IPEC Position Paper

Pharmaceutical Lactose used in oral preparations is a low-risk excipient

01 March 2021

Purpose of Position Paper

This paper describes IPEC's position on the risk classification of lactose in all oral preparations.

NOTE: Within this paper, pharmaceutical grades of Lactose refer to those materials which are the subject of pharmacopoeial monographs or otherwise approved by regulatory authorities for use in medicinal products.

The Issue

Increasingly, regulatory authorities worldwide seek to classify pharmaceutical excipients according to the risk they may present to patients when used in dosage forms. For example, according to their origin and application. Although lactose is derived from an animal derived material (whey), this position paper seeks to support pharmaceutical grade lactose as a low-risk excipient in oral dosage forms. This paper could help to advocate this classification status with regulatory authorities and consequently result in fewer dossier requirements for lactose when applying for marketing authorisations, thus facilitating the availability of medicines.

Background Information

In the Chinese pharmaceutical legislation, a distinction is made between low-risk excipients and high-risk excipients. Definitions are found in Annex 1: "Provisions for Bundling Review and Approval of Chemical Drug Substances, Pharmaceutical Excipients, Pharmaceutical Packaging Materials and Drug Product (Draft for Comments)" [1]:

"High-risk pharmaceutical excipients: high-risk pharmaceutical excipients generally include **animal-derived** or human-derived pharmaceutical excipients; pharmaceutical excipients used for injections, ophthalmic drug products, and inhalation drug products; the pharmaceutical excipients subject to regulation as specifically required by NMPA based on monitoring data. The pharmaceutical excipients not currently used in drug products marketed both domestically and overseas shall be managed as per standard for high-risk pharmaceutical excipients."

This distinction is also made in the Guideline for the Production and Quality Control of Pharmaceutical Excipients of Animal Origin (ChP2020).

Pharmaceutical grade lactose should be considered as a low-risk excipient for the following reasons:

1. Pharmaceutical grade lactose is a single well-defined chemical compound and is described in the following pharmacopoeias:

- European Pharmacopoeia
- USP-NF
- Japanese Pharmacopoeia
- Chinese Pharmacopoeia

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 – 1000, Brussels, Belgium
www.ipec-federation.org -- +32 (0)2 213 74 40 -- info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73 3630 6812 5160 - RPM Brussels Capital Region

- Indian Pharmacopoeia
- Brazilian Pharmacopoeia
- International Pharmacopoeia

Pharmaceutical grade lactose has a purity between 98.0 and 102.0 w/w % (ChP 2020)
Potential contaminants have been eliminated by a double crystallization and a refining procedure and trace amounts of related sugars identified (e.g., galactose, glucose) therein have a high safety.

Lactose is of animal origin as lactose is isolated from whey which is a product derived from cheese manufacturing by dairy companies. It is produced by crystallization from whey with a subsequent refining procedure and a second crystallization. Refining is conducted by adding processing aids (activated carbon and inorganic filter auxiliaries) to a hot solution of the unrefined lactose. On cooling, the desired crystals grow and exclude other kinds of particles and impurities. Thus, refining is a purification process leading to a higher purity.

Given these purification steps, Lactose is a chemically pure sugar substance with a purity of > 98.0%. In this context, the animal origin is of low importance and the risks due to its origin are no longer relevant.

2. Due to the described manufacturing process, residues and contaminants which might be present in the raw material like pesticides, veterinary drug residues, dioxins, PCB's heavy metals, melamine, are present at low levels in pharmaceutical grade lactose.
Furthermore, only water is used as solvent. Residual organic solvents are not present.

3. Pharmaceutical grade lactose has been used as an excipient in pharmaceutical preparations for more than 50 years. It is used worldwide in many licensed pharmaceutical products.

4. Lactose is used as an ingredient in a large variety of different foods but also in infant formulae. In China, lactose for food and infant consumption has been defined in the recently published GB 25595-2018. Lactose is not regarded as a milk product in Chinese legislation (e.g., AQSIQ, 2015,152). The amounts used in food and thus eaten by the consumer are much higher than those in pharmaceutical preparations.

5. Pharmaceutical grade lactose is produced by a process where in addition to a legally required pasteurization (15 secs at 72 °C) an intensive heat step is applied during the crystallization process (e.g., 95 °C for 30 minutes). This heat treatment assures a very low bio burden i.e., TAMC less than 100 cfu/g, TYMC less than 100 cfu/g.
The treatment is also effective in eliminating viruses like Foot-and-Mouth disease.

6. Pharmaceutical grade lactose is derived from milk. In an extensive risk assessment performed by the European Union competent authorities it is concluded that for pharmaceutical grade lactose the BSE/TSE risk is negligible. This includes the use of calf rennet during cheese making processes where raw whey material is obtained as by-product.

- " Taking all these factors and the scientific assessment performed by the BWP into consideration, the CPMP concludes that the BSE risk in pharmaceutical lactose is negligible.", EMEA (EMA) [2];

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 – 1000, Brussels, Belgium
www.ipec-federation.org -- +32 (0)2 213 74 40 -- info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73 3630 6812 5160 - RPM Brussels Capital Region

Other regulators have drawn similar conclusions:

- "Milk from cattle does not contain prions and has no infectivity", WHO [3];
- "Milk and certain milk derivatives, such as lactose, are generally considered non-infectious, regardless of geographic origin, provided that the milk is from healthy cows fit for human consumption and no other potentially infectious ruminant-derived materials were used in the manufacturing process", WHO [4];
- "We also confirm that milk and milk products, hides and hide-derived products, tallow that contains no more than 0.15 percent insoluble impurities, and tallow derivatives are not prohibited cattle materials", FDA [5];

7. Pharmaceutical grade lactose is exclusively sourced from cow's milk and thus homogeneous with respect to species.
For milk this is assured by local legislation and compliance is ensured by the continuous monitoring of the local competent authorities. Strict controls are performed throughout the supply chain for milk and dairy products including surveillance of cow farms.

8. IPEC/PQG GMP Guide for Excipients [6] is used by the manufacturers of pharmaceutical grade lactose that are members of IPEC. This includes a requirement for change management where all changes including those for raw materials will be evaluated.

9. Storage requirements for pharmaceutical grade lactose are defined by manufacturers of pharmaceutical grade lactose based on stability studies based on the IPEC Stability Program Guidance [7].

IPEC Federation Position

IPEC considers that pharmaceutical grade lactose has a low risk profile with respect to chemical and biological risks when used in oral pharmaceutical preparations.
It should be considered as such where regulations require excipient risk to be classified for the following reasons:
- the typical risks of pharmaceutical excipients of animal origin are not relevant;
- it is a single compound with a well-defined chemical structure;
- lactose has a long and well-documented history of safe use in oral pharmaceutical preparations, and in food and infant food preparations;
- its impurity profile is well defined;
- pharmaceutical grade lactose has a low bioburden and as confirmed by many regulatory authorities, has a negligible BSE/TSE risk;
- lactose is manufactured according to appropriate GMP and shelf life is supported by stability studies performed under suitable conditions.

References

1. NMPA, Annex 1: "Provisions for Bundling Review and Approval of Chemical Drug Substances, Pharmaceutical Excipients, Pharmaceutical Packaging Materials and Drug Product (Draft for Comments)".

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 – 1000, Brussels, Belgium
www.ipec-federation.org -- +32 (0)2 213 74 40 -- info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73 3630 6812 5160 - RPM Brussels Capital Region

2. The European Agency for the Evaluation of Medicinal Products (EMEA), Public Statement – Lactose prepared from calf rennet: Risk assessment in relationship to bovine spongiform encephalopathies (BSE), 27 February 2002
https://www.ema.europa.eu/documents/public-statement/public-statement-lactose-prepared-using-calf-rennet-risk-assessment-relationship-bovine-spongiform_en.pdf
3. World Health Organization, WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (Updated 2010), 2010
http://www.who.int/bloodproducts/tablestissueinfectivity.pdf
4. WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Product, 2003, page 7
http://www.who.int/biologicals/publications/en/whotse2003.pdf
5. Food and Drug Administration, FDA Final Rule: Use of Materials Derived from Cattle in Human Food and Cosmetics, 18 March 2016
https://www.federalregister.gov/documents/2016/03/18/2016-06123/use-of-materials-derived-from-cattle-in-human-food-and-cosmetics
6. IPEC-PQG Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients, version 3, 2015
https://ipec-federation.org/resources/
7. IPEC Excipient Stability Program Guide, version 1, 2010
https://ipec-federation.org/resources/

The International Pharmaceutical Excipients Council – Federation (IPEC Federation) asbl
Rue Marie de Bourgogne 52 – 1000, Brussels, Belgium
www.ipec-federation.org -- +32 (0)2 213 74 40 -- info@ipec-federation.org
VAT: BE 0823931361 - IBAN: BE73 3630 6812 5160 - RPM Brussels Capital Region