US OFFICE PRODUCTS

Product Quality Research Institute

Particle Size Distribution Profile Comparisons Working Group

Summer 2002

WORK PLAN

Investigation of an Optimized Chi-square Method for Comparing Particle Size Distribution Profiles Obtained by Cascade Impactors with Specific Reference to Equivalence Testing of Orally Inhaled and Pressurized Nasal Drug Products

Finalized by WG Chair on 28 May 2002
Finalized by Working Group on 4 June 2002
Forwarded for review to DPTC on 4 June 2002
DPTC comments incorporated on 28 June 2002
Present version approved by WG on 18 July 2002

Approved by DPTC on 14 August 2002

Forwarded for review to SC on 14 August 2002
Approved by SC on 29 August 2002

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I. BACKGROUND[1]

The FDA draft Guidance for Industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*[2] (1999) sets forth recommendations for product quality studies on locally acting nasal aerosols and sprays intended to evaluate bioequivalence between the Test and Reference products. One of the in vitro studies recommended by the draft Guidance involves a statistical comparison of the particle size distribution (PSD) profiles based on Chi-square difference ratios.

The procedure described in the 1999 draft Guidance was further developed and presented by Dr. Yi Tsong[3] (FDA) at the 26 April 2000 meeting of the Advisory Subcommittee for Orally Inhaled and Nasal Drug Products (OINDP). In addition, the Agency expressed an interest in examining the use of this method for orally inhaled as well as pressurized nasal drug products.

Since the draft Guidance's Chi-square method was developed using simulations based on an albuterol MDI cascade impactor data, it would benefit from a more complete evaluation of its capabilities over a wider variety of product types and measuring devices. Such evaluation would assess robustness, sensitivity and discriminating ability of the test, and may point to a strategy for determining equivalence limits, which play a critical role in practical application of the method.

In July 2001, the PQRI Steering Committee considered the proposal to investigate appropriate methods, including the Chi-square method, for comparisons of PSD profiles for bioequivalence testing of OINDP. The Steering Committee approved the formation of a Working Group (WG) on this topic, with participation from industry, academia, FDA and USP. The present document represents a Work Plan developed by this Working Group.

II. RESEARCH OBJECTIVES

A. General Considerations

The overall research objective is to develop the Chi-square method proposed by the FDA into a robust, rugged, statistically-based method for testing equivalence of normalized (as % of total recovery) PSD profiles. The Working Group emphasizes that it is NOT its intention to investigate or develop a method for routine quality control/batch release testing.

Initially, the Working Group will focus on propellant-driven nasal and orally inhaled aerosols, and then on DPIs and other OINDP.

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1 The format of this Work Plan follows the general outline suggested by the *Guidance for Working Groups/PQRI* (see Appendix A).

2 Available at http://www.fda.gov/cder/guidance/2070dft.pdf.

3 Dr. Tsong's presentation can be viewed at http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1e.ppt.

Important issues to be addressed include:

- more complete evaluation of the discriminating ability and other properties of the test;
- evaluation of consistency of performance of the test across various products and configurations of cascade impactors, initially focussing on Andersen CI; and
- investigation of an approach that generalizes the determination of "goalposts".

In developing a concrete Work Plan, the Working Group recognized several challenges, such as:

- A variety of equipment types are used for particle sizing of pharmaceutical aerosols (*e.g.*, Andersen cascade impactor, modified Andersen impactor, Marple-Miller impactor, *etc.*). Current USP Chapter <601> includes several impactors. Specific impactor configurations can affect the results of the Chi-square analysis.
- The Chi-square profile comparison is intended to examine the similarities or differences in mean profiles and within- and between-batch variabilities. Chi-square results may be affected by factors yet to be investigated, which may affect the outcome of this comparison. Such factors include the number of triplets, the number of resamples, and other possible factors.

B. Goals

The Working Group proposes to achieve the following:

- *To test, characterize and document the properties of an optimized Chi-square method when used to compare cascade impactor generated PSD profiles of propellant-driven nasal and orally inhaled aerosols;*
- *Develop and document an approach for determining "goalposts" (generalizable to the extent possible) against which equivalence of PSD profiles will be assessed; and*
- *Develop validatable software which can be used to perform Chi-square equivalence testing.*

C. Work Plan Outline

To address the above objectives, the Working Group envisions a two-step approach: first, understand capabilities and potential limitations of the test as presented in the 1999 draft Guidance; and second, develop an optimized, robust Chi-square method that is thoroughly characterized, tested and documented.

Thus, the Working Group proposes to undertake the following steps:

To understand capabilities and potential limitations of the draft Guidance Chi-square test:

1. Develop and test a computer code and algorithm reflecting the Chi-square test of the 1999 draft Guidance. **(March-June 2002)**

2. Explore the algorithm and code-related factors affecting outcome of the Chi-square test; begin development of an approach for determining goalposts. **(June – September 2002).**

3. Identify different scenarios (product types, profile types, impactor types and configurations) to be investigated using the software tools developed in step 1; continue development of an approach for determining goalposts. **(October – December 2002).**

4. Perform calculations to investigate performance of the draft Guidance's test under identified scenarios and explore differences in test performance; continue development of an approach for determining goalposts. **(January – March 2003).**

5. Prepare a paper which will outline an agreed methodology of the chi-square method and will summarize results of the above investigations. **(April – September 2003).**

To develop optimized method for PSD profile comparisons:

6. Identify desired characteristics of an optimized method of PSD profile comparisons; consider newer products and the imminent broad use of the Next Generation Pharmaceutical Impactor (NGI); continue development of an approach for determining goalposts. **(October 2003 – February 2004).**

7. Develop an optimized test method and associated goalpost determination method. **(March-August 2004).**

8. Determine scope and extent of testing the proposed methods. **(September – December 2004).**

9. Test proposed methods. **(1-2 Q 2005).**

10. Summarize results in a paper. **(3 Q 2005).**

11. After approval by DPTC and SC, make recommendations to FDA. **(4Q 2005).**

An outcome of the above steps will be validatible software that can be used to implement the test method.

III. REQUIRED RESOURCES

A. Human Resources

Members of the Working Group include several scientists from the FDA, pharmaceutical industry, academia and USP; these provide expertise in statistics, analytical testing of aerosols and nasal sprays, product development, academic research and regulatory affairs. The Working Group is currently looking to strengthen the representation of generics industry.

B. Laboratory Resources

To thoroughly test and document the Chi-square method and address a generalized determination of "goalposts," simulations will be very useful. However, comparative data of actual products differing in mean profiles, within- and between-batch variability, and the combination of differences in mean profiles and variability is essential. These data may be obtained through data-mining and/or further laboratory work. Updated versions of the work plan will be submitted to the PQRI DPTC and Steering Committee for review and approval.

C. Financial Resources

No additional financial support from PQRI is requested at this time.

IV. POTENTIAL IMPACT

Based on results of this investigation, a standard method could be established for in vitro bioequivalence comparisons of PSD profiles of OINDP. This will provide a sound scientific base for the Agency's regulatory requirements for BE testing, and both industry and patients will benefit from consistent application of such regulatory guidance.

Guidance for Working Groups
Product Quality Research Institute

The Working Groups of the Product Quality Research Institute (PQRI) are essential to the success of the Institute. As such, each Working Group should understand what it is expected to do in carrying out its charge from the Technical Committee. The PQRI Steering Committee is therefore providing this guidance for Working Groups to help establish what the expectations are for the Working Groups. This guidance will be revised if necessary based on the on-going experience gained by each Working Group.

The Technical Committees will define the research objectives of the project as approved by the Steering Committee that the Working Group will study. The Technical Committee will nominate Working Group members from the names provided by the constituent PQRI member organizations. The Technical Committee chair may recommend additional Working Group members after assessing the expertise of member organization nominees. If a member organization nominee is not selected by the Technical Committee to be on the Working Group, the reason for that rejection will be provided. Nominations to Working Groups should be made based on the technical expertise of the candidates and their willingness to devote the time and effort necessary to successfully complete their assigned project according to the project timeline. The Technical Committee also will designate a Working Group chairperson from the members of the nominated Working Group and a Technical Committee member will be assigned to the Working Group to provide a continual link between the Working Group and the Technical Committee. The PQRI Steering Committee will approve the membership and chair of each Working Group recommended by the Technical Committees.

Once a Working Group has been established and approved the Group should meet within thirty (30) days to begin development of a work plan to address its assigned topic and establish a definitive timeline when the plan will be completed. It is the responsibility of the Steering Committee to provide each Working Group with an orientation to PQRI and an explanation of the PQRI research process.

A formal work plan should be prepared for the topic assigned to the Working Group. It is anticipated that each plan will contain at a minimum the following:

1. Background*

    - What is the specific topic being addressed?
    - What is the regulatory/compendium history of this topic?
    - What are the scientific issues surrounding the topic and what specific questions are being addressed?

2. Why is the work being done?*
    - What regulation or guidance is impacted by this research?

* *Items 1 and 2 should be provided by the Technical Committee.*

- What is the current guidance/regulation?

3. Research Objective**

- What is the specific research objective that this work plan would address? (Include a statement of hypothesis.)

4. Work Plan

- What specific work will be needed to address the research question?
- Will the study utilize data mining or prospective research?
- Can the work be conducted using "sweat equity" from the Working Group membership or does the work have to be contracted? Any decision to contract work will be made by the Steering Committee.
- What is the plan timeline? (Should include milestones, data analysis and report preparation)
- What are the anticipated costs of the project?

5. Potential Impact

- How will this regulation/guidance change if the research is "positive"?
- What will the impact of this change be on FDA and/or Industry? (Should try to address safety, timing and financial considerations)

It should be noted that the PQRI process is intended to be a very public exercise. Study plans, meeting minutes and all reports will be made public on the PQRI web site. Additionally, Working Groups should consider by what mechanisms they would solicit necessary public input. The Working Group must consider the impact of public solicitation for comment on project timelines.

Once the Working Group completes the formal proposal, it will be reviewed and approved by the Technical Committee and the Steering Committee. The Steering Committee will then recommend project funding to the Board of Directors.

As the project evolves, the Working Group is to keep the Technical Committee informed on a monthly basis of plan status relative to the timeline. Any issues that cannot be resolved at the Working Group level should be raised to the Technical Committee and/or the Steering Committee to insure timely progress and completion of the project. The Technical Committee shall inform the Steering Committee of status and/or issues associated with each project at the regularly scheduled Steering Committee meeting at least two (2) weeks prior to each Steering Committee meeting. If necessary, a Technical Committee may request a special ad hoc meeting of the Steering Committee to address specific, urgent issues. The Steering Committee may at any time recommend changes to the Working Group study plan based on study progress and/or information obtained from other sources.

** *Item 3 will be provided by the Working Group and incorporated into the overall document, which will be sent to the Steering Committee for approval.*

Once the work is completed, the Working Group will prepare a comprehensive report and make a recommendation regarding potential changes to existing or draft guidance/regulation. The report should be suitable for publication in a peer reviewed scientific journal. The Technical Committee will review, recommend any changes if necessary, approve the report and send it to the Steering Committee for review and approval. The Steering Committee is responsible for sending the completed report and regulatory recommendation to FDA for consideration.

Under the PQRI process, FDA has agreed to review the report and regulatory recommendation. If the Agency rejects the conclusions and recommendations made by PQRI, a written explanation for the rejection will be provided to the PQRI Steering Committee. These results will be communicated to the Technical Committee and Working Group. If there is an opportunity to revise the report and/or conduct additional work to make the initial recommendation acceptable based on feedback from the Agency; the Working Group will take necessary actions to successfully revise the report. The process will continue until the Working Group recommendation is accepted by FDA or it is determined by the Steering Committee that further work will not result in successful resolution of remaining issues. In any case, the report and actions taken by FDA will be made available to the public via the PQRI web site and publication in an appropriate scientific journal.

Abbreviations

DPTC	(PQRI's) Drug Product Technical Committee
NGI	Next Generation Pharmaceutical Impactor
OINDP	Orally Inhaled and Nasal Drug Products
PQRI	Product Quality Research Institute
PSD	Particle Size Distribution
SC	(PQRI's) Steering Committee
WG	Working Group