



Approved by the SC on May 13, 2004

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WORK PLAN PROPOSAL

PROJECT NAME ___Process Robustness of Oral Solid Dosage
Forms_____

Name of Working Group: Manufacturing Science

Technical Committee: Manufacturing Date: 23 March 2004

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I. BACKGROUND

The definition of manufacturing science varies across the industry, academia and the FDA. The complexity of oral solid dosage forms has increased over time, as has the expectations of the FDA on processing controls and the level of detail required to assure a robust manufacturing process.

Guidance is needed to define and understand those factors that are critical to robust processes and standards.

A universal framework for this definition and the critical factors would result in the level of scientific rigor expected for a thorough understanding of processes.

II. GUIDANCE OR REGULATION TO BE ADDRESSED

- None

III. DESCRIPTION OF OBJECTIVE

- Develop and define an industry-wide understanding of factors that influence complexity and robustness of processes for oral solid dosage forms. A methodical unit operation approach will be utilized to describe in detail the possible process/formulation principles and factors that lead to understanding and/or optimization to assure a product is robust and can be manufactured reproducibly throughout its lifecycle. Attachment 1 is an example of a high-level chart that could be used to itemize minimal expectations in this process. The Working Group must decide the level of detail to be added and the best way to present the information.
- Utilize the above factors to develop a model which can be used across industry, academia and FDA to assure that the appropriate scientific principles and accompanying expectations are applied during the product lifecycle. For example, setting of specifications, identifying measures of robustness (e.g., CpK, retrospective analysis of process success following x commercial lots, proactive process monitoring of critical process parameters), and defining critical process parameters [CPPs] and critical quality attributes.

An additional chart to be developed will outline which potential CPPs exist per unit operation. It also must be understood that the selected CPP for a given product will be formulation and process dependent and not generic to all products. For example, for a given formula, tablet hardness may not be a CPP if there is adequate material flow and the formulation has an adequate compressibility

index, whereas another formulation that has a poor compressibility index and whose hardness is important to dissolution, hardness could be a CPP. This concept will be elaborated on and case studies may be developed.

- Develop the approach on how to determine which parameters are CPPs. This may be a statistical approach. The Working Group may develop case studies of parameters that are CPPs and those that are not, and show in detail how the decision was made. This concept may also be applied to new and novel processes and technologies.
- Develop and agree on definitions for terms in this area of process robustness, e.g., Manufacturing Science, critical quality attributes, critical process parameters, process capability, and manufacturing technologies.
 - Example: Manufacturing Science – the body of knowledge available for a specific product or process, including critical quality attributes, critical process parameters, process capability, manufacturing technologies, process control technologies and the quality systems infrastructure.

IV. POTENTIAL IMPACT

- Use as a basis for understanding the level of manufacturing science expected during development through commercialization phases of oral solid dosage forms.
- Alignment and understanding on the definition of critical processing factors, how they are controlled and how specifications are developed to assure product quality.
- Use as a basis for sharing knowledge on process robustness. (Wording)

V. WORK PLAN OUTLINE

- Appoint WG leader, members, MTC sponsor – 30 Apr 2004
- WG kick-off meeting – 14 May 2004
- Brainstorm factors & prioritize – 15 June 2004
- Clear definitions, examples of each factor – 30 June 2004
- Develop protocol for benchmarking – 30 July 2004
- Collect data and collate – 31 Aug 2004
- Analyze results – 30 Sept 2004
- Write draft report – 15 Oct 2004
- Review and incorporate comments – 22 Oct 2004
- Present to MTC for comments – 28 Oct 2004
- Incorporate comments from MTC, finalize report and submit to SC – 19 Nov 2004
- Presentation to SC – 2 Dec 2004
- Incorporate comments from SC and finalize report – Jan 2005

- Review and approval by MTC of final report – Jan 2005
- Submit final report for approval by SC for Publication – Jan 2005
- Submit final report for Publication – Feb 2005

VI. WHAT WILL BE IN FINAL REPORT

- White Paper with charts similar to SUPAC guidances (i.e., showing key areas where process robustness should be studied, listing the potential areas where CPPs could be found).

VII. DETAILED WORK PLAN

- What Specific Work Will be Needed to Address the Research Question? *A survey of industry will be conducted to collect information.*
- What Are the Required Resources?
 - Human Resources – *WG members (approximately 10 people)*
 - Laboratory Resources - *None*
 - Financial Resources (Budget) – *This has to be developed depending on how benchmark survey is conducted, use internal resources or consultant.*
- Will the Study Utilize Data Mining or Prospective Research? *Yes. The work plan will utilize benchmarking of existing practices for process robustness.*
 - What data /information will be needed to complete the objective of this work? *Benchmarking of practices and examples of process robustness.*
 - Will the study utilize existing data (Data Mining)? If data mining is to be used, please review the established PQRI protocols for the submission of data. *We will utilize existing practices for process robustness and not data for specific products.*
 - Will the study require that new data be generated (Prospective Research)? *No*
 - Please explain the data collection or generation process and protocol. *This will be developed by the WG.*

Attachment 1: **Critical Process Point Checklist**

Item/Unit Operation	Variable/Potential CPP
Formulation Optimization	Ratio of excipients
Weigh/Dispense <ul style="list-style-type: none"> • API • Excipients 	Particle size Surface area Compressibility index
Pre-blend	Time Order of addition
Wet Granulation	Plow speed Chopper speed Rate of solution addition End point Solution temperature
Granulation Solution	Temperature Time of mixing Method of mixing
Wet Milling	Screen size Mill speed
Drying	Inlet temperature Outlet temperature Airflow Drying time
Material Transfer	Distance of transfer Granule friability Tendency to segregate
Milling	Screen size Rate of feed Knives/impact Mill speed
Lube blend	Time Particle size of lubricant
Compression	Pre-compression Main compression Hardness
Coating	Pan RPM Spray Rate Hardness Temperature
Printing	Speed of printer
Encapsulation	Slug hardness Machine speed

Approval:

Working Group Chairman _____ Date: _____

Technical Committee Co-Chairs Bruce Bird/Nick Maselli Date: March 18, 2004

Steering Committee Chairman _____ Date: _____