QbR Lessons Learned & Common Deficiencies in Abbreviated New Drug Applications

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QbR as a platform for QbD for Generic Drugs

• The Office of Generic Drugs (OGD) developed Question based Review (QbR) in 2007 as a tool to implement the concepts and principles of FDA’s cGMPs for the 21st Century Initiative for the Abbreviated New Drug Applications (ANDAs).

• It was OGD’s first step toward providing the generic industry with a platform for sharing information, justifying specifications and building quality into generic drugs.

Reference: Srinivasan and Iser, JVT, June, 2009
The QbR Experience in OGD

-The Positives-

• Product & Process Development summary in QbR-QOS provides insight into sponsor’s rationale for product design and development of manufacturing process

• Justifications in QbR-QOS reduce the number of questions to sponsor

• Critical parameters identified in QbR-QOS enhance product and review assessment

• Electronic QbR-QOS reduces transcriptional errors and saves documentation time
The QbR Experience in OGD

-The Drawbacks-

• Limited product and process development information

• Applicants have provided response to the QbR-QOS questions with no supporting information in Module 3

• Lack of clear rationale behind setting specifications

• Minimal justification of scale up process
Fundamental Questions

- Will the product design ensure desired performance?

- Will the applicant be able to scale-up to commercial size; and ensure comparable quality with bio batch(es)?

- Will the applicant be able to manufacture the product with defined quality parameters over time?
In spite of introduction of the QbR and submission of more information in the Pharmaceutical Development Section (3.2.P.2) of the ANDA by the applicant, there are some deficiencies that are being frequently cited.
Nature of the common deficiencies in current ANDAs

– There are some “traditional” information which are not being addressed in ANDA submissions

– With an increased focus on product and process understanding, there are more questions asked regarding product design, critical quality attributes, critical material attributes, critical process parameters.
Common Deficiencies

3.2.S.1 Drug Substance

• The Drug Master File (DMF) related to your drug substance is deficient, and the holder has been notified. Please do not respond until the DMF holder has responded to all the deficiencies.

• Please revise the unknown impurities criteria to be in-line with ICH Q3A recommendations based on Maximum Daily Dose. Impurities observed above the recommended identification threshold should be identified, and impurities observed above the recommended qualification threshold should be suitably qualified.

• Based on the literature, multiple polymorphic forms are possible. Please provide the form used and add a suitable control to ensure its consistency in the drug substance.
Deficiencies related to the drug substance contd.:

• Residual solvent criteria should be in-line with the DMF holder’s limits as they are process related impurities. Please consult your DMF holder and revise your criteria accordingly.

• Please include a suitable test and justified criterion for water content of the drug substance.

• Based on the chiral nature of the drug substance, please include a control for the relevant enantiomer and diastereomers.

• In view of the chiral nature of the drug substance, please include a chiral identity.
Some potentially genotoxic impurities

$N$-Hydroxyaryl

$N$-Acylated aminoaryls

Aza-aryl $N$-oxides

Aminoaryl and alkylated aminoaryls

Michael Reactive Acceptors

Alkyl Esters of sulfonates and phosphonates

Urethane or Carbamate

Hydrazines Azo compounds

R = Alkyl, Aryl, or H

EWG = Electron withdrawing groups as C=O, CN, COOR etc.

Drug substance related methods

• **DMF holder’s method**: Adaption of the DMF holder’s method is acceptable. However, the sponsor needs to provide the details of the DMF holder’s validation and their own method verification information.

• **In-house vs. USP**: It is acceptable to use an in-house method for analysis of the drug substance, however demonstration of its equivalence to the USP method is desirable.

• **Process impurities**: The ANDA sponsor needs have a complete list of the possible process impurities in the drug substance and make sure that these impurities are separated from the parent peak and other degradants in their method.
Common Deficiencies & Comments

3.2.P.2 / 3.2.P.4 Excipients

- We would like to inform you that the premise of the excipient-API compatibility studies is to provide justification based on mechanistic understanding of chemical interaction of drug substance and excipients and manufacturing process. Thus, justifying excipient compatibility based on end product testing or monitoring changes in physical appearance are not acceptable. For your future applications, we request that you provide information regarding the possibility of degradation of the API or other interactions of the API in presence of the excipients.

- Due to the presence of carboxyl groups in the API there is a potential of interaction with the glycerin in the formulation. Please demonstrate that the proposed analytical methods are suitable to identify and quantify any ester product that may be formed.

- Please justify the functionality related characteristics of the release controlling (excipient name) in your modified release product, for example, viscosity range. Please address what impact a lot with at the lower end and higher end of the range would have on the drug product critical quality attributes such as release profile.
2.3.P.2.2 QbR-QOS: Excipients

- Inert(?) substances used as a vehicle for drug delivery
  - Chemically inert?
  - Biologically inert?
- Constitutes the majority of dosage form
- Most of the suppliers are Chemical Industry subsidiaries
- Specifications-driven
- Global Market and Manufacturing Base which makes them difficult to control
- Composition and “impurity” profiles are not well defined
2.3.P.2.2 QbR-QOS

Some known incompatibilities between API and excipient functional groups

<table>
<thead>
<tr>
<th>Functional Groups</th>
<th>Incompatibilities</th>
<th>Type of Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Amine</td>
<td>Mono and disaccharides</td>
<td>Amine-aldehyde and amine acetal formation, Maillard Rxn.</td>
</tr>
<tr>
<td>Ester, Lactose</td>
<td>Basic Components</td>
<td>Hydrolysis, ring opening</td>
</tr>
<tr>
<td>Carbonyl, Hydroxyl</td>
<td>Silanol</td>
<td>Hydrogen Bonding</td>
</tr>
<tr>
<td>Aldehyde</td>
<td>Amine, Carbohydrates</td>
<td>Aldehyde-amine, Schiff Base or Glycosamine formation</td>
</tr>
<tr>
<td>Carboxyl</td>
<td>Bases</td>
<td>Salt formation</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Oxygen</td>
<td>Oxidation to aldehydes and ketones</td>
</tr>
<tr>
<td>Sulfydryl</td>
<td>Oxygen</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Phenol</td>
<td>Metals</td>
<td>Complexation</td>
</tr>
<tr>
<td>Gelatin Capsule Shells</td>
<td>Cationic surfactants</td>
<td>Denaturization</td>
</tr>
</tbody>
</table>
2.3.P.2.2 QbR-QOS

• Impurities in Excipients
  – In many cases drugs react with excipient impurities, including reducing carbohydrates
  – Significant Reactive Excipient Impurities include
    • Hydrogen peroxide (other oxidized species)
    • Formaldehyde (other aldehydes)
    • Formic Acid (other acids)
  – Low drug excipient ratio leads to higher risk of reaction
Some reactive impurities in common excipients

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Povidone, crospovidone, polysorbates</td>
<td>Peroxides</td>
</tr>
<tr>
<td>Magnesium stearate, fixed oils, lipids</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>Lactose</td>
<td>Aldehydes, reducing sugars</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Benzoaldehyde</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Aldehydes, peroxides, organic acids</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Lignin, hemicelluloses, water</td>
</tr>
<tr>
<td>Starch</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Talc</td>
<td>Heavy Metals</td>
</tr>
<tr>
<td>Dibasic calcium phosphate dehydrate</td>
<td>Alkaline Residues</td>
</tr>
<tr>
<td>Stearate lubricants</td>
<td>Alkaline Residues</td>
</tr>
<tr>
<td>Hydroxypropylmethyl/ethyl cellulose</td>
<td>Glyoxal</td>
</tr>
</tbody>
</table>

Ref: Crowley P. J.; Martini, L.G., Pharm. Tech, Oct 2001
Common Deficiencies

3.2.P.1 / 3.2.P.2 Description, Composition

• Please justify the overage in your formulation by demonstration of similar or higher overage in the Reference Listed Drug (RLD). We recommend a comparison with multiple lots of RLD to justify the proposed overage.

• We note that there are significant differences in the proposed formulation and that of the RLD. We request you to further comment why these differences do not affect performance and intended use of your drug product as per label claim.
Some examples for consideration of design

- Delayed Release Tablet
  - RLD: DR tablet of enteric coated beads
    - Purpose of Design: Allowing for crushing, to be administered with applesauce while retaining the property of delayed release and also reduce stomach irritation

- Modified Release Tablet
  - RLD: IR + ER tablet
    - Purpose of Design: Allowing for rapid rising and maintenance of high plasma concentration upon administration and during the course of treatment
Common Manufacturing Deficiencies

3.2.P.3 Manufacturing (In-process Controls)

- Please justify the proposed tablet hardness range taking friability and dissolution into consideration.

- Your description of the granulation end point is very subjective. Please provide us with information regarding the steps to be taken if a suitable granulate is not formed by allocated time of mixing and its effect on the quality of your final product.

- Please revise the fill volume to meet the recommendations for excess volume in USP <1151>.
Rationale

• Please justify the proposed tablet hardness range taking friability and dissolution into consideration.
  
  – Examines variability in process
  – Demonstrates robustness of criteria
  – Also leads to understanding of impact of change
Rationale

- Your description of the granulation end point is very subjective. Please provide us with information regarding the steps to be taken if a suitable granulate is not formed by allocated time of mixing and its effect on the quality of your final product.

  - Is the process robust, repeatable?
  - Can consistent product be produced?
  - Is it a critical control?
Rationale

• Please revise the fill volume to meet the recommendations for excess volume in USP <1151>.
  – Part of USP <1> requirements
  – Important to ensure intended use
  – May be justified in multiple ways:
    • Development data
    • Extractable volume test
    • IPC filling controls with criteria in-line with <1151>
Process Development

• Reference: ICH Q8 (R)
• Impact of raw material attributes and process parameter on in-process materials and end product.
• How much of this knowledge is translated in building effective control strategy?
  – To move the further controls (upstream) instead of focus at the final stage(s) of manufacturing.
Process Development

• Demonstrate process understanding to show ability to scale up the process and execute it consistently.
  – Failing to identify critical process parameters (CPP) and the critical process steps indicates lack of understanding.
  – Unidentified critical steps or process parameters may be indicative of a poorly controlled manufacturing process and considered higher risk.
Process Development (QbR)

• Why was the manufacturing process described in 3.2.P.3 selected for this drug product?
  – Why was the process chosen?

• How are the manufacturing steps (unit operations) related to the drug product quality?
  – Relates process to product quality and identified critical steps

• How were the critical process parameters identified, monitored, and/or controlled?
  – Summary of process development studies used to identify CPPs

• What is the scale-up experience with the unit operations in this process?
  – Summary of process development studies and experience that supports scale-up
Summary of process development studies used to identify CPPs

• What is a critical process parameter?
  A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process condition or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency.

• Scale independent CPPs, such as material attributes, are valuable, and can be directly used in scale up.
  – For example, a material attribute CPP, such as moisture content, should have the same target value in the exhibit batch process and the commercial scale process.

• An operating parameter CPP, such as air flow rate, would be expected to change as the process scale changes.
How were the critical process parameters identified, monitored, and/or controlled?

• How should critical process parameters be identified?

• Prior experience or knowledge
  – For example, an ANDA sponsor that used the same blender for multiple products with similar formulations might use that information to support a claim that the key process parameter* mixing speed was not critical.
  – Prior experience may also be used to develop process models and thus reduce the number of experiments needed to establish the critical process parameters for the current product.

• Scientific investigations and controlled variations (Design of Experiments – D.O.E.) of operating parameters.

*A key process parameter is a designation for a potentially critical process parameter.
How were the critical process parameters identified, monitored, and/or controlled?

- Monitoring and Control
  - In-process / End product testing, and/or
  - Continuous Monitoring / PAT, and/or
  - Feedback
    - based on material property variability,
    - process,
    - or environment
What is the scale-up experience with the unit operations in this process?

- **Summary of process development studies and experience that supports scale-up**

- **Examples:**
  - Experience with other products using the same unit operations
  - Literature references/vendor scale-up factors
  - Lab scale (to pilot) to exhibit batch process transfer, exhibit batch production, as well as modeling and dimensional analysis.

- **Link to Scale-up Plan (QbR Questions in 2.3.P.3)**
  - Plan for commercial scale identifying scale dependent operating parameters and process monitoring
  - Comparability of commercial scale process to the exhibit batch process
  - Similarity of equipment, change of scale, physical properties of the API, and similarity of the excipients.
How is the knowledge gained from process development linked to manufacturing process (3.2.P.3)?

- Critical Process Parameter (CPP) are
  - identified
  - ranges are scientifically justified and
  - are flexible (justified ranges wider than without development)

- Automatic, continuous feedback, and/or control strategy in place.

- Higher assurance that process is robust with increased probability of successful scale-up
Common Container Closure Deficiencies

3.2.P.7 Container Closure System

*Please provide moisture permeation data for the proposed blister pack.*

*Please provide extractable and leachable studies for the proposed stoppers.*
Rationale

- Please provide moisture permeation data for the proposed blister pack.

  - Impact on the following:
    - Product quality / aesthetics
    - Product stability / degradation
    - Product Integrity (e.g. ODT)
Rationale

• *Please provide extractable and leachable studies for the proposed stoppers.*
  
  – Impact on product quality / safety
  – Relationship to formulation (pH, etc.)
2.3.P.2.4 Container Closure System

• **What specific container closure attributes are necessary to ensure product quality?**

• Studies conducted to identify necessary attributes including identity, suitability (safety, protection, compatibility, and performance) consistent with the QTPP.
  – *Guidance to Industry – Container Closure Systems for Packaging Human Drugs and Biologics.*

• Solid oral products package is generally driven by identified stability issues:
  – Light sensitivity
  – Moisture protection
  – Inert atmosphere
  – Tablet Integrity – ODT/Chewable
What specific container closure attributes are necessary to ensure product quality?

- If delivery devices are present (nasal sprays, metered inhalers, etc), development studies for designing device should be performed.
- Suitability of proposed system
  - Dosage form compatibility (e.g. extractables, leachables, dye from labeling)
  - Compatibility with the sterilization procedure
  - Performance system (e.g. dropper consistency, calibration of delivery device)
  - Provide studies to support dispensing and/or reconstitution requirement
3.2.P.5 / 3.2.P.8 Drug Product / Stability

- The drug product limit for specified impurity X is not acceptable as it is listed as a process impurity and should be controlled at no higher than the proposed drug substance limit. Please revise or justify.

- Please establish a criterion for reconstitution time based on a comparison with the RLD product.

- Please be informed that based on trends observed in the accelerated stability data, the expiry date for this product will be based solely on the accumulated full long-term stability data.
Rationale

• The drug product limit for specified impurity X is not acceptable as it is listed as a process impurity and should be controlled at no higher than the proposed drug substance limit. Please revise or justify.

  – In many cases the standard identification and qualification thresholds* are used for all specified impurities.
  – Appropriate for degradation products
  – Not appropriate for impurities that are solely linked to the drug substance synthetic route (i.e. process impurities).

* Per ICH Q3B(R) and ANDAs: Impurities in Drug Products (draft)
Rationale

- Please establish a criterion for reconstitution time based on a comparison with the RLD product.
  - Assurance of desired function
  - Based on observed data and RLD comparison
  - Additionally, ICH Q6A states that test for reconstitution time can also be omitted based on development studies.
Rationale

• Please be informed that based on trends observed in the accelerated stability data, the tentative expiry date for this product will be based solely on the accumulated full long-term stability data.

  – In these cases ACC data may not be representative of actual product stability, but this must be confirmed by LT data
  – Tentative expiry date is confirmed post-approval
Fundamental Questions

- Will the product design ensure desired performance?
- Will the sponsor be able to scale-up to commercial size; and ensure comparable quality with bio batch(es)?
- Will the sponsor be able to manufacture the product with defined quality parameters over time?

As we have seen, development studies and the subsequently justified material, product and process choices are directly related to answering YES to these fundamental questions.
Guiding Principles for Generic Products

1. Do not introduce any additional risk to consumers (excipients, design, impurities, container, etc.)

2. Understand the RLD and your proposed product to ensure that the ANDA product design will perform as intended

3. The allowed flexibility in the ANDA manufacturing processes and design, translates to a need for better understanding which will ensure
   • robust design and process; and
   • the ability to manufacture consistent product that meets desired quality / performance over the product life-cycle.
Transparency

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Any Questions?