ITFG/IPAC Collaboration

CMC Specifications Technical Team

Dose Content Uniformity Working Group

Initial Assessment of the ITFG/IPAC Dose Content Uniformity 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.*

- 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) supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge and address key CMC issues in the draft Guidance documents.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 Dose Content Uniformity (DCU) 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 investigate the following question: Can the current state of OINDP technology generally comply with the DCU specifications in the draft FDA CMC Guidances? The DCU Working Group also committed to collect a worldwide database of DCU in OINDP in order to investigate this question.

- The DCU database collected by the ITFG/IPAC Collaboration contains data for 77 products (from 10 companies) with a total of 46016 individual DCU observations. Five products are for nasal delivery and 72 are for oral inhalation.

- Because of the limited number of nasal products available in the database, no valid conclusion can be drawn concerning general characteristics of different product types for nasal delivery.

- The initial assessment of the database supports the hypothesis that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances. The relatively large differences among products and among product types suggest that a single content uniformity specification for all orally inhaled products is not suitable.

- A more detailed analysis will follow employing simulations to address such issues as probability of compliance with complex criteria and which may include studies to compare alternate (statistical) approaches for DCU testing.

II. INTRODUCTION

At the public hearing of the meeting of the Advisory Subcommittee for Orally Inhaled and Nasal Drug Products (OINDP) of the Advisory Committee for Pharmaceutical Science held on 26 April 2000, the ITFG/IPAC Specifications Technical Team put forward the following hypothesis:

> "The current state of OINDP technology may not allow general compliance with the dose content uniformity specifications in the draft FDA CMC Guidances."

Further, at the same meeting, the FDA asked the OINDP Subcommittee the following questions:

- "Should there be a single content uniformity standard for all orally inhaled and nasal drug products (OINDPs)?" and
- "Should the FDA continue development of the proposed statistical approach to evaluating content uniformity?"

To investigate our hypothesis and to provide guidance on the FDA's questions, the Specifications Team committed to collect a worldwide blinded database containing delivered dose content uniformity (DCU) data for OINDP products. Further, the Specifications Team committed to present an initial assessment of the collected DCU data by 31 July 2000. This is the topic of the present report.

This initial assessment is limited to a descriptive analysis of summary characteristics of groups of data. This allows only broad conclusions to be drawn, which nevertheless provides an initial answer to the first question posed by FDA and to the Team's hypothesis. A more detailed analysis will follow in order to maximize the benefits of the database, which is unique in its scope and depth. The detailed analysis will need to employ simulations to address such issues as probability of compliance with criteria on average delivered dose and individual determinations, both for Between Container and for Through Container Life testing. Moreover, the database provides an excellent opportunity to study and compare different tests and sets of criteria for DCU using real data. Thus, although we are not currently in a position to offer any comments on the Agency's second question regarding the development of a statistical approach to evaluating content uniformity, we expect that such considerations may be included in our detailed assessment of the DCU database.

III. DATA COLLECTION

Pharmaceutical companies participating in the IPAC/ITFG Collaboration were asked to submit delivered dose data for as many products as possible. Individual determinations for commercial products and products in late development, obtained at release testing and/or real time stability studies were requested. Data were presented as a percent of delivered dose 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 time-span.

To ensure blinding of raw data and preserve confidentiality, data for each product were separately submitted in a standardized form to the IPAC Secretariat, which assigned a random code to each file. After checking and necessary clarifications, the coded files were merged into a Master Clean File containing all files that had been finalized by 26 July 2000.

IV. STRUCTURE OF DATA

For each individual DCU 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), and months of storage. Furthermore, the following information describing the product was requested in order to provide an opportunity to study relevant groupings of products:

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

Product status	Delivery route	Formulation type	Device type	Metering system	# of actuations for minimal clinical dose	# of actuations for one determination
US commercial	Nasal	Dry Powder	CFC	Device metered	1	1
Non-US Commercial	Pulmonary	Solution	HFA	Pre-metered	2	2
Phase IIB/III/NDA		Suspension	Non-pressurized		3	3
			Power assisted		4	4
			Container only		>4	>4
						Same as labeled dose

For each of the categories, submitting companies had the option not to disclose the information (however, this option was very rarely used). Finally, if data for stored samples was submitted, the real time storage condition could be stated.

Original data were provided by 10 companies. The DCU database contains data for 77 products with a total of 46016 individual observations. The number of determinations per product varies from 24 (all from 1 batch) to 3658 (from 18 different batches). About 46% of the results are collected through initial (release) testing, and the remaining 54% are from stability tests. Five products are for nasal delivery, and 72 products are for oral inhalation.

To investigate the Team's hypothesis in an appropriate manner, it was decided to separate from the main assessment those products for which:

- the delivery route is nasal (results for the few nasal products are presented individually);

- the number of actuations in one determination exceeds the number of actuations constituting the minimal clinical dose (since the draft CMC Guidances require that the number of actuations per determination does not exceed the number of actuations per clinical dose); or

- the overall product mean is outside 90-110% LC (since off-target products cannot appropriately represent the general ability to comply with the proposed uniformity requirements).

In total, 17 products were excluded by these requirements, leaving 60 products and 36296 determinations for the main analysis. The excluded products are treated separately.

For each product, the data were summarized by the following characteristics: the number of determinations, the overall mean dose, the overall relative standard deviation (RSD) of delivered dose, and the frequency of determinations outside 75-125% LC (f25) (this interval equals the outer attribute limits of the DCU specification in the draft Guidances).

V. RESULTS AND DISCUSSION

A. Products Excluded from Main Analysis

In total, 17 products did not meet the criteria for being included in the main analysis. Of these 17 products, 12 were orally inhaled products and 5 were nasal products.

1. Orally Inhaled Products

Four products were excluded from the main analysis because the overall product mean was outside 90-110% LC.

Nine products were excluded from the main analysis because the number of actuations per determination exceeded that of the clinical dose (one of which also had an overall product mean outside 90-110% LC). The number of actuations per determination was two or more times higher than the number of actuations per the minimal clinical dose. All 9 products excluded for this reason were suspension pMDIs, two development products formulated with HFA and seven US Commercial products formulated with CFC. A summary of product characteristics is given in Table 2. For the US commercial CFC pMDIs, the RSD ranged between 5.7-11.2% (mean 7.6%, median 6.4%) with f25 varying between 0.0-2.3% (mean 0.7%, median 0.3%). Because the variability of a determination is reduced by increasing the number of actuations, the variability of a determination defined according to the draft Guidances would be higher than indicated by these figures.

Table 2. Summary characteristics for groups of products using more actuations per determination than in clinical dose.

Product status	*Formulation type*	*# of products*	*Total # of determinations*	*Average # of act. per clinical dose*	*Average# of act. per determ.*	*Grand Mean % LC*
Phase IIB-NDA	HFA	2	580	1.0	2.0	96
US Commercial	CFC	7	1901	1.7	3.7	102

Table 2 Continued.

Product status	*Formulation type*	*RSD %*			*f25 %*		
		Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
Phase IIB-NDA	HFA	8.7	*	6.7-10.6	2.9	*	1.7-4.0
US Commercial	CFC	7.6	6.4	5.7-11.2	0.7	0.3	0-2.3

* not meaningful

2. Nasal Products

Table 3 shows product characteristics for the 5 submitted nasal products. All are device-metered suspensions, either in pressurized (CFC and HFA) or non-pressurized formulations. As seen from the table, the RSD varies between 3.6-11.0% with f25 varying between 0.0-2.3%. The number of actuations per determination is greater, lesser or equal to the number of actuations in the clinical dose. Because of the limited number of products available in the database, no valid conclusion can be drawn concerning general characteristics of different product types for nasal delivery.

Table 3. Nasal products (all are device-metered suspensions)

Product status	*Formulation type*	*# of act. per clinical dose*	*# of act. per determ.*	*# of determ.*	*Mean % LC*	*RSD %*	*f25 %*
Phase IIB-NDA	HFA	2	2	2230	99	11.0	2.3
Phase IIB-NDA	HFA	2	2	900	101	6.7	0.1
US Commercial	CFC	2	4	1310	100	10.2	1.5
US Commercial	Non-pressurized	1	2	520	102	3.6	0.0
US Commercial	Non-pressurized	4	2	1200	100	4.8	0.0

B. Main Analysis (Orally Inhaled Products)

The products were grouped according to product status (Table 4) or product type (Table 5). These groups were summarized by taking the mean, median and range of the individual mean product characteristics. This approach (giving each product the same weight in the analysis) was taken to avoid bias from products with a large number of determinations.

Overall, the frequency of DCU determinations outside 75-125% LC varies between 0-14%, with a mean of 2.3% and a median of 1.1% (see Table 4). Results outside the outer attribute limits were reported for the majority (68%) of the products. The relative standard deviation varies between 3.5-18.1% (mean 9.1%, median 8.6%). Table 4 shows that the lowest variability is displayed by US commercial products, which at least partly is due to the fact that these products also had the highest average number of actuations per determination. As noted above, an additional seven US commercial products did not meet the criteria for being included in the main analysis because the number of actuations per determination exceeded the minimal clinical dose. Of the thirteen US Commercial products (6+7), twelve are CFC pMDIs and one is a pre-metered DPI. All of the submitted CFC pMDI data pertain to US Commercial products.

Table 4. Summary characteristics for different groups of product status.

Product status	*# of products*	*Total # of determinations*	*Average # of act. per determination*	*Grand Mean % LC*
US commercial	6	2626	1.8	97
Non-US commercial	16	12259	1.1	98
Phase IIB/III/NDA	36	21171	1.3	101
Not Disclosed	2	240	1.0	100
All	60	36296	1.3	100

Table 4 Continued.

Product status	*RSD %*			*f25 %*		
	Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
US commercial	6.9	6.8	5.8-8.3	0.5	0.4	0-1.4
Non-US commercial	9.6	9.3	5.3-16.7	3.0	1.2	0-14
Phase IIB/III/NDA	9.1	8.7	3.5-18.1	2.3	1.3	0-11
Not Disclosed	11.4	*	11.1-11.6	2.9	*	2.5-3.3
All	9.1	8.6	3.5-18.1	2.3	1.1	0-14

* not meaningful

Table 5. Summary characteristics for different groups of product type.

Product status	*# of products*	*Total # of determinations*	*Average # of act. per determination*	*Grand Mean % LC*
Device metered DPI	19	22985	1.1	100
Pre-metered DPI	17	2020	1.0	100
CFC suspension pMDI	5	2526	2.0	97
HFA suspension pMDI	18	7533	1.5	99
HFA solution pMDI	1	1232	1.0	107
All	60	36296	1.2	100

Table 5 Continued.

Product status	*RSD %*			*f25 %*		
	Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
Device metered DPI	11.0	11.1	6.2-16.7	4.6	3.3	0-14
Pre-metered DPI	6.3	6.0	3.5-8.6	0.3	0.0	0-1.9
CFC suspension pMDI	7.0	7.1	5.8-8.3	0.6	0.7	0-1.4
HFA suspension pMDI	10.2	9.4	8.1-18.1	2.2	1.3	0-7.8
HFA solution pMDI	11.4	*	11.4	6.7	*	11.4
All	9.1	8.6	3.5-18.1	2.3	1.1	0-14

* not meaningful

A comparison of RSD and f25 of different product types presented in Table 5 reveals that different product types have differing characteristic variabilities. Table 5 also demonstrates that device-metered DPIs on average display greater variability than other product types, and pre-metered DPIs on average display lower variability. For pMDIs, the database appears to indicate that an average HFA formulation shows greater variability than an average CFC formulation. There is only one HFA solution pMDI product in the database and therefore no conclusion can be drawn for this product type at this point.

The difference among product types shown in Table 5 and the fact that the RSD and f25 vary over large ranges demonstrate that the DCU characteristics of different products are significantly different, which thus indicates that a single content uniformity specification for all orally inhaled products may not be suitable. The product types that on average appear to show the highest degree of compliance with the draft Guidance specification are CFC suspension pMDIs and pre-metered DPIs.

To illustrate one consequence of having a certain small portion of the DCU results outside 75-125%, we would like to present the following simple example: Assume a product consistently shows 1% of DCU determinations outside the outer limits. The probability of obtaining at least one such result in a test in which 16 determinations are collected (10 determinations in a Between Container test and an additional 6 determinations to complete a Through Container Life test for three of these containers) is $1-0.99^{16} = 0.15$; that is, 15% of such tests would show non-compliance with the outer attribute limits. Given that a typical stability program comprises more than thirty such tests, it is virtually certain that this hypothetical product would fail at some point of its DCU testing program. It is worth noting here that more than half of the orally inhaled products in the current database have DCU results outside 75-125% with a frequency higher than 1%.

The example above suggests a high rate of non-compliance with the DCU specification in the draft Guidances for the majority of the orally inhaled products in the database. From this initial assessment, the database appears to support the Team's hypothesis that orally inhaled products do not in general comply with the DCU specification in the draft CMC Guidances.

VI. CONCLUSION

The initial assessment of the database supports the hypothesis that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances. The relatively large differences among products and among product types suggest that a single content uniformity specification for all orally inhaled products is not suitable.

VII. GLOSSARY

CMC	Chemistry, Manufacturing, and Controls
DCU	Dose Content Uniformity
f25	frequency of DCU determinations outside 75-125% LC
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 American Association of Pharmaceutical Scientists which is 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
OINDP	Orally Inhaled and Nasal Drug Products
outer limits	75-125% LC as recommended by the draft Guidances
RSD	Relative Standard Deviation