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RECOMMENDATIONS TO THE FOOD AND DRUG ADMINISTRATION: METERED DOSE INHALER TESTS AND METHODS IN THE CHEMISTRY, MANUFACTURING, AND CONTROLS DRAFT GUIDANCES FOR METERED DOSE INHALERS AND DRY POWDER INHALERS

INHALATION TECHNOLOGY FOCUS GROUP/INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM ON REGULATION AND SCIENCE TESTS AND METHODS TECHNICAL TEAM*

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In response to the Food and Drug Administration's (FDA's) Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation *(1), a technical team initiated a scientific evaluation of the tests and methods for MDIs required by that guidance. This technical team was comprised of members of the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). It was called the ITFG/IPAC-RS Tests and Methods Technical Team.*

The team believes that only those tests that have been demonstrated in development studies to provide meaningful information about quality should be included as product quality control tests. The team analyzed the tests required by the draft guidance from this perspective. This article summarizes the results of the team's investigation and provides a critical assessment of how individual tests can add value to the development and quality control of a new product. The goal of the team's initiative is to maximize the value of characterization and control testing, and to minimize testing that does not provide useful information.

Key Words: Metered dose inhaler; CMC; FDA; Guidance; Test

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INTRODUCTION

IN OCTOBER 1998, THE FDA issued the draft *Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation*. Industry commended the FDA for this effort, since for many years there was no regulatory guidance for inhalation drug products. However, many public comments were filed in response to this guidance document. Many of the comments raised similar and significant concerns with the agency's regulatory approach to inhalation drug products. Furthermore, a number of the comments from industry maintained that certain tests recommended by the draft guidance were not scientifically justified.

Subsequent to the issuance of the draft guidance, two groups with expertise in orally inhaled and nasal drug products, ITFG and IPAC-RS, established a collaborative effort to provide a science and consensus-based response to the draft guidance. The ITFG/IPAC-RS collaboration formed several technical teams, consisting of scientists from industry and academia, which addressed key topics of concern. Starting in February 2000, the ITFG/IPAC-RS Tests and Methods Technical Team conducted scientific and data-based investigations and developed recommendations regarding the tests and methods required for finished MDI products.

Throughout this process, the team outlined plans for its investigations and presented its findings at several public advisory committee meetings of the FDA. In May 2001, the team submitted a technical paper describing its findings and recommendations, entitled *Recommendations for Tests and Methods* (2), to the FDA.

STATEMENT OF THE PROBLEM

The draft guidance for MDIs and DPIs requires many individual tests for routine quality control of manufactured drug products. Specifically, the draft guidance requires a total of 20 different release tests for finished product MDIs. Even though these tests are intended to ensure product quality, it would be helpful if the guidance could offer more information on the circumstances in which the various tests would provide meaningful information about product quality.

Use of all the tests listed in the guidance for product release may not be the best approach. Modern quality control theories underscore the fact that quality cannot be "tested into the product" but rather, should be "built in." Thus, the use of an excessive number of tests at the release of a finished product may be wasteful and meaningless.

A broad range of testing is conducted during the design and development stages for a new product. Ideally, the development findings will be used to select the appropriate tests for final product control. Other tests may be identified as best suited for the control of incoming components or in-process controls. Some tests may only be useful for development information or for out-of-specification problem solving, but not for routine release testing.

The ITFG/IPAC-RS Tests and Methods Team investigated these issues considering industry data, literature data, and industry best practices. This paper reviews the team's findings.

THE ITFG/IPAC-RS TESTS AND METHODS TEAM'S APPROACH

During an 18-month period, the ITFG/IPAC-RS Tests and Methods Technical Team investigated whether proper assessment of development studies may eliminate the need to use certain tests as blanket requirements for quality control of the final product. The team reviewed all the tests and methods for MDIs and DPIs required by the draft guidance. Because the guidance covers many tests, the group focused its efforts only on MDIs, and then only on those MDI tests of most concern. These MDI tests are: water content, spray pattern and plume geometry, shot weight, impurities and degradants, dose content uniformity, pressure, and particle size distribution.

The team approached its investigation following two basic principles:

1. The investigation and conclusions had to be based on data and solid scientific principles, and
2. Conclusions had to be corroborated by a consensus view of industry experience.

Thus, the team agreed that its recommendations to the FDA would reflect the current state of knowledge, available data, and best industry practices. Following are the team's consensus position statements on the selected MDI tests:

- *Water Content*: Water or moisture content should only be controlled if it has been demonstrated during development studies to affect product performance,
- *Spray Pattern and Plume Geometry*: These tests may have value in drug product 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 potentially affecting product quality (ie, 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, etc.) influence the spray pattern and plume geometry in a convoluted way. These factors are more appropriately evaluated via straightforward and exacting component controls, rather than by observation of the final spray pattern and plume geometry,
- *Shot Weight*: The shot weight test is appropriate as an incoming valve release test. However, for drug product release, there is no value in repeating shot weight determination in addition to the more informative dose delivery test. Specifications should not be required for the shot weight test,
- *Impurities and Degradants*: Synthetic impurities that are not degradants should be controlled in the drug substance and not in the drug product, as is recommended by the International Conference on Harmonization (ICH) guidelines (3,4). Testing of drug product for synthetic impurities that are not degradants is redundant and, therefore, unnecessary. The ICH approach to process impurities should apply to inhalation drug products,
- *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, that is, during the degradation products assay. The method for dose content uniformity should be validated, unbiased, and specific to its intended use. (In addition, the Dose Content Uniformity Working Group of the ITFG/IPAC-RS collaboration developed statistical recommendations on appropriate test designs for dose content uniformity testing [5]),
- *Pressure Testing*: Pressure testing of MDIs should not be required for single propellant/cosolvent systems. Pressure testing of MDI can contents is a difficult technique and an indirect measure. The integrity of the propellant-cosolvent mixture is much better controlled by direct analysis, and
- *Particle Size Distribution*: A final MDI/DPI guidance should allow suitable and validated alternate approaches to the determination of particle size distribution (eg, time-of-flight mass spectrometry, light scattering), which assure control of the product quality and manufacturing process. Relative humidity and temperature should be controlled during the testing of MDI products only if needed, as judged from the development and validation data. (In addition, the Particle Size Distribution Working Group of the ITFG/IPAC-RS collaboration considered appropriate approaches to particle size distribution specifications [6]).

Where possible, the team collected data from the industry and supplemented that information by data from the literature. All industry data were collected and blinded by a neutral third party, and then organized into a database. Table 1 summarizes the industry data collected by the team.

For water content and shot weight, the

TABLE 1
Summary of Industry Data Collected

Extensive Industry Database	Moderate Industry Database	Literature Data
Water content (11 products)	Spray pattern (8 products)	Plume geometry
Shot weight (14 products)		Spray pattern
		Particle size distribution
		Alternate methods
		Relative humidity and temperature
		Pressure

team conducted analyses solely based on data collected from the industry. For spray pattern, the team considered both industry data and literature data. For plume geometry, pressure, and particle size distribution, the team reviewed literature data. The data were then analyzed, and the results and recommendations presented in the team's technical paper. The position statements for impurities/degradants and dose content uniformity testing did not require examination of data, so the team based its recommendations on examination of existing ICH guidelines and consideration of best industry practices, respectively.

THE TEAM'S FINDINGS

Based on analyses of industry and literature data, and consideration of industry best practices, the team reached the following key conclusions regarding the role of the tests or methods investigated:

1. Some product tests provide little or no value,
2. The usefulness of some tests and methods is product dependant, and
3. Some methods may benefit from consideration of alternative approaches.

Table 2 summarizes these results.

TABLE 2
Summary of the Team's Conclusions for Selected Tests Required by FDA Guidances

Some Tests Provide Little or No Value	Usefulness of Some Tests is Product Dependent	Consider Alternative Approaches to Methods
Spray pattern	**Water content:** Useful development study to test for moisture sensitivity	**Particle Size Distribution (Alternate methods)**
Plume geometry	**Relative Control of Temperature and Humidity during Particle Size Distribution Testing**	**Dose Content Uniformity:** Need not be stability indicating
Pressure (single propellant and cosolvent systems)		
Shot weight: Only to verify quality of incoming components and as a diagnostic tool		
Impurities: Should be controlled in drug substance		

We describe further, as case studies, those tests where significant databases were collected. Details regarding the data are available in the team's technical paper, *Recommendations for Tests and Methods* (2).

Water Content

The team investigated its hypothesis that the test for water content should be performed as a routine drug product control only if the product has been shown to be sensitive to moisture in development studies. Stability data for a variety of MDI products were collected and analyzed. Statistical analysis of the data demonstrated that for a number of products, there is no correlation between increase in water content and change in key performance parameters such as fine particle dose and delivered dose. The team concluded that the data support the above hypothesis and, therefore, the test for water content should be product-dependent.

Shot Weight

The team investigated whether shot weight testing is redundant to the device or component acceptance test used to control the quality of incoming materials. Shot weight, dose delivery, and valve release specification data for a number of MDI products were collected and analyzed. Statistical and comparative analysis of these data demonstrated that shot weight:

1. Shows virtually no variance in stability studies (under a variety of storage conditions),
2. Offers no certainty of adequately controlled dose delivery, and
3. Values are as tight as the valve release specifications.

Figure 1 provides results from statistical analysis of the data, demonstrating that shot weight shows almost no variance in stability studies, and, therefore, is not a sensitive predictor of product performance. The assessment of the database supports the original hypothesis that shot weight is a poor indicator of product performance, offers little assurance of product quality, and is best suited as a test for incoming device components.

DISCUSSION

The team's results demonstrate that indiscriminate use of all of the examined tests for product release may not be the best approach. As our preliminary investigations suggest, development findings should be used to select the most appropriate tests for final product control, control of incoming components and in-process controls. Other tests may only be useful for development information or for out-of-specification problem solving.

Figure 2, a Decision Tree for Orally Inhaled and Nasal Drug Product Tests and Methods, developed by this group, outlines a process by which the most effective stage for application of a given test or method may be determined. First, development studies are assessed. Then, based on this assessment, a determination should be made as to whether a given test should be limited to characterization studies, used for quality control of the final product, or used for component testing or in process controls. This flowchart may be used as a tool to determine the appropriate use of a specific test or method (eg, spray pattern and plume geometry, foreign particles, particle size distribution, etc.) and may, thus, provide guidance as to how a test or method is best used for a particular product.

CONCLUSION

The ITFG/IPAC-RS Tests and Methods Technical Team has developed a critical assessment of how individual tests can add value to the development and quality control of a new product. The team assessed tests to make recommendations and offer guidance on *how* to select tests that are needed to characterize a new product and to control a manufactured product. Through a science-based process, the team has demonstrated that a fixed list of control tests for all products is not appropriate.

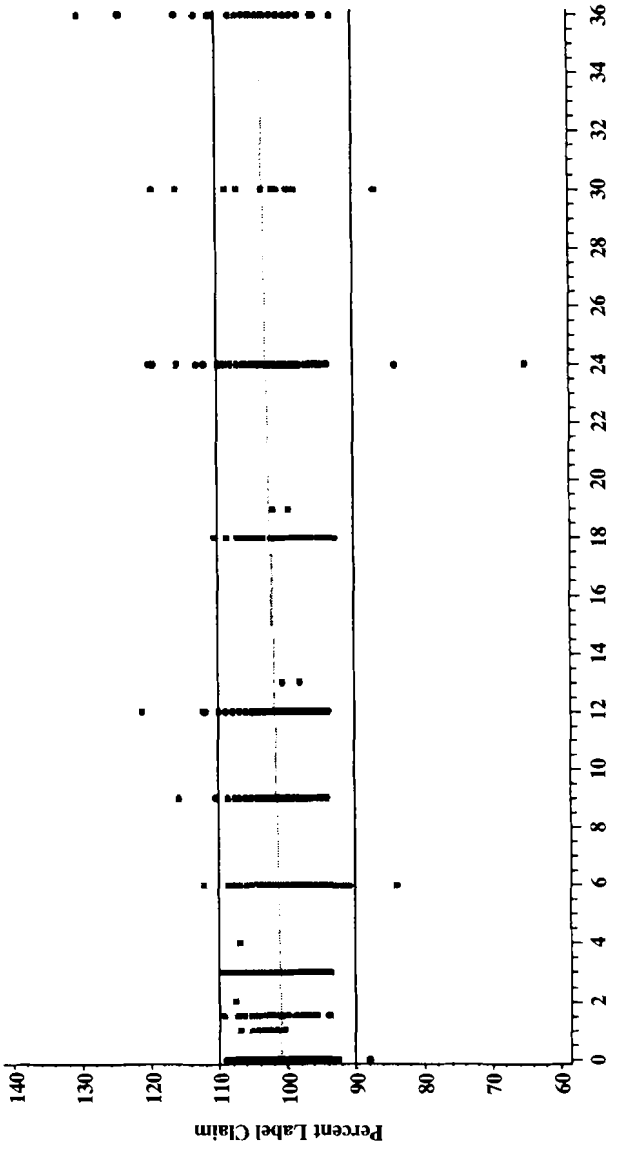

FIGURE 1. Normalized shot weight over time, measured for 11 MDI products. The graph shows the results of a zero order trendline analysis with 95% upper and lower bound confidence intervals. The figure demonstrates that the predicted rate constant is just above zero but not statistically different from zero. Three products from the database were removed from this analysis because their data sets did not contain enough information to conduct normalization of the data.

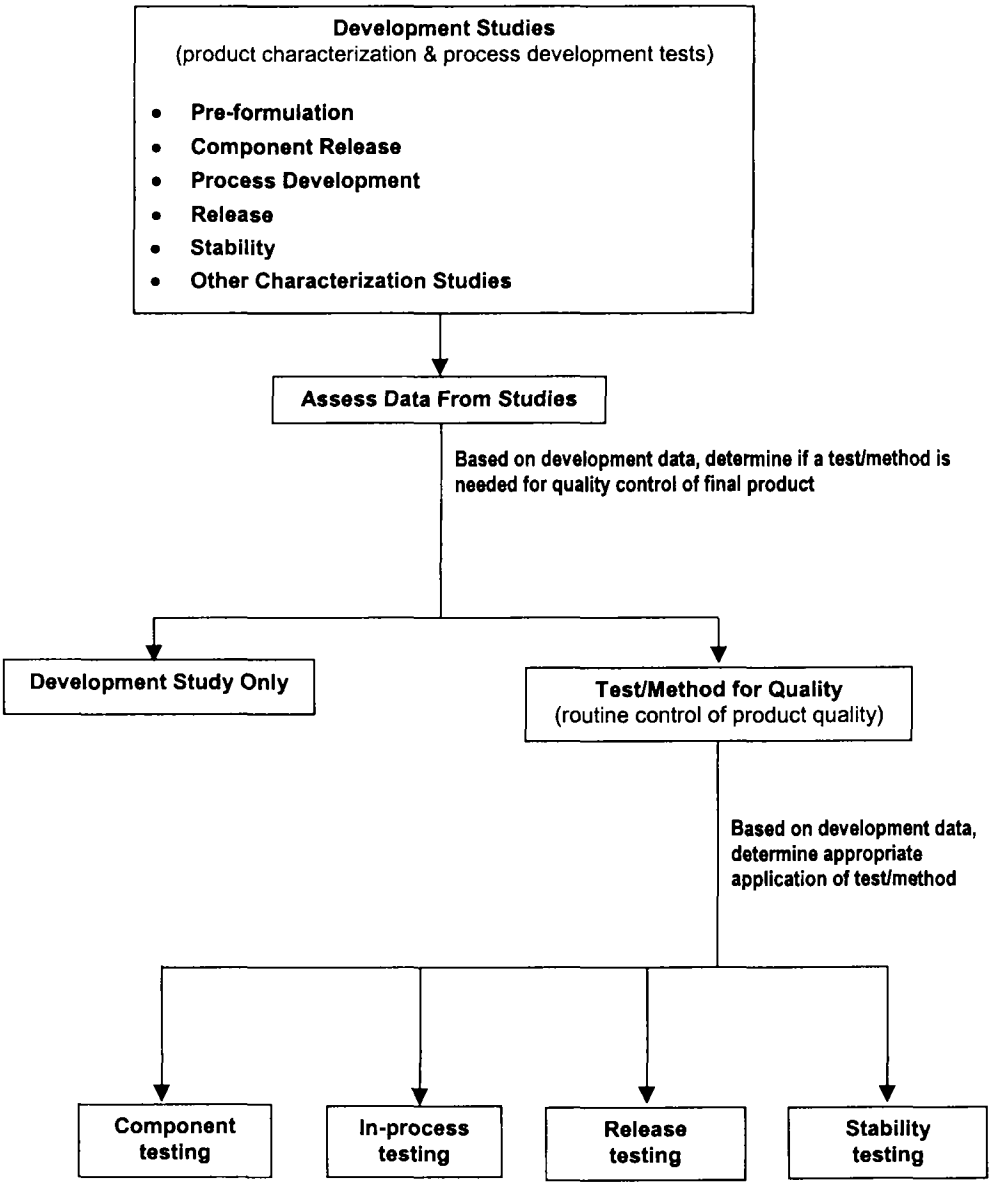

FIGURE 2. Decision Tree for Orally Inhaled and Nasal Drug Product Tests and Methods.

The team's conclusions suggest that an MDI/DPI guidance should support the concept of characterizing a new product in development studies and applying that information to select appropriate control tests for the commercial product. The desired overall goal is to maximize the value of characterization and control testing and to minimize redundant testing.

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