Lost in Terminology of Quality Attributes of Inhalation Products! Terms Currently Used by EPAG Companies to Encourage Harmonization in International Pharmacopeias, Regulatory Guidelines and Literature

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INTRODUCTION AND CURRENT STATUS

Attributes describing the quality of inhalation drug products are contained within international pharmacopeias [1, 2], various regulatory guidances from the US Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA) [3-6], International Conference on Harmonization (ICH) guidelines [7] and International Organization for Standardization (ISO) standards [8]. There are currently wide differences in the use of these attributes between international regulatory guidances, usage in literature, and by companies. Different terms for the same quality attributes were collected from the various sources to make the broad variety visible. In this work, European Pharmaceutical Aerosol Group (EPAG) presents a survey of most commonly used terms for quality attributes by the member companies and proposes harmonization in regulatory guidance and communication.

METHODS

The pharmacopeias, guidances, and guidelines were systematically screened for their quality terms for inhalation drug products. These were descriptive quality terms as well as terms required as testing parameters for quality attributes of one time characterization studies or routine quality testing. The found terms were grouped according to their use and listed together with their source

in a tabular list. A copy of this list was emailed to each of the EPAG company plenary members. They were asked to indicate all the terms in the list that their company uses by denoting them with a number dedicated to their company (e.g., 1) and to introduce and mark respectively with the same number all additional terms they use in their internal and external regulatory submission documents. The EPAG company plenary members responded with their company terminology denoted in the list, some of them after consultation with their development, analytical, quality or regulatory affairs department staff. About two thirds of the 23 EPAG member companies responded.

RESULTS

The screening of the guidelines showed a variety in the terminology used for the same issue, e.g., (foreign) particulate matter is used by FDA in [3, 4] and ICH [7], whereas, the United States Pharmacopeia (USP) proposes foreign particulates [1]. The variability of terminology for quality attributes of inhalation drug products and inhalers is made visible by the survey among the EPAG member companies (Tables 1 and 2). They are not only using the full variety of quality terminology proposed by regulatory guidance for description of quality attributes in submission documentation and communication with regulatory authorities, but in addition, some EPAG companies are using alternate quality terms, e.g., in the case of shot weight: actuation weight, actuation mass, emitted weight and metered mass for this purpose. In some member companies, the terminology for the same drug product and quality attribute even differs for the different regions of submissions, e.g., spray content uniformity for USA and uniformity of delivered dose for Europe.

Table 1.

Example for variability of terms for homogeneity of delivered dose.

Quality parameter	Example Terms	Source	EPAG company using this term*
Homogeneity of delivered dose	Content uniformity	EMA	8, 15
	Delivered dose rate	EMA	
	Delivered Dose Uniformity	EMA, USP	2, 3, 7, 8, 11, 13
	Delivered dose uniformity through container life	EMA	2, 4, 5, 8, 10
	Delivered dose uniformity over patient flow rate range	EMA	6
	Dose content uniformity	FDA, USP	2, 11, 15
	Dose content uniformity through container life	FDA	8, 11, 13
	Emitted dose		9
	Emitted dose content uniformity	FDA	12
	Emitted dose uniformity		8
	Emitted dose uniformity over entire contents	USP	
	Emitted dose content uniformity through container life		12
	Spray content uniformity	FDA, USP	5
	Uniformity of emitted dose		9
	Uniformity of delivered dose	EP	5, 6, 13, 14
	Uniformity of dosage units	ICH	15

* Each EPAG member company was given a dedicated number

Table 2.

Example for variability of terms for particle size and particle size distribution.
The most frequently used terms by EPAG companies given in bold.

Quality parameter	Example Terms	Source	EPAG company using this term*
Particle size parameters and particle size distribution parameters	**Aerodynamic particle size distribution (APSD)**	FDA	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 15
	Aerodynamic size distribution	USP	
	Emitted fraction	USP	
	Fine particle characteristics	EP	
	Fine Particle Fraction (FPF)	USP	2, 3, 4, 5, 6, 7, 8, 10, 11, 13
	Fine Particle Dose (FPD)	EP, USP	2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15
	Fine Particle Mass (FPM)	EMA, EP	2, 6, 9, 13, 14, 15
	Fine particle mass over patient flow rate range	EMA	3
	Fine particle mass through container life	EMA	
	Geometric standard deviation (GSD)	EMA, USP	1, 2, 3, 6, 7, 8, 9, 14, 15
	Mass median aerodynamic diameter (MMAD)	EMA, USP	1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 14, 15
	Multi-point particle size test	EMA	
	Particle size	EP, ICH, USP	2, 15
	Particle size distribution	FDA, ICH	14, 15
	Particle size distribution (of the delivered dose) (PSD)	EMA, EP	5, 8, 15
	Particle size distribution of emitted dose	FDA	12, 15
	Respirable fraction (RF)		1, 15
	Single dose fine particle mass	EMA	5
	Stage groupings		2, 6, 7, 9, 10, 11, 15

* Each EPAG member company was given a dedicated identification number

This difference in terminology creates a burden for internationally operating companies. An approximation to harmonization of quality attributes for inhalation drug products over all regions of the world would be a valuable goal to achieve for ease of compilation of documentation for international submissions or company internal documents like testing specification for drug products and/or inhalers. As a starting point for international attempts to achieve this goal, this survey is published.

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CONCLUSION

The purpose of this work from EPAG is to make the broad variety of terms for quality attributes in international regulatory guidance visible and encourage individuals and organizations that are responsible for the determination of binding terms for inhalation products in pharmacopeias and regulatory guidance to aim for consolidation and harmonization of the terminology in all regions. Since the current difference in terminology creates a burden for internationally operating companies, EPAG is more than willing to support all attempts that aim for harmonization.

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