
BMS Experience with the FDA-EMA QbD/PAT Joint Pilot

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FDA/PQRI Conference on Evolving Product Quality
September 17, 2014



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Discussion Overview

Introduction

Industry perspective on the Pilot

Case study

- ◆ Introduction to the Drug Product Control Strategy
- ◆ Feedback from EMA and FDA
- ◆ Observations and comments

Concluding Remarks



Introduction

- **BMS application contained QbD based development work, including design space, application of PAT for in-process control and real-time release testing (RTRT)**
- **Initial marketing application submitted to the EMA prior to the Pilot**
- **EMA participated in the FDA initiated consultative advice process post-approval**



Benefits of the Pilot– Industry Perspective

- **Helps in ensuring consistent interpretation of the ICH guidelines**
 - ◆ The Pilot has resulted in two question-and-answer documents, which provides clarification on the QbD topics and Agency's thinking
- **Joint review and assessment of the filing will reduce overall cost and resource requirements and can potentially:**
 - ◆ lead to harmonization of the queries, and thus reduce the total number of different types of queries
 - ◆ lead to harmonized regulatory specifications
 - ◆ eliminate divergent feedback
 - ◆ Streamline the overall approval process



Benefits of the Pilot– Industry Perspective

- **Opportunity for joint meetings with the two Agencies**
 - ◆ Can help reduce time and resource
- **Potential for joint inspection of a QbD/PAT application**
 - ◆ Will help in reducing the inspection burden – savings in resource and time
 - ◆ Increased interactions of CMC reviewers and the inspectors from both Agencies

What are the Challenges?

- Is similar outcome feasible given the differences in the regulatory framework?
- Is similar assessment possible taking into account the differences in reviewer's tolerance for risk?
- If the Agency's assessment is divergent on the applicant's proposal then:
 - ◆ what would be the outcome of the joint review?
 - ◆ would the more conservative opinion prevail?
 - ◆ or, would the two Agencies stand by their respective opinions?

A Case Study to Illustrate the Challenges

Tablet Manufacturing Process & Proposed Control Strategy

Drug Substance and Excipients

Control on API and excipients

Blending

**Blending end point by NIR
(>97% of the total tablet composition mixed)**

Roller Compaction/Granulation

Attribute based control on RC ribbons

Final Blending

Tableting (core)

**Potency by NIR (Tablet NIR/RTRT)
Large-N acceptance criteria for CU**

Finished Product (coated)

**ID, Appearance, HPLC as back-up to NIR,
disintegration, dissolution waiver/model**



Large-N Acceptance Criteria for Content Uniformity

NIR Content Uniformity (CU) acceptance criteria (Bergum, Vukovinsky)

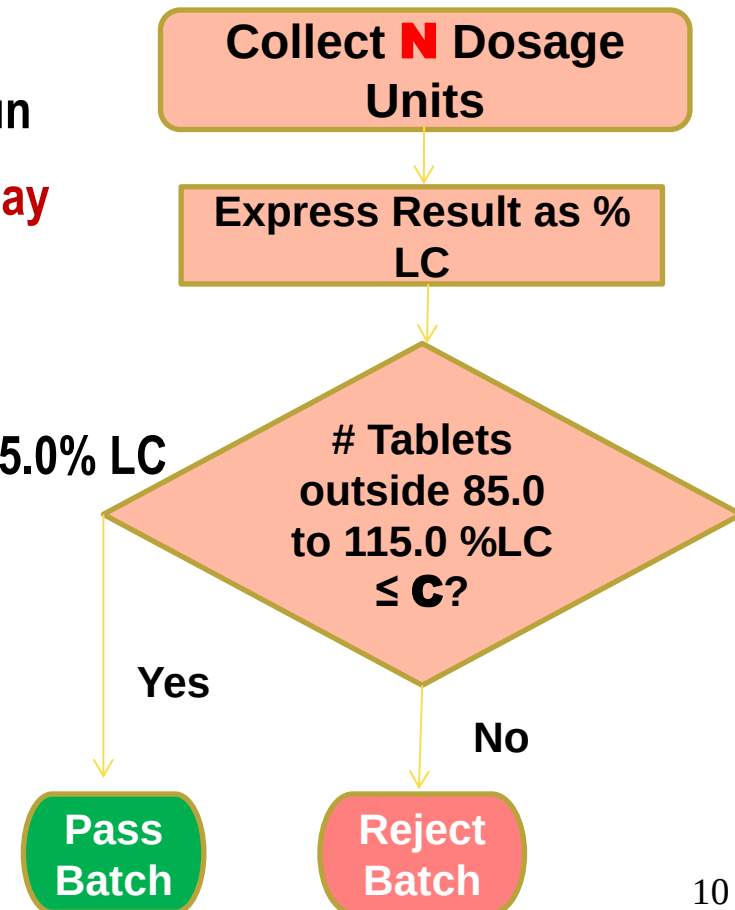
Similar to or more stringent than the ICH UDU test acceptance criteria

- Test at least 100 tablets per batch compared to the 10-30 tablets (ICH UDU test acceptance criteria)
- Tablets collected throughout the compression run

Potency is calculated by averaging the individual assay results from content uniformity testing of tablets

- One tiered counting test
- Count number of results (C) outside 85.0% to 115.0% LC
- Criteria:
 - $C \leq 0.03 \cdot N$

N	100	160	250	500	1000
C	3	4	7	15	30



EMA and FDA Preliminary Feedback Prior to Filing

- **Pre-blend NIR**

- ◆ Both HAs supported but asked questions if the NIR measurement of the sample at blender sight-glass was representative of the entire blend
- ◆ Intrigued by the use of gravimetric calibration; wanted to know why BMS did not use HPLC for calibration

- **Tablet NIR/RTTRT**

- ◆ Limited commercial scale experience with application of in-process tablet NIR for release
- ◆ Continue to collect NIR and HPLC data in parallel
- ◆ Include alternate conventional HPLC method as contingency plan

- **Large – N acceptance criteria**

- ◆ EMA was favorable in accepting the Large-N criteria and commented that EFPIA was looking into it as well.
- ◆ FDA commented that their statisticians have evaluated the PhRMA Large-N approach but preferred the parametric tolerance interval test (PTIT) approach. FDA shared the public record on PTIT to allow BMS to compare the two statistical approaches.



Feedback from the *EMA* on the NIR Based Control Strategy During Review

- **Pre-blend NIR – Method related questions, but accepted the in-process control. Was appreciative of the fact that some level of control was in-place**
- **Tablet NIR/RTTRT – Several method and model related questions and also recommended running HPLC in parallel for sometime due to limited commercial scale batch data in the filing**
 - ◆ BMS decided to gather NIR data on more batches before implementing the NIR/RTTRT control strategy for routine commercial manufacturing
 - ◆ BMS filed tablet NIR/RTTRT post-approval
 - ◆ No additional questions from the EMA during the review of the Type II variation
- **Large-N Acceptance Criteria for CU - It was re-filed as part of the Type II variation. EMA accepted the criteria as is**

Feedback from the *FDA* on the Pre-Blend NIR During Review

Pre-blend NIR

- FDA asked why thief sampling was not done on pilot and commercial scale to confirm the NIR predicted values
- BMS justified that there is a potential for segregation during thief sampling of the batch,

and

- Negotiated to continue to use the pre-blend NIR with a post-marketing commitment to provide HPLC data on samples from XX commercial batches when the NIR based blending end-point was reached. FDA Agreed.
- BMS submitted the comparative data post-approval. The data showed similar uniformity from both tests, however, there was greater variability in the thief sampling results. No further questions from the FDA.



Feedback from the *FDA* on the Tablet NIR/RTRT During Review

Tablet NIR

- Several method and model related questions
- FDA asked for raw NIR and HPLC assay values measured on the same tablets to perform their own assessment of correlation between NIR and HPLC
- FDA commented that the NIR method showed consistently higher predictions relative to HPLC, but also acknowledged that this could be due to availability of limited commercial scale batches
- FDA asked BMS to explain the bias before accepting the method for RTRT
- BMS decided to investigate this further and file tablet NIR post approval



Post-Approval Joint Meetings Prior to Submission of the PAS for Tablet NIR Method

- In 2013, BMS held two Type-C meetings with the FDA and EMA
- The meetings were held following the FDA initiated consultative advice process
- Three reviewers from the EMA attended the Type C meetings via T/C



Feedback from the *FDA* During the Meetings

- **BMS provided additional batch data to demonstrate that the NIR predicted potency results were not consistently higher than the HPLC results**
 - ◆ FDA concurred, but as a risk mitigation strategy, proposed tighter specs for potency than the initially filed specs and asked BMS to conduct parallel testing by HPLC if the NIR results were outside of the proposed tighter specs. This proposal was acceptable to BMS
- **FDA sought feedback from the EMA during the meetings**
 - ◆ EMA said that since they had already granted approval of the Tablet-NIR method for RTRT, they did not have any additional comments or questions

Feedback from the *FDA* During the Review of the PAS

- **FDA recommended to include in the drug product specifications, the description of dual role of HPLC (as an alternative to NIR; and for parallel testing when NIR assay test results are outside of the tighter potency specs)**
 - ◆ **BMS agreed**
- **FDA reiterated their concerns that the Large-N acceptance criterion for CU is much liberal than the PTIT, if the dose content distribution is not normal**
 - ◆ **Further discussion with the FDA statisticians is needed**

BMS Observations and Comments

- Both Agencies open to meetings to provide clarification and guidance during the query responses
- Both Agencies recognize the value of PAT in providing greater assurance of product quality compared to the traditional approaches

However,

- ◆ The EMA reviewers were more driven by the potential of PAT, when comparing it against the traditional methods and accepted it as part of the overall control strategy
- ◆ The FDA reviewers seem to place significant emphasis on establishing equivalency between the PAT and the traditional approach when interrogating the PAT controls



BMS Observations and Comments

- Both Agencies conducted a QbD/PAT based PAI of the manufacturing sites. The CMC reviewers accompanied the GMP inspectors
- Presence of CMC reviewers facilitated a very good learning experience for both the reviewers and the applicant
- Prior to start of the PAI, R&D presented salient aspects of the drug product development and control strategies
 - ◆ These presentations were very well received by the reviewers and the inspectors
 - ◆ It clarified many of the questions they had

Concluding Remarks

- The case study highlights some of the challenges associated with differing opinions and risk tolerance of the reviewers

but,

- The Pilot is certainly a step in the right direction for harmonization of the regulatory requirements, and
 - ◆ has helped in establishing a platform for discussion and increased interactions between the Agency and the Applicant
 - ◆ continued dialog has the potential to “simplify” post-approval changes
- The Q&A documents very helpful in clarifying Agency’s expectations for filing
- A 3-way interaction (between the Agencies and the Applicant) prior to issuing the queries will be very helpful in clarifying Applicant’s thinking
- Very helpful to have participation of the CMC reviewers during the PAI



Acknowledgement

Mark Rosolowsky

Doug Both

Yolanda Carringal

Linda Gambone

Jingpin Jia

Gary McGeorge

Prakash Parab

Jatin Patel

Pankaj Shah

Tim Stevens

Chandra Vema-Varapu

Kim Zerba