Track 2: Achieving Drug Product Quality: Novel Approaches and Applications
Session 1: Oligonucleotide Therapeutics: Quality, Standards, and Regulation

Moderators: Larisa Wu (FDA) and Mohan Sapru (FDA)
Speakers: Joe Guiles (Agilent), Serge Beaucage (FDA) and Mohan Sapru (FDA)
Session Background/Premise/Challenges

• Oligonucleotides
  • Typically short chain DNA or RNA molecules or their chemically modified derivatives
  • Exhibit reproducibility, high potency, specificity, known mechanism of action, rapid onset, durability or effects, and reversibility
  • Are suitable for local or systemic delivery to target tissues
• Oligo therapeutics are rising as a new therapeutic modality; have the potential to be an important class of new medicines to fulfill unmet medical needs
• Currently, no formal guidelines are available for oligonucleotide products from any regulatory authority
• There is a need to establish standards and policy for this class of molecules
Session Schedule/Speakers

- Day 1 – Wednesday, March 22, 2017; TRACK #2: Achieving Drug Product Quality: Novel Approaches and Applications
- Moderators: Larisa Wu, FDA and Mohan Sapru, FDA
- Speakers:
  - Joe Guiles (Agilent): Challenges and Approaches Used in Current Process Development of Oligonucleotide Therapeutic APIs
  - Serge Beaucage (FDA): A High-Throughput Process for the Solid-Phase Purification of Synthetic DNA Sequences
  - Mohan Sapru (FDA): CMC Regulatory Considerations for Oligonucleotide Drug Products: FDA Perspective
- Panel Discussion
Key Themes and Takeaways

- Unique scientific and regulatory challenges in oligo therapeutics
- Majority of oligonucleotides synthetically created by solid phase synthesis
- Purification by anion exchange and then ultrafiltration to remove anion exchange buffers
- Impurities important in early synthesis
  - Total impurity level greatly impacted by coupling efficiency, chain length, and charge similarity to the main oligonucleotide sequence
- Major impurities with structure similarity to the main oligonucleotide difficult to remove
- High-throughput procedures available for the purification of synthetic oligonucleotides
Key Themes and Takeaways

- No ICH or FDA regulatory guidelines that specifically address the quality expectations/standards for oligonucleotide products
- No consensus about impurity identification and qualification thresholds
- Despite their large size, oligos considered more similar to small molecule drugs than biologics
- FDA expectations for oligonucleotide drug applications:
  - determination of oligonucleotide sequence, API designation, calculation of assay, and, in some cases, bioassay
- So far, 5 FDA approved oligonucleotide products, 2 of them in 2016
  - Eteplirsen (Exondys 51)
  - Nusinersen (Spinraza)
Future Directions

- Accumulative regulatory experience
- Advances in impurity qualifications, toxicity & control strategies
- Advances in oligonucleotide chemistry and analytical methods
- Continued progress towards establishing science based regulatory guidelines
Session 2: PQRI PODP Working Group Recommendations on Extractables and Leachables

Moderator: Diane Paskiet (West)
Speakers: Diane Paskiet (West), Dennis Jenke (Triad Scientific Solutions), Christopher Houston (iuvo Bioscience)
Summary Points

- PQRI PODP Working Group developed safety thresholds and best practices for E/L studies
  - Risk communication and management encouraged
  - Built on conceptual foundations of PQRI OINDP E/L work
- Parenterals and ophthalmics represent a large, diverse group of products that had to be considered
  - Small and large molecules
  - Range of delivery and packaging systems, and material characteristics
Thresholds

<table>
<thead>
<tr>
<th>Proposal</th>
<th>Class I No Genotox</th>
<th>Class II No Genotox</th>
<th>Class III Genotox M7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (µg/day)</td>
<td>50 If Systemic</td>
<td>5 If Irritant/Sensitizer</td>
<td>1.5 To Identify</td>
</tr>
</tbody>
</table>

Best Practices

<table>
<thead>
<tr>
<th>Characterization</th>
<th>Simulation</th>
<th>Leachables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material Chemistry</td>
<td>Mimic Actual Use</td>
<td>Actual Drug Product</td>
</tr>
</tbody>
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AET

LVP, SVP, PFS Applications

Considerations Given

Ophthalmics

Biologics
Next Steps

- PQRI PODP Recommendations to be sent to PQRI Development Technical Committee for review in 2 Q 2017
- Target final to public by 3 Q 2017
- PQRI workshops planned
Session 3: Extractables and Leachables: The Future

Moderator: Reggie Saraceno (Boehringer Ingelheim)
Speakers: Mike Hodgson (Baxter), John Iannone (AMRI) and Tim Robinson (FDA)
The Future for E/L is Now - Observations

Dosage forms are more complex
• Biopharmaceuticals (manufacture, product, delivery); Implantable devices; New combinations of existing technologies; Novel materials

Organizations struggle with how to properly do E/L studies
• Difficult to discern what is relevant data/knowledge for their application
• Severity is not well defined
• Fall back to performing large studies; generate lots of data which is ultimately of questionable use
• More than one way to get to an answer; which is best…
• Detailed, specific analysis of the product is important to design appropriate E/L studies
  • MDIs – mouthpiece vs. valves
  • Pre-filled syringe – stopper vs. 316 stainless steel
Risk Assessment Tools – Aiding E/L Study Design

Risk assessment (RA) helps lead to a Toxicology impact assessment – understand what is delivered to the patient.

Many existing examples of using a risk-based approach:
- 1999 FDA guidance on C/C systems, 2005 EMEA guidance on plastic packing materials, 2014 ICH M7 guidance on genotox impurities

Engage ICH Q9 principles to assess severity and guide appropriate studies.

Severity ranking guides the extent of studies from extraction with aggressive conditions versus leachable studies at other end.

Probability of leachables in product also has knowledge hierarchy with leachables studies on specific product at one end; simulated studies at the other.

Chemical analysis becoming more important for Toxicity assessments and biocompatibility -- important for risk mitigation and failure analysis.
To sum up...

RA, applied correctly, provides a systematic approach for understanding new products/systems and planning appropriate E/L studies. The output of the RA exercise should direct experimental work and influence leachable risk management strategy. Experimental work feeds back to further RA for greater product understanding and to justify actual risk. Not all data/knowledge is useful or equivalent - E/L is too complex to manage with a one size fits all approach; education of critical parameters and what they mean is necessary. Controlled extraction studies should be relevant to the clinical application by modeling the clinically relevant conditions. Proper alignment is a goal, not yet achieved, for proper evaluation of multifaceted and regulated assessment technologies. Check out the detailed talks for more examples of RA and case studies.
Session 4: Elemental Impurities

Moderator: Tony DeStefano (PQRI)
Speakers: Nancy Lewen (Bristol-Myers Squibb), Donna Seibert (Perrigo), and Danae Christodoulou (FDA)
Background/Relevance of Topic

- USP <232> and USP<233> will replace USP <231> as the compendial tests for elemental impurities (aka heavy metals) with an implementation date of January, 2018.
- FDA Guidance and ICH Q3D expect compliance beginning June, 2016 for new NDAs/ANDAs
- Implementation across the wide spectrum of drugs on the market and the levels that need to be measured remain concerns for many groups
- An understanding of the opportunities and challenges of the new technology, the practical aspects of making the measurements, and FDA’s short-term and long-term expectations regarding compliance and regulatory submissions are important.
- This session addressed all three of these areas of interest.
Summary of Presentations

Nancy Lewen, BMS – Implementing ICH Q3D and USP 232/233 – Challenges and Opportunities

• Key dates – June 2016 – New drug products, January, 2018 – existing drug products and USP 231 removed from the book via General Notices
• Need – System understanding control/change control strategy, some data
• Mined excipients are an on-going issue due to variability of sources. Data may mean some testing in these cases.
• New vendors do not automatically imply more testing – assess the risk and the robustness of your control strategy.
• Aggressive manufacturing/processing equipment – testing likely needed
• Vendor won’t supply data – testing, literature, Lhasa DB
  • Paper exercise may be ok for well understood materials, processes and no metal intentionally added
Summary of Presentations

Donna Seibert – Perrigo - **PQRI/USP Workshop on Implementation Status and Progress Report on Collaborative Studies**

- PQRI/USP host a successful series of workshops on elemental impurities
- Nov 2016 workshop provided a forum for focused dialogue between regulators, compendial colleagues, drug manufacturers, API and excipient suppliers, and other stakeholders
- Ongoing dialogue needed to promote the understanding of risk assessment strategies in the context of elemental impurity requirements as implementation proceeds.
- Discussion of analytical capabilities and technical challenges is beneficial as labs are building expertise in spectroscopic techniques and/or interpretation of spectroscopic data
- Collaborative studies seek to provide a data driven way to discuss technical aspects and expected variation for the analytical techniques relevant to elemental impurities
Summary of Presentations

Danae Christodoulou, FDA - A Reviewer's Perspective on the Monitoring Elemental Impurities

1. Considerations for risk assessment: EI from mined raw materials, manufacturing processes, container/closure

2. Control strategy for EI: Consistently above the control threshold, options for control in drug product component(s) or drug product.

3. Documentation to be included in an application and at the manufacturing site: Risk assessment summary and support data to the control strategy versus detailed risk assessment, screenings, qualification of supplier(s) and data supporting the manufacturer’s quality system.

4. Suitability of analytical methods to support EI determination.
Action Steps/Discussion Points

- See <661> series and <381> USP general chapter for references to elemental impurities.
- Metals intentionally added in any part of the process should be considered in the risk assessment.
- Execution and reporting of the PQRI Phase II collaborative study.
- Planning Committee is actively engaged for PQRI/USP workshop -- Nov. 2-3, 2017.
- Summary slides from 2016 EI workshop will be posted on PQRI website within next two weeks (presentation slides already posted) -- [http://pqri.org/](http://pqri.org/).
- Work toward demonstrating compliance—Jan 2018 will be here soon.
- Continued dialogue around newly published information/current topics.
  - Recent examples include:
    - Element-specific chapters in compendia—remove or retain?
Session 5: Drug/Device Combination Products: Quality

Moderators:
Nina Cauchon (Amgen) and Laura O’Brien (Boehringer Ingelheim)

Speakers:
Doug Mead (Janssen), Clint Judd (Amgen), & Ramesh Raghavachari (FDA)
Tremendous diversity

- Types of combination products and how they deliver the dose
- Design, development, and control processes
- Device component parameters range from few to thousands; moving or fixed → challenging to identify CQAs / release tests
- Regulatory requirements, review processes
- Criticality assessment, also considering the patient population(s)
- User handling considerations

→ Sponsor’s combination product expertise is specialized and implementation details vary case by case!
Regulatory perspectives on CQAs, CPPs, and Risk Analyses for Combination Prods.

- General guidance is fragmented across countries, organizations, & documents; not comprehensive in any single document, and may not be aligned.
- For success, drug regs & device regs have to be integrated and implemented.
- “Essential Performance Requirements”? – A new term you may see in Authority requests for information. Sponsor should decide how to distinguish between “intended function” and “essential performance.”
- Drug vs device development:
  - process dev’t versus design dev’t (via design controls)
  - devices are changed/ improved more often post-approval
- Need to justify how risk mitigation resulted in “level of acceptable risk”
Life Testing for Device Combination Prods.

- Design inputs/outputs should capture varied conditions potentially impacting performance over time, e.g., humidity, processing, vibrations.
- Design inputs/outputs should capture how to define the start, duration, and end of performance shelf life limiting event.
  
  Example: resin mould-by date, considers shelf life of raw materials.
- Device shelf life is comprised of multiple stages, each with unique durations and conditions. Recommend mapping design controls & recommendations for each stage.
- Not every feature needs to be evaluated over shelf life; consider risks, e.g., content vs legibility/damage for a label.
- Risk assessment outcomes → stress study protocols (testing at nominal versus extreme conditions/parameters); also consider specific cases e.g. thermal transitions of plastics; biologic stability.
- Purchasing control process should capture details relevant to shelf life.
Ensuring the Quality of Some Drug-Device Combination Products - FDA Perspective

Transdermal systems (patch) → uniform, continuous drug delivery
- Adhesion (over a range)
- Precipitation/crystallization → lack of drug delivery, non-uniformity
- Migration; cold flow
- Misuse / labeling

Pulmonary delivery devices
- Coordination of drug delivery and its usage is critical; demonstrate quality attributes as a function of time during administration
- Impurity: risk of lung collapse; e.g., detergent residue in a MDI can
- HF error mitigation (not shaking; coordination with breath; orientation)
Ensuring the Quality of Some Drug-Device Combination Products - FDA Perspective

Auto-injectors

• Device activation reliability is critical, e.g., epinephrine
• Dose delivered, stability of DS, force to fire
• Safety issues: It may take time (e.g., 10 seconds) to administer; difficult to restrain young children → risk of lacerations → Agency recommends shorter delivery time
Session 6: Drug/Device Combination Products: Bioequivalence

Moderators: Bing Li (FDA) and Andrew LeBoeuf (FDA)
Speakers: Bing Li (FDA), Andrea Redd (Fresenius-Kabi), and Irene Chan (FDA)
Thoughts for designing our session

• Selecting critical topics which audiences are interested
• Covering representative combination products to illustrate the points
• Including the most updated advancements happening in the field
• Good representative from two sides of the table
• Principles + case studies
Presentations

1) Bioequivalence of Locally Acting Orally Inhaled and Nasal Drug Products: Regulatory Histories and Milestones
   Bing Li, FDA

2) Understanding BE Requirements for Combination Products – A Focus on Auto Injectors
   Andrea Redd, Fresenius-Kabi

3) User Interface Considerations for Drug-Device Combination Products Submitted in an ANDA
   Irene Chan, FDA
Key Points (1)

• FDA approved about 70 ANDAs for combination products in 2006-2016 (more than half of these for orally inhaled and nasal drug products), and issued a number of product-specific bioequivalence guidances

• “Weight of evidence” approach:
  • Equivalent in vitro performance
  • Equivalent systemic exposure
  • Equivalent local delivery (e.g., clinical endpoints for nasal sprays)
    • Could be “most expensive part of development”
  • Device similarity
  • Formulation sameness

• Emerging technologies could open possibilities for waiving clinical endpoint BE study
  • E.g., Morphology Directed Raman Spectroscopy for nasal suspension characterization
Key Points (2)

- Lessons from case studies of generic autoinjectors:
  - Always compare to an RLD even if other generics are available.
  - Statistically significant differences in dimensions (e.g., needle extension difference of less than 1 mm) could lead to requirement of a PK study.
  - Compare functional attributes (e.g., drug volume delivered, injection time, force to fire).
  - “How close is close enough?” – should discuss with FDA case by case.
  - Human Factors study should be separate from in vivo bioequivalence study (different goals and different design of the studies).
  - Discussing with FDA the generic’s design and differences from RLD as early as possible could have been beneficial.
Key Points (3)

- Therapeutic equivalence is not only bioequivalence but also substitutability
- User interface includes packaging, labeling, instructions for use, device constituent parts such as displays, etc.
- January 2017 Draft Guidance on Comparative Human Factors Studies
  - Focus is on differences in user interface and impact of those differences on safety and efficacy
    - Switch at the pharmacy from RLD to generic
    - Training is often not given
- FDA does not expect that the design of a generic drug-device combination product be identical to the design of its RLD, but it’s prudent to have the same product presentation as RLD
- What is allowable difference? – should discuss with FDA case by case
- Collaborate with FDA in the early development of any proposed generic combination product
Panel Discussion and Q&As

• When will the “changed paradigm” approach (illustrated for nasal sprays) be applied to MDIs and DPIs?
  • Need more consideration because regional deposition is critical for lung delivery.

• If could predict deposition using in-silico models, and dissolution data, could that be a way to eliminate clinical endpoint requirement?
  • Currently simulation approach are used mainly as supportive evidence but cannot yet replace a “REAL” study in regulatory arena.

• If a candidate product has good solubility, could it be considered for eliminating in-vivo testing requirements?
  • There is much discussion about BCS for OINDPs but they stay theoretical for now. Need data. Method validation is also critical
Panel Discussion and Q&As (cont’d)

• Is there a difference between HF studies intended for Health Care Providers (HCPs) vs. patients? Different study designs and requirements?

  • Yes, user population needs to be considered. HCPs have different knowledge/education basis. Would need to test two user populations – depending on the device constituent part and intended use. For HCP-only population, may leverage existing data. It is case specific. Should discuss with FDA.

  • Per the January 2017 Draft Guidance, differences in ANDA combination products have to be evaluated in the context of overall risk profile, and HCP vs patient would be one of considerations.

• How does CDRH and CDER interact?

  • The two centers have same goals, use same principles, do same work. There are mechanisms for inter-center consults when needed.
Panel Discussion and Q&As (cont’d)

- Are there previous examples of comparative Human Factors studies?
  - No
- For comparative HF studies, should patients with previous RLD user be recruited?
  - Depends on your study design. Has to be representative of user population. Also depends on the product
  - “Existing knowledge” is hard to define. For example, for emergency-use products, may have only used the product once a year.
  - Even with naïve subjects, training could be difficult.
  - Sponsors should discuss study designs with FDA, and FDA’s statisticians will evaluate
Panel Discussion (cont’d)

• In auto-injector comparison of functional parameters, the sample size may have been too small to have sufficient power statistically.

• Communication between FDA OGD and ANDA sponsors is important and is improving.
  • Controlled correspondence mechanism still exists, but there is also now a pre-ANDA process. Can request a meeting with FDA for in-depth discussions.

• In a sumatriptan autoinjector example, since it’s a systemic drug, would FDA accept animal PK data instead of human PK in an ANDA?
  • No, not at this time.
Final Comment from the Audience

“I have worked with different regulatory agencies around the world, and FDA is the best – most responsive and productive. Thank You!”