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Guideline on the use of starting materials and intermediates collected from different sources in the manufacturing of non-recombinant biological medicinal products

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1. Introduction

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.^{1,2} Therefore requirements outlined in the European pharmaceutical legislation, for particulars and documents that should accompany an application for marketing authorisation of a biological medicinal product, applied to these specific products too.

In view of the general definition of what a biological medicinal product is, as outlined in Annex 1 of Directive 2001/83/EC³, knowledge of the manufacturing process and its control is needed for the characterisation and determination of the quality for a biological medicinal product. Therefore, for biological medicinal products the interpretation of European legislation adheres to the principle that the product is defined by its physico-chemical and biological characteristics as well as its manufacturing process and as such within one Marketing Authorisation one process is applied to obtain the active substance.

The marketing authorisation dossier should include information that adequately describes the manufacturing process and process controls. All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on quality and control of all starting materials and process reagents used in the manufacture of a active substance should be provided. It is thus relevant to clearly define where the manufacturing process starts.

The requirement that the MAH should have full access to the active 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 certain non-recombinant products undergoing multi-source processes, i.e. where the starting materials or early intermediates are derived from several suppliers and where the initial processing and the quality control could be different from one supplier to another. Examples of such products are heparins (including Low Molecular Mass Heparins (LMMHs)), 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 a single 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 non-recombinant products such as heparins or its derivatives there is an increasing difficulty in finding starting materials suppliers. As manufacturers of these products often need to have several suppliers, it is acknowledged that 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 caused differences in the definition of ‘starting materials’ for the active 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.

2. Scope

This guideline addresses to what extent any variability in the early manufacturing steps is acceptable for non-recombinant biological products which contain active substance extracted from organs, tissues or fluids from living organisms, either of animal or plant origin and for which flexibility in the sourcing in the biological starting material may be needed, to ensure product supply.

Major examples are given which illustrate the concept of accepting process variability.

This document also clarifies the definition of starting materials for these products.

The principles outlined in these examples could be applied to other biological medicinal products for which flexibility of sourcing in the biological starting materials may be needed.

For allergens and plasma derived medicinal products it is acknowledged that extensive regulatory/scientific guidance is already available which covers the main issues as outlined in this document. Therefore, these product classes are not further discussed in this guideline.

Advanced Therapy Medicinal Products (ATMP) are excluded from the scope of this document.

This document provides guidance in support of Marketing Authorisation Applications as well as already licensed products.

3. Legal basis

This guideline should be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83/EC as amended.

4. Discussion

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)."*

The concept of Active Substance Master File, as laid down in Annex I of Directive 2001/83/EC, cannot be applied in the context of biological medicinal products.^{4,5} Furthermore, according to the CMDh and CHMP recommendations,^{6,7} existing Certificates of Suitability (CEPs) for biological substances of non-recombinant origin cannot replace the relevant data in Module 3. The main reason is that the MAH should have full access to the active substance manufacturing data to take full responsibility for the medicinal product and all of its intermediates and starting materials it is derived from. Consequently, this data should be part of the marketing authorisation dossier for new and existing marketing authorisations.

Within the context of this document "a source" means a certain supplier from which the starting material or intermediate is supplied, irrespective whether this supplier is located inside / outside the EU. For specific GMP aspects related to suppliers located outside the EU please be referred to the relevant GMP legislation. "Multi-source" means that the starting materials or intermediate is supplied from multiple suppliers. It is noted that one source could include multiple slaughterhouses which are under the same pharmaceutical quality control system of the medicinal product manufacturer.

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

Relevant information pertaining to the starting materials, but not necessarily to the description of the manufacturing process, should be presented in Module 3.2.S.2.3 Control of Materials.

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.

Examples of two 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.

Hence, pooled porcine intestinal mucosae are defined as the starting material for any heparin or LMMH.ⁱ

Different intermediates may exist and be qualified for use in the manufacture of LMMHs, such as resin bound heparin, partly purified crude heparin or heparin sodium/calcium. However, these intermediates shall not be considered as starting materials according to Directive 2001/83/EC.

Module 3 of the marketing authorization dossier should cover the whole manufacturing process starting from the sourcing of the mucosa. The source materials used for the production of intermediates for the manufacture of medicinal products shall be derived from animals fit for human consumption following ante- and post mortem inspection in accordance with EU or equivalent conditions. Aspects with potential impact on product quality and safety need to be presented in sufficient detail e.g. species and country of origin, traceability from slaughterhouses/abattoirs, prevention of species cross contamination, confirmation that the animals used are fit for human consumption, veterinary certificate, etc.

Urine derived products

As for the heparins, urine derived products (e.g. urokinases, gonadotrophins) fulfil the definition of 'biological substance'. Pooled 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 details should be provided to enable full assessment of the manufacturing steps. Information should be provided in sufficient detail on safety aspects of the starting material/intermediates such as donor selection criteria, traceability and virus testing.

4.2 Variant manufacturing processes

When defining tissues or fluids, such as urine, as the starting material of the manufacturing process, it is acknowledged that some flexibility within the concept of a single manufacturing process starting

ⁱ Pooled porcine intestinal mucosae can be preserved or non-preserved depending on the local process logistics. In case where the pooled mucosa is preserved, the method of preservation should be described, including the raw materials used, in the MA dossier. This would not necessarily be the point where GMP needs to be applied.

from the biological source materials might be needed, particularly for the very early active substance manufacturing steps. Indeed, for the above mentioned examples, large volumes or quantities of starting materials (porcine mucosa, urine) have to be collected and pre-treated before initiating the final active substance manufacturing steps resulting in an active substance of 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 isolated intermediate. The approach of an intermediate derived from the same starting material but possibly using variant manufacturing processes should however be well defined considering the following aspects.

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

Information about the manufacturing process, starting from the sourcing of the starting material (e.g. mucosa, urine) should be given for each intermediate. The level of detail should provide sufficient information depending on the stage of the process, with a focus on critical quality attributes and critical process parameters, traceability of supply and demonstrated MAH oversight of the process.

Particular attention should be drawn to those intermediates for which the Company applies several sources in their MA. Quality Attributes for these intermediates (e.g. purity profile, biological activity) should be defined by the manufacturer of the active substance to allow comparison of the quality of these intermediates where they are obtained by different sources and using variant manufacturing processes. Where it is not possible to determine the critical quality attributes at the stage of these intermediates, testing for these quality attributes may be performed at a later stage in the manufacturing process. Any differences among variant processes, e.g. additional purification/extraction step, process conditions, intermediates, materials and equipment, should be listed and justified. Provided that the quality of intermediates from variant processes is sufficiently assured, and that the final steps of the manufacturing process of the active substance is robust (and validated) and will produce a comparable active substance irrespective of the initial process steps or intermediate used, the application of such variant processes in the active substance manufacturing steps is acceptable.

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 active substances are consistently obtained in terms of relevant quality attributes irrespective of the process applied.

Comparability should also be supported 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)].⁸ Discernable differences in quality attributes should be discussed and justified in terms of product quality (e.g. product heterogeneity) as well as safety and efficacy of the finished product. Where viral safety of the active substance is mainly or solely based on virus inactivation/removal capacity of production process steps for the intermediates from different sources, this deserves particular attention.

The extent of the studies necessary to demonstrate comparability will depend on (1) the complexity of the biological active 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 different intermediates are introduced. Any storage periods and conditions for isolated intermediates should be set and justified by stability data.

GMP measures (e.g. contract between supplier of the starting material/intermediate(s) and manufacturer of medicinal product, audit system) should be adequate to ensure an appropriate control while allowing sourcing of starting materials or intermediate biological products from different suppliers. Respective GMP responsibilities should be clearly defined in a Quality Agreement. 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 active substances and Medicinal Products for Human Use.⁹

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