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DEVELOPMENT PHARMACEUTICS FOR BIOTECHNOLOGICAL AND BIOLOGICAL PRODUCTS (CPMP/BWP/328/99)

ANNEX TO NOTE FOR GUIDANCE ON DEVELOPMENT PHARMACEUTICS (CPMP/QWP/155/96)

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DEVELOPMENT PHARMACEUTICS FOR BIOTECHNOLOGICAL AND BIOLOGICAL PRODUCTS

(ANNEX TO NOTE FOR GUIDANCE ON DEVELOPMENT PHARMACEUTICS)

1. INTRODUCTION

Whilst some of the issues illustrated in the Note for Guidance on Development Pharmaceutics have been elaborated primarily for products containing chemical active substances, the principles stated therein may be applicable to biological or biotechnological products.

2. GENERAL CONSIDERATIONS

There are, however, underlying physico-chemical differences between biological/biotechnological products and chemically synthesised products, for example, lability and complexity inherent in biotechnological and biological substances.. These differences may necessitate special pharmaceutical and biopharmaceutical considerations during the research and development programme.

This document, therefore, focuses on formulation or pre-formulation studies which should be considered in the course of the development of a suitable dosage form for active principles produced by biological or biotechnological means. The objective of these studies is to develop a stable formulation which ensures, by means of appropriate stability indicating assays, that the integrity of the active moiety is preserved both biologically and chemically for i) the intended medicinal use, ii) during the manufacturing process and iii) throughout the defined shelf-life. Furthermore, process parameters which can influence consistency of the product during scale-up should also be carefully evaluated.

As far as the development pharmaceutics of biological/biotechnological products is concerned, three important inter-related areas should be carefully considered, namely, aspects relating to stabilisation, compatibility and biological activity in any pre-formulation or formulation studies. This document should be read in conjunction with any relevant CPMP guidance notes.

3. SPECIFIC CONSIDERATIONS

3.1 Characterisation

Adequate characterisation using modern physico-chemical and biophysical methods appropriate to the nature and properties of the active substances, excipients and the formulated products should be carried out including those relating to molecular size, charge and surface properties. These studies are intended to describe structural elements responsible for the biological activity such as active sites, receptor and ligand binding sites and the features responsible for signal transduction. They can also indicate the relevant parameters which can potentially impact on the *in vivo* disposition of the product following administration including those intended for site specific delivery.

Any physico-chemical interactions between the active principle and its excipients should also be carefully investigated. In the case of certain viral and bacterial vaccines, physico-chemical or biophysical characterisation may not be adequate and biological characterisation, e.g. immunogenicity determination, should be considered, where appropriate.

3.2 Manufacturing process

Biologicals or biotechnological products are distinguishable from their chemically synthesised counterparts with respect to their manufacturing process and its impact on the drug product quality and safety. The quality of biologicals is defined by the chosen production and manufacturing process. Minor changes in the process can affect the quality of the drug product and therefore the development of the manufacturing process is of paramount importance for biologicals, be they vaccines, biotechnological or blood products or oligonucleotide therapeutics such as DNA vaccines and gene therapy products. Manufacturing parameters which can impact on the quality and stability of the drug substance in a formulated product as indicated previously, e.g. pH, heat, shear, should be carefully investigated as part of the development strategy to ensure consistency. Where over-fill is necessary to ensure that adequate amount of the active substance is administered to the patient, e.g. pre-filled syringe formulation, satisfactory justification should be provided with relevant supporting evidence.

Because of their physico-chemical properties, it is usually not possible to terminally sterilise the biological products in the final container by autoclaving. In most instances, they are sterilised by membrane filtration prior to filling. In this context, manufacture the product under defined, well-controlled aseptic conditions is deemed sufficient.

3.3 Overages

As a result of stability considerations, overages could be included in the formulation of certain biological/biotechnological products, e.g. vaccines, to ensure that the required biological activity or potency is maintained throughout the entire shelf-life under the prescribed storage conditions. Any overages to be included should also take into account the variability of the bioassay method employed to determine the potency of the product particularly where an *in vivo* biological assay is required for such determination.

3.4 Compatibility

Substantial evidence exists that proteins can interact chemically with the formulation excipients present in the finished product, for example, the formation of adducts which are potentially immunogenic.

Potential interactions between the primary packaging and the product itself should be investigated in any products development programme in order to minimise any decrease in the potency or biological activity of the finished product arising as a result of sorption during storage. Since proteins are amphiphilic polyelectrolytes, they exhibit some degree of surface activity. In this regard, adsorption denaturation can take place through i) diffusion of the native protein molecules to the interface and their subsequent adsorption ii) uncoiling of the polypeptide chains at the interface and iii) aggregation of the surface denatured protein into coagulum.

Where the formulated product is presented as a powder for injection in two-chamber cartridges for reconstitution, e.g. growth hormone, special attention should be paid to ensure correct re-constitution of the powder or its homogeneous resuspendability and dosage uniformity in the case of a suspension. This should form the basis of the instructions for use in the appropriate sections of the leaflet and summary of product characteristics.

Compatibility with another active substance(s) in combination should also be carefully considered, for example, combination vaccines for subcutaneous, intramuscular or oral use. There are examples of both live attenuated vaccines, e.g. measles, mumps and rubella, and inactivated vaccines, e.g. DTP and Hib, where combining components has altered the antigenicity of the individual elements.

The clinical relevance of any untoward findings should be fully addressed. The effect of adjuvant on mounting the appropriate immunogenic response should be carefully considered.

3.5 Stability of the active substances

In any pre-formulation studies, it is important to establish the stability of the active principle. In the case of a protein molecule, for it to retain its biological functions, it usually must adopt the correct conformation to render it biologically active for the target receptor(s). Due to the hierachical nature of protein structure, there will usually be more than one mechanism of degradation, be it physical or chemical. In this regard, the degradation pathways, including their mechanisms and kinetics, where applicable, should be established by an appropriate array of physico- or bio-chemical methods.

For DNA based products, the stability of the active principle should be investigated with respect to its degradation kinetics relating to, for example, depurination and β-elimination.

The results obtained can be useful in determining how the formulation, and conditions employed in the manufacturing process and storage, including those relating to changes in temperature, pH, salt, pressure and shear, will impact on the integrity of the molecule such that degradation can be minimised.

3.6 Stability of the formulated product

For routine stability testing, reference is made to ICH Q5C Note for Guidance on stability testing for biotechnological products.

Because of the lability inherent in certain biological/biotechnological products, appropriate quantity or quantities of suitable excipients, supported by experimental data,are frequently incorporated into the formulated or finished product. This is intended to render the active moiety more stable, for example, with respect to its primary or tertiary structure, both of which may have direct impact on the biological activity of the final product e.g. coagulation factors. Such changes may arise during the manufacturing process and/or during storage.

The stability of the formulated product or the drug substance under various process conditions, such as lyophilisation, should be investigated in order to optimise the formulation with respect to the amount of, for example, lyoprotectant required to preserve the integrity of the drug substance.

Excipients and/or reagents used in the manufacture or formulation of drug substances or products may be of human or animal origin. It is desirable that in development pharmaceutics work on labile biological products such as live attenuated vaccines, alternatives to the use of materials of human or animal origin should be developed and evaluated for use in production and in formulation. Substitute for albumin as an excipient, where possible, should be investigated.