European Pharmaceutical Aerosol Group (EPAG): Safety, Quality and Functionality Related Aspects of Lactose for Inhalation

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INTRODUCTION

Lactose is the second most used excipient after water. It is widely used in tablets and capsules and it is also increasingly used in dry powder inhalation products as a filler, diluent or carrier. Therefore, it is recognized as a safe excipient even if inhaled and plays a key role for the quality of a dry powder inhalation drug product. Regulatory considerations in recent years have led to an ongoing revision of proposed monographs for Lactose for Inhalation, namely lactose monohydrate and anhydrous lactose.

The EPAG lactose subgroup is considering such developments and presenting a consolidated industry view on Lactose for Inhalation, using a scientifically based and best practice approach to categorize potential compendial testing parameters.

DISCUSSION

Different potential testing parameters for inhalation grade lactose are discussed with respect to safety, functionality, quality and supply chain control.

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Safety

Lactose, as the monohydrate and anhydrous forms, is in general, regarded as a safe material and appropriate identification is very important for safety reasons. General lactose monographs (monohydrate and anhydrous) based on current knowledge reflect this already (1-3). The Handbook of Pharmaceutical Excipients (4) has recently expanded its monographs to include Lactose for Inhalation. Ongoing monograph revisions may propose changes in specifications, or even additional tests for Lactose for Inhalation. Any proposed specification and method should be appropriately justified based on safety considerations.

Functionality

Excipients are used in pharmaceutical development to impart quality, performance and robustness of a drug product and to allow successful manufacturing of drug product. A pharmacopoeial monograph provides standards to control the safety and quality of an excipient. However, no functional characteristics for which common specifications are appropriate for different drug products have been identified. Therefore, specific functionality related testing parameters and acceptance criteria are established between suppliers and drug product manufacturers, which assure drug product manufacturing and performance.

A number of physicochemical properties of Lactose for Inhalation may be of no concern regarding safety, but of great value to investigate in order to optimize formulation work for an inhalation product. Thus, the characterization work is closely linked to the individual formulation being developed and may require different requirements and testing methodology on a case by case basis. Certain characteristics may be of high relevance for one type of formulation and of very low relevance for another (5). A number of properties of Lactose for Inhalation can be considered to affect the quality and performance of the drug product and the functionality of the formulation, e.g.: particle size distribution, shape and morphology, amorphous content, β-anomer content, bulk and tapped density. The importance of each parameter and the impact of its variation on the performance of the finished drug product have to be investigated and established in development studies on a case by case basis, following the regulatory requirements as laid out in ICH Q8 (6).

As they are purely product related and often specific for a given product these testing parameters should be developed and agreed between suppliers and drug product manufacturers and should therefore not be a mandatory part of any lactose monograph. Each of these characteristics may be included into a product specific testing specification for Lactose for Inhalation. As such, it would be filed and open to the reviewers and complement the requirements of the monograph or even as part of any drug master file. In support of this view, the importance of functionality has been recognized by the regulatory bodies by the recent introduction of chapters such as "Functionality-related Characteristics of Excipients" (Ph. Eur. 7.0; 5.15.) and "Excipient Performance" (USP 33-NF28; <1059>) (5, 7).

Quality

The fact that the manufacturing of Lactose for Inhalation is reproducible defines its quality, and guarantees a robust manufacturing of the drug product. These quality parameters are in most cases distinct from safety parameters. One example of a quality testing parameter not relevant for safety is chromatographic purity which detects related sugars. Another parameter to be considered as quality related is the protein content in lactose because, even if there is limited evidence, there may remain some concerns regarding its content (8). Different tests have been categorized in the following table:

Table 1.

Categorization of testing parameters.

	Safety	Functionality	Quality
Identification	X	-	-
Loss on drying	-	-	X
Heavy Metals	X	-	-
Residue on ignition	X	-	-
Chromatographic purity (HPLC)	-	-	X
Protein and light absorbing impurities	X(1)	-	X
Colour and clarity of solution	X	-	X
Optical Rotation	X	-	X
HPLC-assay(2)	-(2)	-	-
Particle size distribution	-	X	-
Hausner Factor	-	X	X
Particle shape and morphology	-	X	-
Amorphous content	-	X	-
Anomeric content	-	X	X
Karl Fischer	X(3)	-	X
Microbiological Testing	X	-	-
Endotoxins	X	-	-
Acidity and alkalinity	X	-	-

(1) = when considered as a test to indicate gross contaminants, (2) = safety aspect already covered by optical rotation, (3) = when considered as an ID test for Lactose for inhalation

Supply Chain Implications

The complexity of testing of functional related characteristics may induce pressure on suppliers, and may further limit marketed Lactose for Inhalation qualities due to the specifications and/or the methods to be required. For example, the introduction of a specification of anomeric content for the monohydrate form may limit the use of spray-dried lactose or agglomerated lactose which may be relevant for certain drug products. Such qualities may not be covered by the monographs and may lead to an agreement between manufacturer and regulatory bodies as "new excipients."

CONCLUSIONS

Any Lactose for Inhalation monograph provides standards for the supplier to guarantee safety for the patient. Therefore, only safety related testing parameters should be mandatory or specified.

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Functionality related characteristics and specifications may be different for various drug products and should therefore be defined by the manufacturer of the drug product. Complexity of testing of functional related tests may induce pressure on suppliers and may limit marketed Lactose for Inhalation qualities due to the specifications and/or the methods to be required.

Functionality and quality related characteristics are a matter of agreement between the lactose manufacturer and the manufacturer of the finished drug product, although certain testing parameters must also meet the requirements of the monograph, as in the case of the European Pharmacopeia.

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