The Impact of SEND Data on FDA Review of Nonclinical Studies

PhUSE US Connect 2019

Matthew Whittaker, Ph.D.
Kevin Snyder, Ph.D.
FDA Center for Drug Evaluation and Research, Office Of New Drugs
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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA’s views or policies.
Outline

- Overview of nonclinical review at FDA
- Janus Nonclinical
- Impact of SEND on nonclinical review
- Ongoing and future development initiatives
FDA: OND & OCS Relationship

Office of Medical Products and Tobacco

Center for Biologics Evaluation and Research (CBER)

Office of New Drugs (OND)

Clinical reviewers (medical officers)

Nonclinical reviewers (Pharm/Tox)

Center for Drug Evaluation & Research (CDER)

Center for Tobacco Products

Center for Devices & Radiological Health (CDRH)

Office of Translational Sciences

Office of Computational Science (OCS)

Tools & training for review of study data

Define functionality requirements for review tools
<table>
<thead>
<tr>
<th>Discipline</th>
<th>Role</th>
<th>Office</th>
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<tbody>
<tr>
<td>Regulatory project manager</td>
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<tr>
<td></td>
<td>communicate with sponsor</td>
<td></td>
</tr>
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<td>Clinical</td>
<td>Primary reviewer</td>
<td>Office of New Drugs</td>
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<td>Chemistry, Manufacturing &amp; Controls (CMC)</td>
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<td>Office of Pharmaceutical Quality</td>
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</table>
Nonclinical Reviewers in OND

- 247 Reviewers
- 17 review divisions
- All are Ph.D.s
  - Pharmacology (areas of research vary widely)
  - Toxicology
- Come from post-docs, academic research, or industry positions
Nonclinical toxicology studies

- Objectives
  - Define toxic effects of a drug that could potentially be seen in **humans**
  - Define the doses/exposures at which these effects might be expected to occur
Nonclinical studies in support of clinical development

**PRE-CLINICAL**
(before drug is tested in humans)

- In vitro Pharmacology
- Genetic Toxicology
- Safety Pharmacology
- “IND-enabling” toxicology studies
  - Rat
  - Non-rodent (dog or monkey)
  - Dose animals up to the duration of the proposed opening clinical study (i.e. 14-days or 28-days)

**CLINICAL**
(testing of drug in humans)

- **IND Phase**
  (several years)

  - **IND submitted**
  - **30 d safety review**
  - **NDA submitted**

  - Chronic toxicology
    - 6 month rat
    - 9 month dog/monkey
  - Reproductive toxicology studies
    - Fertility
    - Embryofetal development

**Approval**

- 10-month review period
- Carcinogenicity
- Pre & postnatal development
Major review principles

(1) Look for findings that show a dose-response relationship

(2) Of those findings, which ones are considered adverse?

- These 2 components are main factors in limit-dose determination
Challenges with current approach to review of nonclinical studies

- Nonclinical study reports (NCSRs) submitted in pdf format
  - Data analysis requires re-typing of values from summary tables into Excel
  - Variable formats used for organization of NCSRs - 1000+ page documents very difficult to navigate
  - Nonclinical study data is not readily searchable across studies

- SEND datasets can address each of these issues
Electronic study data regulations

- FD&C Act Section 745A(a): Sponsors must use the data standards defined in the **FDA Data Standards Catalog** starting 24-months after final guidance is issued for a specific submission type

<table>
<thead>
<tr>
<th>Standard</th>
<th>Application type</th>
<th>Dates that standard is accepted</th>
<th>Dates that standard is required*</th>
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<td>NDA/BLA/ANDA</td>
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<td>8/21/17-</td>
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*Requirement dates refer to the nonclinical study *initiation* date (not the date that the study is submitted to the Agency)
## SEND submissions to FDA

<table>
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<th>Application type</th>
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<th>2018</th>
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<td>47 (30)</td>
<td>319 (145)</td>
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<tr>
<td>NDA</td>
<td>54 (32)</td>
<td>8 (3)</td>
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<td>BLA</td>
<td>3 (3)</td>
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</table>

*As of 12/28/18

- All SEND submissions to date have been in SEND 3.0
Janus Nonclinical
Janus Nonclinical

- FDA-specific, web-based application that allows users to analyze and visualize SEND datasets
- Pharm/tox reviewers from OND are guiding development of Janus NC by OCS

Why?
Janus Nonclinical

**Current**
- Table & figure format – consistent with general FDA reviewer practices
  - Review documents – consistent formatting across reviewers & review divisions

**Ongoing**
- Interface with IND Smart Template

**Future**
- Cross-study analysis (nonclinical)
- Nonclinical – clinical data correlation
Janus NC Dashboard

- User assigns group alias, control group, **set type** in the Study Sets Table
  - 5 possible Set Types: interim, terminal, recovery, toxicokinetic, satellite

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<tr>
<th>Sponsor Group</th>
<th>Group Label</th>
<th>Group Alias</th>
<th>Control Group</th>
<th>Set Code</th>
<th>Set Description</th>
<th>TK Description</th>
<th>Set Type</th>
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<tr>
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<td>Group 1 - Reference Item</td>
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### Janus NC Summary Table - BW

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<tr>
<td>2M</td>
<td>286.1</td>
<td>352.1</td>
<td>386.1</td>
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<tr>
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<th>Day-1</th>
<th>Day-4</th>
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<tbody>
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<td>Mean</td>
<td>Std Dev</td>
<td>Mean</td>
<td>Std Dev</td>
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<td>Male</td>
<td>Control [Terminal,Recovery]</td>
<td>Body Weight</td>
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<td>±15.17</td>
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<td>Male</td>
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<td>354.18</td>
<td>±15.38</td>
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<td>Body Weight</td>
<td>g</td>
<td>284.93</td>
<td>±9.34</td>
<td>353.38</td>
<td>±13.96</td>
</tr>
</tbody>
</table>
Janus Nonclinical: Now

- Janus NC summary tables reflect summary tables in NCSR
  - Mean calculations based on Set Types defined in Dashboard
  - Highly customizable

- Dynamically filter & sort summary table data
  - Greatest impact: LB & MI

- Switch from Mean ± SD view to % change from control in 2 clicks
  - Eliminates need for re-typing & analysis in Excel

- Individual animal data available from summary table (click on mean)
Impact of SEND data on nonclinical review
## Current impact: Time Savings

- **Summary table preparation time**

<table>
<thead>
<tr>
<th>Data table</th>
<th>Traditional methods – pdf</th>
<th>Janus NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Chemistry</td>
<td>3+ hrs</td>
<td>30 – 45 mins</td>
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<tr>
<td>Histopathology</td>
<td>6 – 8 hrs</td>
<td>1 – 2 hrs</td>
</tr>
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</table>
Improved review efficiency: benefits

- More time to critically consider observed findings in tox studies
  - Risk assessment
  - Sponsor’s perspective & potential explanations for findings

- Potentially earlier engagement with sponsors on specific review issues (rather than at the last minute before the 30 d review clock is about to expire)
Improved review efficiency: benefits

- P/T Reviewers: 50+ INDs/NDAs/BLAs in their portfolio at any given time
  - Submissions are constantly coming in to each IND
  - P/T reviewers: Must keep up with new clinical protocols, clinical protocol amendments, nonclinical inquiries, new study reports...

- Reality: Prioritize PDUFA deadline-related assignments

- More efficient review of tox studies → more time to keep up with ongoing portfolio
  - More timely responses to inquiries with non-PDUFA mandated timelines?
Improved review efficiency: benefits

- More time to engage in non-review activities
  - Subcommittees within FDA
    - Examine topics of scientific interest
  - Engagement with industry/academic community
Future impact

- More informed regulatory decision-making
  - Janus: Warehouse of nonclinical datasets
    - Robust historical control databases
    - Understand class effects on different nonclinical species
Ongoing & future development initiatives

- Training – for all nonclinical reviewers in OND
  - SEND standard (how nonclinical study data is modeled in SEND)
  - Practical use of Janus Nonclinical

- Janus Nonclinical
  - Optimize summary table displays for all domains
  - Graphing/ data visualization enhancements
  - Cross-study analyses
Summary

- Nonclinical reviewers in OND work closely with staff in OCS to guide development of Janus Nonclinical (FDA-specific software application for visualization/analysis of SEND data)

- Janus Nonclinical – increased review efficiency
  - Much faster identification of treatment-related findings than traditional methods with pdf NCSRs

- Increased review efficiency - expected to benefit both FDA and Sponsors
SEND submissions to FDA

- Nonclinical studies initiated after 12/18/17 that did NOT include SEND datasets
  - Difficult to quantify this (no automated flag to identify studies by study initiation date)
  - 3-week sample size: 9/13/18 – 10/6/18; Stephanie Leuenroth-Quinn, (FDA/OND/IO)
  - 16% (15/96 INDs) of INDs during this time period failed to follow SEND requirement
  - 26 total studies that should have had SEND (as defined by study initiation date) did not
    - Studies submitted to modules 4.2.3.1, 4.2.3.2, and 4.2.3.4
    - Draft, interim, final, GLP, Non-GLP studies
    - Companies were both small and large
    - CROs (both in US and outside of US)

- Technical rejection criteria are not yet turned on
Major review principles

- **Additional Factors contribute to determination of the Limit Dose**
  
  (1) Can the finding(s) be monitored clinically?
  
  - So: could doctors see evidence of this toxicity during regular examinations and stop treatment if necessary?
    - Toxicity to brain cells: not clinically monitorable
    - Skin inflammation: clinically monitorable
  
  (2) Is the finding reversible if you stop treatment?
  
  (3) What level of risk is considered acceptable based on the indication?
  
  - This is established in collaboration with the clinical review team
  - Example: Lupus (severe disease, no available treatments) vs. Seasonal allergic rhinitis (many available treatments).
    - Review division may allow clinical dosing beyond the NOAEL dose under certain circumstances