biological Medicinal Substances and Products for Human, Part B.

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