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CHICAGO, ILLINOIS

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18 May 2001

BY COURIER

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

     Re: <u>Docket No. 98D-0997</u>

Dear Sir or Madam:

    Please find enclosed two originals and one photocopy of each of the following documents: (i) **Recommendations for Tests and Methods** and **(ii) Appendices to Recommendations for Tests and Methods,** submitted by the International Pharmaceutical Aerosol Consortium on Regulation and Science (WAC-RS) and the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists. These documents contain comments and recommendations regarding the FDA's draft Guidance for *Industry: Metered Dose Inhaler (MDI) and D y Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing and Controls Documentation,* dated November 13, 1998.

    Please file the originals and time/date stamp the photocopies and return them to the messenger. Thank you for your consideration.

                  Sincerely,

                  Ballard Jamieson, Jr.
                  IPAC-RS Legal Counsel and Secretariat

Enclosures

98D-0997

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ITFG/IPAC-RS Collaboration

CMC Tests and Methods Technical Team

8349

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Recommendations for Tests and Methods

A Response to the FDA draft Guidance for Industry:

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products **Chemistry, Manufacturing, and Controls Documentation**

18 May 2001

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APPENDICES (see accompanying document: *Appendices to Recommendations for Tests and Methods,* 18 *May 2001)*

I. OVERVIEW

- Between November 1998 and June 1999, the FDA issued three draft Guidances for orally inhaled and nasal drug products. Following the issuance of the draft Guidances, two organizations with expertise in inhalation and nasal drug products - the Inhalation Technology Focus Group of the American Association of Pharmaceutical Scientists (ITFG) and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) - initiated a scientific, data-driven collaboration to address specific issues in the draft Guidances in order to contribute constructively to the Agency's development of guidance documents for orally inhaled and nasal drug products.

- The CMC Tests and Methods Technical Team of the ITFG/IPAC-RS Collaboration has carefully reviewed the draft *Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI)* Drug *Products Chemistry, Manufacturing, and Controls (CMC) Documentation*[1] (here referred to as the "draft MDI/DPI Guidance"). The Team has focused its efforts on developing recommendations for tests mentioned in the draft Guidance in order to create a testing process that provides the most effective controls for product quality, and eliminates the need for redundant testing. In this paper the Team presents recommendations for each of the following MDI tests:[2]

    (1) Water Content
    (2) Spray Pattern and Plume Geometry
    (3) Shot Weight
    (4) Impurities and Degradants
    (5) Dose Content Uniformity
    (6) Pressure
    (7) Particle Size Distribution

  For water content, spray pattern and plume geometry, shot weight, pressure, and particle size distribution, the recommendations are based on the analysis and consideration of collected industry data (garnered through confidential industry surveys) and/or literature data. For impurities/degradants and dose content uniformity testing, the Team makes recommendations through consideration of best industry practices.

- Based on its findings, the Team proposes alternate language addressing each of these MDI tests, for inclusion in the revised draft MDI/DPI Guidance. In general the Team believes that only those tests which have been demonstrated in development studies to influence the drug product performance, should be included in the list of tests for the drug product. The proposed changes are summarized below:

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[1] http://www.fda.gov/cder/guidance/2180dft.pdf
[2] The Team plans to address the draft Guidances' tests and methods requirements for non-MD1 inhalation and nasal dosage forms in a separate document.

SUMMARY OF RECOMMENDED CHANGES TO DRAFT MDI/DPI GUIDANCE

The Team suggests the following alternate language for inclusion in the revised draft MDI/DPI Guidance:

.ines in draft ADI/DPI ;uidance	*Recommended Changes to Draft MDI/DPI Guidance (new language in bold; phrases recommended for deletion are shown with strikethrough)*
	WATER CONTENT
21-425	*Methods of Manufacture and Packaging* The moisture content, particle size distribution, particle morphology (shape and texture), bulk density, as well as impurities, degradants, and contaminants in the drug substance and drug products should be controlled with appropriate acceptance criteria and test methods to ensure lot-to-lot reproducibility. **However, moisture content need only be controlled in the final drug product if it has been demonstrated to affect product performance during development studies.**
93-496	*Specifications for the Drug Product – Water or Moisture Content* ~~Testing for the presence of water in the container should be performed, particularly for suspension formulations. Water or moisture should be strictly limited to prevent changes in particle size distribution, morphic form, and other changes such as crystal growth or aggregation.~~ **If water has been demonstrated to affect product performance during development studies, then routine control of water content and appropriate specifications should be established for water content in drug product.**
473-1476	*Drug Product Characterization Studies – Temperature Cycling* At minimum, test parameters for MDIs after cycling studies should include particle size distribution, microscopic evaluation, physical appearance of the content, valve component integrity, dose content uniformity, water content, and leak rate. **However, if development studies show that water content does not affect product performance, then the test for water content does not need to be performed after cycling studies.**

,ines in draft ADI/DPI Guidance	*Recommended Changes to Draft MDI/DPI Guidance (phrases recommended for deletion are shown with strikethrough)*
	PLUME GEOMETRY
521-1522	The Team recommends that *lines 1521-1522* and *lines 1533-1538* of the draft Guidance for MDIs/DPIs, be removed: ~~A study should be performed to characterize the plume geometry to help evaluate the performances of the valve and the actuator.~~
533-1538	~~For assessing the performance of the valve and actuator, the study of plume geometry is complementary to the spray pattern test, which may directly examine the drug substance particles from the plume. The resulting baseline may be used to compare similar drug products by different manufacturers or when introducing certain changes to an already approved drug product.~~

~~Lines in draft~~ ~~MDI/DPI~~ ~~Guidance~~	*Recommended Changes to Draft MDI/DPI Guidance (new language in* **bold***; phrases recommended for deletion are shown with strikethrough)*
	SPRAY PATTERN
655-678	~~Characterization of spray pattern and plume geometry is important for evaluating the performances of the valve and the actuator.~~
	Various factors **may** affect the spray pattern and plume geometry, including the size and shape of the actuator orifice, the design of the actuator, the size of the metering chamber, the size of the stem orifice of the valve, the vapor pressure in the container, and the nature of the formulation.
	~~Currently, it is recommended that spray pattern testing should be performed on a routine basis as a quality control for the drug product.~~
	Therefore, proper controls should be performed on these factors during development studies and component evaluation. Spray pattern and plume geometry testing may be used for component evaluation during development studies, but need not be performed for quality control of drug product.
	~~However, the characterization of plume geometry should be established during the development of the product and is not necessarily tested routinely thereafter (refer to discussion of plume geometry testing in section IV.A.10). The proposed test method for spray pattern, including sampling plans, should be provided in detail to allow their duplication by Agency laboratories. For example, in the evaluation of the spray pattern, the actuation distance between the mouthpiece and the plate, number of actuations per spray pattern, position and orientation of the plate relative to the mouthpiece, and visualization method should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of uniform density) as well as the size of the pattern (e.g., no axis is greater than x millimeters (mm) and the ratio of the longest to the shortest axes should lie in a specified range, for example, 1.00-1.20). The spray pattern should be determined, preferably by a method specific for the drug substance, at different distances (e.g., two) from the mouthpiece to provide greater discriminatory capability to the test. Variability in the test can be reduced by developing a sensitive detection method and by providing method-specific training to the analyst.~~

lLines in draft MDI/DPI Guidance	Recommended Changes to Draft MDI/DPI Guidance (new language in bold; phrases recommended for deletion are shown with strikethrough)
	SHOT WEIGHT
707-714	This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility ~~of the drug product.~~ The proper performance of a metering valve should be ensured primarily by the valve manufacturer, who should assemble the valve with parts of precise dimensions. Valve delivery should be verified by the applicant for **incoming components** ~~each drug product.~~ ~~In general, metered-dose valves should have a valve delivery acceptance criteria of NMT ±15 percent for individual actuations and NMT ±10 percent for the mean of the actuations relative to the target.~~ **Valve delivery may also be used as a diagnostic tool for evaluating drug product.**

Lines in draft MDI/DPI Guidance	Recommended Changes to Draft MDI/DPI Guidance (new language in bold)
	IMPURITIES AND DEGRADANTS
514-520	The levels of degradation products and impurities should be determined by means of stability indicating methods. Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance. Individual impurities or degradation products appearing at levels 0.10 percent or greater should be specified. Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification. **However, following the ICH Q3B guideline, it is not necessary to control impurities that are not degradants, and which are only present in the finished dosage form as introduced from the active ingredient, provided that the development database shows no further increase in these** impurities **during the manufacturing process or on stability.**

Lines in draft MDI/DPI Guidance	Recommended Changes to Draft MDI/DPI Guidance (new language in bold; phrases recommended for deletion are shown with strikethrough)
	DOSE CONTENT UNIFORMITY[3]
528	~~A stability indicating method~~ **A validated, unbiased and specific method** should be used.

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[3] The Tests and Methods Team, unlike the ITFG/IPAC-RS Dose Content Uniformity Working Group, is not addressing the specifications for dose delivery.

Lines in draft MDI/DPI Guidance	Recommended Changes to Draft MDI/DPI Guidance (new language in bold; phrases recommended for deletion are shown with strikethrough)
	PRESSURE TESTING
699-705	This test **is** recommended for MDI products that are formulated using a ~~co-solvent and/or~~ more than one propellant. The test verifies the internal pressure of the container and ensures the use of proper propellants or propellant mixture ratio. A **reasonable** and achievable acceptance criteria may be 5 percent variation around the target pressure at specified conditions. An appropriate sampling plan should be used that selects a representative number of canisters from the batch (e.g., beginning, middle, **and end** of a fill run). **However, for co-solvent/propellant blends, the correct blend may be assessed by co-solvent content analysis and determination of net fill.**

Lines in draft MDI/DPI Guidance	Recommended Changes to Draft MDI/DPI Guidance (new language in bold; phrases recommended for deletion are shown with strikethrough)
	PARTICLE SIZE DISTRIBUTION
592-596	A multistage cascade impactor fractionates and collects particles of one or more drug components by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle size fraction of the dose. **Alternate particle sizing methods may be developed and optimized for the evaluation of the particle size distributions of inhalation formulations. The particle sizing method should be validated for routine use for the inhalation formulation.**
609-610	~~Other critical variables that should be specified and controlled in such a test proced relative humidity and temperature.~~ **The** effect of **temperature and relative humidity on particle size determination of the inhalation product should be evaluated and characterized during development. The need to specify and control these two parameters for the individual product should be determined based on the data acquired during development.**

Alternatively, the Team proposes that these comments be combined to produce cohesive new text describing a proposed new approach to testing and method development, for inclusion in the revised draft MDI/DPI Guidance (new language in **bold**):

TESTING

The moisture content, particle size distribution, particle morphology (shape and texture), bulk density, as well as impurities, degradants, and contaminants in the drug substance should be controlled with appropriate acceptance criteria and test methods to ensure lot-to-lot reproducibility.

Only those tests, which have been demonstrated in development studies to influence the drug product performance, should be included in the list of tests for the drug product. For instance, moisture content need only be controlled in the final drug product if it has been demonstrated to affect product performance during development studies.

Furthermore, following the ICH Q3B guideline, it is not necessary to control impurities that are not degradants, and which are only present in the finished dosage form as introduced from the active ingredient, provided that the development database shows no further increase in these impurities during the manufacturing process or on stability.

Likewise, the effect of temperature and relative humidity on particle size determination of the inhalation product should be evaluated and characterized during development. The need to specify and control these two parameters for the individual product should be determined based on the data acquired during development.

Additionally, pressure testing should not be required for co-solvent/propellant blends, where the correct blend may be assessed by co-solvent **content analysis and determination of net fill.**

Tests that may be useful in evaluating component quality are best assessed during development **studies. For instance, some evaluation of spray pattern and plume geometry may be undertaken, at the applicant's discretion, during metered dose** inhaler **development tests as a screening tool for component evaluation. However, these studies need not be performed for quality control of drug product. Component controls, such as dimensional analysis, performed during development studies and component evaluation, are most appropriate for controlling the quality of components in the finished drug product.**

As an example, valve delivery (shot weight) is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility. The proper performance of a metering valve should be ensured primarily by the valve manufacturer, who should assemble the valve with parts of precise dimensions. Valve delivery should be verified by the applicant for incoming components.

Valve delivery testing may also be used as a diagnostic tool for evaluating drug product.

METHODS

Methodology for dose content uniformity and particle sizing is not prescribed. The method for dose content uniformity should be validated, unbiased and specific for its intended use.

An appropriate particle sizing method should be developed for the product. A multistage cascade impactor fractionates and collects particles of one or more drug components by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle size fraction of the dose. Alternate particle sizing methods may be developed and optimized for the evaluation of the particle size distributions of inhalation formulations. The particle sizing method should be validated for routine use for the inhalation formulation.

II. INTRODUCTION

The Tests and Methods Technical Team of the ITFG/IPAC-RS Collaboration presents its findings regarding requirements for certain tests described in the FDA CMC draft MDI/DPI Guidance. The Team proposes alternate language recommended for inclusion in the revised draft MDI/DPI Guidance.

The Team agrees with the Agency that industry should produce high quality orally inhaled and nasal drug products. The Team therefore recommends an approach to testing and methodology such that the manufacturer thoroughly understands the parameters important for controlling product quality via assessments of development studies. Based on these assessments, the manufacturer can determine the most effective points of quality control in the production chain. This process would ensure that tests and methods provide the most effective product quality controls and therefore ensure the highest standards of product quality. This approach would also eliminate redundant testing, thereby saving significant resources for the Agency, the consumer, and industry. The recommended approach is based on science, data and current capabilities of inhalation technology and analytical tools.

Specifically, the Team believes that (i) certain tests may be effective in assuring product quality and should .be evaluated during drug development studies, and (ii) proper assessment of development studies may eliminate the need to use certain tests as blanket requirements for quality control of the final product.

These ideas underlie the Team's position statements for each of the tests examined in this document:

- **Water Content:** Water or moisture content should only be controlled if it has been demonstrated during development studies to affect product performance. [Section III]

- **Spray Pattern and Plume Geometry:** These tests may have value in development. However, for finished MDI drug products, they are not effective tests for routine analysis of MDI product quality. Those factors specified in the draft MDI/DPI Guidance as affecting product quality (i.e., size and shape of the actuator orifice, etc.) are better evaluated via exacting component controls, rather than by spray pattern and plume geometry testing. [Section IV]

- **Shot Weight:** It is not appropriate to set specifications for this test since it is redundant to the incoming valve release tests, and furthermore, it is less sensitive to product performance changes than the dose delivery test. [Section V]

- **Impurities and Degradants:** Synthetic impurities that are not degradants should be controlled in the drug substance and not in the drug product. The testing of the drug product for synthetic impurities that are not degradants is redundant and therefore unnecessary. This approach is consistent with the ICH approach to process impurities. The ICH approach to process impurities should apply to inhalation drug products. [Section VI]

- **Dose Content Uniformity:** **The dose content** uniformity test need not be "stability indicating" as required in the draft MDI/DPI Guidance. The chemical stability of the formulation is **assessed** elsewhere in product testing, i.e., during degradation products assay. The method for dose **content** uniformity should be validated, unbiased, and specific for its intended use. [Section VII]

- **Pressure Testing:** Pressure testing of MDIs should not be required for single propellant/co-solvent systems. The integrity of the propellant-co-solvent mixture is better controlled by co-solvent content and net fill analysis.. [Section VIII]

- **Particle Size Distribution:** (i) The draft MDI/DPI Guidance should allow suitable and validated alternate approaches to the determination of particle size distribution (e.g., time-of-flight mass spectrometry, light scattering), which assure control of the product and manufacturing process, and (ii) relative humidity and temperature should be controlled during the testing of MDI products only if needed. The requirement to control these parameters should be evaluated in the validation of the method and based on the development data for the product. [Section IX]

These recommendations are based on analyses of data from industry and the current literature, and on best industry practices. The Team encourages the Agency to consider these recommendations when revising the draft Guidance.

III. WATER CONTENT

A.   Introduction

The draft MDI/DPI Guidance includes reference to Water Content in Section E, *Methods of Manufacture and Packaging;* Section F, *Specifications for the Drug Product* sub-section d *Water or* Moisture Content; and Section *IV, Drug Product Characterization Studies* sub-section A.3 Temperature *Cycling*

Methods of Manufacture and Packaging
420   The moisture content in the micronized material should be tightly controlled for drug
421   substances or formulations that are chemically or physically sensitive to moisture. The
422   moisture content, particle size distribution, particle morphology (shape and texture), bulk
423   density, as well as impurities, degradants, and contaminants in the drug substance and
424   drug products should be controlled with appropriate acceptance criteria and test methods
425   to ensure lot-to-lot reproducibility.

Specifications for the Drug Product – Water or Moisture Content
493   Testing for the presence of water in the container should be performed, particularly
494   for suspension formulations. Water or moisture should be strictly limited to
495   prevent changes in particle size distribution, morphic form, and other changes such
496   as crystal growth or aggregation.

Drug Product Characterization Studies – Temperature Cycling
1471   At the end of predetermined cycles, the
1472   samples should be analyzed for appropriate parameters and compared with the
1473   control drug product. At minimum, test parameters for MDIs after cycling
1474   studies should include particle size distribution, microscopic evaluation, physical
1475   appearance of the content, valve component integrity, dose content uniformity,
1476   water content, and leak rate.

The Team believes that water content should be routinely controlled and specified for drug product <u>only if water has been demonstrated to affect product performance in development studies</u>. The Team acknowledges that for some products, water content may have a significant impact on product performance. However, for other products, water content may have no effect on product performance. For moisture insensitive products, process validation controls and product performance tests such as dose delivery and fine particle dose determination provide ample control of water content.

To investigate their position, the Team collected stability data (included in development studies) from a variety of products and compared the effect of increases in water content on what the Team considers to be the key product performance parameters – dose delivery and fine particle dose (as defined by individual sponsors).

B.   Data Collection

Pharmaceutical companies participating in the ITFG/IPAC-RS Collaboration were asked to submit moisture data, accompanied by data that assesses key performance characteristics, for as many products as possible. Individual determinations for commercial products and products in late development, obtained through real time and accelerated stability studies were requested.   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-RS Secretariat, who blinded the data and assigned a random code to each file.

C.   Structure of Data

The Team has collected data for 12 different metered dose inhalers. Stability data have been collected where the following parameters have been monitored on storage:

- Moisture *(i.e.,* water)
- Dose delivered (% label claim)
- Fine particle dose as defined by each company

The Team chose these parameters because they are the key measures of performance for metered dose inhalers, and are also those most likely to be affected by moisture changes on storage.

In order to examine relevant categories of products, the survey requested the following product information (Table 111.1):

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

Product status	Delivery route	Formulation type	Device type	Metering system
Not Disclosed	Not Disclosed	Not Disclosed	Not Disclosed	Not Disclosed
US Commercial	Local Pulmonary	Solution	Pressurized CFC	Device Metered
Non-US Commercial	Systemic Pulmonary	Suspension	Pressurized HFA	Pre-metered
Phase IIB/ III/ NDA				
Before Phase IIE				

D. Summary of Data

Table III.2 summarizes the status and types of products for which data was submitted.

Table III.2. Summa y matrix of status and types of products in the water content database

Product status	Delivery Route	Metering	Suspension CFC	Suspension HFA	Solution HFA	Total
u s Commercial	Local Pulmonary	Device Metered	3	3	1	7
Non-US Commercial	Systemic Pulmonary	Device Metered	None	1	None	1
Non-US Commercial	Local	Device Metered	None	2	1	3
Phase IIB/III/NDA	Not Disclosed	Pre-Metered	None	1	None	1
Total			3	7	2	12

Data from a total of 47 batches containing individual determinations of moisture and accompanying key performance characteristics were submitted by participating companies. The final analysis included 11 different products. A suspension HFA development product was not included in the final analysis because the file did not contain enough storage time data points to produce meaningful results.

E.   Results and Discussion

As a first step, the Team qualitatively assessed the effects of water content on dose delivery and fine particle dose by plotting water content and these key product performance parameters against storage period. Representative graphs for some of the products are shown below (Figures 111.1-5).

For each graph, the left y-axis contains the scale for water content, the right y-axis contains the scale for delivered dose and fine particle dose. Each product is given a 5 digit numerical code name which appears at the top of the graph.   The trendlines are fitted to a second order polynomial. The legend for all graphs is below.
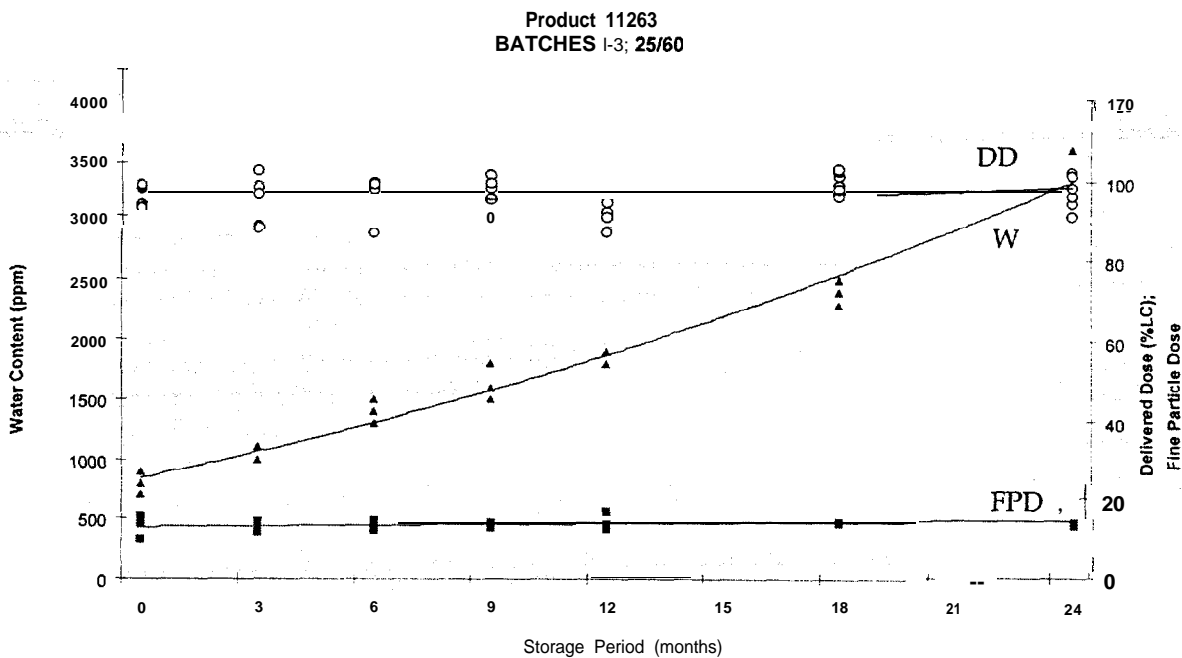
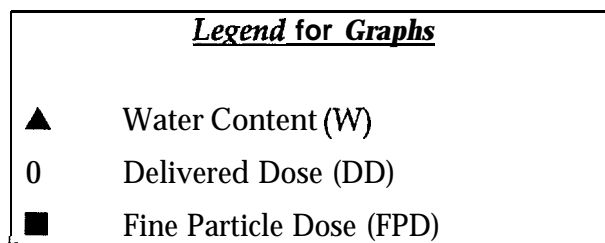| *Legend* for *Graphs*	
▲	Water Content (W)
0	Delivered Dose (DD)
■	Fine Particle Dose (FPD)

Figure 111.1. HFA suspension, product 11263, under standard conditions. Graph shows values from one batch with water content, delivered dose and fine particle dose measured at beginning and end of product lifetime.
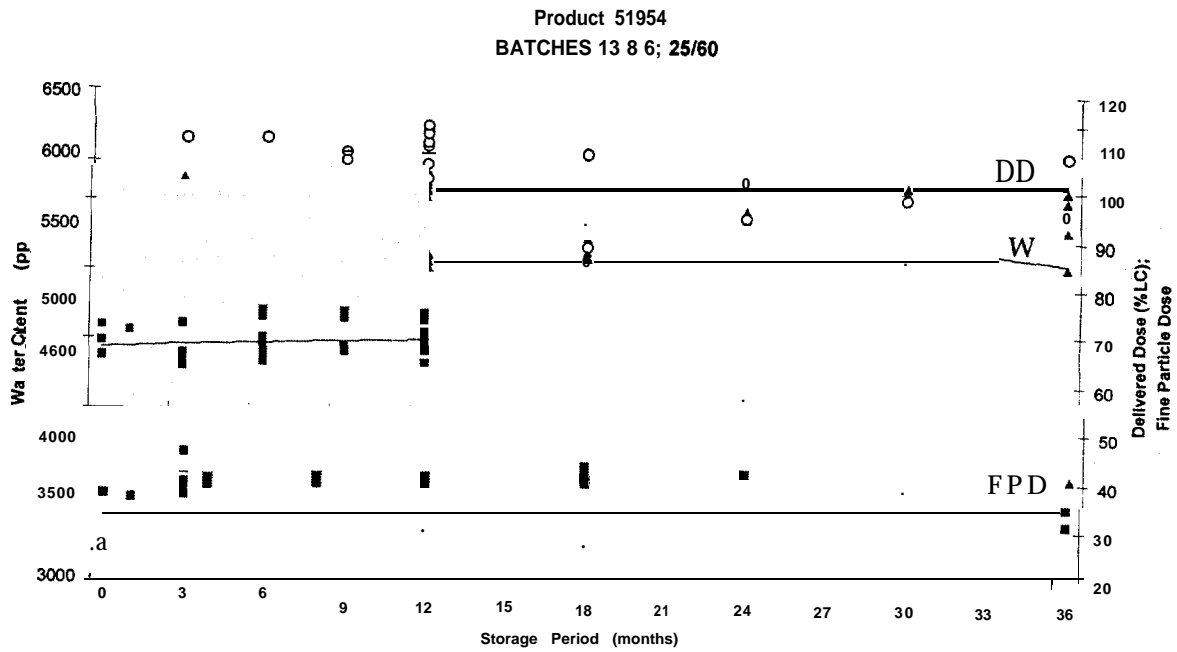
Product 51954
BATCHES 13 8 6; 25/60

Figure 111.2. HFA Solution, product 51954, under standard conditions. Graph shows values from six different batches.

Product 51954
Batches 1-3 & 6; 30/70
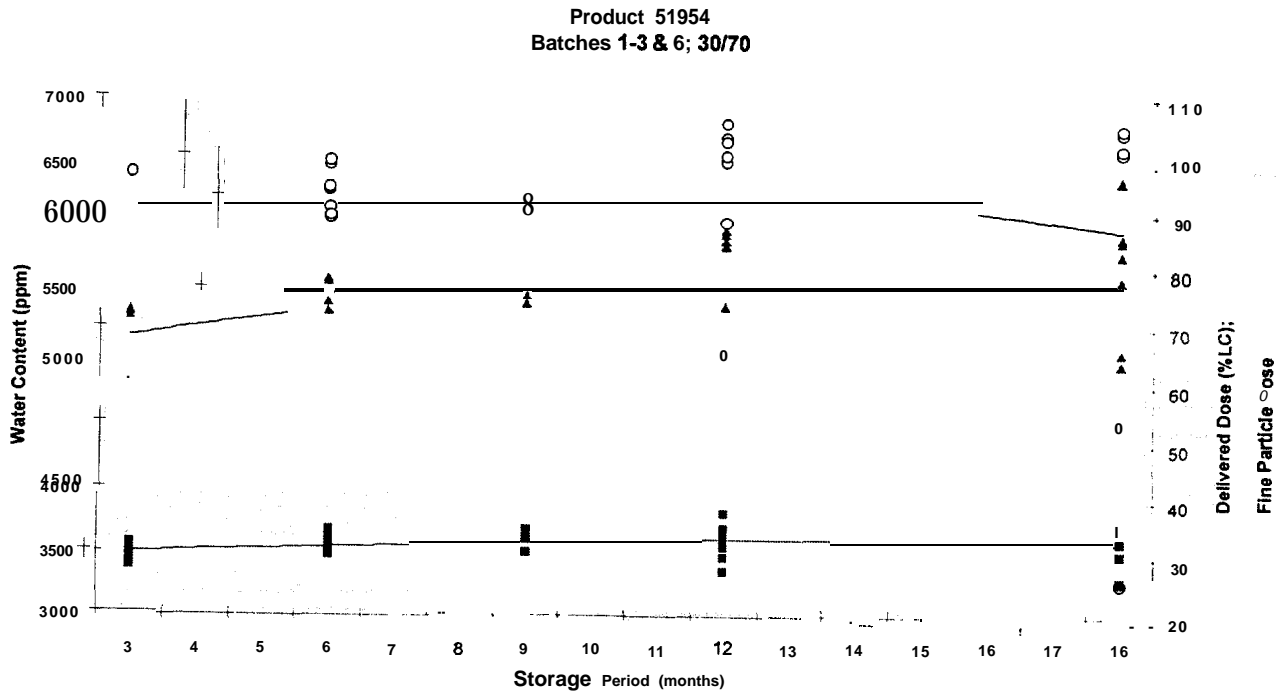

Figure 111.3. HFA Solution, product 51954, under accelerated conditions. Graph shows values from four different batches.

Product 74131
BATCHES 5 & 6; **25/60**

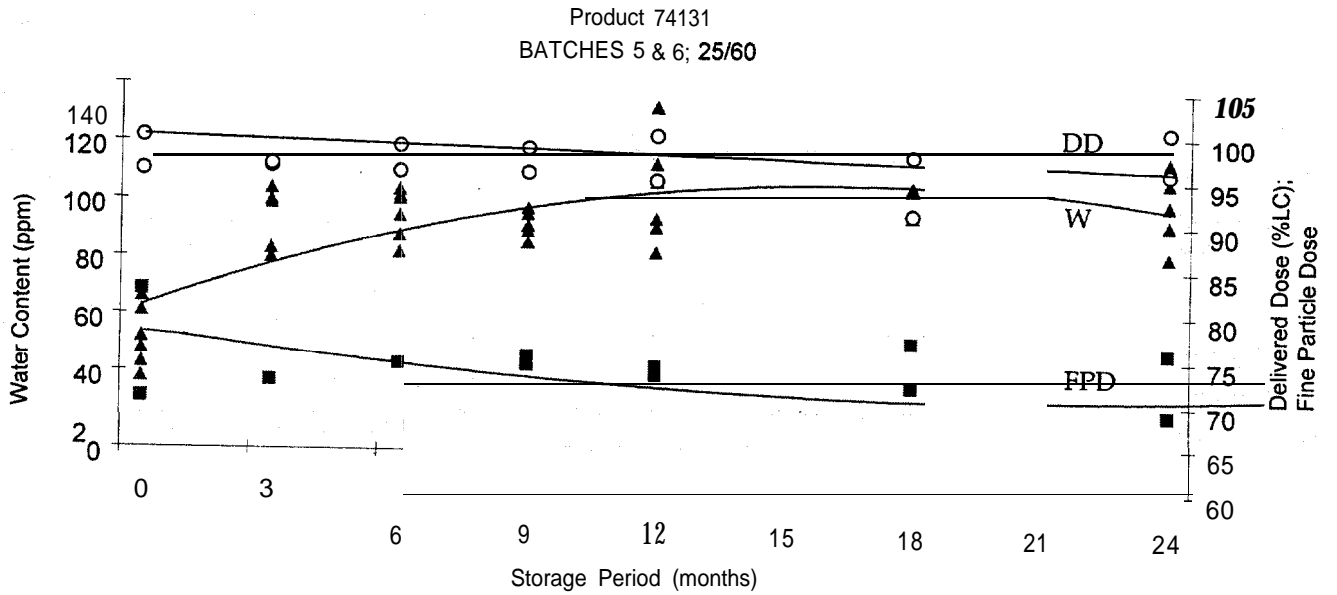**Figure III. 4.** CFC Suspension, product 74131, under standard conditions. Graph shows values from two different batches.
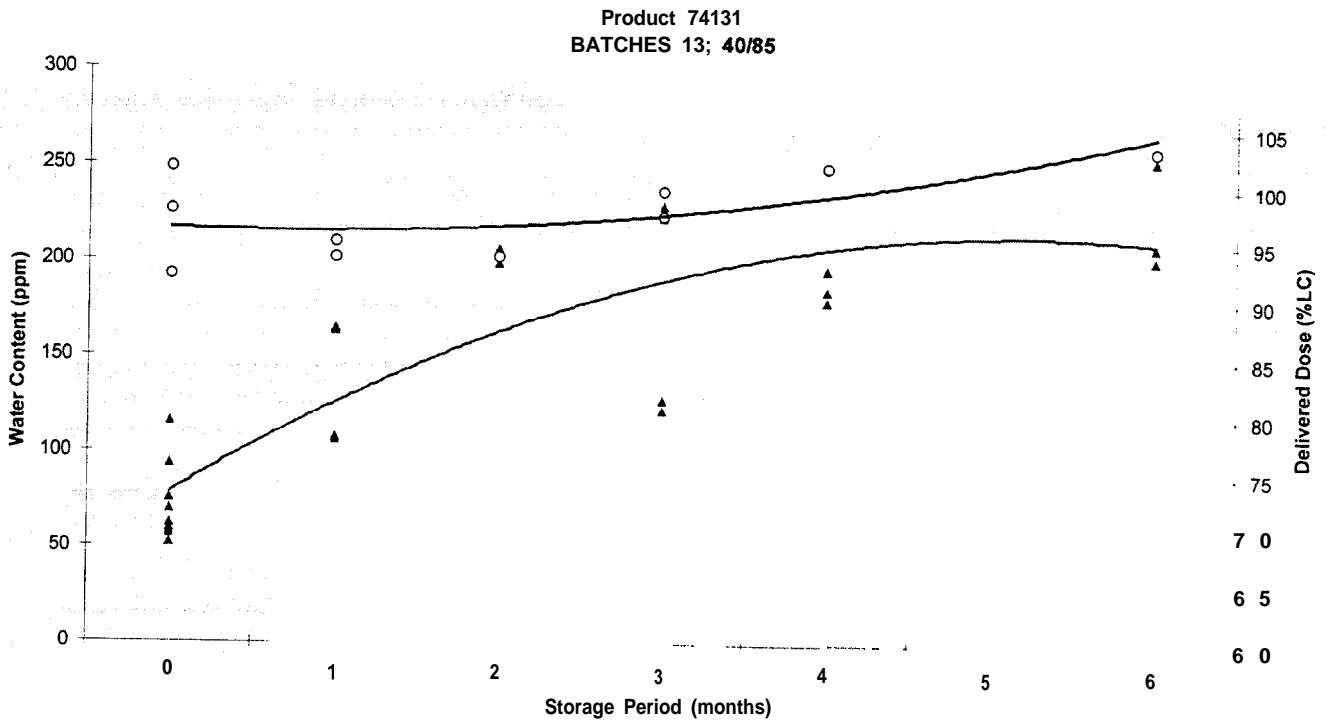
Product 74131
BATCHES 13; 40/85

Figure III. 5. CFC Suspension, product 74131, under accelerated conditions. Graph shows values from three different batches. Batches were tested more than once over the same storage period.

The charts <u>sualitativelv</u> demonstrate that for a variety of MDI products, a notable change in moisture content with increasing storage time does not produce a notable change in key performance characteristics such as delivered dose or fine particle dose.

Even comparing across products, moisture appears to have little impact on product performance. For example, **HFA** suspension products are more hygroscopic than the CFC suspensions, however, no discernable difference is seen in the effect of moisture on delivered dose and fine particle dose between these two types of products. Furthermore, for most of the examined products there appears to be no notable effect of moisture content on key product performance parameters under both real time and accelerated storage conditions.

To investigate this further, we performed a statistical analysis of each product in the database to consider if there might be any significant (up to the 99% confidence level) relationship between delivered dose and water content, and fine particle dose and water content. Table III.3 summarizes the results of this analysis.

Table III.3. Summary Table of Results from Statistical Analysis

	Formulation	Product #; Storage Condition (°C/%RH)[a]	Delivered Dose Slope[b] (change in %LC per ppm)	Delivered Dose p-value	Fine Particle Dose Slope[b] (change in %LC per ppm)	Fine Particle Dose p-value
**Products with Significant Amount of Data**					
1	HFA Suspension	11263; 25/60	0.0011	0.1951	0.0006	0.1374
2	CFC Suspension	35489; 30/45	0.0290	0.1365	0.0192	0.3658
		35489; 40/85	-0.0229"	0.0010	-0.0012	0.9318
3	HFA Suspension	00524; 25/60	0.0007	0.6461	-0.0039**	0.0002
4	HFA Suspension	49131; 25/60	0.0008	0.8217	-0.0016	0.1807
5	HFA Solution	51954; 25/60	0.0031	0.7130	0.0027	0.1361
		51954; 30/70	-0.0154	0.3135	-0.0073	0.2259
		51954; 4/NR[c]	0.0004	0.9434	0.0027	0.2488
6	CFC Suspension	01016; 30/45	0.0014	0.9326	0.0201	0.2655
		01016; 40/85	-0.0212**	0.0020	-0.0263	0.0630
7	CFC Suspension	74131; 25/60	0.0257	0.4184	-0.0404	0.4632
		74131; 30/45	-0.0165	0.5066	-0.0207	0.7193
		74131; 40/85	0.0087	0.6847	n/a	n/a
**Products With Limited Number of Data Points**					
8	HFA suspension	50267; 30/60	0.0013	0.0830	0.0001	0.9315
		50267; 40/75	0.0032	0.2139	-0.0020	0.6104
9	HFA suspension	88596; 25/60	0.0119	0.1710	-0.0030	0.1922
		88596; 30/70	0.0067	0.2653	-0.0012	0.4879
		88596; 40/75	0.0031	0.3939	-0.0005	0.5306
10	HFA suspension	20091; 25/60	0.0098	0.1521	-0.0037	0.1417
		20091; 30/70	0.0075	0.1628	-0.0009	0.6460
		20091; 40/75	0.0055	0.0764	0.0000	0.9790
11	HFA solution	81952; 30/60	0.0055*	0.0135	0.0032	0.4577
		81952; 40/75	0.0113	0.2103	0.0024	0.1285

[a] Storage condition: Temperature in Celsius/percent Relative Humidity (RH)
[b] Slope = Change in measurement per 1 ppm increase in water content
[c] NR = Not Regulated
* p-value $\leq$ 0.05 indicates statistical significance at the 95% confidence level
** p-value $\leq$ 0.01 indicates statistical significance at the 99% confidence level

The data summarized in Table III.3 indicate that for several of the evaluated products, the effects of moisture content on the critical product performance parameters (delivered dose or fine particle dose) are not statistically significant.

In the case of products #35489 (40°C/85% RH), #00524 (25°C/60% RH), # 81952 (30°C/60% RH) and #01016 (40°C/85% RH), the effects of moisture on delivered dose and fine particle dose was determined to be statistically significant at the 95% or the 99% confidence level. The statistical analysis thus confirms that for a variety of MDI products, changes in moisture content over the shelf-life have no significant impact on the critical product parameters of delivered dose or fine particle dose. Therefore, routine control of water content should not be a blanket requirement for all products.

Data for four of the eleven products contain a limited number of data points, making the statistical results for these four products less meaningful. These products and corresponding analysis results are listed in the bottom half of Table III.3 (numbers S-11). For these products, we place more emphasis on conclusions derived from the graphical comparisons of water content, delivered dose, and fine particle dose *in Appendix A* (see accompanying document). For these four products, the charts show a negligible 0-10% overall change in delivered dose and fine particle dose while the water content increases 4-5 fold *(see Appendix A).*

F. Conclusion

The collected data suggest that for several of the examined MDI formulations, moisture content does not significantly affect product performance. The Team therefore concludes that control and specification of water content should not be a general requirement for all pressurized metered dose inhalers. Water content should only be controlled in the drug product if it has been demonstrated to affect product performance during development studies. This approach ensures the quality of the drug product and eliminates redundant testing. For moisture insensitive products, process validation controls and product performance tests such as dose delivery and fine particle dose determination provide ample control of water content.

The Team therefore suggests the following alternate language to the draft Guidance for MDIs (new language in bold. Language recommended for deletion is struck through):

Methods of Manufacture and Packaging (lines 421-425)

The moisture content, particle size distribution, particle morphology (shape and texture), bulk density, as well as impurities, degradants, and contaminants in the drug substance and drug products should be controlled with appropriate acceptance criteria and test methods to ensure lot-to-lot reproducibility. **However, moisture content need only be controlled in the final drug product if it has been demonstrated to affect product performance during development studies.**

Specifications for the Drug Product – Water or **Moisture Content (lines 493-496)**

~~Testing for the presence of water in the container should be performed, particularly for suspension formulations. Water or moisture should be strictly limited to prevent changes in particle size distribution, morphic form, and other changes such as crystal growth or aggregation.~~

If water has been demonstrated to affect product performance during development studies, then routine control of water content and appropriate specifications should be established for water content in drug product.

Drug Product Characterization Studies – Temperature Cycling (lines 1473-1 476)

At minirnum, test parameters for MDIs after cycling studies should include particle size distribution, microscopic evaluation, physical appearance of the content, valve component integrity, dose content **uniformity, water content,** and leak rate. **However, if development studies show that water content does not affect product performance, then the test for water content does not need to be performed after cycling studies.**

IV. PLUME GEOMETRY AND SPRAY PATTERN

In this section, the ITFG/IPAC-RS CMC Tests and Methods Technical Team presents its positions regarding the tests for plume geometry and spray pattern as required by the draft MDI/DPI Guidance. Part I examines the effectiveness of the plume geometry test as a meaningful measurement of product performance, primarily using relevant data from current literature and presentations. Part II examines the same for the spray pattern test using data collected from an industry-wide survey and information from the literature.

I. PLUME GEOMETRY

A. Introduction

In the draft MDI/DPI Guidance, some discussion is devoted to the characterization of plume geometry for pressurized metered dose inhalers and a suggestion is made that

> 662 the characterization of plume geometry should be established during the
> 663 development of the product and is not necessarily tested routinely thereafter

However, in the preamble to this statement, the draft Guidance also states that:

> 656 Various factors can affect the
> 657 spray pattern and plume geometry, including the size and shape of the actuator
> 658 orifice, the design of the actuator, the size of the metering chamber, the size of the
> 659 stem orifice of the valve, the vapor pressure in the container, and the nature of the
> 660 formulation.

Furthermore, the draft Guidance states the following:

> 1521 A study should be performed to characterize the plume geometry to help evaluate
> 1522 the performances of the valve and the actuator.

> 1527 Plume geometry may be evaluated by a variety of methods, (e.g., the time
> 1528 sequence sound-triggered flash photography method, video tape recording and
> 1529 detailed study of the aerosol and droplet development...

> 1533 For assessing the performance
> 1534 of the valve and acutator, the study of plume geometry is complementary to the
> 1535 spray pattern test, which may directly examine the drug substance particles from
> 1536 the plume. The resulting baseline may be used to compare similar drug products
> 1537 by different manufacturers or when introducing certain changes to an already
> 1538 approved drug product.

Thus, the draft MDI/DPI Guidance recommends that plume geometry testing should be performed during development tests. Furthermore the draft Guidance states that plume geometry

testing is a capable measure of product quality through its ability to evaluate valve and actuator performance. However, the Team believes that the plume geometry test does not provide assurance of product quality nor does it offer meaningful functional performance characterization.

Aspects of **inhalation** product testing and their relevance to current CMC section requirements have been presented, and certain limitations regarding plume geometry measurements noted.4 Specifically it has been noted that (i) plume geometry testing is performed on an unconstrained aerosol plume **that** is allowed to develop into a space that far exceeds the mouth or nasal cavities, (ii) that the image represents a frozen moment in aerosol plume development, which may be viewed from both axes perpendicular to the axis of plume development, and (iii) to a large extent plume geometry determinations are subjective tests that yield a qualitative assessment of product performance.

B. Review of Relevant Data

In order to investigate the Team's position, we review here relevant data pertaining to aerosol plume characterization. Results of the survey of current industry practices conducted by the ITFG/IPAC-RS Collaboration are discussed in Section C, and review of the scientific literature related to factors that may affect aerosol plume development are presented in Section D.

Several techniques have been utilized and proposed for the imaging of aerosol plumes. These range from high-speed flash photography with manual actuation of the subject MDT,. high-speed video, often at several hundred frames per second, or digital imaging coupled with laser strobe illumination, with speeds of several thousand frames per second. An example of the latter is provided by Kodak's EktaPro HS Motion Analyzer, Model 4540, that can record up to 4,500 full frames/second. The video imaging can be synchronized with an ultra short pulse width, high intensity visible light source, e.g., Oxford Lasers' Laserstrobe™ copper laser. Real-time aerosol plume development can, therefore, be captured for subsequent frame-by-frame analysis, which attempts to maximize the information obtained for a single image or series of images.

However, in any of the techniques used for plume geometry observations, <u>there is always an **aspect** of subjective analysis and interpretation which is present, even when digital image processing methodologies are applied.</u> Specifically, it is necessary to identify the boundary of a dynamic plume and to determine the edge of an aerosol cloud where only a transient edge exists.

In an attempt to demonstrate the potentially subjective nature of aerosol plume geometry testing, even when more sophisticated methods are applied to the data, a typical image captured for **an** aerosol plume generated for a CFC based pMDI is provided (Figure IV. 1).5

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4 Evans, RM; *Spray Pattern and Plume Geometry,* AAPS/FDA/USP Workshop: Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery, 3 - 4 June 1999
5 Evans, RM and Alcorn, GJ; Drug Delivery to the Lungs VI, 14th/15th December, 1995, London, *Aerosol Plume Imaging and Image Processing Techniques.*
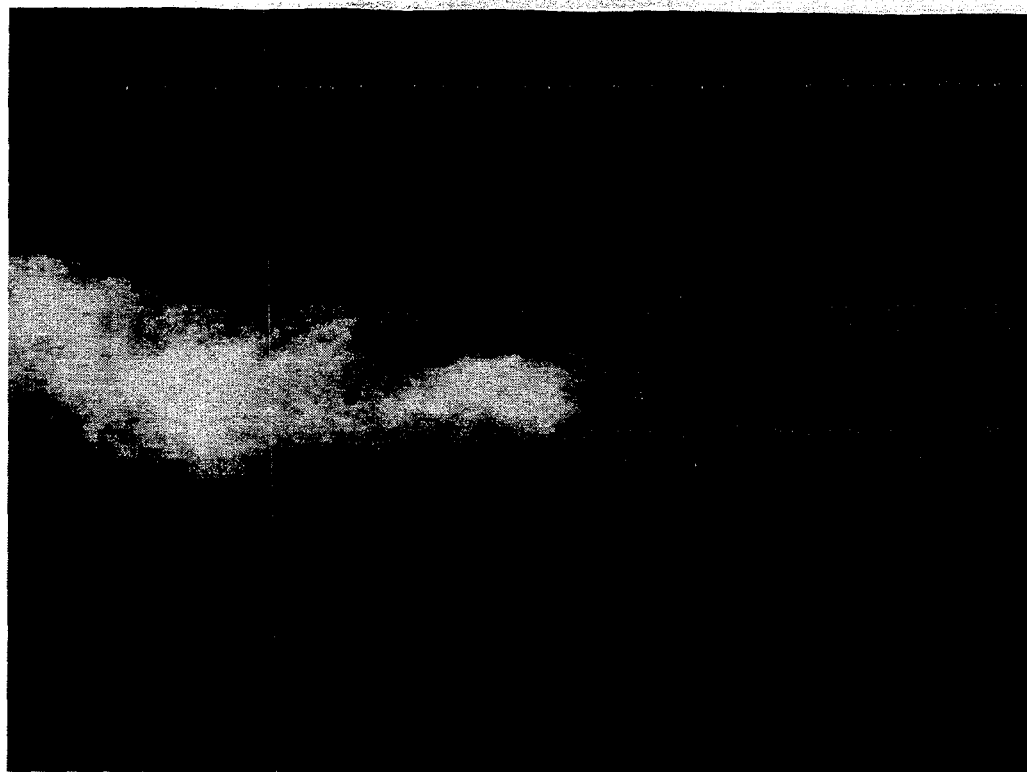
Figure IV.l. Aerosol plume produced from a CFC based pulmonary pMDI.

The sample image was captured using a Pulnix TM7EX CCD video camera equipped with a 12.5 to 75 mm f1.2 Fujinon-TV zoom lens and the video image was fed into a Perceptics Pixel Buffer frame grabber. Aerosol plume illumination was provided from above and below using dual line Dolan-Jenner area strobe panels that were fed by a bifurcated fibre optic cable from a single Dolan-Jenner strobe light illuminator. The length of each Fiber-Lit& panel was 15 cm with an illumination aperture width of 0.5 mm.

Subsequent image processing was performed using Acuity's Image Analyst™ software running on a Macintosh computer and the overlay resulting from this technique is shown in the second image (Figure IV.2). The image-processing algorithm relied upon the fact that the image is composed of pixels with numerical values between 0 and 255 and that within a region of interest, blocks of pixels may be scanned row-by-row or column-by-column. By arbitrarily selecting a pixel transition value for the captured image it was possible to identify the aerosol plume boundary or edge of the plume. The software used also allowed the transition points along the length of the plume to be joined, using linear regression, to define a best straight-line plume. Information such as the angle of the plume boundary relative to the axis of plume development, the magnitude of areas with similar pixels value, or continuous groups of pixels can be determined.
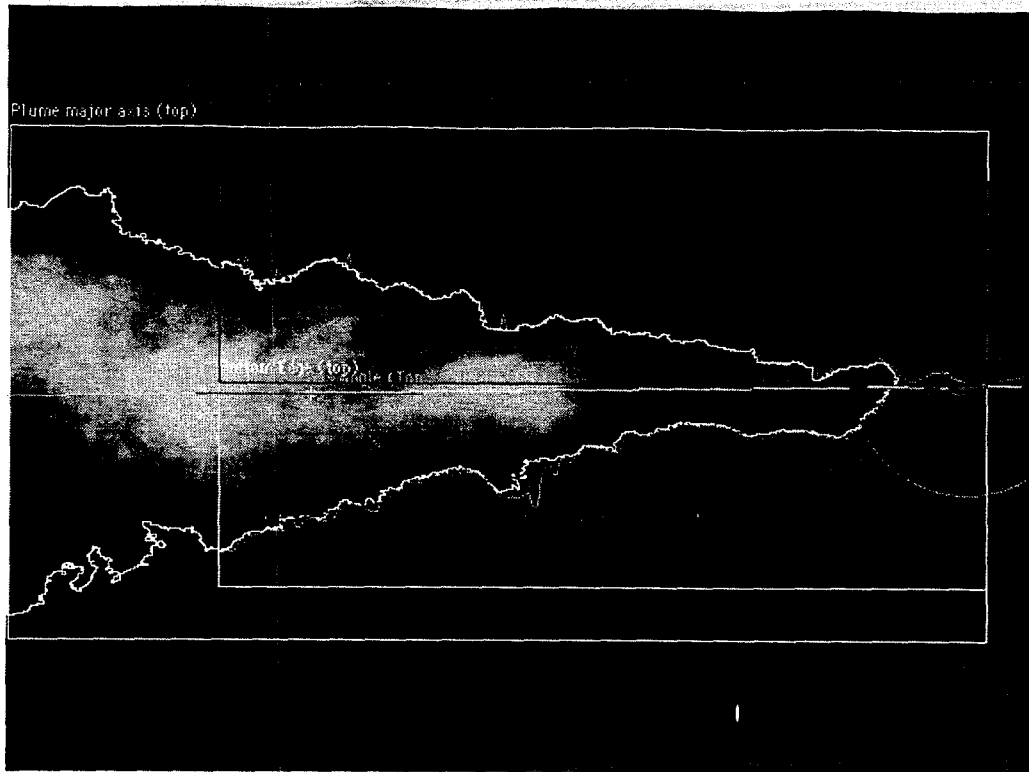
Figure IV.2 Aerosol plume with image processing overlays.

Figure IV.1 shows that the edges of the plume are diffuse and indistinct. The image is more indicative of a general axis of plume development, portraying a general expansion of the plume profile as the constituent elements of the aerosol cloud are slowed by resistance to forward motion and the propellant system evaporates.

The second image illustrates the application of digital image processing techniques to the initial plume image. Here an arbitrary boundary has been identified, based on a transition of pixel values from dark to light, and a 'best fit' straight line approximates the upper and lower plume boundaries.

It **is** obvious from Figure IV.2 that portions of the developing plume lie both within and without the boundary line. It is also evident that the line so derived could be easily modified, thereby significantly changing the angle between the upper and lower plume boundaries, by simply increasing or decreasing the particular pixel value that is selected prior to processing of the image. Thus, even using this technique, the results of the plume test are highly subjective.

C.   **Summary of Results of Industry Survey**

A questionnaire was provided to all members of the ITFG/IPAC-RS Collaboration containing a series of questions regarding the characterization of plume geometry. Specifically, the following questions were posed:

1. Do you *quan titate plume ?*
2. Do you *validate the method?*
3. *How do you define the leading edge of the plume?*
4. *Do you have data on sensitivity of plume geometry to formulation changes?*
5. *How sensitive to lighting is the plume geomety measurement ?*
6. *How tightly do you control the methods in order to get reproducible results?*
7. *When and how frequently do you perform plume geometry testing?*

The number of responses was low. Nevertheless, from the responses received, it appears that industry uses a variety of methods to measure plume geometry, consistent with the draft MDI/DPI Guidance *(lines 1527-1530)*. However, because of the limited response, no other definite conclusions regarding the test could be drawn from the industry survey. The Team therefore concluded that recent literature would be the most appropriate area to focus its efforts. The results of literature review and analysis are presented in section D.

D.   Review of Scientific Literature

We reviewed published literature to investigate how plume geometry and spray pattern might reveal important information about formulation and component parameters, *i.e.,* product quality. The literature shows that when single parameters are varied individually, while measuring the resultant plume of a particular product, plume geometry can reveal information about the changes to the relevant parameter. However, when these parameters are allowed to vary simultaneously (as may be the case in real life), then the combined effect cannot be deconvoluted into separate factors to yield any meaningful indication of the underlying changes. Thus, the plume geometry and spray pattern tests have very limited value.

Summarized below is a review of the relevant literature regarding parameters that may affect plume geometry or spray pattern:

i.   *The size and shape* **of** *the actuator orifice.*

The diameter of the actuator orifice controls the rate of spray formation[6] and the shape of the orifice affects the spray; whereby actuator orifices with a standard taper produce moderate width sprays, while reverse taper actuators provide wider sprays[7].

The molding of the actuator orifice is crucial, as the orifice plays a vital part in the breaking up of the liquid into droplets. It is also important with regard to the velocity and the direction of the emitted aerosol particles.[8] The molding process of the actuator can be checked by determining drug retention in the actuator after releasing doses through it into the air.[9]

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[6] Byron, PR; *in Respiratory* Drug *Delivery* (PR Byron, ed.) CRC Press, Boca Raton, Fla., 1990, pp. 167-205
[7] Sanders, PA; in Handbook of Aerosol Technology. PA Sanders. Robert E. Krieger Publishing Company, Malabar, Fla., 1979a, pp. 111
[8] F Morén, F; Chapter 10. *Aerosol dosage* **forms** *and formulations in Aerosols in Medicine. Principles, Diagnosis and Therapy.* Eds. Moren, F; Newhouse, MT; Dolovich, MB;. Elsevier, 1985, pp. 278
[9] Morén, F and Jacobsson, S-E, *Int J Pharm* 3, 1979, pp. 335-340

Evidence of the contribution of orifice profile, including diameter and length, have also been provided for aerosol formulations designed for pulmonary delivery.[10,11,12]

ii.   *The design of the actuator.*

The equilibration of the propellant with atmosphere results in rapid propulsion of the contents of the metering chamber through the actuator orifice with concurrent evaporation of the propellant. Once the droplets are formed, the plume begins to expand and it has been demonstrated that a proportion of the droplets of large mass are emitted along the axis of the actuator orifice.[13]

The orifice geometry and dimensions will have an effect on the droplet formation. Functionally, the orifice region of the actuator consists of the "sump" a small region beneath the valve stem in which expansion occurs, and the orifice through which the mixed vapor/liquid is emitted (in the book the actuator orifice for four actuators is seen). The dimensions of both the expansion chamber and the orifice may be varied, and will have an effect on the aerosol plume generated.[14] Morén[7] concluded that the actuator of a pressurized inhalation aerosol plays an essential part when it comes to generating the aerosol particles and directing the dose to the patients.

iii.   *The size of the metering chamber and the stem orifice of the valve.*

The metering chamber volume and actuator geometry can have a significant effect on the output from a metered dose inhaler. The volume of the metering chamber and the orifice size of the valve stem and actuator dictate the volume and rate of emission of the aerosol formulation. The dead space between the actuator orifice and the metering chamber act as an expansion chamber in which the propellant forms a mixture of liquid and vapor phases before exiting.[15]

iv.   *The vapor pressure in the container.*

Spray characteristics may be varied by changing the concentration or type of propellant, valve, actuator or solvent. The two most important propellant variables that affect the spray are vapor pressure and concentration in the product. An increase in propellant concentration decreases particle size. At high propellant concentration, a comparatively large quantity of energy is available to break up a relatively low amount of concentrate producing small particles.[16]

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[10] Evans, RM; Solubilization of Drugs within Chlorofluorocarbon Based Pressurized Aerosols, Doctoral Thesis, University of Wales, 1990.

[11] Evans, RM; Farr, S.J.; Armstrong, N.A.; Chatham, S.M.;*Formulation and In-Vitro Evaluation of Pressurized Inhalation Aerosols containing Isotropic Systems of Lecithin and Water, Pharm. Res.;* 8, 1991, p. 629.

[12] Hickey, AJ; Quigley K; and Evans, RM; *Spray Formation at the Actuator of a Metered Dose Inhaler,* Abstract accepted for publication at the American Association of Pharmaceutical Scientists Annual Conference to be held in November 1993.

[13] Hallworth, GW; *Drug Delivery to the Respiratory Tract,* Ganderton, D; Jones TM, eds.; New York; VCH Publishers; 1987, pp. 87-118.

[14] Hickey, AJ and Evans, RM; Inhalation Aerosols. Physical and *Biological* Basis *for Therapy.* Edited by AJ Hickey in the Lung Biology in Health Disease series, 94. Marcel Dekker, New York. 1996.

[15] Hickey, AJ; *Inhalation Aerosols. Physical and Biological Basis* for *Therapy.* Edited by AJ Hickey in the Lung Biology in Health Disease series, 94. Marcel Dekker, New York. 1996, pp. 426.

[16] Sanders, PA; *in Handbook of Aerosol Technology.* PA Sanders. Robert E. Krieger Publishing Company, Malabar, Fla. 1979b, pp. 147.

v.   *The nature of the formulation.*

Droplet formation is significantly influenced by the vapor pressure of component propellants and by the presence of solids, surfactants, or cosolvents in the system. In fact, the concentration of ethanol in MDI formulations has been shown to have a profound influence on the aerosol droplet size distribution and the overall nature of the aerosol plume.[17]

The available literature indicates that while the factors mentioned above may contribute to the aerosol plume generation, the studies usually start with the premise that a given factor may have some effect on the plume geometry. A single factor is then varied to study the resultant effect on the aerosol plume.

In contrast, use of the plume geometry test as required in the draft Guidance, starts with the premise that a given aerosol plume can reveal useful information about an individual factor that influences the performance of the final product. This approach is problematic because not only is the plume geometry test inherently subjective, as shown above, but the effects of all relevant factors are convoluted in the resultant plume so that no meaningful information can be extracted from the test.

E.   Discussion

As the data in section B shows, the subjective selection of the experimental parameters (for example, plume edge detection) introduces significant variability and subjectivity into the plume geometry determination.

The available literature, outlined in section D, indicates that there are factors that may contribute to the aerosol plume generation (such as the size and shape of the actuator orifice, the actuator design, the size of the metering chamber and the stem orifice of the valve, the vapor pressure inside the container, and the nature of the formulation).

However, as stated above, these factors are identified in studies where a single factor is varied to study the resultant effect on the aerosol plume. In contrast, the plume geometry test, as described in the draft Guidance, assumes that the aerosol plume itself can reveal useful information about a particular factor, given no a priori knowledge of device component or formulation changes, This approach is problematic because the plume geometry test is inherently subjective, and the effects of all relevant factors are convoluted in the resultant plume.

A better, more objective and exacting approach to product quality would therefore be through separate evaluation and control of these individual factors during development studies. Companies regularly perform such studies. In addition, manufacturers of metered dose inhalers place rigorous controls on the acceptance and use of actuator and valve components. Actuators and valves are moulded to exacting standards and critical dimensions are controlled to the tightest tolerances to ensure performance of the drug product. Any variation within these tolerances

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[17] Bell, JH; Brown, K; and Glasby, J; Variation in delivery of isoprenaline from various pressurized inhalers. *Journal of Pharmacy & Pharmacolog;* 25, December 1973, Suppl: 32P-36P.

would not be detected by plume geometry testing. Gross noncompliance would be more readily detected by other physical and functional performance tests.

F.   Conclusion

Although it may be possible to apply more objective interpretation of collected plume geometry data, the value of the data, given the ability to control the physical factors that influence aerosolization, is questionable. The determination of plume geometry may be of some use during the development of new inhalation formulations during which time screening and acceptance criteria are being developed for the testing of appropriate components such as actuator and metering valve or pump. However, the qualitative nature of the data generated during these tests, coupled with the potentially complicated methodology disqualifies plume geometry and spray pattern tests as tools for product quality assurance purposes.

Since it is possible to independently select and measure each of the tangible factors that contribute to the development and characteristics of the emergent aerosol plume - for example metered volume or actuator orifice - it seems prudent to apply controls to the individual factors and not the dynamically changing aerosol plume. Pharmaceutical companies, when developing inhalation dosage forms, do not consciously select an aerosol plume profile. Rather, they develop a formulation that provides a suitable aerosol size distribution for deposition at the intended site of action, and then prove the clinical efficacy of the formulation during subsequent clinical studies, In addition, generic companies are more likely to match the tangible *in-vitro* testing parameters (such as dose and aerosol size distribution) than intangible measurements such as plume geometry. Thus, because of its subjectivity the plume geometry test should not be required, but rather should be used at the company's discretion.

We conclude, therefore, that:

> *Some evaluation of plume* geometry *may be undertaken, at the company's discretion, during metered dose inhaler development as a screening tool for component evaluation. However plume geometry testing for MDIs is not an appropriate means of controlling formulation and device parameters as suggested by the draft Guidance, and therefore should not be required either during development or on stability.*

Factors affecting plume geometry could be measured more objectively, quantitatively and more reproducibly than the resultant plume, and therefore these factors, rather than the resultant plume geometry, should be evaluated and controlled. In fact, the objective factors, e.g., size/shape of orifice, are convoluted in both plume geometry and spray pattern testing, which makes both of these approaches less meaningful than the separate controls on the more objective factors. We examine Spray Pattern further in part II below, using data collected from several companies.

The Team recommends that *lines* X21-1522 and *lines* 1533-1538 of the draft MDI/DPI Guidance be removed:

> 1521 A study should be performed to characterize the plume geometry to help evaluate
> 1522 the performances of the valve and the actuator.

1533 ~~For assessing the performance~~
1534 ~~of the valve and actuator, the study of plume geometry is complementary to the~~
1535 ~~spray pattern test, which may directly examine the drug substance particles from~~
1536 ~~the plume. The resulting baseline may be used to compare similar drug products~~
1537 ~~by different manufacturers or when introducing certain changes to an already~~
1538 ~~approved drug product~~.

II.   SPRAY PATTERN

A.   Introduction

The FDA draft MDI/DPI Guidance requires spray pattern testing of finished products (See sections III.F.1.m and III.G.l.c.iv.). In particular, the draft Guidance recommends routine spray pattern testing of the finished drug product as a method to control component performance:

> 654 *m. Spray Pattern and Plume Geometry*
> 655 Characterization of spray pattern and plume geometry are important for evaluating
> 656 the performances of the valve and the actuator. Various factors can affect the
> 657 spray pattern and plume geometry, including the size and shape of the actuator
> 658 orifice, the design of the actuator, the size of the metering chamber, the size of the
> 659 stem orifice of the valve, the vapor pressure in the container, and the nature of the
> 660 formulation. Currently, it is recommended that spray pattern testing should be
> 661 performed on a routine basis as a quality control for the drug product.

B.   Purpose of Survey

The ITFG/IPAC-RS Tests and Methods Technical Team conducted an, industry-wide survey to obtain data from MDIs to examine whether spray pattern analysis is an appropriate means to control the quality of the finished product. In particular, the Team wanted to determine if the device parameters, including the size and shape of the actuator orifice, the design of the actuator, the size of the metering chamber, the size of the stem orifice of the valve, the vapor pressure in the container, and the nature of the formulation, outlined by the FDA in the draft Guidance, show a correlation with spray pattern measurements.

The data collected by the Team is surnmarized in section C below. Analysis of data showed that for representative products, spray pattern measurements exhibit high intra-product variability, suggesting that the test is subjective. Furthermore, this high variability may mask changes in the parameters identified by the draft Guidance as affecting product performance. Finally, we discuss the relevance of the literature data previously referenced in section I.D. for plume geometry testing. *In Appendix B* (see accompanying document) we examine the apparent lack of inter-product correlation shown between the parameters proposed by the FDA as potentially affecting spray pattern, and the actual spray pattern data.

C.   Structure of Data

For each product submitted, the following information describing the product was requested in order to provide an opportunity to study relevant categories of products:

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

Product status	Delivery route	Formulation type	Device type	Metering system
Not Disclosed	Not Disclosed	Not Disclosed	Not Disclosed	Not Disclosed
US commercial	Nasal	Solution	CFC	Device metered
Non-US Commercial	Pulmonary	Suspension	HFA	Eke-metered
Phase IIB/ III/ NDA			Non-pressurized	
			Power assisted	
			Container only	

For each of the categories, submitting companies had the option not to disclose the information (however, this option was very rarely used).

In order to specifically address the parameters listed in the FDA's draft Guidance relating to spray pattern, the following information was also requested for each product:

- Size of Actuator Orifice
- Shape of Actuator Orifice
- Actuator Design
- Size of Metering Chamber
- Size of Valve Stem Orifice
- Vapor Pressure of Container
- Nature of Formulation

For each individual spray pattern determination in the database, the following information was provided by the submitting company: batch number (coded to preserve confidentiality), Spray Distance(s), Spray Pattern Diameters (e.g., Short (S) and Long (L) or Vertical (V) and Horizontal (I-I)), Ratio of Diameters (S/L or H/V) and visual observation.

D.   Summary of Data

Original data were provided representing 8 different products and a total of 20 batches.

Three data sets were submitted which were not included in the analysis. One of these data sets included a specification but no data, another did not provide any real time data and a third was withdrawn at the request of the sponsor.

A summary matrix of the submitted data is included in Table IV.2.

Table IV.2. Summa y matrix of spray pattern data submitted.

Product status	Suspension CFC	Suspension HFA	Total
u s Commercial	3	1	4
Non US Commercial	0	2	2
Phase IIB/ III/ NDA	1	1	2
Total	4	4	8

All of the products in the database are device metered MDIs and all are intended for local pulmonary delivery.

E. Results and Discussion

A summary of the device parameters for the submitted products is included in Table IV.3, along with the range of values reported for each parameter.

Table IV.3. Summa y of Device Parameters

Parameter	Range of Values
Nature of Formulation	CFC Suspension, HFA Suspension,
Size of Actuator Orifice (mm)	0.22-0.6
Shape of Actuator Orifice	Cylindrical, Conical
Actuator Design	No meaningful data submitted
Size of Valve Stem Orifice (mm)	0.5-0.7
Vapor Pressure of Container (psi)	40-70
Size of Metering Chamber (μl)	25-63

E.1 General Ovetview

For the 8 products included in the analysis, 5 products were measured at more than one spray distance, typically 3, 5, and 7 cm or 2.5, 5.0 and 7.5 cm. The remaining 3 products were measured at 5 cm only.

For 6 of the 8 products, the spray patterns were measured along the shortest and longest diameters, while two of the products were measured along the horizontal and vertical diameters.

In order to provide a like-with-like comparison of the data for the investigation of correlation of spray pattern with component/formulation variables only the data from the 5 cm spray distance is presented in this report. The 5 cm distance was chosen as it was the most commonly measured distance. Additionally as the data presented in Figure IV.3 demonstrates, the spray distance did not in general affect the spray diameter measurement. For data set 70043 no 5 cm data was submitted. In this case the 7 cm data was used.
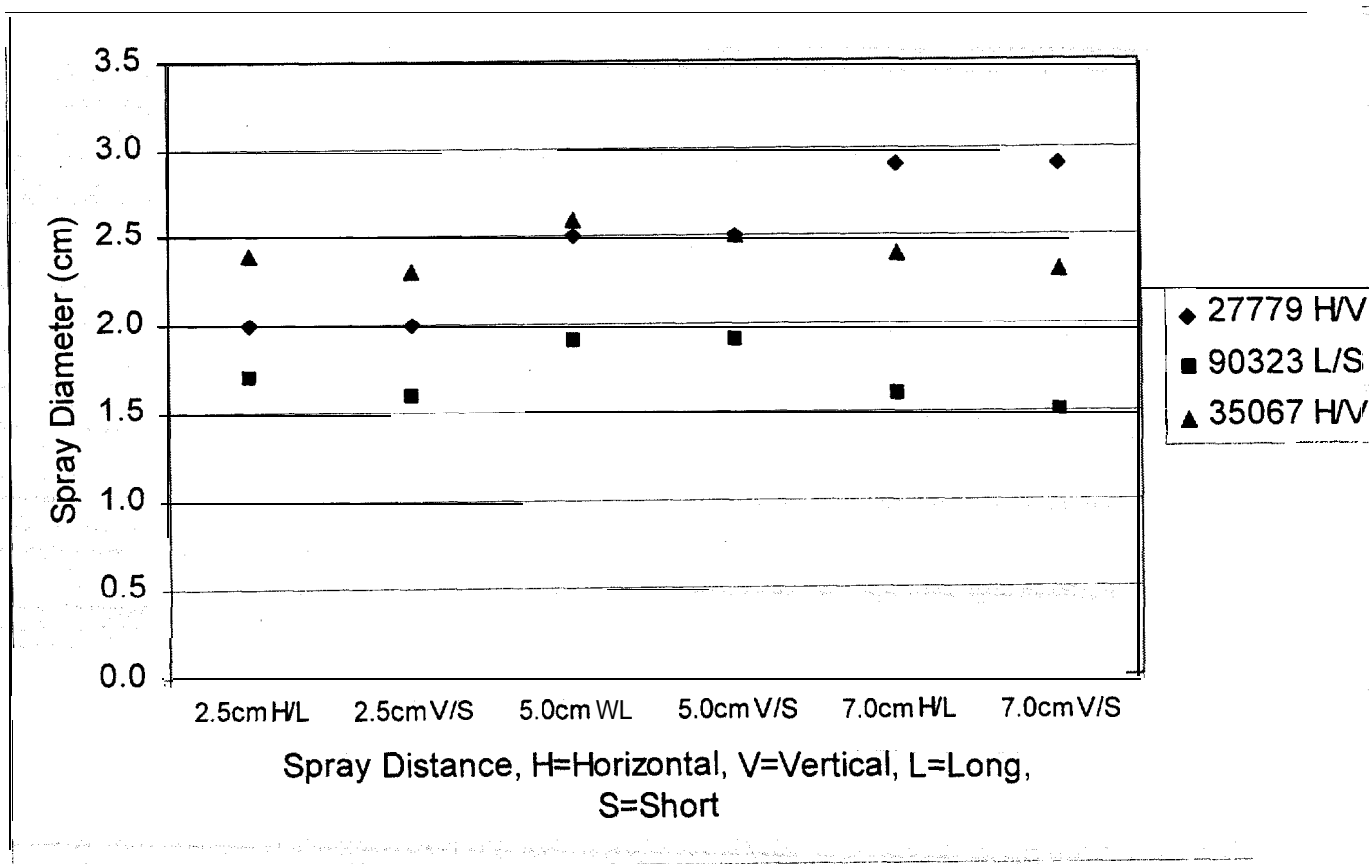

Figure IV.3 Comparison of spray distance to spray diameter for three products.

E.2. Intra-product Variability

A large degree of intra-product variability of spray pattern diameters (both short and long, and horizontal and vertical) was observed for the data submitted. This variability is seen clearly in products for which there are more than two data points (spray diameter measurements).

For example, a range of 1.1-2.6 cm of spray pattern diameters was observed for one data set (22374) and a range of 0.76-2.3 cm for another (88579). For one product (88579), a range of 1.3-2.3 cm was observed for 3 batches while a range of 0.76-1.02 cm was observed for a further 3 batches. This clearly demonstrates the subjectivity in the test measurement.

Products 93452 and 90323 likewise demonstrate a large range in intra-product variability. For 93452, the spray diameter ranges from 1.2-2.2 cm for three determinations. For product 90323, the spray diameter ranges from 1.7-2.2 cm for three determinations.

A graphical summary of all the values obtained for the database is presented in Figure IV.4. These values are also summarized in Table IV.4, which lists the number of batches used in the analysis, and the number of determinations. A graphical summary of the mean values obtained for the database is shown in Figure lY.5.

Table IV.4. Summa y of product data

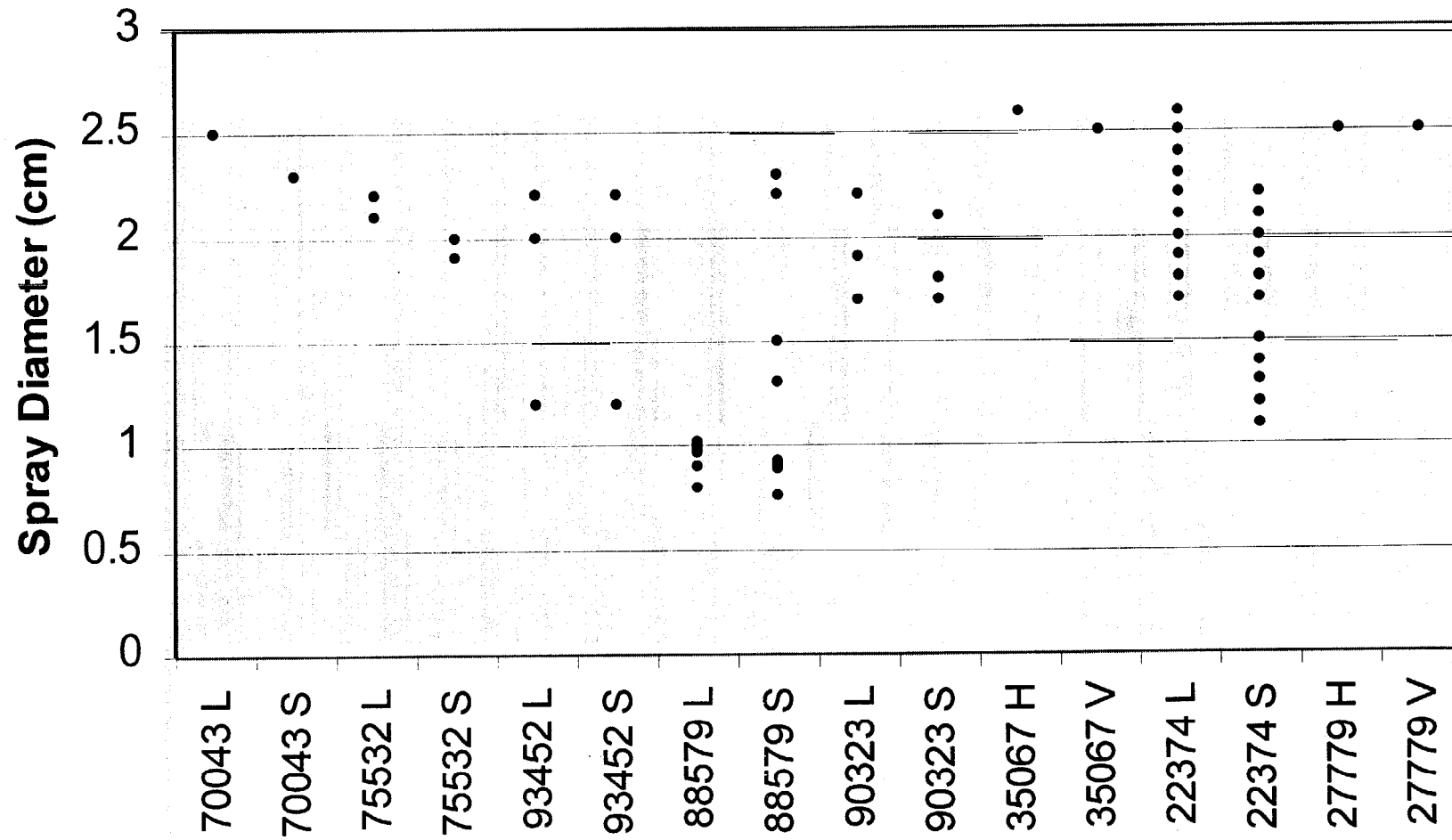| Data File	Number of Batches	Number of Measurements	Spray Diameter Range (cm)	Spray Diameter Mean (cm)	Ratio	Ratio Calculation
70043	1	*1*	2.3-2.5	2.4	1.1	L/S
75532	1	3	1.9-2.2	2.1	1.1-1.1	L/S
93452	1	3	1.2-2.2	1.8	1.0-1.0	L/S
88579	6	21	0.76-2.3	1.1	1.0-1.1	L/S
90323	1	3	1.7-2.2	1.9	1.0-1.1	L/S
35067	1	1	2.5-2.6	2.6	1.0	H/V
22374	8	24	1.1-2.6	1.9	1.1-2.0	L/S
27779	1	1	2.5-2.5	2.5	1.0	H/V

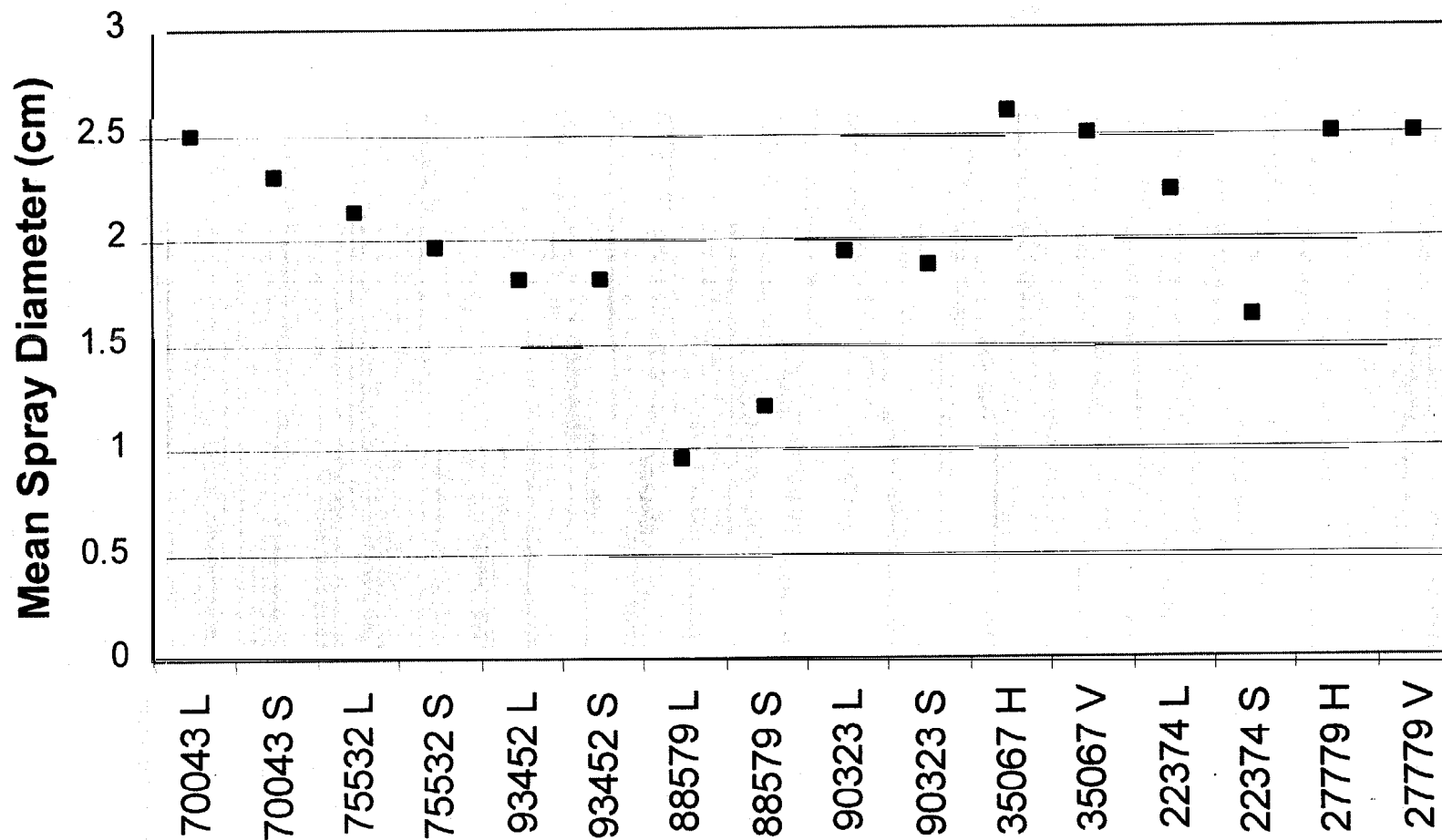Figure IV.4 Summary of individual spray pattern data for all products in database.

Figure IV.5. Summary of mean spray pattern data for all products in database.

This large degree of intra-product variability suggests that the test is not a sensitive or objective determinant of changes in formulation or device parameters. Any difference in spray pattern that may be present, due to formulation or component changes, may be masked by the high variability in measurements within a single product.

We can examine this further by making a comparison among products that differ only in one of the relevant parameters – in this case, formulation type. Table IV.5 lists these products (93452, 88579, and 22374) and their relevant parameters. As shown in Table IV.5, the high intra-product variability in the spray pattern measurements does not allow determination of differences or similarities between these products.

Table *IV.5. Comparison of Products with Different Formulation Type.*

Parameter	93452	88579	22374
Formulation Type	HFA Suspension	CFC Suspension	CFC Suspension
Orifice Diameter (mm)	0.48	0.48	0.48
Valve Stem Orifice (mm)	0.5	0.5	0.5
Orifice Shape	Cylindrical	Cylindrical	Cylindrical
Vapor Pressure (psi)	55	55	55
Metering Volume (µl)	50	50	50
Actuator Design	Standard Type	Standard Type	Standard Type
Spray Measurements			
Spray Diameter Range (cm)	1.2-2.2	0.76-2.3	1.1-2.6
Spray Diameter Mean (cm)	1.8	1.1	1.9
Ratio	1.0-1.0	1.0-1.1	1.1-2.0
Ratio Calculation	L/S	L/S	L/S

For instance, product 93452 is an HFA suspension product, while both 88579 and 22374 are CFC suspensions. Other relevant factors are identical. Comparing 93452 and 88579, spray diameter means are quite different (1.8 *vs.* 1.1) but ratios appear to be similar (1.0-1.0 *vs.* 1.0-1.1). Comparing 93452 and 22374, the spray diameter means are quite similar (1.8 'us. 1.9), but the ratios are very different (1.0-1.0 *vs.* 1.1-2.0).

Products 88579 and 22374 have the same device and formulation parameters defined in the draft Guidance as affecting product performance. However, there appears to be little similarity between their spray diameter means (1.1 vs. 1.9). Moreover, their ratio ranges appear to be quite different (1.0-1.1 vs. 1.1-2.0).

Comparison among these three products thus suggests that because of the high intra-product variability in spray pattern measurements, the spray pattern test cannot clearly reveal definitive information about changes in formulation among products. Factors such as orifice length or drug substance concentration might also influence the results, however the influence of these effects would also be difficult to definitively determine due to the variability in the spray pattern measurements.

The high intra-product variability of some of the spray pattern data, along with data presented in Table IV.5, suggests that spray pattern testing is not a sensitive measure of product quality. Even if the examined parameters (i.e., formulation type, orifice size and shape, valve stem orifice size, vapor pressure, and metering chamber size) do influence spray pattern, their effects may not be discerned by the test because of high intra-product variability in the measurements, and because their individual effects are convoluted in the resultant pattern.

The highly variable and subjective nature of this technique makes the test insensitive to rninor changes in the formulation or components that would be detected by more precise control of the manufacturing process, and the individual components that comprise the drug product.

E.3   Discussion of Literature

The literature reviewed in Section I.D. also pertains to spray pattern. That is, the relevant literature suggests that if certain components or formulation type are varied within a given product, it is possible to discern variations in the resultant spray pattern. However, as with plume geometry testing, the draft Guidance language for spray pattern testing requires that changes or defects in these components and/or the formulation should be checked by examination of the final spray pattern with no *a priori* knowledge of such changes. As shown above, the subjectivity of the test precludes it as a meaningful test, used in this way.

E.4   Comparison of Parameters *Across All Eight Products*

In Appendix B (see accompanying document) we examine the apparent lack of inter-product correlation shown between the parameters proposed by the FDA as potentially affecting spray pattern, and the actual spray pattern data. This apparent lack of inter-product correlation might suggest a lack of intra-product correlation between these parameters and spray pattern measurements.   Additionally, this examination further emphasizes the fact that spray pattern testing on final product only demonstrates the convoluted influences of all the parameters, and not the influence of the individual parameters.

F.   Conclusion

Analysis of the database submitted to the ITFG/IPAC-RS Tests and Methods Technical Team and the relevant literature data, suggests that spray pattern is not **a meaningful test** for product quality analysis of MDI products.   Therefore the spray pattern test should not be required for routine quality control and as a specification for drug product. High intra-product variability in spray pattern measurements strongly suggests that the test is highly subjective. This variability diminishes its usefulness as a sensitive measure of formulation and device parameter changes, and therefore product quality/performance.

As previously discussed in sections I.D -I.E, the literature suggests that the formulation and device parameters mentioned in the draft Guidance may affect spray pattern (and plume geometry). However, as stated above, literature studies usually start with the premise that a given factor may **have** some effect on the spray pattern and plume geometry. A single factor is then varied to examine the resultant effect on the aerosol plume. In contrast, the draft Guidance suggests that the aerosol plume itself can reveal useful information about a particular factor. This approach is problematic because the spray pattern and plume geometry tests are inherently subjective, and the effects of all relevant factors are convoluted in the resultant plume.

A more objective and exacting approach to product quality would therefore be to evaluate and control these individual factors during development studies. As stated in section I for plume geometry, manufacturers of metered dose inhalers place strict controls on the acceptance and use of actuator and valve components.   Actuators are moulded to exacting standards and critical dimensions are fixed to very narrow tolerances to ensure performance of the drug product.   Any variation within these tolerances would not be detected by spray pattern testing and gross non-compliance would be more readily detected by other physical and functional performance tests. Similar exacting controls are put in place for metering valves. This approach to quality testing is more reliable, accurate, and informative than spray pattern testing. Companies regularly perform these evaluations during development.   Spray pattern testing is therefore redundant, less meaningful, and should be eliminated as a specification for the drug product.

The Tests and Methods Team therefore offers the following recommendations for the spray pattern and plume geometry section of the draft MDI/DPI Guidance, lines 655-678 (new language in bold. Language recommended for deletion is struck through):

> ~~Characterization of spray pattern and plume geometry is important for evaluating the performances of the valve and the actuator~~.

> Various factors **may** affect the spray pattern and plume geometry, including the size and shape of the actuator orifice, the design of the actuator, the size of the metering chamber, the size of the stem orifice of the valve, the vapor pressure in the container, and the nature of the formulation.

> ~~Currently, it is recommended that spray-pattern testing should be performed on a routine basis as a quality control for the drug product~~.

> **Therefore, proper controls should be performed on these factors during development studies and component evaluation. Spray pattern and plume**

geometry testing may be used for component evaluation during development studies, but need not be performed for quality control of drug product.

However, the characterization of plume geometry should be established during the development of the product and is not necessarily tested routinely thereafter (refer to discussion of plume geometry testing in section IV.A.10). The proposed test method for spray pattern, including sampling plans, should be provided in detail to allow their duplication by Agency laboratories. For example, in the evaluation of the spray pattern, the actuation distance between the mouthpiece and the plate, number of actuations per spray pattern, position and orientation of the plate relative to the mouthpiece, and visualization method should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of uniform density) as well as the size of the pattern (e.g., no axis is greater than x millimeters (mm) and the ratio of the longest to the shortest axes should lie in a specified range, for example, 1.00-1.20). The spray pattern should be determined, preferable by a method specific for the drug substance, at different distances (e.g., two) from the mouthpiece to provide greater discriminatory capability to the test. Variability in the test can be reduced by developing a sensitive detection method and by providing method-specific training to the analyst.

V. SHOT WEIGHT

A. Introduction

The draft MDI/DPI Guidance includes reference to shot weight in section III.F "Specifications for the Drug Product." In particular, the draft Guidance states:

706 *p. Valve Delive y (Shot Weight)*
707 This test is directly related to the metering ability of the valve, and it evaluates
708 valve-to-valve reproducibility of the drug product. The proper performance of a
709 metering valve should be ensured primarily by the valve manufacturer, who should
710 assemble the valve with parts of precise dimensions. Valve delivery should be
711 verified by the applicant for each drug product. In general, metered dose valves
712 should have a valve delivery acceptance criteria of NMT | ±15 | percent for
713 individual actuations and NMT | ±10 | percent for the mean of the actuations
714 relative to the target.

B. Industry Survey

The Team conducted a confidential industry survey in order to obtain data from MDIs to examine whether shot weight testing provides meaningful information about product performance and therefore, whether it is appropriate to set specifications for this test. The Team agrees that shot weight testing, as a device or component acceptance test, should be used to control the quality of incoming materials. It is also a good diagnostic tool. However, the Team's position on formulated products is that it is not appropriate to set specifications for shot weight since the test is redundant to incoming valve release tests, and furthermore, it is less sensitive to product performance changes than dose delivery testing.

The Team collected MDI shot weight data from several companies and analyzed it with respect to dose delivery, stability conditions, and valve release specifications. Careful examination of the data revealed no clear, consistent correlation between product shot weights and dose delivery values. Further, shot weight showed virtually no variance relative to stability storage conditions, suggesting that any trends existing in the data could not be stability indicating. Importantly, product shot weight values demonstrated at least the, same degree of compliance to specifications as the valve release specifications used for incoming materials.

Industry data therefore strongly suggest that shot weight may be used as a device or component diagnostic tool, as well a qualification or acceptance test for incoming supplies. However, the results demonstrate that the shot weight test is neither stability indicating nor sensitive to product storage conditions recommended in stability guidelines, unlike functional performance tests such as dose delivery. Therefore, shot weight should not be required as a specification.

C.   Structure of Data

Each submitting company provided the following information on individual products for the database: batch number (coded to preserve confidentiality); unit number *(i.e.,* container/can/device number); shot weight (reported as percent target weight); storage time; life stage of canister (beginning, middle, end, or N/A); dose delivered (percent label claim); and particle size distribution.   Of the product performance parameters, dose delivery data was the most complete. Therefore, only dose delivery data was used in the analysis of the ability of shot weight testing to reveal useful information about product performance.

Furthermore, the following information describing the product was requested in order to provide an opportunity to study relevant groupings of products (Table V.l):

Table V.1. Product information categories and options for answers.

Product Status	Delivery Route	Formulation Type
US commercial	Local Pulmonary	Suspension
Non-US Commercial	Systemic Pulmonary	Solution
Phase IIB/III/NDA		

For each of the categories, submitting companies had the option not to disclose the information. This option was rarely used.   The survey also asked for valve metering volume, incoming valve release specifications, product density, and the number of actuations per measurement. Finally, if data for stored samples was submitted, the real time storage condition could be stated.

D.   Summary of Data

Table V.2 provides a summary of the number and types of products included in the shot weight database.

Six companies provided original data for the database, which comprised fourteen products and a total of 1775 individual observations. The number of, determinations per product ranged from 4 (from 3 different batches) to 432 (from 7 different batches). All of the products are for oral inhalation, twelve of which are intended for local action, one for systemic delivery and one undisclosed.   Eleven of the products are suspension formulations, the remaining three are solutions.

Data for one suspension product did not include information for valve release, and therefore was not included in the valve release analysis (section E.3). Three products were removed for the analysis of shot weight behavior on stability (section E.l) because these data sets did not contain enough information with which to normalize the shot weight data.

Table V.2. *Summa y matrix of shot weight data submitted.*

Product status	Suspension Local	Solution Local	Suspension Systemic	Suspension Delivery Route Not Disclosed	*Total*
US Commercial	7	2	**None**	None	9
Non US Commercial	1	1	*1*	None	*3*
Phase IIB/ III/ NDA	1	None	None	1	2
Not disclosed	None	None	None	None	0
Total	*9*	3	*1*	*1*	14

E.   Analysis, Results, and Discussion

1.   *Statistical Analysis of Shot* Weight *on Stability*

A general SAS-based kinetic program was used to assess shot weight stability data on multiple batches of eleven MDI products, involving multiple lots of commercial as well as developmental batches. Statistical treatment of the data was based upon FDA guidelines.[18] A SAS/PC program STAB, previously released to industry in 1992 by FDA, **was** adapted for this analysis. The program estimates the expiration dating period for a typical batch based on linear regression analysis, provided certain rules are taken into consideration, i.e., zero and first order kinetics using common slope or parallel slope models. Results and conclusions summarized in this report were based upon zero order kinetics, common slope, and common intercept criteria.

i.   *Analytical Approach*

The kinetic projections utilized 0 to 36 months shot weight storage time data obtained under ambient and accelerated stability storage conditions. The data included beginning, middle and end-of-canister-life results. The shot weight data were normalized individually based upon the theoretical labeled dose weight. No shot weight projections for canisters stored in upright, sideways, or inverted storage configurations were made as no specific storage orientation information was received with the respective batches.

The analysis was initially based upon individual product groups, but no statistically meaningful difference was measured in the dose weight change rates. Therefore all product groups were pooled and analyzed.

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[18] Ng, Moh-Jee, *Guideline for Submiffing Documenfafion for the Sfabilify of Human* Drugs *and Biologics,* FDA, February 1987.

Zero and first **order** kinetics were employed in the analysis but there was no departure from what would be expected from first principles. Therefore, results from zero order kinetics have been assembled in this report. The theory and equations used for zero order and first order calculations, are described in Appendix C (see accompanying document).

The storage time and shot weight results (reported as percent target valve shot weight) from all 11 product data files were entered into the SAS program. Sensitivity analysis of the data to various kinetic models was then performed in order to enable selection of the best model for shot weight analysis. The sensitivity analysis yields optimal estimates for the regression line by least squares, standard error, ANOVA (analysis of variance), t-tests for pooling of data based upon null hypotheses. A summary of the key considerations for the algorithm are given below:

1. Best linear regression fits when normalized shot weight (i.e., logarithm of normalized shot weight for first order mode) or percentage label claim is plotted as a function of time for each lot based on data from the individual product lots. Values generated include rate constants together with their associated confidence intervals, correlation coefficient, and projected 95% confidence values for each product batch at each time/ temperature condition.

2. An analysis of covariance test to evaluate the appropriateness of (i) using a common (parallel) slope model or (ii) pooling data from all lots based on both a common slope and intercept.

3. Linear regression fits for each lot based upon fitting the weighted mean slope from the parallel slope model to the data. Values generated include the mean rate constant, the mean intercept, individual rate constant, and individual intercept ± their respective projected 95% confidence values at any target time.

4. Regression data tables and graphed kinetic summaries obtained by pooling all values as if they came from the same population.

5. Summary tables containing highlighted data from all lots using either the individual regressions or the common slope model.

6. Comparative graphs showing the slopes from all lots using either the individual regressions or the common slope model.

7. t-Tests to compare whether the slopes and intercepts of any two lots are significantly different.

Linear Regression

Since both zero and first order kinetics describe straight line relationships between C or Ln C and time, standard linear regression treatment is used to obtain the critical values and associated confidence limits.[19,20,21] The term C is the normalized shot weight of drug remaining (see *Appendix* C in the accompanying document for descriptions and equations). Estimates of values desired from the algorithm include rate constant ± 95% limits, intercept ± 95% limits, correlation coefficient, 95% confidence range for predicted lines and points. The degree of sensitivity of the values to changing storage or stress conditions demonstrates the relevance of the test as a stability-indicating tool that could bring additional assurance of product quality.

Common (Parallel) Slope Model

Since stability data for individual lots is often sparse, it is advantageous to evaluate data from similar lots of a formulation simultaneously to obtain more accurate rate constants and tighter confidence limits.[22] An analysis of covariance test using Brownlee's method is used to test whether the pooled lots may have similar slopes, similar intercept and slope, or different slopes.   If the analysis of covariance indicates the slopes for the individual lots are not different based on an, F-test or accepted probability (FDA recommends $P > 0.25$), a parallel slope model may be used. ln the latter case the data from each lot is fitted to a weighted mean slope to obtain the regression values. The individual lots in the combined group will have identical rates and confidence limits, but different intercepts, projected potencies at target times and $t_{fraction}$ projections. The collected data supported pooling and common slope-common intercept modeling.

Results

Figure V.l presents the composite regression results for all eleven products using the common slope-common intercept model.   Figure V.l demonstrates that the predicted rate constant is just above zero but not statistically different from zero.

Outlier analysis was performed, but no specific exclusion criteria were used to eliminate these in the database, as no out of specification (OOS) investigation reports were available. The resulting projected 'results from the trend line, together with the 95% confidence intervals, are shown in *Appendix D,* **Table** *D1* (see accompanying document).

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[19] Snedecor, GW and Cocran, WG, *Statistical Methods,* Iowa University Press, Ames, 1967.

[20] Brownlee, *KA, Sfatisfical Theory and Methodology,* Robert E. Krieger, Malabar, FL, 1984.

[21] Schuirmann, DJ, *Current Statistical Approaches in fhe Center for* Drug *Evaluation and Research,* FDA, Proceedings of Stability Guidelines, AAPS and FDA Joint Conference, Arlington, VA, Dec. 11-12, 1989.
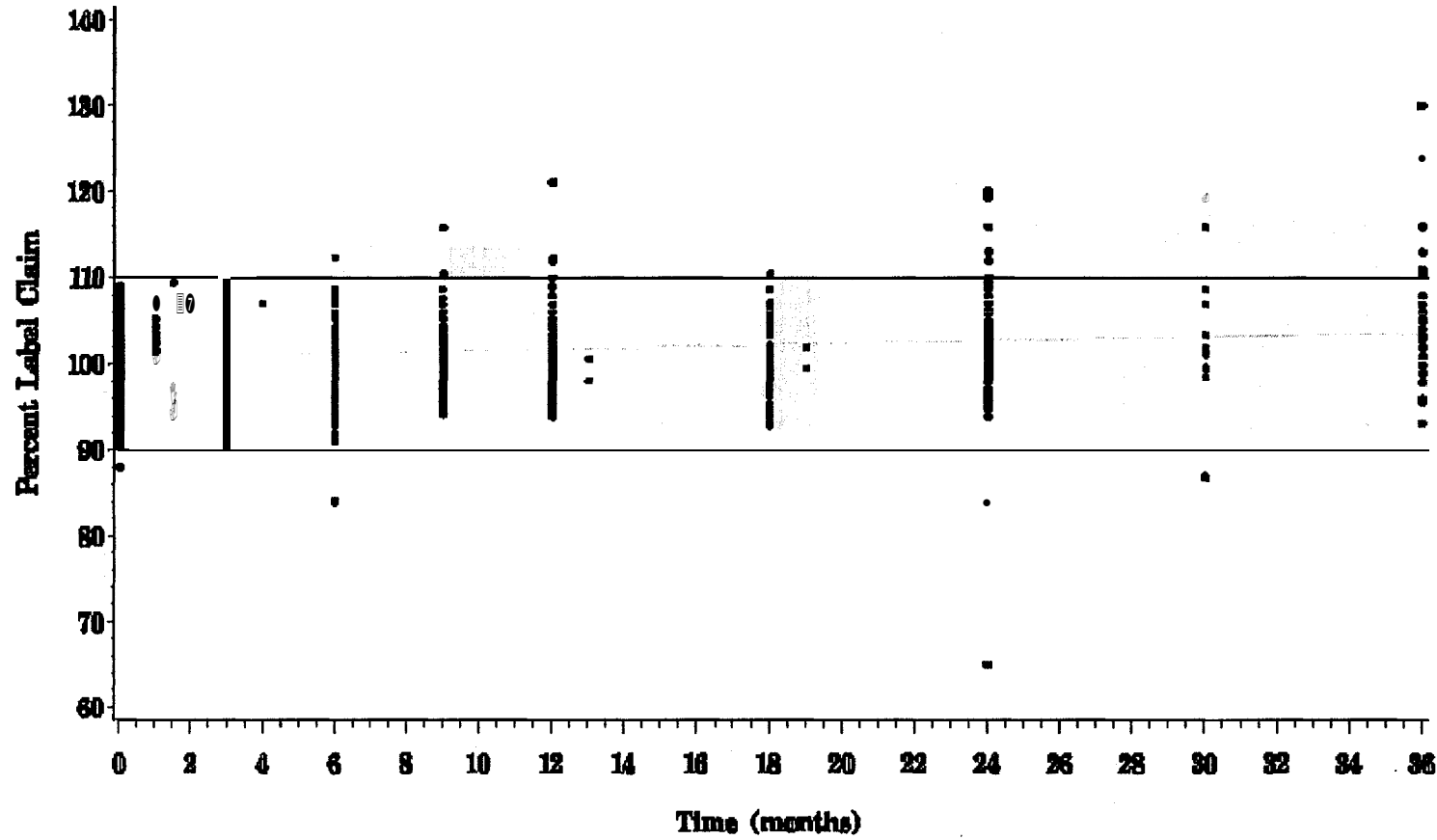
[22] *Ibid.*

Figure **V.1.** Shot weight summary. Normalized shot weight over time was measured. Graph shows results from a zero order trendline analysis with 95% upper and lower bound confidence intervals for pooled batches using common slope and common intercept model.

ii. Comparison to Dose Delivery

The lack of sensitivity when shot weight analysis is correlated with other functional criteria for pMDIs should not be surprising as mass per unit dose is often far greater than emitted dose of the drug product. To demonstrate this lack of sensitivity in the shot weight test, we examine the delivered dose behavior of a representative pMDI suspension product on stability.

Our objective was to perform the kinetic analysis on all 14 products. However, this could not be performed on pooled results as the content and nature of all products in the database is different (*e.g.*, the complete list includes solutions as well as suspensions). Nevertheless, it was felt that kinetic analysis of emitted dose for one product should be sufficient to show how the model can provide a clear relationship between functional performance of these products and time.   For this reason, we selected product 92443 as a demonstration model for this group of products. We chose this product because its data set contained multiple replicate data from multiple lots.

Results

Initial analysis indicated delivered dose data for the product would meet common slope and intercept requirements.   Therefore, emitted dose results on all batches represented in product 92443 data were pooled and the kinetics conducted using 95% confidence limits to estimate the rate constant for degradation. The trend line yielded a linear curve with a slope of -0.0563 months-* (see Figure 2) implying that both time and temperature would have a deleterious impact on delivered dose. The predicted results for this product, including 95% upper and lower bound confidence values for the delivered dose are shown in *Appendix D, Table D2* (see accompanying document).

It is evident from the lower 95% confidence limit that this product is degrading with time, which the shot weight analysis could not demonstrate (i.e., the shot weight analysis yielded slopes that include zero as a valid number). Therefore, using typical kinetic modeling approaches as described above, we conclude that unlike the delivered dose test, shot weight testing is not a meaningful metric of product quality. Tests such as dose delivery, i.e., emitted dose, are more effective than shot weight testing in evaluating product performance.

iii. Discussion

The insignificant change in the slope of the line in Figure V.l compared to that for Figure V.2 demonstrates that:

(a)   Normalized shot weight data cannot discriminate one product from the other based upon dose volume, drug normalized shot weight, and drug type.

(b)   Shot weight is an insensitive predictor of product quality over the maximum duration used in the statistical modeling, i.e., 36 months.

(c)   The predicted shot weight change rate and its 95% confidence limits are not statistically different from zero.

(d)   Storage temperature and humidity conditions do not have any measurable impact on dose weight values or on the predicted dose weight change over the 36-month duration upon which these products are stored.

(e)   Kinetic analysis of shot weight results is not stability indicating and therefore would not be **a** statistically meaningful method for setting technically justifiable expiration periods for these products.

These five observations, derived from statistical analysis of the data, strongly suggest that shot weight testing is a poor indicator of product performance.
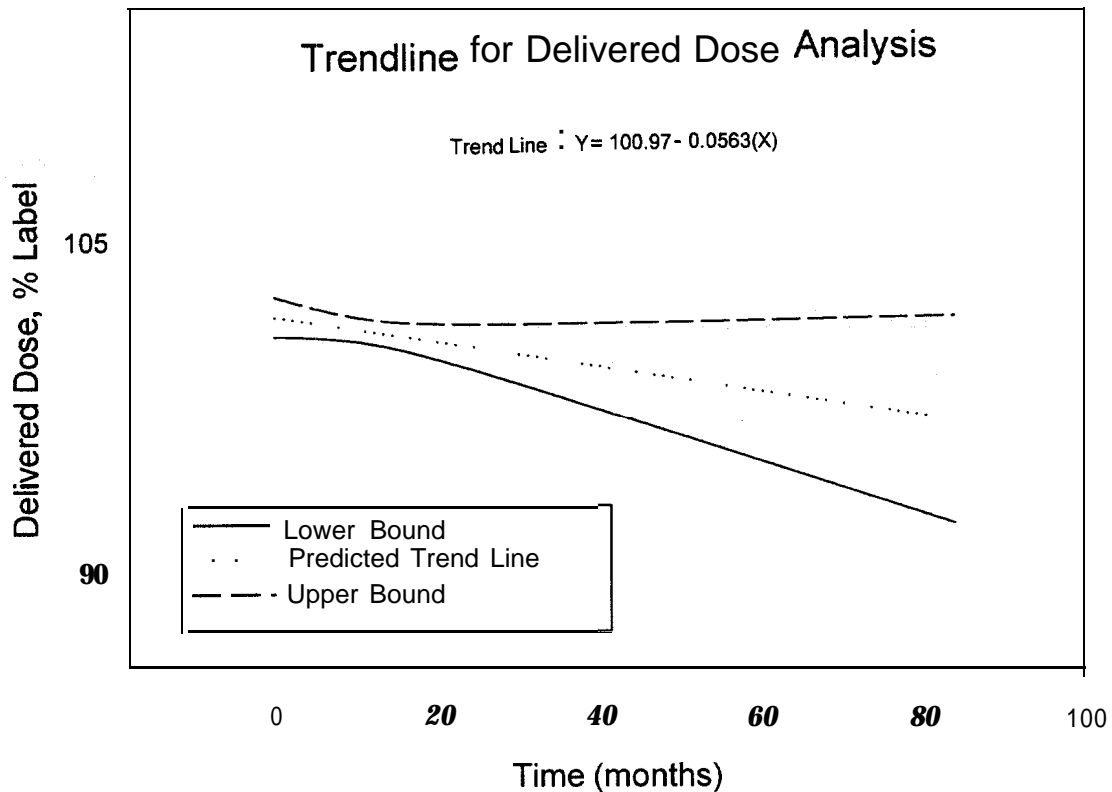
Figure V.2. Delivered dose summary for product 92443. Graph shows results from a zero order trendline analysis with 95% upper and lower bound confidence intervals for pooled batches using common slope and common intercept model.

2.　　**Comparison of shot weight data to dose delivery.**

　　　While a relationship between shot weight and dose delivered may be expected for a single can at a single point in its life stage, many factors may influence the dose delivery independently of the shot weight.　Can-to-can variation, lot-to-lot variation, loss of propellant on stability and through-life changes in the concentration of the formulation may all reduce the relationship between dose and shot weight. The collected dose delivery data were plotted against shot weight to determine if there is a clear correlation between these parameters.　All graphs of dose delivered versus shot weight are shown in *Appendix E* (see accompanying document).

　　　The charts demonstrate that there is no clear, consistent correlation between shot weight and dose delivered. R^2 values for all products examined range from 0.000000 to 0.847756. One suspension product was not examined due to its limited number of data points.

　　　Representative examples are shown below.　For instance, for the suspension product 11470 there is no good correlation between delivered dose and shot weight (Figure V.3).　R^2 for a linear fit was only 0.120669, for delivered dose and shot weight from a single batch.　Graphs from other data sets also show no strong correlation between delivered dose and shot weight. Regression lines are shown on the graphs for those products with a limited number of batches.

Product 11470
Valve acceptance specifications are +l- 15% for individuals and +/- 10% for the Average.
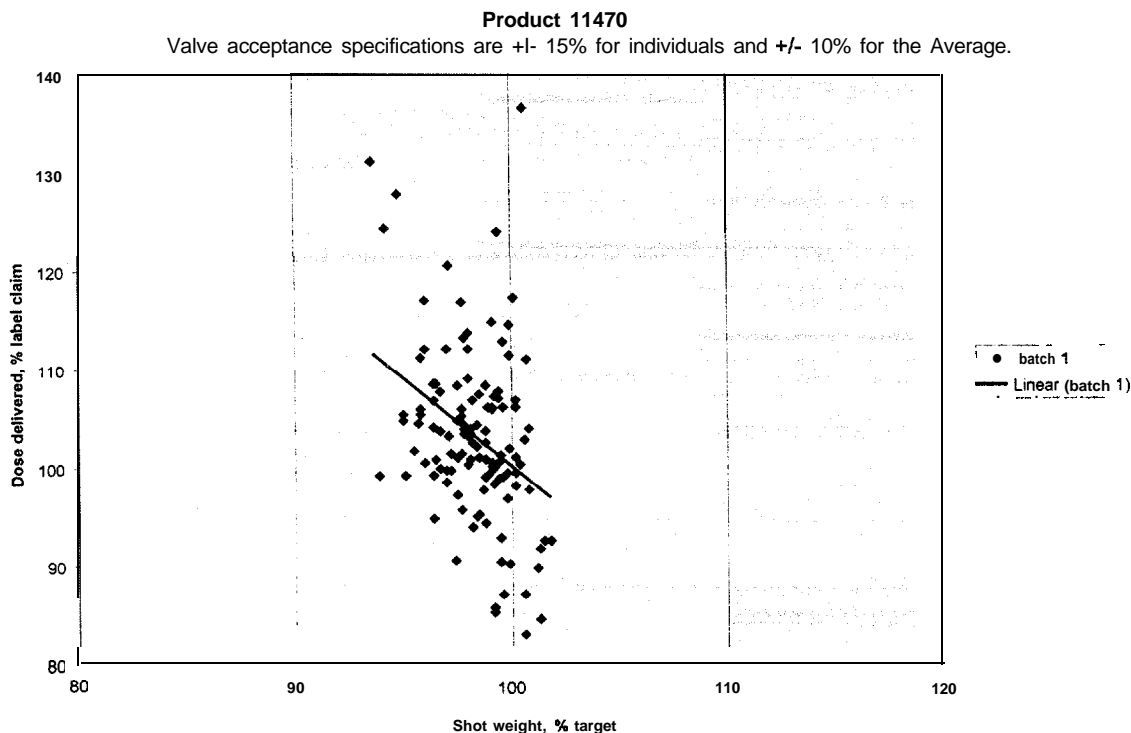

Figure V.3. Graph showing the lack of correlation between dose and shot weight for product 11470. The R^2 for a linear regression analysis of shot weight and dose is 0.120669.

Furthermore, in the data sets for the solution products, where one might expect a clear relationship between dose and shot weight, there was no apparent relationship between dose and shot weight. Figure V.4 shows the lack of correlation in product 13609, which is representative of this product group (the two other solution products in the database showed similar results).

Product 13609
Valve acceptance specifications are **+/-** 15% for individuals and **+/-** 10% for the Average,
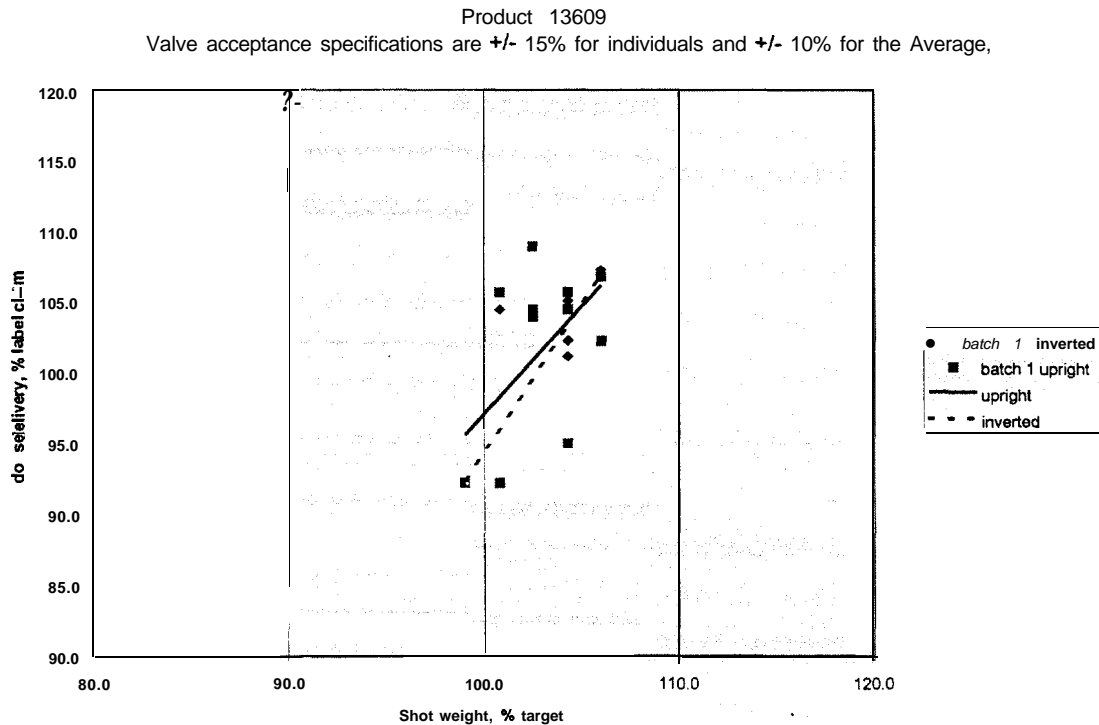

Figure V.4. Graph showing the lack of correlation between dose and shot weight for solution product 13609. R^2 for the inverted canisters is 0.640729. R^2 for upright canisters is 0.330342.

Discussion

There is poor correlation between shot weight and dose delivery for all products. Thus shot weight is not a good predictor of product performance.

3.   Comparison of shot weight data for product to valve acceptance criteria.

In this analysis, we examine whether shot weight is more variable than the incoming valve acceptance criteria.   One product was excluded from this part of the analysis, as the valve acceptance specifications were not supplied. Nine of the products had shot weights, as determined on the product, within the valve acceptance criteria for all determinations (total of 358 determinations).   -The remaining four lots had 19 values out of 1100 outside of the acceptance criteria for the incoming valves.

In general the collected data show that for each product, shot weights were within the range of valve acceptance specifications *(see Appendix* E, in accompanying document). In the following discussion, we present the details of four products that contain data outside the incoming valve specifications. The vertical lines on the graphs show the incoming valve acceptance criteria for average shot weight. The number of **shots** per determination is not disclosed for all products. Thus, the comparison to the average shot weight specification represents a conservative approach.

The majority of the data outside of the incoming valve acceptance criteria for product 739 were associated with two lots which were exposed to accelerated conditions for prolonged periods (6 or more months at 40°C/85%RH or 18 or more months at 30°C/70%RH). Only one data point for this data set represented a shot weight value outside the valve acceptance criteria, but the associated dose delivery was within an acceptable range (Figure V.5).   It should also be noted that there were several low doses associated with acceptable shot weights.

Product 739
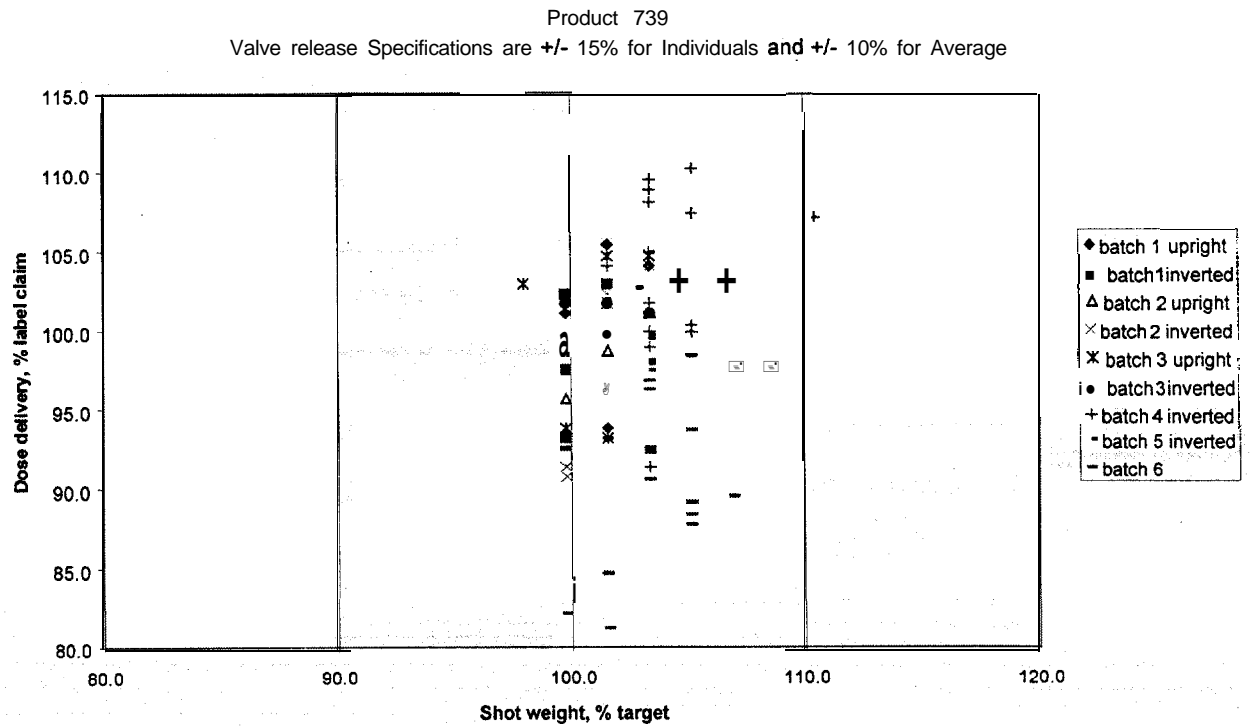Valve release Specifications are **+/-** 15% for Individuals **and +/-** 10% for Average

Figure V.5. Product 739. Comparison of shot weight obtained during dose delivery testing and incoming valve specifications (shown as vertical lines on both sides of the mean).

The R² for the various batches are shown in the Table V.3 below:

Table V.3

Batch/Orientation	R²
Batch 1 upright	0.102797
Batch 1 inverted	0.278984
Batch 2 upright	0.181513
Batch 2 inverted	0.628195
Batch 3 upright	0.030539
Batch 3 inverted	0.022624
Batch 4 inverted	0.000968
Batch 5 inverted	0.000000
Batch 6	0.000028

The data series for product 27854 contained one shot weight at 87% of target, outside of the normal incoming valve specifications (Figure V.6). The dose associated with this shot weight was 102% of label claim. In contrast the low dose of 49% of label claim was associated with an acceptable shot weight (97% of target).

Product 27854
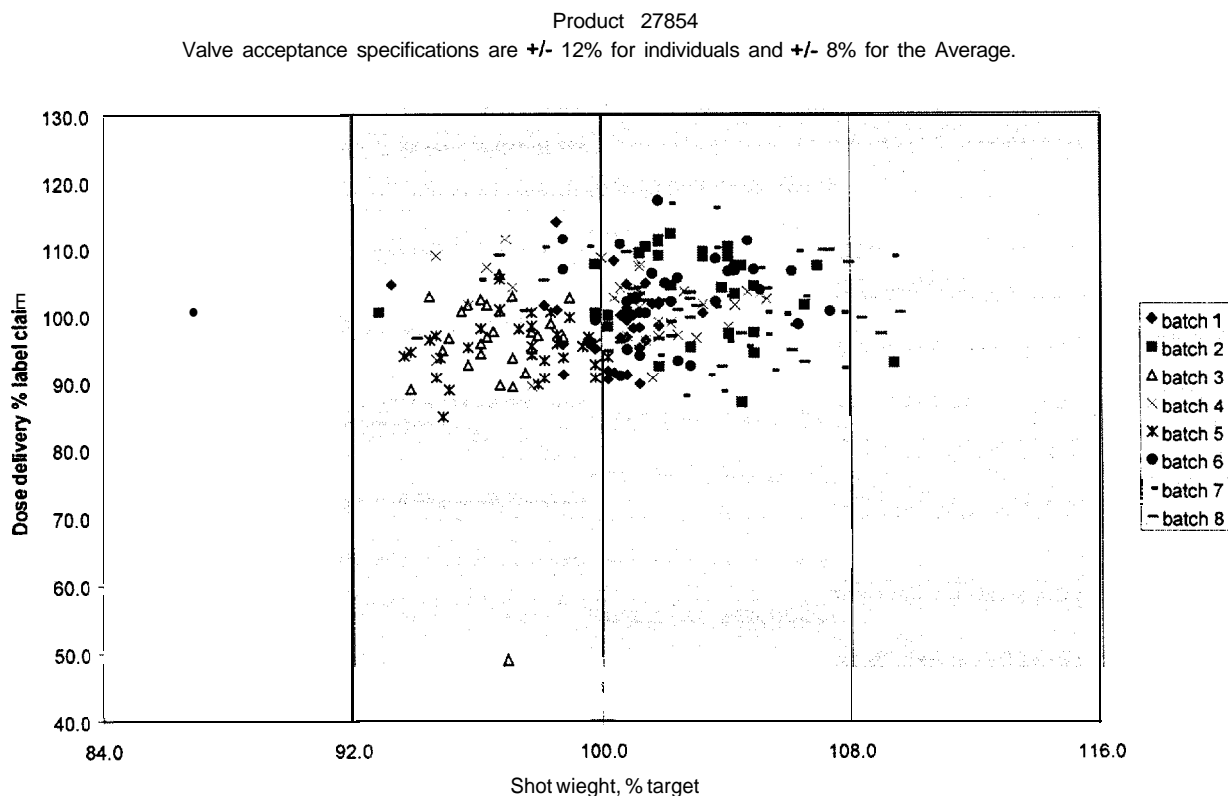Valve acceptance specifications are **+/-** 12% for individuals and **+/-** 8% for the Average.

Figure V.6. Product 27854. Comparison of shot weight obtained during dose delivery testing and incoming valve specifications (shown as vertical lines on both sides of the mean).

The R^2 for the various batches are shown in the Table V.4 below:

Table V.4

Batch/Orientation	R^2
Batch 1	0.023973
Batch 2	0.015286
Batch 3	0.000005
Batch 4	0.017681
Batch 5	0.041415
Batch 6	0.007861
Batch 7	0.024209
Batch 8	0.020321

The data series for product 92443 contained 5 data points outside of the valve acceptance specifications. These are shown in Figure V.7. All of these data were associated with acceptable dose deliveries.

Product 92443
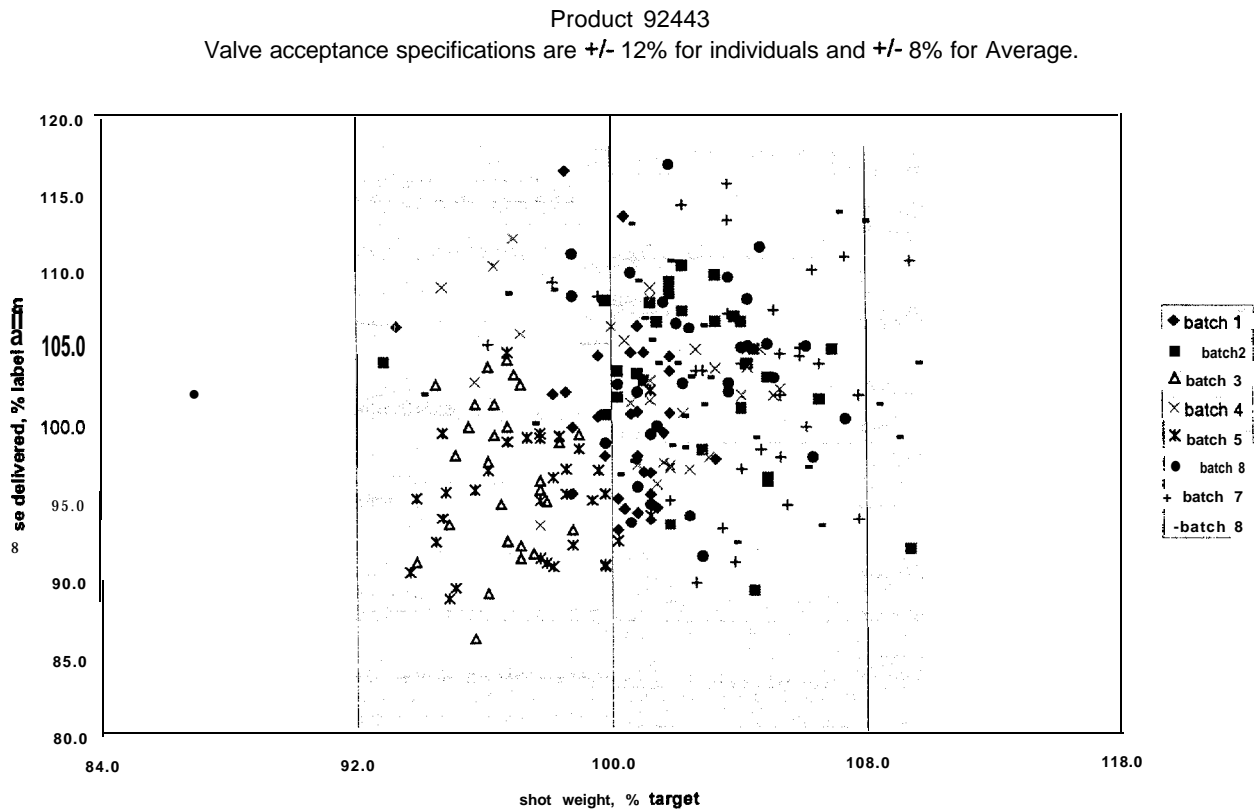Valve acceptance specifications are **+/-** 12% for individuals and **+/-** 8% for Average.

Figure V.7. Product 92443. Comparison of shot weight obtained during dose delivery testing and incoming valve specifications (shown as vertical lines on both sides of the mean).

The R^2 for the various batches are shown in the Table V.5 below:

Table V.5

Batch/Orientation	R^2
Batch 1	0.039219
Batch 2	0.093900
Batch 3	0.000020
Batch 4	0.057027
Batch 5	0.018393
Batch 6	0.000002
Batch 7	0.004335
Batch 8	0.009314

The data for product 68040 contained 13 data points outside of the valve acceptance specifications. These are shown in Figure V.8. Most of these data were associated with acceptable dose deliveries. There were two instances of data for high shot weight associated with low dose delivery. There were three very high shot weight values. The supplier of this data indicated that the high shot weights were thought to be associated with a weighing error but that this could not be confirmed. The sponsor further indicated that they regarded the dose delivery as the primary specification and indicator of product performance, while shot weight was obtained for information only.

Product 68040
Valve acceptance specifications are **+/-** 10% for individuals.
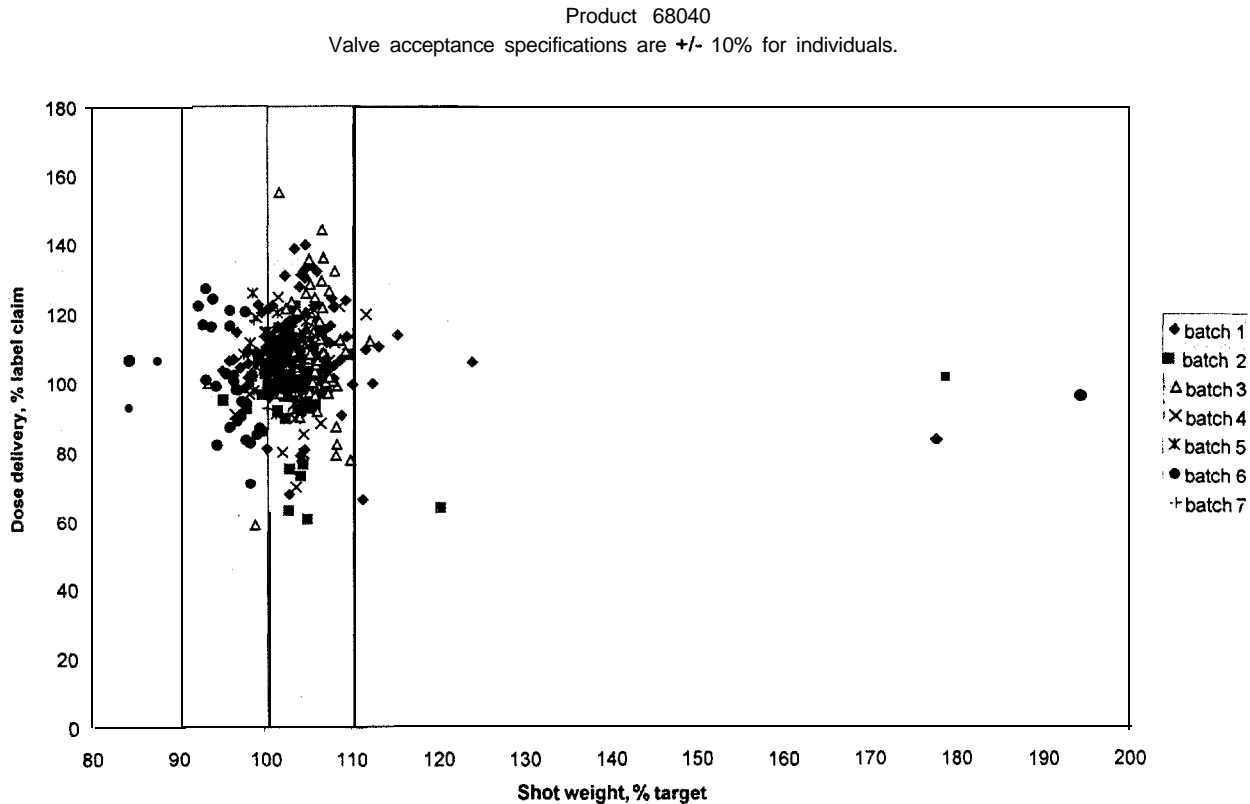
Figure **V.8.** Product 68040. Comparison of shot weight obtained during dose delivery testing and incoming valve specifications (shown as vertical lines on both sides of the mean).

The R^2 for the various batches are shown in the Table V.6 below:

Table V.6

Batch/Orientation	R^2
Batch 1	0.010639
Batch 2	0.003208
Batch 3	0.000224
Batch 4	0.185147
Batch 5	0.014682
Batch 6	0.022028
Batch 7	0.008223

Discussion

The majority of data submitted for all products showed that shot weight data obtained for product was within the range set for incoming valve acceptance. Less than 1% of the data were outside these acceptance criteria. In cases where the shot weights were outside the acceptance criteria the performance of the product with respect to dose delivery was generally in the acceptable range.

VI.   Conclusions

The Team agrees with the Agency that shot weight is a test that evaluates valve-to-valve reproducibility and that both the valve manufacturer and applicant should confirm appropriate valve performance.

However, the Team has investigated the benefit of shot weight analysis by collecting MDI shot weight data from several companies and analyzing it with respect to dose delivery, stability conditions, and valve release specifications. The collected data shows the following:

- Shot weight shows virtually no variance on stability and under a variety of storage conditions;

- There is no clear, consistent correlation between shot weight and dose delivery; and

- Shot weight values are at least as tight as the valve release specifications.

The assessment of the database supports the hypothesis that shot weight may only be a poor indicator of product performance and offers little assurance of product quality. Valve performance is adequately controlled by incoming valve specifications as shot weight testing on product does not appear in general to be more variable than the incoming valve release specifications. Furthermore, shot weight is not correlated with dose data nor is it a discriminating test on stability. These conclusions strongly suggest that shot weight may be used as a component/device acceptance test and a diagnostic tool, but is an insensitive measure of product performance. Thus the database supports our hypothesis that:

> *Shot weight testing is a device or component acceptance test used to control the quality of incoming materials. Although shot weight testing may be a good diagnostic tool, it is not appropriate to set specifications for this test since it is redundant to incoming valve release tests and is less sensitive to product performance changes than dose delivery testing.*

We therefore propose that the Guidance indicate that shot weight is a valve acceptance test and that it is not a test requiring a specification for final product as it is neither stability indicating nor is it sensitive to product storage conditions, such as storage configuration (inverted or upright), temperature (stress and accelerated), and time. Other performance tests are more appropriate measures of proper product performance.

The Team suggests the following for the draft Guidance regarding shot weight testing for MDIs.

- Lines 707-708 and 710-711 should **not** refer to "drug product:"

  This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility ~~of the drug product~~.

  Valve delivery should be verified by the applicant ~~for each drug product~~

- Lines 711-714, which describe shot weight (valve delivery) specifications for the drug product, should be removed.

- The Team therefore recommends the following overall changes for the MDI shot weight section, lines 707-714 (new language in **bold.** **Language** recommended for deletion is struck through):

  This test is directly related to the metering ability of the valve, and it evaluates valve-to-valve reproducibility ~~of the drug product~~. The proper performance of a metering valve should be ensured primarily by the valve manufacturer, who should assemble the valve with parts of precise dimensions. Valve delivery should be verified by the applicant **for incoming components** ~~each drug product~~.

  ~~In general, metered dose valves should have a valve delivery acceptance criteria of NMT |±15| percent for individual actuations and NMT |±10| percent for the mean of the actuations relative to the target.~~

  Valve delivery may also be used as a diagnostic tool for evaluating drug product.

VI. IMPURITIES AND DEGRADANTS[23]

A.   **Introduction**

The draft MDI/DPI Guidance requires that the levels of degradation products and impurities be determined in the final product.   Specifically, the draft Guidance states that for the drug product:

514   The levels of degradation products and impurities should be determined by means
515   of stability indicating methods. Acceptance criteria should be set for individual and
516   total degradation products and impurities. For identification and qualification
517   thresholds, refer to the appropriate guidance. Individual impurities or degradation
518   products appearing at levels 0.10 percent or greater should be specified. Specified
519   impurities and degradation products are those, either identified or unidentified, that
520   are individually listed and limited in the drug product specification.

The draft Guidance thus recommends this testing for the final MDI product in addition to testing of degradation products and impurities in the active pharmaceutical ingredient (API).

B.   **Position**

Impurities and degradation product testing is conducted on the API, as consistent with the Agency's guidelines and the International Conference on Harmonization's (ICH) guidelines Q3A, *Impurities in New Drug Substances* and Q3B, *Impurities in New Drug Products.24* As stated in ICH guideline Q3B, section I.C., impurities present in the new drug substance need not be monitored in drug products unless they are also degradation products. Furthermore, in section II.C. of guideline Q3B, a provision is given for excluding impurities which are not degradation products (e.g., they are process impurities from the drug substance), provided a scientific rationale is presented. The Team agrees with this approach for process impurities and believes that this approach should be followed in the FDA's draft Guidance for metered dose inhalers as well. Further quantitation of process impurities that are not degradants, and which are only present in the finished dosage form as they are introduced from the API, does not further enhance product quality.

C.   **Discussion**

In certain instances, impurities which are degradation products arising from the synthetic process used for the API may also be formed (or may occur at increased levels) in the finished

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[23] Impurities as stated in this paper are related to process impurities only. The ITFG/IPAC-RS CMC Leachables and Extractables Technical Team is addressing approaches to leachables testing.
[24]http://www.ifpma.org/ich5q.html

dosage form. Under such conditions these impurities should always be controlled in the finished dosage form at both release and on stability. These products should also be appropriately qualified, based upon thorough toxicological assessments.

However, there are other instances where process impurities are not degradants originating from the synthetic process, and are only present in the finished dosage form as they were introduced from the API. In this situation, where it can be demonstrated from the development database that no further increases of these process impurities take place as a result of either the manufacturing process or on stability, it is not considered necessary to further control them in the drug product. These impurities will be elucidated in the release testing of the drug substance. Thus, further testing in the final MDI drug product is redundant.

These approaches are fully consistent with the ICH guideline Q3B *Impurities in New Drug Products.* The team is in agreement with the Q3B approaches to process impurities and believes they should be followed for metered dose inhalers as well.

D.   Conclusion

Impurities and degradation product testing is conducted on the API, as per both the Agency's and the ICH guidelines. The quality of the drug product is not enhanced by further quantitation of process impurities that are not degradants, and which are only present in the finished dosage form as they are introduced from the API.

The Team thus proposes the following new, clarifying language for the impurities and degradants section of the draft MDI/DPI Guidance, lines 514-520 (new language in bold):

The levels of degradation products and impurities should be determined by means of stability indicating methods.   Acceptance criteria should be set for individual and total degradation products and impurities. For identification and qualification thresholds, refer to the appropriate guidance.   Individual impurities or degradation products appearing at levels 0.10 percent or greater should be specified.   Specified impurities and degradation products are those, either identified or unidentified, that are individually listed and limited in the drug product specification.

However, following the ICH Q3B guideline, it is not necessary to control impurities that are not degradants, and which are only present in the finished dosage form as introduced from the active ingredient, provided that the development database shows no further increase in these impurities during the manufacturing process or on stability.

VIII. PRESSURE

A. Introduction

The draft MDI/DPI Guidance recommends that pressure testing be conducted for metered dose inhalers where either (a) more than one propellant is used or (b) a single propellant with a co-solvent is used. Specifically it states:

699   This test is recommended for MDI products that are formulated using a co-solvent
700   and/or more than one propellant. The test verifies the internal pressure of the
701   container and. ensures the use of proper propellants or propellant mixture ratio. A
702   reasonable and achievable acceptance criteria may be 5 percent variation around
703   the target pressure at specified conditions. An appropriate sampling plan should
704   be used that selects a representative number of canisters from the batch (e.g.,
705   beginning, middle, and end of a fill run.

As stated above, the aim of this test is to ensure that the proper propellant mixture ratio is used during product manufacture. In the case where more than one propellant is used (as is the case historically with CFC metered dose inhalers), this testing is rational. However, in the case of MDIs using a single propellant and co-solvent, data from the literature show that pressure testing during development is not a reliable means of measuring propellant mixture ratio. In this case, the Team's position is that the integrity of the propellant-co-solvent mixture is better controlled by co-solvent content analysis and determination of the net fill. Pressure testing of the final product in this case is redundant.

B. Discussion

Literature and industry practice supports that internal pressure testing of pMDIs is possible, although the results depend on the method used (e.g., can piercing *vs.* through valve). Even when test variations are overcome, it is still a difficult task to test small volume aerosols (approximately 10 ml).[27] In the case where ideal behavior is observed, as is the case with blends of propellants, literature values (theoretically predicted from Raoult's law) closely match those of experimentally obtained values, even taking into consideration the small volume. [28,29]

However, this is not the case when a single propellant and a co-solvent such as ethanol are used. The addition of alcohol lowers the vapor pressure of the propellant. The pressure is negligibly affected by the addition of drug substance.[30] The lowering of the vapor pressure is

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[27] Gorman, W and Carroll, F; *Pharm. Tech.,* August 1993, pp. 24-58
[28] Tzou, T; *Proceedings from Respiratory Drug Delive* y; **6**, 1998, pp. 439443
[29] Williams, R and Liu, J; *Int. J. Pharm.;* **166**, 1998, pp. 99-103
[30] *Ibid. (24 & 25)*

relatively small and positively deviates from ideal behavior. Consequently, a predicted value is not reliably known *a priori.*

The draft Guidance suggests that pressure testing results should lie within 5% of target pressure. However, it is questionable that pressure testing is sensitive enough to detect differences in ethanol content. For example, **in the literature, a** 2.37% ethanol/HFA 134a blend MDI had a vapor pressure of approximately 60 psia (4.1 bar) **as** compared to a 3.95% ethanol/HFA 134a blend MDI which had an experimental vapor pressure of approximately 59 psia (4.0 bar). Thus despite nearly doubling the alcohol content, which would readily be detected by alcohol analysis of the MDI, the difference in the pressure testing results are negligible. In the case of an HFA-227 MDI, the pressure of the 2.37 % ethanol and 3.95% ethanol/HFA-227 blend formulations are approximately 92 psia (6.3 bar) and 89 psia (6.1 bar), respectively. These comparisons, as well as vapor pressure values at higher ethanol contents are shown in Table VIII.1.[31]

Table 1. *Change in vapor pressure with ethanol content*

Ethanol (% w/w)	HFA 134a/Ethanol Blend Vapor Pressure, psia (bar)*	HFA 227/Ethanol Blend Vapor Pressure, psia (bar)*
0	65 (4.5)	99 (6.8)
2.37	60 (4.1)	92 (6.3)
3.95	59 (4.0)	89 (6.1)
7.9	56 (3.8)	85 (5.8)
11.85	53 (3.6)	82 (5.6)

*Approximate values

Thus, it appears that the Agency-recommended testing for dehydrated alcohol content (which is also required under the Federal Food, Drug and Cosmetic Act, Section 502. (e)) is a more reliable test method than pressure testing for control of propellant/co-solvent ratio.

C.   Conclusions

Pressure testing during development of single propellant plus co-solvent MDIs is not a reliable product quality test. Rather, the integrity of the propellant-alcohol mixture is better controlled during development by alcohol content analysis, and determination of net fill. Pressure testing of the final product in this case is redundant.

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[31] *Ibid. (25)*

The Team therefore proposes the following alternate language for the draft MDI/DPI Guidance, lines 699-705 (new language in **bold.** Language recommended for deletion is struck through) :

This test is recommended for MDI products that are formulated using ~~a co-solvent and/or~~ more than one propellant. The test verifies the internal pressure of the container and ensures the use of proper propellants or propellant mixture ratio. A reasonable and achievable' acceptance criteria may be 5 percent variation around the target pressure at specified conditions. An appropriate sampling plan should be used that selects a representative number of canisters from the batch (e.g., beginning, middle, and end of a fill run). **However, for co-solvent/propellant blends, the correct blend may be assessed by alcohol content analysis and determination of net fill.**

IX. PARTICLE SIZE DETERMINATION

INTRODUCTION

The Tests and Methods Technical Team of the ITFG/IPAC Collaboration has examined the requirements for the use of inertial impactors and the control of relative humidity and temperature for particle size determination. These are mandated in the Agency's draft MDI/DPI Guidance.

The draft Guidance appears to specify a multistage cascade impactor as the only acceptable method for MDI particle size distribution testing:

> *580 Particle Size Distribution*
> 592 A multistage cascade impactor fractionates and collects particles of one or more
> 593 drug components by aerodynamic diameter through serial multistage impactions.
> 594 Such a device with all associated accessories should allow determination of a size
> 595 distribution throughout the whole dose including, in particular, the small particle
> 596 size fraction of the dose.. .
>
> 605 Additionally, criteria should be provided in the application for the
> 606 qualification of each cascade impactor. It is recommended that all cascade
> 607 impactors used in support of the drug product in the application be of the same
> 608 design.

Furthermore, the draft Guidance requires that relative humidity and temperature should be specified and controlled:

> 609 Other critical variables that should be specified and controlled in such a test
> 610 procedure are relative humidity and temperature.

The Tests and Methods Technical Team has discussed these issues in depth, and has developed the following position statements:

(i) The draft MDI/DPI Guidance should allow suitable and validated alternate approaches to the determination of particle size distribution (e.g., time-of-flight mass spectrometry, light scattering), which assure control of the product and manufacturing process.

(ii) Relative humidity and temperature should be controlled during the testing of MDI products only if needed. The requirement to control these parameters should be evaluated in the validation of the method and based on the development data for the product.

In order to investigate the validity of these positions, Team members evaluated scientific articles related to these position statements. The conclusions in this paper are based upon currently available information.

The Team has prepared this paper on particle size distribution test requirements in the draft Guidance in order to:

- highlight areas where there are not enough data at present to draw conclusions; and

- review available technical documentation related to particle size determination issues addressed by the Team, and offer the Team's conclusions based on that documentation.

I. ALTERNATE APPROACHES TO PARTICLE SIZE DETERMINATION

A. Draft Guidance cascade impaction recommendation for particle size distribution tests

The draft MDI/DPI Guidance, Section III.F.1.k for Particle Size Distribution, specifies a <u>multistage cascade impactor</u> as the only option for particle size distribution (line 592).

The Team has surveyed the current literature to investigate the possibility that while inertial impaction may be a suitable means of particle sizing for MDIs, alternate validated particle sizing methods may be equally suitable for accurate determination of particle size distribution.

B. Test and Methods Team's analysis

B.1 Inertial impaction, while having certain advantages, is not always reliable due to its complexity.

Inertial impaction methods require carefully controlled techniques and method validation. In one study[32] various collection surfaces were used to collect aerosol from an MDI in an Andersen cascade impactor (ACI) and the resulting mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were compared. MMADs ranged from 5.7 μm to 4.8 μm for the untreated stainless steel plates and silicon-coated plates respectively, and the GSD changed from 1.7 to 2.4. Aluminum foil and filter paper surfaces yielded intermediate results. These data indicate particle bounce and re-entrainment. Comparison was also made to a Delron impactor (Delron research products DCI-6) with glass collection plates. The results were in good agreement with the Andersen with the stainless steel plates, but were quite different from the results obtained with the coated plates.

LeBelle, ef. *al.*[33] compared the particle size distribution determined using the ACI and the Marple Miller Impactor, (MMI, MSP corporation Model 160[34]). The two impactors were compared

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[32] Hickey, AJ; Factors influencing aerosol deposition in inertial impactors and their effect on particle size characterization; *Pharm. Tech.;* 14 (9), 1990, pp. 1X3-130.
[33] LeBelle, MJ; Metered dose inhalers. II. Particle size measurement variation; *International Journal of Pharmaceutics;* 151, N2, May 1997, p. 209

when used to size aerosols from four salbutamol MDI products currently on the Canadian market. The MMADs determined using the ACI were in all cases larger, the average difference being 18%. The GSDs were comparable. However, both methods appeared to be able to distinguish particle size differences between the four products.   Thus, in comparing alternate methods to inertial impaction, as with comparison among different inertial impaction techniques, precision and power to distinguish changes in aerosol size distribution should be the criteria for accepting the method, not absolute accuracy.

Stein and Olson35 compared the performance of several separate ACIs, both theoretically (based on jet diameters) and experimentally. Five ACIs sampled identical aerosols consisting of oleic acid and beclomethasone dipropionate dissolved in methanol. The size distribution of the aerosol was varied in order to compare the deposition characteristics of all of the stages of the ACIs that were tested. After evaporation of the methanol, the aerosols consisted of 95% oleic acid and 5% beclomethasone. Large differences were measured in the amount collected per stage. For example, for an aerosol with MMAD of 1.70 μm and GSD of 1.94, as measured with a recently calibrated Micro-Orifice Uniform Deposit Impactor (MOUDI, MSP corporation), the values collected on stage 5 of the ACI ranged from 31.6% of the collected aerosol to 42.2%. These values were in good agreement with the theoretical predictions based on measured jet diameters. The predicted range of collected mass was 31.6% to 42.2%.

Particle size distributions from six different MDIs were determined for comparison by the ACI and the Quartz Crystal Microbalance (QCM, California Measurements Inc., Model PC2) inertial impactor.36 The QCM senses the mass on each stage in real time, but is not drug specific. Because of the lack of specificity, the QCM tended to underestimate the particle size relative to the ACI by an amount that tended to vary with the amount of non-volatile excipient, such as surfactant.   However, better agreement, and in some cases, near identity, was achieved by correcting the results by subtracting the amount per stage, measured in placebo shots that contained propellant and excipients but no active.   This is a technique that may be applicable to alternate sizing methods, such as time of flight or light scattering techniques that are also non-specific.

> **B.2**   Alternate particle sizing **methods exist that may present the opportunity for precise control of some MDI and DPI drug products**

Many methods are presently used to size aerosol particles. Examples include light scattering, phase doppler, time of flight, differential mobility, time of flight/mass spectrometry, **scanning electron** microscopy, and others.   These methods in general respond to different measures of particle size, such as physical diameter, mobility equivalent diameter, optical diameter, or aerodynamic diameter.   Although in general, aerodynamic diameter is theoretically the most predictive of lung deposition, because airway impaction during inhalation and

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[34] Marple, VA; Olson, BA; and Miller, NC; A low-loss cascade impactor with stage collection cups: calibration and pharmaceutical inhaler applications; *Aerosol Sci. Technol*; **22**, 1995, pp. 124-134.

[35] Stein SW; Olson, BA; Variability in size distribution measurements obtained using multiple Andersen Mark II cascade impactors; *Pharmaceutical Research;* 14, N12 (DEC), 1997, p. 1718-1725.

[36] Tzou, Tsi-Zong; Aerodynamic particle size of metered-dose inhalers determined by the quartz crystal microbalance and the Andersen cascade impactor; *International Journal* of *Pharmaceutics* (Amsterdam); 186 (1), Sept. 10, 1999, p. 71-79.

sedimentation during breath-hold are both determined by aerodynamic diameter, knowledge of the composition and morphology of the particles allow calculation of this size from the optical or physical diameter. Several studies have been conducted comparing particle size distributions measured by various techniques.

One study[37] compared the particle size determined by an inertial impaction method (using the USSR Institute of Biophysics Impactor, a design similar to the Berner Impactor) to an aerodynamic particle sizer, the APS 3310[38]. Liquid oil droplets in the size range pertinent to inhalation aerosols (0.4-5.6 μm) were generated for comparison between the two methods. Additionally, these two methods were compared to a differential mobility analyzer, (DMA 10/1000), although this method is applicable in a size range (less than 0.7 μm) that is smaller than generally delivered by inhalation aerosol systems. Although a slight correction (0.8 to 0.9) needed to be applied to previously published calibrations,39 in general the correlation between the methods was quite good.

Another study40 (Srichana, et. *al.,* 2000) analyzed powdered albuterol sulfate particles and lactose carrier particles collected in an ACI by scanning electron microscopy (SEM, Philips EM501b) and by time of flight (TOF, Amherst Process Instruments Aerosizer Mach 2, cf Niven, 1993). The ACI was equipped with a pre-separator, and aerosol **was introduced at flow rates of** 28.3 and 60 liters per minute. The aerosizer was used with an aerodisperser. This study was designed to investigate drug carrier interactions, and thus no attempt was made to quantify the size distributions by SEM or TOF. However, significant differences were demonstrated between the time of flight spectra for particles collected on different stages of the ACI, and for particles collected on the same stage at different flow rates. Qualitative differences in particle size on different stages were observed by SEM, and x-ray microanalysis demonstrated specificity by distinguishing between the carrier and drug particles.

Peters, et. *al.*[41] combined data from a differential mobility particle sizer (TSI Inc. DMPS model 3932C) and an aerodynamic particle sizer (TSI Inc. model APS3310). They also combined data from an electrical aerosol analyzer (EAA, TSI Inc. model 3030) and the APS. These hybrid data were then compared to data from an inertial impaction method using a low pressure impactor (LPI).[42] Aerosols were specifically chosen to have size ranges in the "data gap" between the APS

[37] Frank, G; Kashparov, V; Protsak, V; Tschiersch, J; Comparison measurements of a Russian standard aerosol impactor **with several** western standard aerosol instruments; *J. Aerosol Sci.; 27* (3), *1996,* p 477-486.

[38] Remiarz, RJ, Agarwal, JK, Quant, FR, and Sem GJ; Real time aerodynamic particle size analyzer; in *Aerosols in the Mining and Industrial Work Environments;* edited by VA Marple and BYH Liu; 3, Chapter 62, 1983, p. 879-895.

[39] Shuravel, NF; Development, production and supply of the cascade impactors for the determination of the dispersion of radioactive aerosols; published by Ukrainian Academy of Science, North-Eastern Scientific Center, Khurkov (in Russian); 1993.

[40] Srichana, T.; Brain, A.; Marriott, C; Martin, GP; A study of drug-carrier interactions in dry powder inhaler formulations using the Andersen cascade impactor, x-ray microanalysis and time of flight aerosol beam spectrometry (TOFABS); *Chem. Dharm. Bull.; 48*(2), Feb. 2000, p. 167-174.

[41] Peters, TM; Chein, HungMin; Lundgren, DA; Keady, PB; Comparison and combination of aerosol size distributions measured with a low pressure impactor, differential mobility particle sizer, electrical aerosol analyzer, and aerodynamic particle sizer; *Aerosol Science and Technology; 19,* 1993, p. 396.

[42] Vanderpool, RW; Lundgren, DA; Kerch, PE; Design and Calibration of an in-stack low pressure impactor; *Aerosol Science and Technology; 12,* 1990, pp. 215-224.

and the EAA, and were generated by using Collison nebulizers with 5% and 20% sodium chloride solutions. In spite of this choice of size range, excellent agreement among the three methods was obtained. For example, for the 5% solution, the data were very well fit by a log normal distribution. The MMAD and GSD were determined to be 0.69 μm and 1.81 by the LPI, 0.72 μm and 1.67 using the DPMS/APS system, and 0.75 μm and 1.74 using the EAA/APS system. Another comparison using the 20% solution and a virtual impactor, the LPI measured an MMAD of 2.14 μm and a GSD 1.78, while the APS measured values of 2.11 and 1.82 for these parameters.

Jager, et. al.43 present a'comparison of various MDI formulations as sized using a right angle light scattering method (Polytec Optronics Inc. HC-15/2 optical particle counter). Three MDI suspension formulations were compared: a once micronized formulation (Lot 1); a twice micronized formulation (Lot 2) that was otherwise identical to Lot 1; and in a second test, a different formulation (Lot 3) was compared before and after exposure to conditions of elevated temperature and humidity (36 months at 40" C and 75% RH). The system was capable of distinguishing particle size differences between Lot 1 and Lot 2, and also between stressed and unstressed samples from Lot 3, with very high statistical significance.

In another study data have been compared to particle size distributions determined using the ACI. In this study,44 a new aerodynamic particle sizer (TSI Inc. model 3320) was used. This APS incorporates new features that can eliminate errors due to coincidence counts and particle recirculation. Aerosols were generated using solution and suspension MDIs with an HFA propellant. Aerosols were introduced into the instrument through a USP induction port. Excellent agreement between the ACI and the APS were obtained using solution MDIs over the studied range of MMADs (0.8-1.9 μm). Good agreement was also obtained using a suspension MDI with small amounts of surfactant. Small but significant differences (20%) in MMAD were measured with a beclomethasone dipropionate suspension MDI, due to a second mode of smaller surfactant droplets. The authors suggest that this discrepancy could be corrected using bimodal distribution fitting software.

Kwong, et. *al.*45 compared size distributions of aqueous droplets measured with an Andersen cascade impactor and a Malvern laser diffraction analyzer, the Malvern Mastersizer X (MMX, Malvern Instruments Inc., Worcestershire, UK). The aerosols where generated with a Pari LC Star Nebulizer (PAR1 Respiratory Equipment Inc., Mississauga, ON) with salbutamol solution (12.5 mg of 5 mg/ml salbutamol +2.5 mL normal saline). Some differences in particle size distribution were seen when the ACI was maintained at 21" C. The authors attributed this to evaporation in the ACI, a non-physiological effect, as aerosol particles would not be expected to evaporate in the high relative humidity environment of the lung. However, when evaporation was controlled by maintaining the ACI at 10" C, excellent agreement between the ACI and MMX was seen.

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43 Jager, PD; DeStefano, GA; McNamara, DP; Particle size Measurement using right-angle light scattering; *Pharmaceutical Technology* (USA); 17, (Apr), 1993, pp. 102-120.

44 Stein, SW; Beck, TJ; Gabrio, BJ; Evaluation of a new aerodynamic particle sizer for MDI size distribution measurements; *Respiratory Drug Delivery VII;* **2**, 2000, p. 283.

45 Kwong, JWT; Ho, SL; Coates, AL; Comparison of nebulized particle size distribution with malvern laser diffraction analyzer versus Andersen cascade impactor and low-flow Marple personal cascade impactor; *J. Aerosol Medicine;* 13 (4), 2000, pp. 303-314.

Gard and others[46] at the University of California at Riverside, demonstrated a system that combines particle sizing with chemical detection. In their Aerosol Time of Flight Mass Spectrometer (ATOFMS) system, aerosol particles are introduced into a sonic jet, and light scattering is used to determine the time of flight. A calibration is used to determine aerodynamic particle size. The particles are then introduced into the desorption/ionization region, where a frequency tripled Nd:YAG laser is used to create ionized species that are characterized using mass spectrometry. The technique is similar to GCMS, with the column retention time replaced by the time of flight, thus yielding particle size data. The technique presently is limited to aerosol densities that are quite a bit lower than those presently used in the pharmaceutical aerosol industry due to computational limits. However, with future improvements in algorithms and processing speeds, this technique may be useful.

Dyksterhouse, ef. *al.*[47] demonstrated that laser diffraction can be used for reliable particle sizing of aerosols generated using the AERx™ Pulmonary Drug Delivery System. In this study laser diffraction particle sizing (Sympatec HELOS BF instrument) was compared to cascade impaction (Andersen Mark II) for aerosols generated from the AERx™ Pulmonary Drug Delivery System for solutions containing small molecules and for solutions containing protein peptide formulation. The laser diffraction results correlate well with cascade impaction results. The deposition on the various impactor stages can also be predicted with accuracy by appropriate binning of particle size distributions for both small molecules and protein peptide formulations.

Ding, et. *al.*[48] developed a method to measure the particle size distribution (PSD) of aerosols generated from commercially available metered dose inhalers using a Malvem diffraction particle sizer. A 100 mm receiving lens that covers a particle diameter range of 0.5-180 μm was used for these determinations. The effect of the USP induction port and spacers on the PSD of drug aerosols was determined. The effect of distance between the exit of mouthpiece and laser beam was investigated. Finally, the effect of flow rate on the PSD of breath activated MDIs was also determined. The mass median diameter (MMD) of aerosols exited from the metered dose inhalers was reduced from 6.0-8.0 μm at the mouthpiece to 1.0-3.0 μm at the exit of the USP induction port. For MDIs with an integral spacer, about 10% reduction in MMD was observed at the USP induction port. There were no differences in MMD for the breath activated metered dose inhaler at three different inhalation flow rates. A sharp reduction in MMD was observed at a distance smaller than 150 mm between the device exit and the laser beam, and gradually reached steady state about 200 mm from the exit of the device. The study also demonstrates that a particle sizing method using a Malvern particle diffraction sizer can be developed and optimized for the evaluation of inhalation aerosols.

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[46] Gard, E; Mayer, JE; Morrical, BD; Dienes, T; Fergenson, DP; Prather, KA; Real-time analysis of individual atmospheric aerosol particles: design and performance of a portable ATOFMS; *Anal. Chem.;* 69, 1997, pp. 40834091.

[47] Dyksterhouse, M; Wilbanks, T; Roach, M; Comparison of Cascade Impaction and Laser Diffraction Particle Sizing for Characterization of Protein Aerosols Delivered from AERx Pulmonary Drug Delivery System, *American Association of Pharmaceutical Scientists Annual Meeting,* 2000, Abstract # 3166.

[48] Ding, JY; McVeety, BD; Placke, ME; Zimlich, WC; Measurement of Particle Size distribution from Metered Dose Inhalers by Malvern Diffraction Particle Sizer; American *Association of Pharmaceutical Scientists Annual Meeting,* 2000, Abstract # 1213.

Recently, Hu ef. al.[49] compared the Aerosizer ® and Andersen cascade impactor as devices used to determine the influence of the formulation type, metering chamber volume, or spacer device on the aerodynamic particle size distribution for pressurized metered dose inhalers (pMDIs). The model drugs investigated were betamethasone valerate (BMV) solution and triamcinolone acetonide (TAA) suspension. MMAD and GSD were determined using the Aerosizer ® and Andersen cascade impactor. Similar results were obtained using the Aerosizer® and the Andersen cascade impactor methods for the aerodynamic particle size distribution of BMV solution or TAA suspension pMDIs. Furthermore, the formulation type, metering chamber volume, or spacer device influenced the aerodynamic particle size distribution of the pMDIs investigated.

C.   Conclusion

The available literature appears to support the Teams initial hypothesis that while inertial impaction may be a suitable means of particle sizing for MDIs, other validated particle sizing methods may be equally suitable for accurate determination of particle size distribution.

The particle sizing test method, developed and validated for a particular product is used to measure and monitor particle size changes within a batch and to ensure batch to batch consistency. The cascade impactor technique is intended to measure aerodynamic particle size distributions of most inhalation aerosols. However, the requirement for a multi-stage cascade impactor for determination of particle sizes should not be mandated by the FDA guidance document, since for some products, properly validated alternate techniques may be equally suitable.

The Team concludes that the draft Guidance should be revised to provide general requirements for the particle size distribution measurements that are consistent with the scope of the test and technique, and meaningful for routine applications and product control.

The Team therefore suggests the following alternate language to the draft Guidance regarding MDI particle sizing methods, lines 592-596 (new language in bold):

> A multistage cascade impactor fractionates and collects particles of one or more drug components by aerodynamic diameter through serial multistage impactions. Such a device with all associated accessories should allow determination of a size distribution throughout the whole dose including, in particular, the small particle size fraction of the dose. Alternate **particle sizing methods may be developed and optimized for the evaluation of the particle size distributions of inhalation formulations. The particle sizing method should be validated for routine use for the inhalation formulation.**

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[49] Hu, J; Rogers, TL; Williams III, RO; Comparison of Aerodynamic Particle Size Distribution of pMDIs Obtained Using the Aerosizer and Andersen Cascade Impactor, *American Association of Pharmaceutical Scientists Annual Meeting,* 2000, Abstract # 3012.

II. THE EFFECT OF RELATIVE HUMIDITY AND TEMPERATURE ON PARTICLE SIZE DETERMINATION

A. Draft Guidance relative humidity and temperature requirement for particle size distribution test

The FDA draft MDI/DPI Guidance, Section III.F.1.k for Particle Size Distribution states that relative humidity and temperature should be specified and controlled (line 610).

The Team has surveyed the current literature to investigate the hypothesis that specification and control of relative humidity and temperature in particle sizing should be based on the individual product and data acquired during development, and should not be universally mandated.

B. The effect of relative humidity and temperature on aerosol size determination with MDIs

A review of the current literature shows that the effect of relative humidity and temperature varies among different products. Wilson, ef. *al.*[50] studied the effect of temperature on the performance of an MDI. They measured the aerosol particle size distribution for a CFC MDI containing metaproterenol. The aerosol was sized using an optical aerosol monitor (Climet Instruments Co. LO8 particle analyzer). They found that the MMAD of the aerosol changed from 3.65 to 2.50 μm when the canister temperature was changed from O-37" C. They attributed the larger size to the lower vapor pressure of the propellant, which caused less fragmentation of the particles exiting the valve orifice.

However, other MDI products have been shown to have no dependence on temperature. Williams and Barron[51] studied the performance of an MDI product containing beclomethasone dipropionate (BDP) in a mixture of CFC propellants (Freon-11 and Freon-12) and oleic acid at 4, 23, and 40 °C. Particle size was determined using an ACI. ANOVA was used to compare the results, and results were judged to be significant based on the 95% probability values ($p < 0.05$). No effect on the metered dose was seen over this temperature range. A slight downward trend was observed in the particle size with increasing temperature, but this trend lacked statistical significance ($p > 0.05$). Additionally, there was no significant effect of temperature on the geometric standard deviation.

June, et. *al.*[52] demonstrated that an HFA salbutamol product showed no change in the respirable mass until the lowest temperature studied, -20°C, was reached. Other products in that study (CFC salbutamol, CFC budesonide dipropionate, and HFA-BDP) did show an effect with

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[50] Wilson, AF; Mukai, DS; Ahdout, JJ; Effect of canister temperature on performance of metered dose inhalers; *American Review of Respiratory Disease;* 143 (5), May 1991, pp. 1034-1037.

[51] Williams, R.O; Barron, M.K.; Influence of temperature on the emitted dose of an oral metered dose inhaler; *Drug Development and Industrial Pharmacy; 24,* N11, *1998,* p 1043-48.

[52] June, D; Carlson, S; Ross, D; Reduced effect of temperature on drug delivery characteristics of CFC-free metered dose inhalers (MDIs) compared to current CFC metered dose inhalers; The *European Respiratory* Journal, *Abstracts;* ERS Annual Congress, Stockholm, Sweden, 9 (Supp. 23), 1996, p. 255s.

temperature, although the effect was less'pronounced for the HFA products.

In addition to temperature, the effect of relative humidity has also been studied. Schultz, et. al.[53] looked at the effect of temperature, relative humidity, and percent co-solvent on particle size from a solution and a suspension MDI. Relative humidity was shown to have no effect on particle size distribution for the solution MDI, although temperature did have a statistically significant effect. Temperature alone had no effect on the suspension MDI, although humidity, and humidity multiplied by temperature did have an effect. The authors conclude, "small fluctuations of temperature and humidity would not alter the results under routine laboratory conditions."

Lange and Finlay[54] studied the effect of relative humidity and temperature on MDIs when used in ventilator circuits. They developed a model ventilator in which temperature and relative humidity could be controlled. Aerosols were introduced into this system using a metered dose inhaler containing salbutamol sulfate at 100 µg/puff through either a commercially available spacer (Trudell Medical Aerochamber MV) or a larger prototype of length 29 cm and diameter 4.5 cm. Particle sizing was done with an ACI at 28.3 LPM. Aerosols were generated at 25, 30, and 37°C, and low (-10%) and high (100%) relative humidities. Over this range, no changes where observed in the particle size with either spacer device (p > 0.1).

C.   Conclusion

This review of the current literature suggests that relative humidity and temperature will affect particle size distribution *for* some *but not all* types of products. In some cases both parameters had no effect, and in other cases either one or the other produced an effect. Based on this evidence, the Team believes that the requirements for control of relative humidity and temperature in the product test method should be based on the individual product and data acquired during development, and should not be universally mandated.   The requirements for the test method should also be consistent with the standards of USP and EP pharmacopeias.

The Team suggests the following alternate language regarding temperature and relative humidity requirements for MDI particle sizing in the draft MDI/DPI Guidance, lines 609-610 (new language in bold. Language recommended for deletion is struck through):

> ~~Other critical variables that should be specified and controlled in such a test procedure are relative humidity and temperature.~~ **The effect of temperature and relative humidity on particle size determination of the inhalation product should be evaluated and characterized during development. The need to specify and control these two parameters for the individual product should be determined based on the data acquired during development.**

[53] Schultz, DW; Schultz, RK; Dow, MM; The effect of temperature and humidity on the spray characteristics of solution and suspension MDI's; AAPS, Sixth Annual Meeting and Exposition, Washington, DC, Nov. 17-21, 1991; *Pharm. Res.* (NY); 8 (10 Suppl.), 1991, p. S120

[54] Lange, CF; Finlay, WH; Overcoming the adverse effect of humidity in aerosol delivery via pressurized metered-dose inhalers during mechanical ventilation; *Respiratory and Critical Care Medicine;* 161 (5), May, *2000,* pp. 16141618.

X. CONCLUSION

The Tests and Methods Technical Team respectfully encourages the Agency to consider the recommendations developed by the Team and to incorporate the same in the next version of the draft CMC Guidance for MDIs.

The Team would like to meet with the Agency in order to discuss and **agree** on the proposals contained in this document. The Team believes that this report will assist the Agency in ensuring high standards of product quality, while eliminating redundant testing. Further, the Team believes that its suggestions of alternate language for the draft Guidance will help clarify testing criteria and make such criteria specific to particular dosage forms. In this regard, the Team plans to undertake similar analyses of tests and methodology for non-MD1 dosage forms.

The ITFG/IPAC-RS Collaboration supports the Agency's efforts to develop scientifically sound guidances for OINDP that will serve the needs of the Agency, patients, and industry.

XI. GLOSSARY

ACI	Andersen Cascade Impactor
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
APS	Aerodynamic Particle Sizer
CMC	Chemistry, Manufacturing, and Controls
GSD	Geometric Standard Deviation
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MMAD	Mass Median Aerodynamic Diameter
SAS	Statistical Analysis System, SAS Institute