□□ 2 [Annex 2]：

《中国药典》2020 年版通则征求意见稿反馈意见单

Chinese Pharmacopoeia 2020 Comment Template

□□□□（□□）Name	Inhalations (0111)
□□□□□□	International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) https://ipacrs.org/

□□□□ [Feedback]：

Thank you very much for this opportunity to comment on the Chinese Pharmacopoeia 2020. We are an international association that seeks to advance the science, and especially the regulatory science, of orally inhaled and nasal drug products (OINDP) by collecting and analyzing data, and conducting joint research and development projects. Our members include innovator and generic companies that develop, manufacture or market orally inhaled and nasal drug products for local and systemic treatment of a variety of chronic diseases. Based on our organization's experience and perspective, we would like to offer some specific comments on Inhalations (0111) as well as some general comments on several chapters that are closely related to Chapter 0111 for the Pharmacopoeia's consideration. If you have any questions regarding these comments, please do not hesitate to contact us at any time and we would welcome the opportunity to discuss with you further.

1. Specific comments related to chapter 0111.

Current content in each chapter	**Suggested content in each chapter**
0111 Preparations for Inhalation Page 1, section 5 The text currently says 'The particle size of the active substances must be not more than 10 µm, most of them should be less than 5 µm'	Please consider revising the text to state only that, "Most of the particles of the active substances should be less than 5µm in size." If this statement pertains to the active pharmaceutical ingredient (API) it is better to refer to the D50. Each product will define an appropriate particle size distribution for both input API (as appropriate) and product performance. If this statement pertains to the product, it is not possible to state that materials be not more than 10 microns because for inhalation products, the ACI or NGI are not used to measure particles above 9 microns. Instead, such material is deposited

	in the area of the apparatus that does not measure sizes.
0111 Preparations for Inhalation Page 2, section 8 (2) The text currently states 'The content of active ingredient in a dose* and delivered dose' *The assumption is that dose is equivalent to metered dose in this text	Please clarify whether the dose means metered dose. If it is, please consider revising this sentence to state "the content of active ingredient in a **metered** dose ~~**and**~~ **or** delivered dose." We would be interested to learn your perspective on why both should be included.

2. Please consider harmonizing testing approaches, where possible with other Pharmocopoeia. This is done in some parts of the chapters but not others. For example, it is noted in the chapters that the European Pharmacopoeia approach is adopted for uniformity of delivered dose (within inhaler / intra-inhaler). We suggest that the approach for uniformity of delivered dose between inhalers (inter-inhaler) also adopt this approach. Another example of potential harmonization is in the application of sterility. Please consider that sterility requirements could also be harmonized with other regional pharmacopoeia. For example, in the United States Pharmapoeia chapter 5, the United States Code of Federal Regulations 21 CFR 200.51, and the European Pharmacopoeia 9.6 04/2018:0671, only nebulized products are required to be sterile.[1, 2, 3]

1. USP <5>, definitions for inhalation solution, inhalation suspension, solution for inhalation and [drug] for inhalation solution are all described as 'sterile'.
2. 21 CFR 200.51, Aqueous-based drug products for oral inhalation must be sterile.
3. EP 9.6 04/2018:0671, Liquid preparations for nebulisation: Liquid preparations for nebulisation supplied in multidose containers that do not contain an antimicrobial preservative, and where the preparation itself does not have adequate antimicrobial properties, are sterile and are supplied in containers preventing microbial contamination of the contents during storage and use. Liquid preparations for nebulisation supplied in single-dose containers are sterile and preservative-free, unless otherwise justified and authorised.

Specific areas where harmonization with, for example, the European Pharmacopoeia can be considered are noted in the following table:

Current content in each chapter	**Suggested content in each chapter**
0111 Preparations for Inhalation Page 2 Section 1. Inhalation Aerosols, Apparatus	Please consider adding the statement, "Other types of collection apparatuses could be used if justified" to be consistent with the European Pharmacopoeia.
0111 Preparations for Inhalation Page 4 Section 1 Inhalation Aerosols, DDU Criteria	Please consider that DDU limits should continue to reference the average delivered dose rather than the labelled delivered dose as this is consistent with European

	Pharmacopoeia.
0111 Preparations for Inhalation Page 4 Section 1 Inhalation Aerosols, DDU Criteria	Please consider amending the statement, “The preparation should comply with the test..” by adding the additional statement, “unless otherwise authorized and justified.” This would be consistent with EMA guidelines where different criteria can be applied if suitably justified.
0111 Preparations for Inhalation Page 6 Section 2 Inhalation powders Apparatus	Consistent with the recommendation for inhalation aerosols, please consider adding the statement, “Other types of collection apparatuses could be used if justified” to be consistent with the European Pharmacopoeia.
0111 Preparations for Inhalation Page 8 Section 2 Inhalation powders, Criteria	As for inhalation aerosols, please consider that the average delivered dose should be referenced rather than the labelled delivered dose and that the statement, “The preparation should comply with the test..” is amended by adding the additional statement, “unless otherwise authorized and justified.” This would be consistent with EMA guidelines where different criteria can be applied if suitably justified.
0111 Preparations for Inhalation Page 11 Section 4 Liquid preparations for inhalation rate Active substance delivery rate and the total active substance delivered, Criteria Fine particle dose	We suggest that this test be a characterization test and not a release test, to be consistent with the European Pharmacopoeia and the United States Pharmacopoeia, in which this is described as a characterization test. The results of these tests are dependent on the model of nebulizer used, that is, different nebulizer types will give different delivery rates and fine particle dose values. If this test were performed as a release test, it would be necessary to specify a particular nebulizer for each product, which would make it unsuitable for inclusion in a Pharmacopoeia since the nebulizer designs can change.

3. In addition to the above specific comments on Chapter 0111, please allow us to share the following feedback regarding the structure and format among Chapter 0111 and a few chapters (Nasal Preparations (0106), Sprays (0112), Aerosols (0113)) that are closely related to Chapter 0111:

First, within the chapters, once an item is fully detailed in one chapter (for example, Inhalation chapter), then consider cross-referencing this item in subsequent chapters rather than repeating the same information or presenting partial information. This will improve consistency. Second, please consider arranging content within chapters such that products are more appropriately categorized. For example, all nasal drug products can be the focus of Chapter 0106 (Nasal Preparations) and all inhalation drug products (with lungs as the target) can be the focus Chapter 0111. Any other sprays, which are not for nasal delivery can be the focus of Chapter 0112, and any other aerosols, which are not intended for drug delivery to the lungs can be the focus on Chapter 0113. This rearrangement would improve clarity of the Chapters. An example of this rearrangement is shown in the following table (we have included Chapter 0106, in the table, for clarity):

Current content in each chapter	**Suggested content in each chapter**
0106 Nasal Preparations …… nasal aerosols, nasal sprays, nasal dry powders……	0106 Nasal Preparations …… nasal aerosols, nasal sprays, nasal dry powders……
0111 Inhalations pMDI, DPI, inhalation sprays, Liquid preparations for inhalation, Preparations to be converted into vapor	0111 Inhalations pMDI (hand actuated, and breath actuated), DPI, inhalation sprays (including soft mist), Liquid preparations for inhalation, Preparations to be converted into vapor
0112 Sprays Inhalation sprays, nasal sprays, topical or oromucosal sprays	0112 Other sprays (except nasal and inhalation sprays) Sprays that are intended for topical or oromucosal use.
0113 Aerosols Inhalation aerosols, nasal aerosols	0113 Other pressurized aerosols (except nasal and inhalation) Aerosols that are intended for topical or oromucosal use.

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联 系 人：長尾李, 国际药用气雾剂联盟

□□□□：**+1 202 230 5165**

□□□□：**lee.nagao@dbr.com**

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