

Project 1 – Angelos Dovletoglou – 45 min

Issues: How does one arrive at a set of specifications for allowing post approval changes and influence established and developing guidelines?

Action Items:

Outline all possible changes: Changes in 1) manufacturing: scale, equipment, controls and process; 2) route of synthesis; 3) packaging and 4) supplier(s) of API. [Hussain, Mehta, Schultz]

Considerations for Setting Specifications and Evaluating Manufacturing Changes: Focus on the science required and the process for defining analytical tests and acceptance criteria used for evaluating changes regarding a) Polymorphism, b) Particle Size and c) Impurities. [Hoag, Olsen]

Identify research projects that will help establish low risk changes in the manufacture of API's, keeping in mind the impact on critical attributes, and proper test methods and specifications [*need someone to lead*]

Keep the WG updated about USP Working Group on API monographs [Lin]

Update the WG on the direction and progress at the FDA and elsewhere on the risk based CMC review initiative [Mehta]

Munir Hussain and Jai Mehta updated the group regarding their teleconferences. A draft document prepared by Munir Hussain has been circulated to Jai Mehta and Tom Schultz. This document will be expanded upon and categorized into various categories of possible changes (i.e. equipment, process, intermediates, raw materials, packaging, etc.) Under each category all possible changes will be listed and an attempt will be made to classify each such change as in significant/major or insignificant/minor or indeterminate. This categorization may also depend on the use of the API. Hussain, Mehta and Schultz will try to compile the first draft by the next working group meeting.

Bernie Olsen had updated the previous draft of "considerations for setting specifications and evaluating manufacturing changes" with a section on impurities. This additional section describes the various conditions in which the impurity profile may change (i.e. new impurities may get added or some impurities may get increased or decreased). The existing methods would need to be evaluated for suitability of any changes in the impurity profile. It was discussed whether this document should be further refined, reviewed and critiqued by the working group. It was the general consensus that we should wait for the "changes" document to be drafted.

The working group discussed the possibility of identifying research projects to have an impact on the hypothesis. It was generally agreed that we needed to have the two documents finalized and linked with the Biopharmaceutics Classification System (BCS) Guidance before we can identify specific research projects. Angelos mentioned that we would need a volunteer to lead that task force - preferably one of the FDA lab members of the working group.

Lih-Yang Lin reiterated the previous update to the group regarding the 15 projects at the USP. The first one is the one where she is representing GPhA is working to harmonize the USP monograph against the EP, JP & ICH. Lin was asked to update the group as necessary if there was any overlap with the activities with the DSTC WG.

Jai Mehta will update the working group on the risk-based CMC review initiative presentation at the DIA seminar and the ensuing conversations. John Smith gave the group an update on BACPAC II

Project 2 – Angelos Dovletoglou – 45 min

Issues: For a given category of drug products are a set of specifications together with impurity profile and physical property evaluation a reliable determinate of performance of the drug product?

Action Items:

Identify cases of API and/or categories of drug product (formulation types or therapeutic areas) where the appropriate physical-chemical properties of the API were not captured by the specifications leading to failures in dissolution, stability, content uniformity and processability (especially for high dosage). Data mining of sponsor databases. [Team]

The discussion pertaining to this project had already started during the discussion of the second action item of project one, but the minutes belong more against this project. Bernie Olsen had initiated the discussion by writing a stimulus regarding the discussion for the causes of drug failures or recalls that could be related back to specification deficiencies. As he put it, "as we may not be able to find examples where recalls and failures of drug products that can be tied back to the API specifications, maybe we should think about failure modes and think about whether these could be caught ahead of time by retrospective analysis including drug substance specs." His e-mail had examples of different failure modes (i.e. safety problems, formulation dissolves too fast or too slow; change in efficacy, stability, etc.

This stimulus provided a lively discussion where a number of real life examples were "put on the table" by the attendees. The examples are captured in brief below. Tom Schultz, Munir Hussain and Hitesh Chokshi volunteered to work separately to summarize the discussion in greater detail.

- Tom Schultz - talked about a common steroid manufactured as the anhydrate. However, it was discovered that the hemi-hydrate is the most stable form under ambient conditions. In addition, the size and shape of the crystalline drug substance changes during the conversion. The corresponding USP method for Water Content determination (i.e. Loss on Drying) is unable to discriminate between the anhydrate and hemi-hydrate. However, the non-compendial particle size method developed is capable of detecting the solid state conversion. The drug substance generally fails to meet the proposed particle size specification when the hemi-hydrate content exceeds 30 - 40%. The particle size specification inadvertently became a surrogate test for an inferior USP procedure intended to determine Moisture Content.
- Jai Mehta - talked about cyclobenzepine failure with superpotent stability samples, where the investigation led to the change in API supplier and the particle size distribution. The particle size specification was met with the new supplier, but the material was much finer and there was no lower limit on the specifications. The formulation process was dry blend and thus there was more segregation of the blend leading to the superpotent tablets at the end of

Review of a literature search conducted with Nerac [Lin, Mehta]

Retrospective review of publicly available information and FDA records under the Freedom of Information Act? [Dovletoglou]

Prepare a questionnaire and contact the companies on the Blend Uniformity Survey Contact List [Dovletoglou]

the run.

- Munir Hussain - talked about carbamazepine. A well known case where the carbamazepine hydrate was formed in the finished dosage form and resulted in decreased dissolution. The slower dissolution profile led to some deaths.
- Jai Mehta - talked about phenytoin capsule dissolution profiles - the API exhibits different hydrate forms in different environments leading to inconsistent dissolution profiles.
- Munir Hussain - IVIVC data would be needed on drug products to correlate the physical chemical properties of the API in dosage form vs. BCS Class II or Class IV.
- Hitesh Chokshi - we may want to consider situations where physical properties that are not adequately captured by a standardized set of specifications and that there may be "other" physical properties that may capture API characterization more appropriately.
- It needs to be kept in mind that a dosage form or a drug tends to reach the lowest thermodynamic stage of minimal energy to achieve a more stable form (i.e. solution dosage form).
- We need to think about the impact of the excipients in a tablet or capsule dosage form, with respect to API characteristics like polymorphism.

Jai Mehta's literature search with NERAC did not yield any significant lead. After the conference call Lih-Yang Lin established a one-month experimental contract with NERAC and performed additional literature searches, which were forwarded to Jai Mehta and Munir Hussain. Update on these literature searches will be provided at the next meeting.

Angelos is actively searching the Merck database with respect to quality issues that have arisen for their products. The inherent problem with respect to negative quality issues is that a company would get district FDA citations, despite the end product being of good quality, so therefore it is difficult to look at the compliance record to come up with real problems. Angelos still plans to go ahead with the review of internal data and requested other WG members to do the same.

Angelos did leave a message with Ajaz Hussein at FDA regarding FDA assisting the WG with data mining through FOI available data. He requested Ajaz to see if someone at the FDA could review the amendments and supplements filed with respect to APIs. Which areas are "hot buttons" where industry is having trouble meeting the criteria to qualify the changes?

Angelos is not very certain that the best approach would be to ask companies about their problems with product quality with respect to API specifications. He needs to confirm with John DeFoe the strategic approach to this action item. It may be better to arrive at a position paper

Analyze these cases to determine a classification system
[Team]

out of the WG and come up with a series of suggestions or hypothesis. Thus specific questions could be proposed to the interviewee companies as to whether they agreed with the analysis of the DSTC WG as far as their experiences were concerned or if they have a different point of view?

Full Review and Edit of Action Item List– Jai Mehta – 10 min

Future Agenda and/or Action Items	Responsible Team Member	Due Date	Comments
Analyze literature search -earlier by Mehta and subsequent by Lin after the October 16 meeting.	Lin, Mehta, Hussain, Dovletoglou	Nov-2001	
Preliminary work plans to the DSTC and the Steering Committee	Dovletoglou	Oct-2001	Completed
Outline all possible changes in API	Hussain, Mehta, Schultz	Nov-2001	
How do we evaluate changes in API?	Hoag, Olsen	Nov-2001	Draft Completed
Summarize examples of product problems with respect to API specifications	Schultz, Hussain, Chokshi	Nov-2001	
Prepare a questionnaire and contact sponsors	Dovletoglou	TBD	
Identify research projects based on analysis of the working group	TBD	TBD	
<i>Evaluate possibility of FDA's database available through FOI</i>	Ajaz Hussein	TBD	

Next Meetings:

**PQRI-Specifications and BACPAC Working Group
Meeting Schedule Remaining for Year 2001**

Date	Time	Location
Wednesday, 21-Nov-2001	2:00 – 4:00	teleconference
Wednesday, 19-Dec-2001	2:00 – 4:00	teleconference