
ITFG/IPAC Collaboration

CMC Specifications Technical Team

Particle Size Distribution Working Group

***Initial Assessment of the
ITFG/IPAC Aerodynamic Particle Size
Distribution Database
by the CMC Specifications Technical Team
of the ITFG/IPAC Collaboration***

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I. OVERVIEW

- Between October 1998 and June 1999, the FDA issued the following CMC draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*; and 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*. (These draft Guidances are available at <http://www.fda.gov/cder/guidance/index.htm>).
- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft CMC Guidances.
- The Inhalation Technology Focus Group (ITFG) of the AAPS supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge of both organisations and address key CMC issues in the draft Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration.
- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.
- At the 26 April OINDP Subcommittee meeting, the Particle Size Distribution (PSD) Working Group of the CMC Specifications Technical Team of the ITFG/IPAC Collaboration reported that, based on the collective experience of its members, it deemed it important to examine the relevancy of the mass balance requirement as a product specification versus a system suitability requirement, and to investigate if fewer than 3-4 stage groupings can provide equivalent control. The PSD Working Group also committed to collect a worldwide database of PSD in OINDP in order to consider these issues.
- The PSD database collected by the ITFG/IPAC Collaboration contains data for 35 products (from 7 companies) with a total of 3606 individual observations. One product is for nasal delivery and 34 are for oral inhalation.
- Because there is only one nasal product in the database, no valid conclusion can be drawn concerning this class of drug product.
- The initial assessment of the database indicates that orally inhaled products do not in general comply with the mass balance requirement proposed in the FDA's draft Guidances and that the proposed requirement is not suitable as a drug product specification. Only 4 out of 35 examined products showed no results outside the proposed mass balance limits.
- A more detailed analysis will follow, which will further address such issues as the relevance of the mass balance criterion as either a specification or system suitability criterion and which may include studies to compare different metrics and sets of criteria for characterizing the PSD of OINDP.

II. INTRODUCTION

During the 26 April 2000 meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science, the ITFG/IPAC Specifications Technical Team reported that, with respect to aerodynamic particle size testing in the draft FDA CMC Guidances, it intended to:

- Examine the relevancy of the mass balance requirement as a product specification versus a system suitability requirement; and
- Investigate if fewer than 3 to 4 stage groupings can provide equivalent control.

In order to carry out these investigations, the Specifications Team committed to collect a worldwide, blinded database containing particle size distribution (PSD) data for OINDP. Furthermore, the Specifications Team committed to present the Agency and the Subcommittee with an initial assessment of the collected PSD data. This is the topic of the present report.

This initial assessment contains i) a descriptive analysis of summary characteristics of products grouped by different categories and ii) an investigation of the suitability of the mass balance requirement proposed in the draft CMC Guidances. The initial assessment allows only broad conclusions to be drawn. A more detailed analysis, which is to follow, will further examine the relevancy of the mass balance requirement as a product specification versus system suitability requirement and will also consider if fewer than 3-4 stage groupings can provide adequate control of PSD.

Moreover, the collected PSD database provides a unique opportunity to study and compare different metrics and sets of criteria for characterizing the PSD of OINDP. A subsequent detailed analysis will maximize the benefits of the database, which is unique in its scope and depth. The Specifications Team is continuing to solicit additional data to augment the current database.

III. DATA COLLECTION

Pharmaceutical companies participating in the IPAC/ITFG Collaboration were asked to submit aerodynamic particle size data for individual stages for as many products as possible. Individual determinations for commercial products and products under development (*i.e.*, before Phase IIB through NDA and later), obtained at release testing and/or for real time stability studies were requested. Data were presented as a percent of the label claim (LC). To avoid bias, it was recommended that companies submit either:

- all available data for the product, or
- data for a random selection of batches, or
- data for all batches manufactured during a defined timespan.

To ensure blinding of raw data and to preserve confidentiality, data for each product were separately submitted in a standardized form to the IPAC Secretariat, which assigned a random code to each datafile. After checking and necessary clarifications, the coded files were merged into a Master Clean File containing all files that had been finalized by 9 August 2000.

IV. STRUCTURE OF DATA

For each individual PSD determination in the database, the following information was provided by the submitting company: batch number (coded to preserve confidentiality), unit number (*i.e.*, container/can/device number), life-stage (beginning, middle, end, or N/A), months of storage, apparatus used and particle size ranges for all stages. Furthermore, the following information describing the product was requested in order to provide an opportunity to study relevant groups of products: product status, delivery route, formulation type, device type, metering system and number of actuations per determination. Table 1 lists these categories along with the options for answers. For each of the categories, the companies had the option not to disclose the information; however, this option was very rarely used. Finally, if data for stored samples were submitted, the real time storage conditions could be stated.

Table 1. Product information categories (top row) and options for answers.

Product status	Delivery route	Formulation type	Device type	Metering system	Number of actuations per determination
US commercial	Local pulmonary	Suspension	CFC	Pre-metered	1
Non-US commercial	Local nasal	Solution	HFA	Device metered	2
Phase IIB/III/NDA	Systemic pulmonary	Dry Powder	Non-pressurized		3
Before phase IIB	Systemic nasal		Power assisted		4
			Container only		5
					6
					7
					8
					9
					10
					>10

Seven companies provided original data. The current PSD database contains data for 35 products with a total of 3606 individual observations. The number of determinations per product varies from 9 (all from one batch) to 279 (from five batches). About 49% of the results are collected through initial (release) testing, and the remaining 51% are from

stability tests. One product is for nasal delivery and 34 products are for oral inhalation. The PSD data supplied by the companies were obtained using one of the following apparatus: Andersen cascade impactor, modified Andersen cascade impactor, multistage liquid impinger or IMPAQ (a type of multi-stage cascade impactor).

To examine the mass balance (MB) requirement in an appropriate manner, it was decided to separate from the main assessment those products for which:

- the delivery route is nasal (the single nasal product is presented individually); or
- the MB mean is outside 90-110% LC (since these products cannot appropriately represent the general ability of the product category to comply with the MB requirement proposed in the draft CMC Guidances).

In total, 12 products were excluded because of these considerations, leaving 23 products and 2927 determinations for the main analysis. All of the 23 products included in the main analysis are for local pulmonary delivery. The excluded products were treated separately and the results are presented in Section V.A below.

For each product, the mass balance obtained in each determination was calculated as a sum of the results on all stages and accessories. These individual MB values were then rounded to the nearest integer before the statistical analysis.

For the initial analysis presented here, the data for each product were summarized by the following characteristics: the number of determinations, the mass balance mean, the relative standard deviation (RSD) of the mass balance and the frequency of determinations outside 85-115% LC (f15) (this interval equals the outer limits of the proposed PSD mass balance specification in the draft Guidances).

V. RESULTS AND DISCUSSION

A. Products Excluded from Main Analysis

As stated above, 12 products were excluded from the main analysis. Tables 2a and 2b summarize characteristics of these products. In the case of the single nasal product submitted, this product was eliminated because it was the only product in this class (this product is described in the first row of Table 2a). As a result, we concluded that there was insufficient data to comment on this class of drug products.

The remaining 11 products excluded from the main analysis were separated because their mean mass balance fell outside 90-110% LC. It is obvious without statistical treatment that products in this category will have difficulty meeting the MB requirement of 85-115% LC. In particular, all eight of the power assisted devices demonstrated mass balances on the order of 50% (Table 2b). In this class of drug products, there were no results that met the proposed mass balance requirement. These very low MB values may relate to the interpretation of the draft CMC Guidance. The draft CMC Guidance states that:

The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.

(Lines 624-626 of the *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation* draft Guidance); and

The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per spray basis.

(Lines 759-761 of the *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation* draft Guidance).

The interpretation of this recommendation is problematic because the label claim on a product may not necessarily refer to the amount of drug collected on all the stages and accessories. (As one example, for DPIs that use pre-metered blisters or capsules, the label claim may be based on the amount in the blister or capsule rather than the amount emitted by the device. Since the capsule or blister residual is not quantitated during a particle size determination, obtaining 100% LC mass balance is not possible.) Therefore, it is recommended that the draft Guidances acknowledge the diversity of products and allow the mass balance metric - if it is retained in the Guidances at all - to be defined for each product individually.

Table 2a. Summary characteristics for products excluded from the main analysis.

<i>Product status</i>	<i>Number of products</i>	<i>Formulation</i>	<i>Number of actuations per determination</i>	<i>Total number of determinations</i>	<i>Mean Mass Balance % LC</i>	<i>RSD</i>	<i>f15*</i>
IIB – NDA	1	HFA pMDI	2	159	100.1	9.9	12.6
IIB – NDA	1	Device-metered DPI	10	83	89.2	10.3	28.9
Non-US Commercial	1	Device-metered DPI	1	192	83.8	9.7	51.0
US Commercial	1	CFC pMDI	>10	96	77.7	4.1	100.0

* frequency of mass balance determinations outside 85-115% LC

Table 2b. Summary characteristics for the group of power-assisted solution drug products excluded from the main analysis

<i>Product status</i>	<i>Number of products</i>	<i>Number of actuations per determination (range)</i>	<i>Total number of determinations</i>	<i>Mean Mass Balance % LC</i>	<i>RSD %</i>		
					<i>Mean</i>	<i>Median</i>	<i>Range</i>
before Phase IIB	8	1-10	149	56.5	9.3	8.9	2.5-14.5

B. Main Analysis (Orally Inhaled Products)

The products were grouped according to product status (Table 3), product type (Table 4) or the number of actuations used per determination (Table 5). The summary characteristics of each group are represented by the mean MB and the mean, median and range (for RSD and f15) of the corresponding mean product characteristics. This approach (*i.e.*, giving each product the same weight in the analysis) was taken to avoid bias from products with a large number of determinations.

The results presented in Tables 3, 4, and 5 suggest that there is relatively little difference in the mean MB or the variability of MB (as assessed by RSD) among different groups of products. In particular, the number of actuations per determination does not seem to influence the mean MB or the variability in the range of 1 to >10 actuations per determination (see Table 5).

The mean MB for the 23 products in the main analysis (97.0%, see Table 3), is less than 100% LC. This is probably explained by the nature of a mass balance determination where the analyst is faced with recovering all of the aerosolized dose from a complex device containing a large surface area. This would imply that any acceptance criteria for mass balance should reflect these inherent losses and not be centered on the absolute recovery criterion of 100% LC.

The frequency (f15) of MB determinations outside 85-115% LC varies between 0.0-28.6%, with a mean of 6.6% and a median of 4.8%. Results outside the MB limits proposed in the draft Guidances were reported for the majority (19 out of 23) of the products included in the main analysis. The relative standard deviation varies by product between 3.6-16.7% (mean 7.6%, median 7.1%).

To illustrate a consequence of the MB requirement being applied as a drug product specification, we present the following example: Assume a release test stipulates that 2 units should each be characterized through-life (in the beginning and in the end); that is, 4 determinations are to be made. If the risk to fail the MB requirement (85-115% LC) in an individual determination is 4.8% (equal to the median f15 for products in the main analysis), the risk of failing any arbitrary batch (at least one determination outside 85-115% LC) is $1-(1-0.048)^4 = 0.18$; that is, on average, 18% of batches will fail to comply with the MB requirement. Given that a typical stability program includes a battery of such PSD tests, it is virtually certain that an average product would fail the 85%-115% LC criterion at some point of its PSD testing program.

The actual results from the surveyed products and the example above suggest a high rate of non-compliance with the proposed PSD mass balance specification in the FDA's draft CMC Guidances for the majority of the orally inhaled products. From this initial assessment, the database appears to indicate that the mass balance requirement proposed in the draft CMC Guidances is not suitable as a specification.

We believe that it is not appropriate to use the mass balance requirement in this way (*i.e.*, where it is essentially measuring the emitted dose rather than a characteristic of the size distribution of the batch). For certain products, obtaining adequate information about the particle size distribution may not require achieving an 85-115 % LC mass recovery. We also note that emitted dose is adequately controlled by appropriate specification tests.

Table 3. Summary characteristics for different groups by product status.

<i>Product status</i>	<i>Number of products</i>	<i>Total number of determinations</i>	<i>Mean MB* % LC</i>	<i>RSD %</i>			<i>f15*** %</i>		
				<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
US commercial	6	866	96.7	5.4	5.2	3.6-8.4	1.8	0.5	0.0-4.9
Non-US commercial	6	622	96.8	7.5	8.0	4.4-10.0	7.2	6.2	0.0-16.8
Phase IIB/III/NDA	10	1404	97.8	8.7	7.8	5.2-16.7	6.9	4.7	0.0-23.8
Not Disclosed	1	35	91.5	11.8	**	**	28.6	**	**
All	23	2927	97.0	7.6	7.1	3.6-16.7	6.6	4.8	0.0-28.6

Table 4. Summary characteristics for different groups by product type.

<i>Product type</i>	<i>Number of products</i>	<i>Total number of determinations</i>	<i>Mean MB* % LC</i>	<i>RSD %</i>			<i>f15*** %</i>		
				<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
Device metered DPI	13	1706	97.4	8.7	8.1	5.2-16.7	8.1	6.7	0.0-23.8
CFC suspension pMDI	5	854	97.7	5.6	5.3	3.6-8.4	2.1	0.6	0.0-4.9
HFA suspension pMDI	4	166	93.6	7.3	6.5	4.3-11.8	8.4	2.5	0.0-28.6
HFA solution pMDI	1	201	101.4	6.2	**	**	1.5	**	**

Table 5. Summary characteristics for different groups by numbers of actuations per determination.

<i>Number of actuations per determination</i>	<i>Number of products</i>	<i>Total number of determinations</i>	<i>Mean MB* % LC</i>	<i>RSD %</i>			<i>f15*** %</i>		
				<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
1	5	890	98.9	7.1	6.9	5.8-8.6	4.7	4.3	0.7-12.2
2	2	267	100.9	6.9	6.9	5.3-8.4	2.8	2.8	0.6-4.9
10	5	536	95.9	9.8	10.4	7.1-11.8	15.0	13.6	1.7-28.6
>10	11	1234	95.9	7.0	5.5	3.6-16.7	4.3	1.5	0.0-16.8

* mean of the product MB means

** not meaningful (n=1)

*** frequency of mass balance determinations outside 85-115% LC

VI. CONCLUSION

The initial assessment of the database indicates that orally inhaled products do not in general comply with the proposed mass balance requirement in the draft CMC Guidances (85-115% LC) and that the proposed requirement is not suitable as a drug product specification but could be appropriate as a system suitability test defined on a case by case basis.

VII. GLOSSARY

AAPS	American Association of Pharmaceutical Scientists
CFC	Chlorofluorocarbon, a type of propellant used in pMDIs
CMC	Chemistry, Manufacturing, and Controls
DPI	Dry Powder Inhaler
f15	frequency of mass balance determinations outside 85-115% LC
HFA	Hydrofluoroalkane, a type of propellant used in pMDIs
IMPAQ	a brand name for a commercially available multi-stage cascade impactor used for aerodynamic particle sizing
IPAC	International Pharmaceutical Aerosol Consortium, an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes
ITFG	Inhalation Technology Focus Group of the AAPS, comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes
LC	Label Claim
MB	Mass Balance
MDI	Metered Dose Inhaler
OINDP	Orally Inhaled and Nasal Drug Products
outer limits	85-115% LC as recommended by the draft Guidances
pMDI	pressurized Metered Dose Inhaler
PSD	Particle Size Distribution
RSD	Relative Standard Deviation