Manufacturing Process and Controls

How to Avoid Major Review Issues Turning into Potential Deficiencies / Approvability Issue – Case studies

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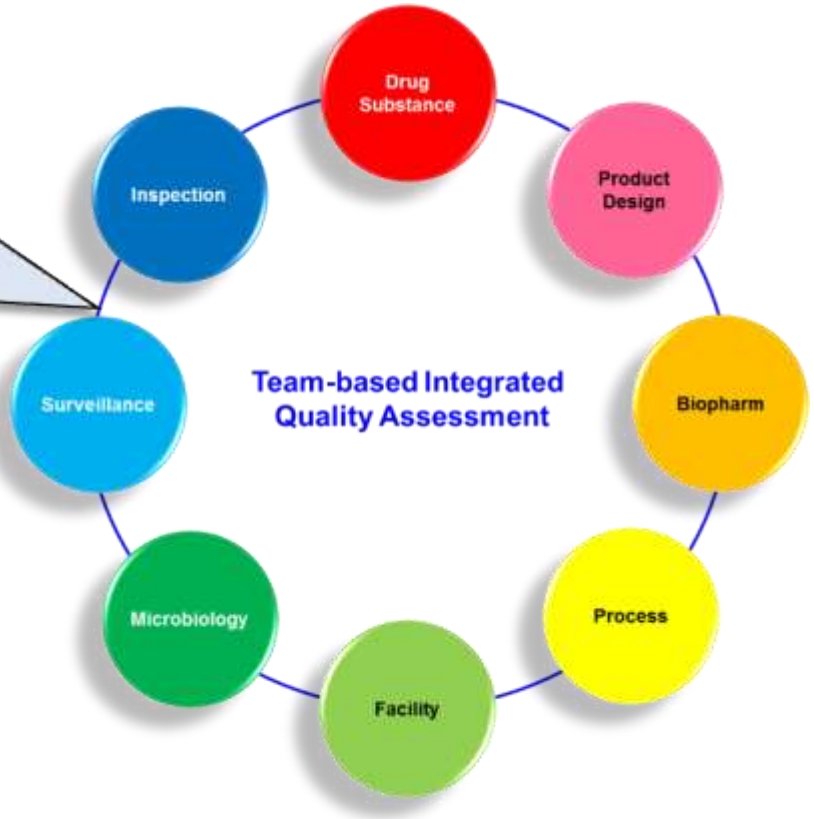
Outline

- IQA, Review Team and OPF (Office of Process & Facility) in OPQ
- Major and Minor Amendment/Deficiencies
- Impact of Major Deficiencies
- Examples of Major Deficiencies
- Case studies on major deficiencies/approvability issues
- Recommendations
- Acknowledgements

Team-based Integrated Quality Assessment (IQA)

Inclusive of drug substance, drug product, and manufacturing (process, facilities, microbiology), and maximizes each team member's expertise

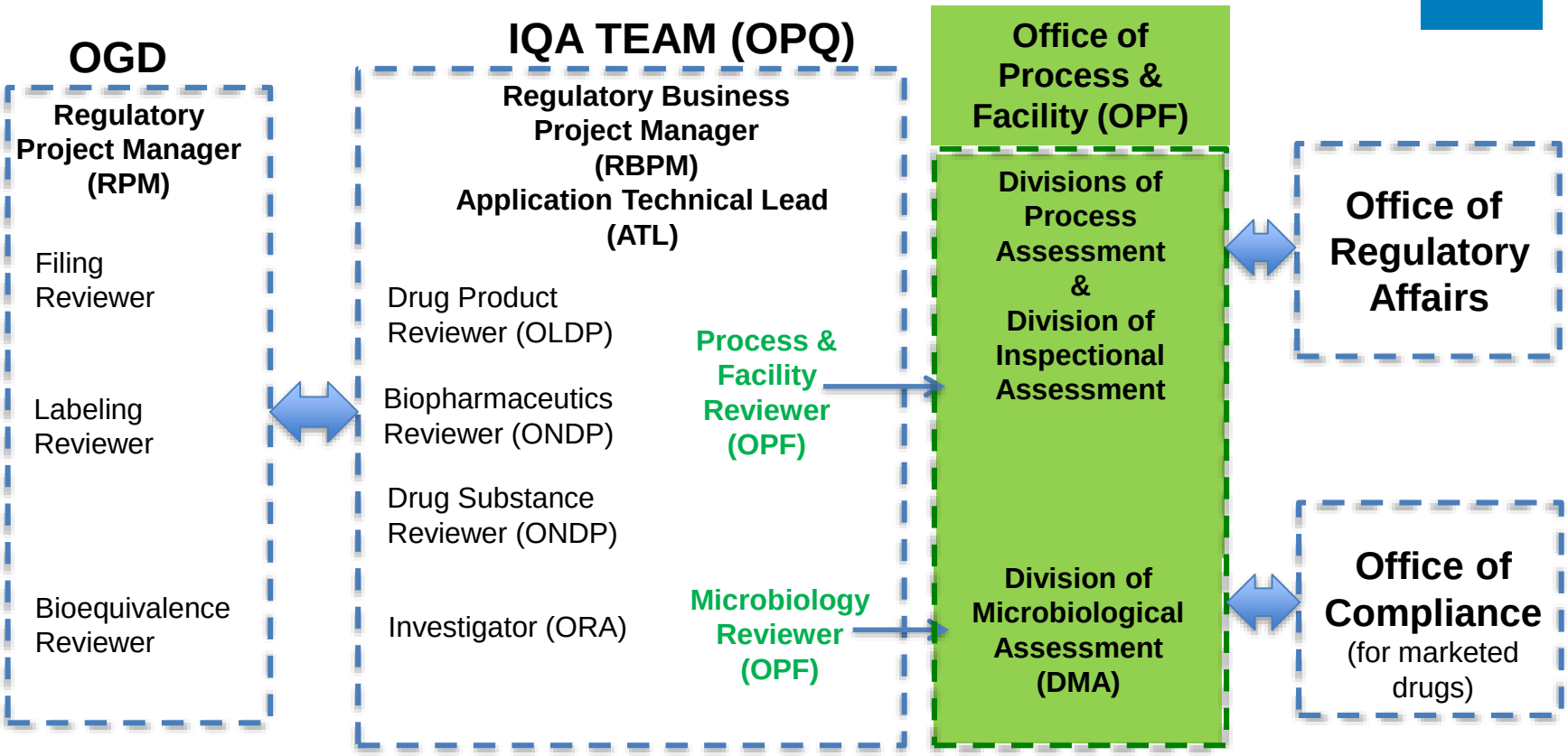


OPF's Role within the IQA Team

- OPF conducts application assessment in coordination with pre-/post- approval inspections as needed to ensure that manufacturing is adequate to deliver quality products for the patient.

- Manufacturing assessment includes the process, sterility assurance, and facilities.

Review Team for ANDAs & OPF



Major and Minor

- **Major amendment**
  - Amendment, *solicited or unsolicited,* that contain a substantial amount of new data or new information not previously submitted to or reviewed by FDA, requiring, in FDA's judgment, a substantial expenditure of FDA resources
  - Major deficiency: Deficiencies that applicant's response to them would be classified as major amendments

- **Minor Amendment**
  - Amendment that are not classified as major or are a response to a deficiency that could be adequately resolved through an information request (IR) or discipline review letter (DRL).
  - FDA review of it requires, in FDA's judgment, fewer FDA resources than are necessary to review a major amendment
  - Minor deficiency

This classification **does not reflect the time it takes an applicant to respond** to the complete response letter (CRL) but is **based on a determination by FDA** that the content of the information or data provided will require extensive assessment.

Impact of Major Deficiencies

On Goal Dates

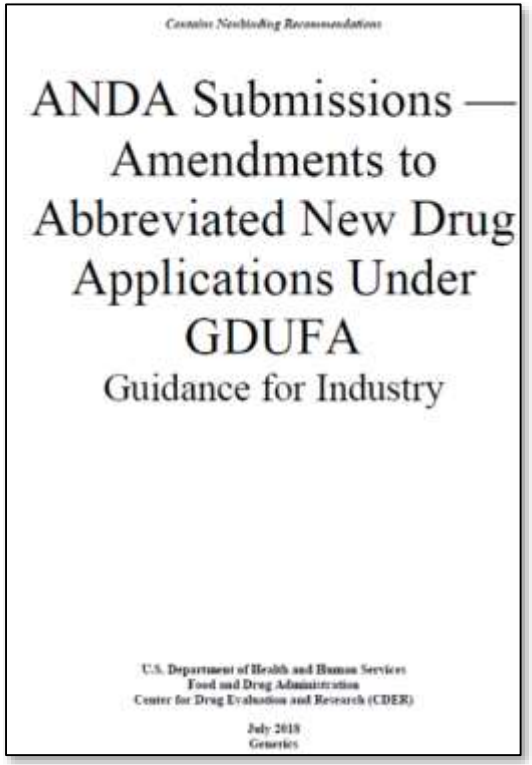
- **Minor amendments:**
  - 3 months, 90%, standard and priority
- **Standard major amendments:**
  - 8 months, 90%, PAI not required
  - 10 months, 90%, PAI required
- **Priority major amendments:**
  - 6 months, 90%, PAI not required
  - 8 months, 90%, PAI required & PFC complete, accurate and remain unchanged
  - 10 months, 90%, PAI required & PFC incomplete, inaccurate or change

Efforts and cost from the applicants

- **New batches**
- **New BE study**
- **New analytical method …….**

Referenced Documents

- 2000 – Major, Minor, FAX, and Telephone Amendments to Original Abbreviated New Drug Applications
- 2001 - *Revised* Guidance for industry - Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications
- 2012 – MaPP 5241.1 Reviewer Determination of Major/Minor Amendments to Abbreviated New Drug Applications (ANDAs).
- 2014 – *Draft* Guidance for Industry - ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA
- 2018 - Guidance for Industry - ANDA Submissions — Amendments to ANDAs Under GDUFA (current final)



ANDAs with Major Deficiencies (Original ANDAs only)

Function	Review Discipline	Submission Status			
		Complete Response	Pending	Withdrawn	Approved
Quality	Drug substance	275			
	Drug product	329			
	Manufacturing process and controls	46			
	Facility	347			
	Microbiology	28			
	Biopharmaceutics	21			
Other	Bioequivalence	191			
	Clinical	4			
	Statistical	1			
	Labeling	0			

* Survey from 2015/1/1 to 2019/2/26

** These survey numbers are not exclusive by review disciplines. For example, 6 quality disciplines have 716 CRs, instead of mathematical sum of 6 disciplines as 1046 CRs.

ANDAs with Major Deficiencies (All submissions)

Function	Review Discipline	Submission Status			
		Complete Response	Pending	Withdrawn	Approved
Quality	Drug substance	441	2	1	2
	Drug product	729	1	2	
	Manufacturing process and controls	52		1	
	Facility	573		1	
	Microbiology	51			
	Biopharmaceutics	45		2	
Other	Bioequivalence	371		1	
	Clinical	8		1	
	Statistical	1			
	Labeling	11			

* Survey from 2015/1/1 to 2019/2/26

** These survey numbers are not exclusive by review disciplines. For example, 6 quality disciplines have 1377 CRs, instead of mathematical sum of 6 disciplines as 1846 CRs.

Examples of Major Deficiencies

- Request of manufacturing a **new batch** of drug product **for any reason, such as:**
  - a composition change or reformulation,
  - a change in the source of a drug substance,
  - a change in the manufacturing site,
  - a change in a major manufacturing process,
  - a new strength of the product,
  - unacceptable impurities or impurity levels,
  - unacceptable excipients found during assessment,
  - failed stability data,
  - a change in the container-closure system (other than solid oral dosage forms)
- Request of performing a new BE study whether or not related to the manufacture of a new batch or different formulation of the drug product
- Request of developing new analytical procedures and providing full validation data

Examples of Major Deficiencies

- FDA has the discretion to consider the responses to additional deficiencies not included this list as major amendments as long as the “major amendment” classification receives concurrence by the appropriate division director.
- FDA developed a **non-exhaustive list** of examples in Appendix A, 2018 Guidance for Industry

Examples of Major Process Deficiencies

1. Major change in drug product manufacturing process (e.g., change from wet to dry granulation) used in manufacturing of registration batches and commercial production
2. Change in specification that would require changes to the manufacturing process
3. Significant differences between the manufacturing process proposed for commercial batches and exhibit batches
4. Size of exhibit batches is less than the minimum requirement without appropriate justifications
5. Change in or lack of information about the form of the drug substance during drug product manufacturing, which could adversely affect CQAs of the drug product

2018 – Guidance for Industry, Appendix A, Section A.3

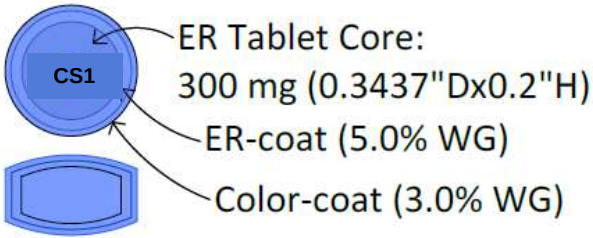
Examples of Major Process Deficiencies

6. Product quality adversely affected by interaction of API and excipients during manufacturing
7. Product quality adversely affected by inadequately scaling up manufacturing process (e.g., process parameters)
8. Commercial manufacture at risk by scaling up any unit operation >10 times
9. Requirement to manufacture a new batch (e.g., stability failure)
10. Significant differences between process descriptions, in-process controls, or scale-up information in Module 2 and Module 3
11. Need for safety assessment based on the risk of extractables and leachables from formulation contacting polymeric components of manufacturing equipment, inadequate assessment of extractables and leachables, or submission of the assessment in an unsolicited amendment

2018 – Guidance for Industry, Appendix A, Section A.3

Case study - 1

Facts: The proposed drug product CS1 is an extended-release tablet.

Tablet Schematic (not to scale)	Characteristics
	Blue to light Blue, round, film-coated tablets, imprinted with "CS1" on one side and plain on other side.

- a matrix-based tablet core
- a semipermeable ER-coat
- a blue color-coating over the ER-coating
- The color-coated tablet is **ink imprinted with "CS1"** on one side of the tablet for commercial production
- **however, the three exhibit batches were manufactured without the imprint identifier**

Deficiency:

Your proposed commercial manufacturing process includes an imprinting step; however, your exhibit batches were not manufactured with an imprint. Provide data **from at least one imprinted batch** to demonstrate that the imprinting process is well controlled and does not adversely affect the ER functional coating/tablet dissolution and stability.

#3 Significant difference between manufacturing process for exhibit batches and commercial

Case study - 2

Facts: The proposed drug product CS2 is an IR capsule.

- The proposed manufacturing process involves wet granulation where sodium hydroxide is used in the granulating fluid.
- Since the drug substance is a free acid, it will be converted to sodium salt in the finished dosage form.
- According to section 2.3 of the Drug Product labeling – Non-Interchangeability with other Formulations of CS2 – finished dosage forms containing the CS2 free acid should not be substituted with similar dosing strengths of other CS2 products containing a salt of CS2, i.e., CS2 potassium or sodium.

Deficiency:

……. the proposed generic drug product which contains the CS2 Sodium Salt in the finished dosage would not be considered pharmaceutically equivalent to the Reference Listed Drug which contains CS2 free acid in the finished dosage as stated in the labeling per the 21 CFR 314.94 (a)(5). We strongly recommend that you reformulate your drug product to contain the same active ingredient and amount in the same dosage form as the RLD, and to provide all supporting CMC information and a new bioequivalence study of the reformulated drug product to demonstrate that your drug product is pharmaceutically equivalent and bioequivalent to the Reference Listed Drug

***Section III-A.1* New BE study.**

#5 - Change in or lack of information about the form of the drug substance during drug product manufacturing.

Case study - 3

Facts: The proposed drug product CS3 is an immediate-release tablet with low API loading

- The manufacturing process involves dry mixing, wet-granulation, fluid-bed drying, milling-and-sieving, lubrication, compression, film-coating and packaging.
- Two sub-lots were used in wet granulation step for exhibit batches. A single lot will be used for commercial batch.

Item	Exhibit Batch	Largest Commercial Batch	Scale-up factor
Granules	2 lots of 6.89 kg	1 lot	**20×**
Core Tablets	13.77 kg	137.70 kg	10×
Number of Tablets	135,000 Tablets	1,350,000 Tablets	10×

Deficiency:

The scale-up factor for the largest commercial batch (137.7 kg), based on the batch size of final blend and/or uncoated tablets, will be 10-fold. However, your exhibit batches were manufactured in two lots of granules, while the commercial batch will be manufactured in one lot of granules. As a result, the actual maximum scale-up factor at the wet-granulation step is 20-fold. This is higher than the maximum scale-up allowed (10×), which poses a high risk in the manufacturing of quality drug product and is considered a major deficiency. Please **provide data from exhibit batches of adequate size** to justify your proposed commercial batch size.

#8 Scaling up of any unit operation >10 times

Case study - 4

Facts: The proposed drug product CS4 is an oral or rectal solution

- Drug product is manufactured by dissolution, filtration, filling, labeling and packaging.
- **Impurity A** was reported from **Tubing/Filter Extractable-Leachable Study**
- Pharm/Tox review has concerns regarding the proposed safety threshold of Impurity A for rectal use

Deficiency:

You have not adequately addressed the safety of **Impurity A** as a leachable from Tubing/Filter for the rectal route of administration. Based on your assessment and the information available to the Agency, we determined that the proposed maximum exposure to **Impurity A** as a leachable at 0.552 mg/day is not acceptable.

We recommend that you submit nonclinical information and/or clinical information on prior human experience with Impurity A for rectal use….or conduct toxicology study in an appropriate species…..

Alternately, please consider replacing the current filter/tubing with a more suitable ones. Submit adequate Chemistry Manufacturing Controls data for three new batches manufactured using the new filter/tubing component including executed batch records, qualification data for the components of the manufacturing equipment, release and stability data.

#11 Safety assessment of extractables and leachables

Case study - 5

Facts: The proposed drug product CS5 is 100 mg and 400 mg (free base) IR tablet

- The proposed process consists of three unit operations: dry blend and direct compression followed by non-functional coating.
- Final Blend has very poor powder flowability (cohesive material)

	100 mg product	400 mg product
Exhibit batch	1,400,000	45,000 *
Commercial batch	1,400,000	45,000 *

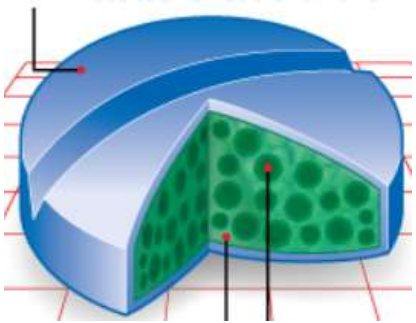
- The firm did not demonstrate good control at compression stage for the high strength 400 mg tablets as reflected by low yield, i.e. 60%-70% in some exhibit batches. The firm attributed this to "high online reject quantity" due to "weight variation".
- The firm manufactured one additional Batch#CS5 at the same scale for the problematic 400 mg strength with one major equipment modification, i.e., addition of an agitator in the bin-blender for more consistent die filing. The yield value for this batch is ~ 91.7% at compression stage.

Deficiency: The development data to support the selection of the agitator speed and its range was not included for Batch-CS5. Please provide batch record and supportive development data for our review. We recommend to add two (2) additional 400 mg strength tablet batches for demonstrating the feasibility of consistent compression and manufacturing DP at the proposed scale.

 # *Section III-A.1* New batches required due to new process element in commercial production and concerns on robustness

Case study - 6

Facts: The proposed drug product CS6 is a scored **ER tablet with MUPS (Multiple unit pellet system)**



- A notable number of out of specification (OOS) dissolution testing results were observed across all the dose strengths at release and stability for exhibit batches.
- The majority of the OOS results are associated to 8 hour dissolution data with most cases drug release exceeding the upper limit and some cases drug release less than the lower limit.

Deficiencies:

1. Drug product: There are OOS (out of specification) testing results for dissolution and content uniformity in your drug product at release and stability. They are also found in the Tablet Scoring Study Report. This is not acceptable. Please manufacture exhibit batches that meet all the quality specifications.
2. Process: ……. We recommend that you investigate the root-cause for failing to meet the dissolution specifications for whole and/or half-tablets, including evaluations of adopted equipment and unit operations, critical process parameters, and critical material attributes of in-process intermediates. Provide a comprehensive control strategy with supporting data from new registration batches to ensure that the critical quality attributes can be achieved.

 # *Section III-A.1* New batches required due to OOS in release and stability

Case study - 7

Facts: The proposed drug product CS7 is an IR tablet, **NTI drug with very low API loading**

- The manufacturing process involves **stepwise geometric mixing, compression** and packaging
- The in-process blend uniformity appears acceptable (mean, RSD), however its sampling size is 5× to 10× of the unit dose weight.
- The in-process content uniformity acceptance criteria used for the exhibit batches is based on USP <905> and cannot provide statistical inference to the entire batches. High AVs observed in exhibit batches.

Strength	Batch Number	Content Uniformity, Mean/AV		
		Initial/Full Hopper	Middle/Half Hopper	End/End Hopper
25 mcg	1	100.9/12.7	98.3/12.2	97.7/10.9
	2	99.3/6.1	101.7/14.5	98.4/11.0
	3	97.9/7.1	101.8/12.1	103.0/14.7

- **Scale-up x10. No in-process CU is proposed for commercial.**

Deficiency: ……In light of the potential high risk in content uniformity for commercial manufacturing, provide three commercial scale batch data (including in-process testing data such as blend uniformity and stratified content uniformity at the compression stage, and the final batch release data) for each of the lowest two strengths (x mcg and y mcg) and the highest strength (z mcg) to demonstrate that the proposed process is capable of producing quality drug products. Note that you should revise the in-process test methods/acceptance criteria for blend uniformity and stratified content uniformity according to the Agency's comments.

#7 Inadequate scaling-up of manufacturing process; Safety concern on sub-/over-potency

Case study - 8

Facts: Proposed drug product CS8 is an ER tablet with functional coating and laser drilled holes. No scale-up.

- Development study (manual drill) cannot support CPPs adopted in actual manufacturing process (laser drill).
- Exhibit Batches were poorly characterized and no data were provided on the actual laser setting.
- IRs were issued in May, with one **deficiency** specifically asking for development study using laser drill, how the applicant established CPPs/IPCs and how they ensure them for laser drilling unit operation.
- The applicant responded *in later June* with plenty of actions and updates, including a programmed recipe not accessible to the operator to ensure proper hole size and penetration, a microscope to examine and camera system for defect detection and rejection.
- A Pre-Approval Inspection was performed on DP manufacturing facility *in July*. OPF reviewer found that the firm was not implementing what was stated in the IR response. Two CPPs were either not monitored or running outside of qualified ranges. Visual inspection system failed to work. Same issues were observed in other products manufactured in this facility.

Consequence:

- Process Major: During the FDA inspection that took place from July, we have found serious control, and quality system issues regarding your laser drilling unit operation and its visual inspection system. Address those concerns and respond to our **previous deficiency**…..with three new exhibit batches.
- 10 Citations on Form 483. **Application Withhold; OAI for product manufacturing facility**

Recommendations

To avoid major deficiencies, we recommend the following:

- ✓ Spend more efforts on process development and the understanding of potential risks of each unit operation on product quality;
- ✓ Select proper process and equipment for proposed manufacturing process;
- ✓ Establish comprehensive control strategy, e.g. adequate material controls, Critical Process Parameters and In-process Controls for both exhibit and commercial batches;
- ✓ Registration batches meet the in-process, release and stability specifications;
- ✓ Adequately justify the operating ranges of scale-dependent process parameters. Do NOT leave process development work to Process Validation stage;
- ✓ Have facilities conform to submitted information;
- ✓ Submit all required information and data for review.

Readiness for Commercial Manufacture

Questions you should address:

- Do all registration batches meet the release specifications?
- Do all critical in-process testing meet the proposed specifications?
- Does the manufacturing process have adequate in-process controls?
- Is there significant batch-to-batch inconsistency among the three registration batches? Such as batch reconciliation, yields for unit operation and overall production, batch formulae etc.
- Are the proposed operating parameters supported by data collected from manufacturing of development and/or registration batches?
- Have all scale-dependent process parameters been identified? Have justifications been provided for those parameters based on their scale-up strategy?

Acknowledgement

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- Shujun Chen, Quality Reviewer, OPF
- Tim Zhou, Quality Reviewer, OPF
- Nathan Davis, Quality Reviewer, OPF

U.S. FOOD & DRUG ADMINISTRATION

Questions?

They will be addressed in the panel shortly….