# Meeting Minutes

## CDISC-HL7 Stage I-B
## March 19, 2008
## 8:30 am – 2:00 pm (EST)

**Attendees / Affiliation**

Dave Iberson-Hurst/CDISC (Co-Chair)
Jay Levine/FDA (Co-Chair)
Patty Garvey/FDA
Scott Getzin/Eli Lilly
Armando Oliva/FDA
Jason Rock/Global Submit
Lise Stevens/FDA
Diane Wold/GSK

**Background**

The Clinical Data Interchange Standards Consortium (CDISC) formed a Stage IB group to develop the requirements for the CDISC - Health Level 7 (HL7) Content to Message Project. It was agreed by FDA and CDISC to conduct a series of regular conference calls for sub-team members as the initial path forward on the CDISC HL7 IB activities.

The purpose of this meeting was to discuss the Study Participation storyboards.

**Discussion**

- The use cases should describe (focused for Release 1 Bullets 1-4):
  - annual update of the study:
  - subject demographics (per subject level)
  - subject disposition information (subject level data)
  - start of the study (sponsor, IND holders, CROs, central labs, safety monitoring boards, data management organizations)
  - investigator participation (linking to FIREBIRD information) (Form 1572)

  ** **NOTE**: Separate and future messages (future release)
  - study disposition/conclusion – study planned, study stop due to AEs, etc
  - overall recruitment status (study opened for enrollment or not)

- Scott responsible for drafting the roles and responsibilities for organizations:
  - Data handlers/managers
  - Central Labs – basic info, certification
  - Site monitoring – basic info
  - DSMB (Data Safety Monitoring Board)
  - IRBs – authentication/certification
  - CROs – basic information

- The following need further brainstorming: study subject – look at a boarder picture i.e. animal and product (device).

- The group would like to capture the following types of scenarios:
    - Complex (oncology - chemo vs rx. vs surgery - Diane to provide example)
    - Simple
    - Animal Toxicity study
    - Stability study
    - Veterinary study
    - Device performance study

*Attachment: DRAFT Study Participation storyboards*

***Drafted: PGarvey/4-7-2008***
***Approved: 5-6-2008***

**Some thoughts on CDISC-HL7 storyboards. Each can be broken down into multiple, simpler real-life scenarios with more detail.**

# 1. New Protocol Submission

Acme Pharmaceuticals plans to study the effects of their new topical pharmaceutical product, Drug A in two available strengths, a 1% topical lotion and a 5% topical lotion, compared with placebo lotion, to treat sunburn. Study A1234 will enroll 100 subjects with a pre-specified demographic composition. Each subject will serve as their own control. Three areas of sunburn will each be treated, in a random manner, with placebo, 1% lotion, and 5% lotion. All planned local clinical observations will be associated with the experimental intervention at the site of application. Acme must submit a new protocol to the FDA before beginning the investigation. The protocol submission contains a CDISC-HL7 study protocol message containing: a) study summary information including planned enrollment information b) eligibility criteria, c) trial design (including planned arms, elements, visits, epochs, planned interventions and assessments) and d) the statistical analysis plan as currently defined by the CDISC standard.

We should create the minimal amount of storyboards needed to cover the following scenerios:

1. Arms
    1.1. Single Arm
    1.2. Multiple Arms
    1.3. Single treatment in Arm
    1.4. Multiple treatments in Arm
    1.5. 1 Arm per patient
    1.6. 2 or more Arms per patient
    1.7. Arm switching based upon response.
    1.8. Treatment(s) in Arm is not completely determined by Arm assignment
2. Investigators
    2.1. Single
    2.2. Multiple
3. Treatments
    3.1. Drug(s)
    3.2. Device(s)
    3.3. Surgery(ies)
    3.4. Drug/Device
    3.5. Drug/Surgery
    3.6. Device/Surgery
    3.7. Drug/Device/Surgery
4. Epoch
    4.1. Single epoch
    4.2. Multiple epochs
5. Previous studies
    5.1. Continuation from previous study or studies? (Sometimes the last Epoch is an open label extension that contains patients from multiple studies)

6. Allocation to Arms
   6.1. observational
   6.2. randomized
   6.3. adaptive randomization

## 2. Study Participation

2a. Study Progress

Discussion 3/19:
Use Case describes (focused for Release 1 Bullets 1-4)

- annual update of the study
  - subject demographics (per subject level)
  - subject disposition information (subject level data)
- start of the study (sponsor, IND holders, CROs, central labs, safety monitoring boards, data management organizations)
- investigator participation (linking to FIREBIRD information) (Form 1572)

** **NOTE**: Separate and future messages (future release)
  - study disposition/conclusion – study planned, study stop due to AEs, etc
  - overall recruitment status (study opened for enrollment or not)

ROLES: (Scott will work on this, pick list of roles)
Data handlers/managers
Central Labs – basic info, certification
Site monitoring – basic info
DSMB (Data Safety Monitoring Board)
IRBs – authentication/certification
CROs – basic info

Need further brainstorming:
Study subject – look at a boarder picture i.e. animal and product (device)

New Wave Pharmaceutical has committed to perform a phase 4 multi-center study to investigate the effects of their recently approved Drug B on cognitive function and level of alertness, because of inconclusive causal reports in phase 3 clinical trials of drowsiness and motor vehicle accidents. As part of their phase 4 commitment, they must notify the FDA annually on the progress associated with conducting the trial. With their annual report submission, they will use the CDISC-HL7 study participation message to identify each subject enrolled to date, including all relevant demographic and other information as defined by the CDISC DM domain:

- Unique Subject Identifier
- Subject Identifier for the Study
- Subject Reference Start Date/Time
- Subject Reference End Date/Time

- Study Site Identifier for the Subject
- Investigator Identifier associated with the Subject
- Investigator Name associated with the Subject
- Date/Time of Birth of the Subject
- Age
- Age Units
- Sex
- Race
- Ethnicity
- Planned Arm Code (if known)
- Description of Planned Arm
- Country
- Date/Time of Collection
- Study Day of Collection

as well as the cutoff date used for the report.

## 3. Spontaneous Adverse Event Report

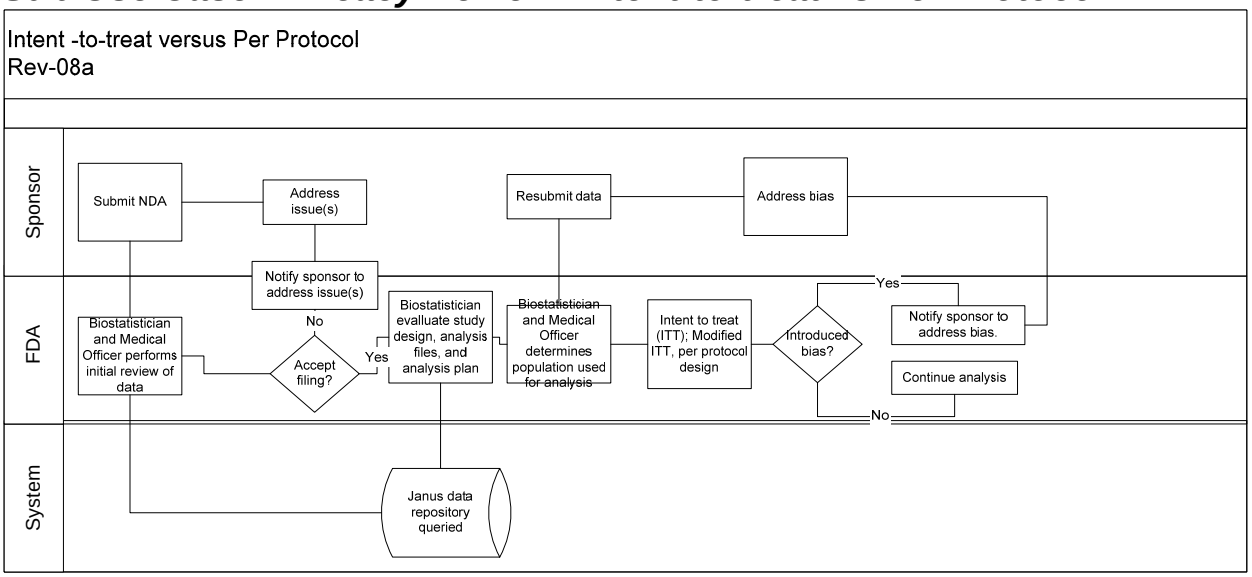
An experimental subject in Acme's Study A1234 develops right upper quadrant pain and jaundice two weeks after starting treatment for sunburn. She undergoes and unscheduled clinical visit at the investigator site. The investigator identifies right upper quadrant tenderness, an enlarged liver. He performs a liver function test, which reveals an elevated ALT, AST, Alkaline Phosphatase and Total Bilirubin. The findings are serious and unexpected. These assessments are unscheduled and the findings are reportable as an expedited adverse event report. The sponsor uses the HL7 ICSR to report the adverse event to the FDA, and all related findings and interventions.

## 4. Subject Data Submission

Study A1234 is complete and Acme Pharmaceuticals now wants to send to the FDA all the observations recorded for each subject during the study as part of their study report submission. Acme uses the CDISC-HL7 subject data message to provide all the recorded observations, as well as all the derived parameters resulting from those observations, as defined by the CDISC SDTM and ADaM standards. The message contains all important relationships, such as the relationship between an observed and planned assessment (or lack thereof), and the relationship between unplanned assessments and other observations (*i.e.* physical exam finding of jaundice led to a bilirubin measurement). Those observations that were previously reported in a spontaneous adverse event report are not re-submitted, but rather updated and referenced.

# FDA Review

## *Sub Use Case: Efficacy Review: Intent-to-treat vs Per Protocol*

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| Use Case Name: | **Efficacy Review: Intent-to-treat Sub Use Case** |
| Use Case ID: | Rev-08a |
| Description: | Compare if there are differences between Intent-to-treat and Per Protocol groups.<br><br>*Intent-to-treat*: Includes all randomized patients (e.g., eligible for study). Exclusions are permissible on pre-specified data (e.g., modified intent-to-treat).<br>*Per protocol:* Addresses what happens to patients who remain on therapy. Typically excludes patients with problematic data. This introduces selection bias that is often difficult to assess.<br><br>Risk: Important to determine if any bias is introduced by using the proper analysis group and used for meaningful conclusions. |
| User(s)/Roles(s): | **Reviewer:**<br>• FDA: Biostatistician<br>• FDA: Medical Officer |
| Trigger: | NDA accepted for review after initial 60-day review and initial review is complete including completion of study design evaluation. |
| System Preconditions: | Availability of demographics, response, exposure, disposition, and response data is in repository. |
| Flow of Events: | 1. Sponsor submits NDA<br>2. FDA conducts initial review from JANUS data (initial 60 days) and accepts filing<br>3. Evaluate study design, analysis files, and analysis plan available in JANUS.<br>4. Confirm what population analysis was based upon on: intent-to-treat group, modified intent-to-treat (based on factor established at randomization) or per protocol group.<br>5. Use Commercial tool integrated with JANUS to analyze |

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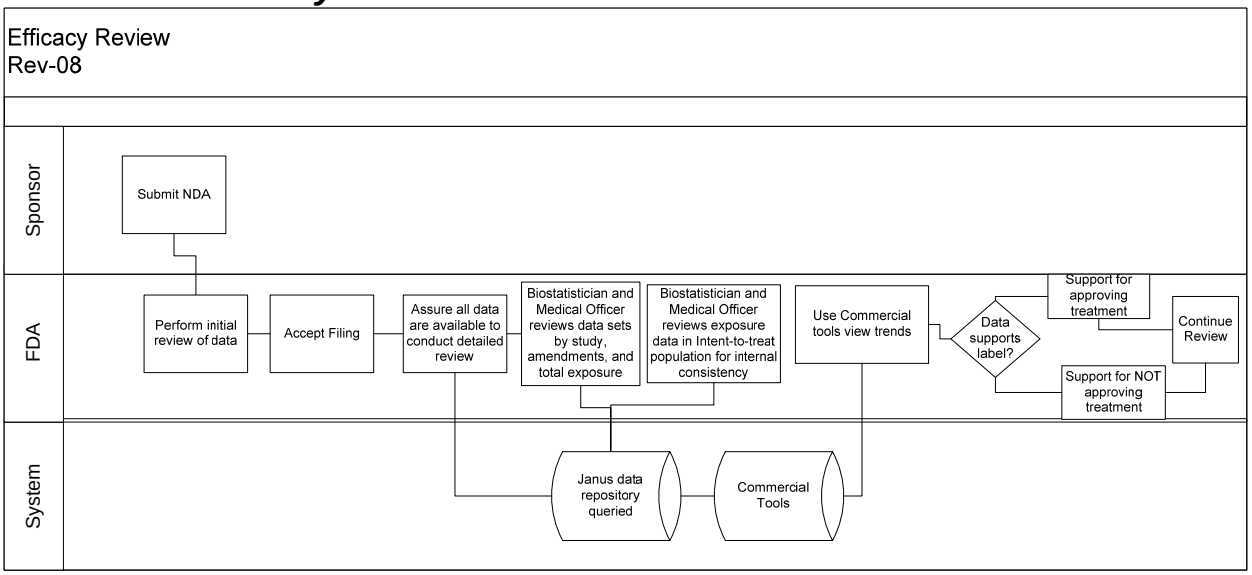
| | differences (if any) between intent to treat (ITT) and per protocol (PP) patient groups.<br>6. If sponsor used per protocol population, then evaluate if any bias was introduced.<br>7. Determine if omission of any subgroups (e.g., drop out or discontinued patients) was appropriate.<br>8. Contact sponsor, as necessary. |
| System Post Conditions: | Not applicable: Use cases are all read only access to the database. |
| Data View/Security: | Review by study, but have access across studies |
| Special Requirement(s): | Data available to execute Use Case Rev-08<br>Use Commercial tools to analyze data. |
| Related Use Case(s): | Rev-8 (Efficacy Review) |
| Related Extension(s): | NA |
| Relevant Requirements: | Both types of populations are important for approval. Results should be logically consistent. Should reduce selection bias. |

## *Use Case: Efficacy Review*

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| Use Case Name: | **Efficacy Review** |
| Use Case ID: | Rev-08 |
| Description: | Using Intent-to-treat group: Look for unusual trends and determine if data support outcomes and conclusions.<br><br>Risk: This review is critical to determine if the data supports the label and primary outcomes of the study. |
| User(s)/Roles(s): | **Reviewer:**<br>• FDA: Biostatistician<br>• FDA: Medical Officer |
| Trigger: | NDA accepted for review after initial 60-day review and initial review is complete including completion of study design evaluation and intent-to-treat versus per protocol populations have been evaluated and reviewer is comfortable that no bias has been introduced at this stage. |
| System Preconditions: | Execute Rev-08a before this use case to assure all required intent-to- |

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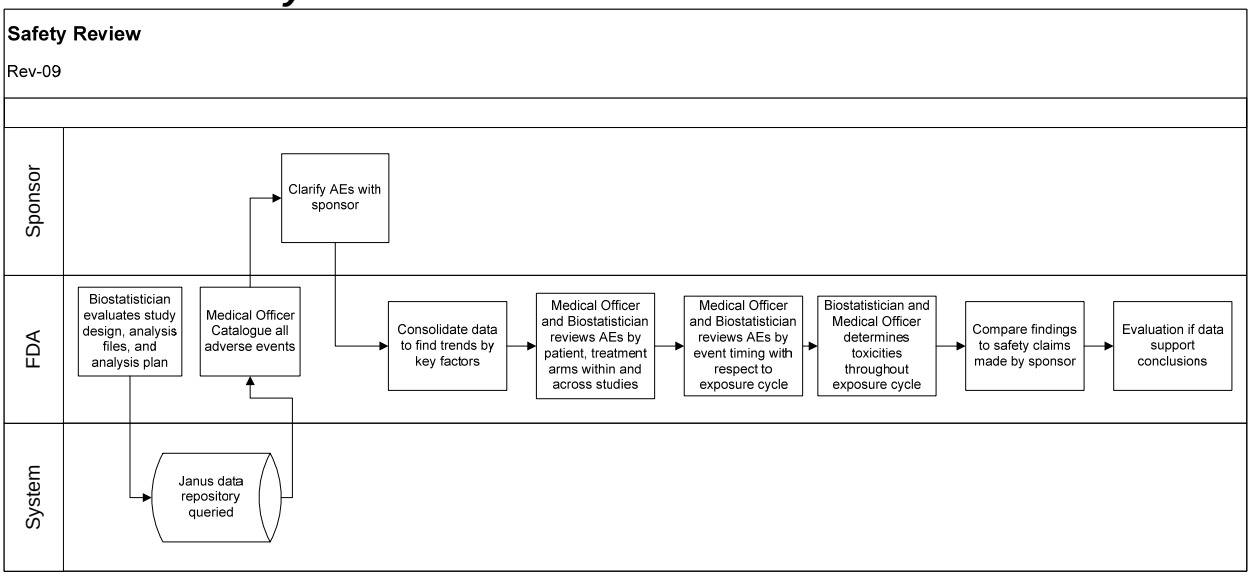
| | treat patients are included. |
| Flow of Events: | 1. Review tables to assure all data tables and review sections are included necessary to conduct a detailed review.<br>2. Become acquainted with data and variable names (JANUS can facilitate this step)<br>3. Review study data sets in JANUS by study, amendments, and total exposure.<br>4. Review exposure in intent-to-treat population looking for internal consistency of exposure and endpoints – visualize trends.<br>5. Review other supporting information, working with Medical Reviewer<br>6. Use Commercial tool to evaluate if data supports claim for label – very important. |
| System Post Conditions: | Not applicable: Use cases are all read only access to the database. |
| Data View/Security: | Review by study, but have access across studies |
| Special Requirement(s): | Use Commercial tools to view data trends and analyze data, as needed.<br>Analysis tools compatible with JANUS. |
| Related Use Case(s): | Rev-8a (Intent-to-treat) |
| Related Extension(s): | • Include pharmacokinetic (PK) data to enable data modeling and trend analysis, relating metabolites to response and safety.<br>• Need standard query process through JANUS between FDA and sponsor; between sponsor/cooperative groups/lead sites and satellite study sites. Create audit trail to capture data changes, which created change, date of change, and reason..<br>• Standardize analysis algorithms |
| Relevant Requirement(s): | • Standardization is critical to efficiently review data across studies, support standardized analysis algorithm.<br>• Use accepted, consistent toxicity scales for Oncology.<br>• Use Common Terminology Criteria (CTC) for adverse events.<br>• Look for outliers, unusual trends and recreate study findings.<br>• Product label is influenced by subpopulation and their AE profile. |

## *Use Case: Safety Review*

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| Use Case Name: | **Safety Review** |
| Use Case ID: | Rev-09 |
| Description: | Review across all Phase 3 studies (must drop blind on data). Look across all studies to even out data. Note: Need to know if data was blinded or open label study. No need to maintain blind on data. |
| User(s)/Roles(s): | **Reviewer:**<br>• FDA: Biostatistician<br>• FDA: Medical Officer |
| Trigger: | NDA accepted for review after initial 60-day review and initial review is complete including completion of study design evaluation and intent-to-treat versus per protocol populations have been evaluated and reviewer is comfortable that no bias has been introduced at this stage. |
| System Preconditions: | Availability of demographic and adverse event, and medical comorbidity data is in repository |
| Flow of Events: | 1. Evaluate study design, analysis files, and analysis plan.<br>2. Catalogue all adverse events<br>3. Perform data clean up to resolve inconsistencies between terms and synonyms (Standardized data in JANUS would eliminate this step)<br>4. Clarify with sponsor, as needed.<br>5. Summarize and review data in JANUS to find trends by key factors (e.g., sites, dose, sub-populations).<br>6. Review by patient, treatment arm within study, and across study.<br>7. Review for when event appeared, resolved compared to cycle of exposure.<br>8. Determine toxicities occurring at initial dose, throughout therapy, or cumulatively.<br>9. Compare data to any safety claims made by the sponsor.<br>10. Evaluate if data supports conclusions. |
| System Post Conditions: | Not applicable: Use cases are all read only access to the database. |

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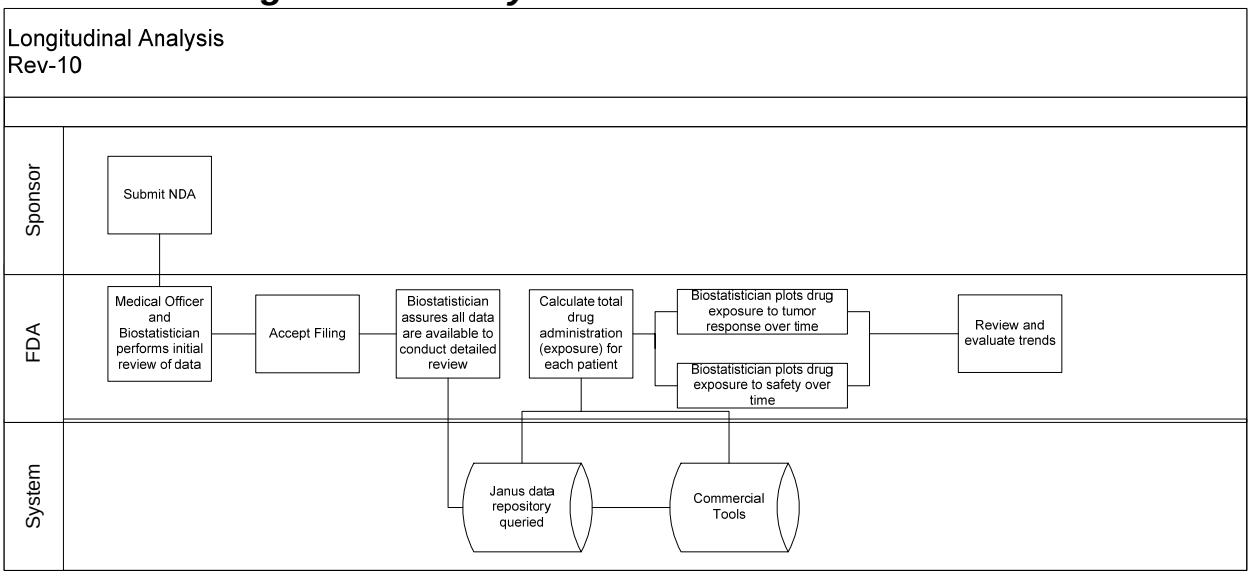
| Data View/Security: | Across studies |
| Special Requirement(s): | Identify top 3 adverse events<br>• Use Commercial tools to view and analyze data, as needed. |
| Related Use Case(s): | Mng-04 (Safety Reporting) |
| Related Extension(s): | • Include pharmacokinetic (PK) data to enable data modeling and trend analysis, relating metabolites to response and safety.<br>• Apply business rules to submitted data to assure proper format, missing values, and alert errors.<br>• Need standard query process through JANUS between FDA and sponsor; between sponsor/cooperative groups/lead sites and satellite study sites. Create audit trail to capture data changes, which created change, date of change, and reason.<br>• Standardize analysis algorithms.<br>• Priority to include Serious Adverse Events (SAE) in same repository as non-serious adverse events to eliminate the need to reconcile data across separate databases |
| Relevant Requirement(s): | • Standardization is critical to efficiently review data across studies, support standardized analysis algorithm.<br>• Use accepted, consistent toxicity scales for Oncology.<br>• Use Common Terminology Criteria (CTC) for adverse events.<br>• Look for outliers, unusual trends and recreate study findings.<br>• Product label is influenced by subpopulation and their AE profile |

## *Use Case: Longitudinal Analysis*

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| Use Case Name: | **Longitudinal Analysis** |
| Use Case ID: | Rev-10 |
| Description: | Identify safety and response trends by visualizing the number and types of events across time and exposure level.<br><br>Risk: Safety and efficacy trends must be viewed over various levels of exposure to provide additional rigor to review process. |
| User(s)/Roles(s): | **Reviewer:** |

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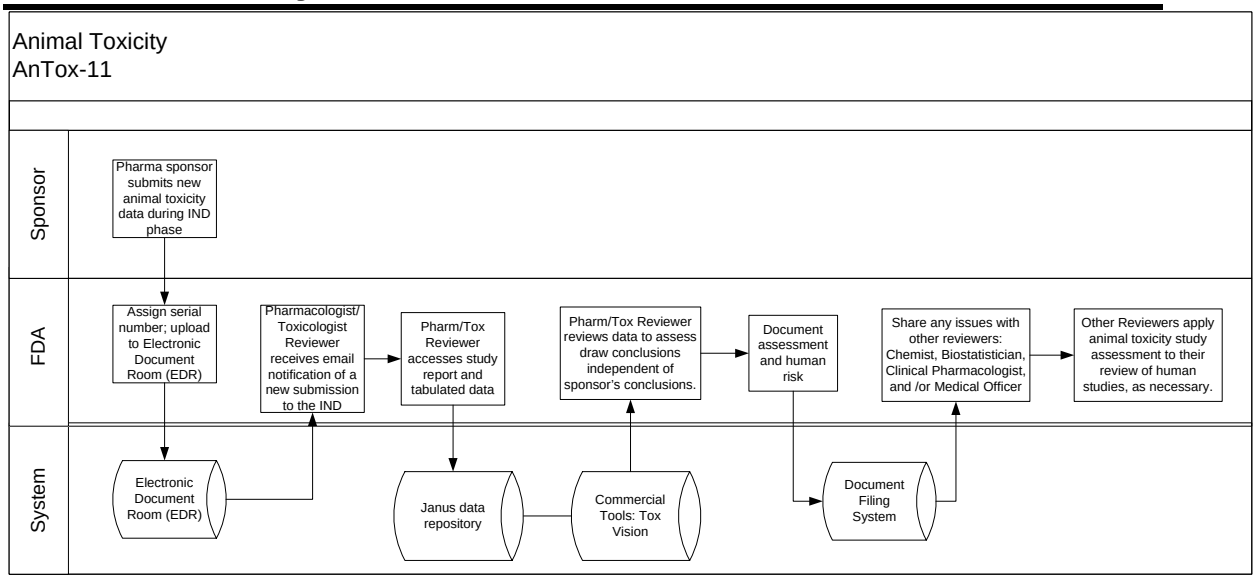
| | • FDA: Biostatistician<br>• FDA: Medical Officer |
| Trigger: | NDA accepted for review after initial 60-day review and initial review is complete including completion of study design evaluation and intent-to-treat versus per protocol populations have been evaluated and reviewer is comfortable that no bias has been introduced at this stage. |
| System Preconditions: | Availability of demographics, response, and adverse event, and exposure data is in repository. |
| Flow of Events: | 1. Conduct all preliminary and initial review steps.<br>2. Calculate total drug administration from data stored in JANUS.<br>3. Correlate and plot (using MS Excel ) to tumor response (for response data) over time<br>4. Identify top adverse events frequency, duration and resolution using Pt. Profile viewer (for safety review) over time.<br>**5.** Review and evaluate trends**.** |
| System Post Conditions: | Not applicable: Use cases are all read only access to the database. |
| Data View/Security: | View by study, but have access across studies |
| Special Requirement(s): | Need interface with **MS Excel** to graph response data generated from JANUS.<br>• Need interface with **Pt profile viewer** to view trends in safety and response data generated from JANUS. |
| Related Use Case(s): | Rev-08 (Efficacy Review) and Rev-09 (Safety Review) |
| Related Extension(s): | NA |
| Relevant Requirements(s): | • Need to understand response trends over time.<br>• Focus on raw data as the primary data, rather than the analysis files to help determine how the variables were derived and if analysis was biased.<br>• Include audit trail in ODM |

# Animal Toxicity



## *Use Case: Animal Toxicity*

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| Use Case Name: | **Animal Toxicity** |
| Use Case ID: | AnTox-11 |
| Description: | Use Case involves data from a repeat-dose (28-day) animal toxicity study in rats. The 28-day study design enables the reviewer to relate the data to other animal toxicity studies of longer or shorter duration.<br><br>Risk: Animal Toxicity review is a critical step during the IND review process to determine drug safety profile of a drug in animal models that might apply to human participants. |
| User(s)/Roles(s): | FDA Reviewer: Pharmacologist/Toxicologist |
| Trigger: | Animal toxicity studies submitted during the IND phase to support human drug trials. (Can also occur during the NDA phase to support a marketing application.) |
| System Preconditions: | Tabulated data containing individual animal line listings. Assume animal data is available in electronic (i.e., SEND) format. |
| Flow of Events | 1. New non-clinical (animal toxicity data) is submitted to the FDA during the IND phase.<br>2. Each study is assigned a serial number and is uploaded to the Electronic Document Room (EDR); includes textual study report and associated summary data in PDF format.<br>3. Reviewer is alerted through email of a new submission to the IND.<br>4. Reviewer accesses all components (i.e., study report and tabulated data) of the new submission through the Electronic Document Room (EDR).<br>5. Access the tabulated data electronically, triggering the launch of Tox Vision, the commercial tool used to display and analyze data submitted in the SEND format.<br>6. Review of submitted study report and data in JANUS to become familiar with content of study: purpose, methodology, results, and key findings.<br>7. Review data independent of sponsor's conclusions (Focus is on safety; animal efficacy data has less impact on clinical trials)<br>8. Document assessment and interpretation of key findings. Also assesses human risk to determine if data has implications to support proposed clinical trials or if it affects ongoing clinical studies.<br>9. Convey key issues, if any, alerting Chemist, Biostatistician, Clinical Pharmacologist, and/or Medical Officer of any relevant findings that might apply to human studies.<br>10. Store assessment (review document) in Document Filing System (DFS).<br>11. Biostatistician, Clinical Pharmacologist, and/or Medical Officer apply animal toxicity study assessment to their review of human studies as necessary. |
| System Post Conditions: | Not applicable: Use cases are all read only access to the database. |
| Data View/Security | Reviewers should be able to access data across all studies, but review process generally involves reviewing one study at a time. |
| Special Requirement(s) | Need ability to authenticate electronic signatures to confirm completion of study for Quality Assurance (QA) and compliance with Good Laboratory Practice (GLP) requirements. Would like to avoid scanned PDF study reports because of reduced text quality and reduced ability of character recognition and copy/paste functions. |
| Related Use Case(s) | Rev- 09 (Safety Review)<br>Results of animal toxicity studies are used to see if similar findings are observed in human studies, if additional clinical monitoring should be performed, or to help in selecting clinical doses. |
| Related Extension(s) | Animal data is in SEND format. (SEND is based on SDTM model adapted for non-clinical data to evaluate animal toxicity data.) |

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| | Key JANUS step is for the electronic document room (EDR) to have access to tools through a central portal that will display data (e.g., integration of ToxVision through centralized access point). Clicking on study data file or icon will trigger the ToxVision tool to open and access data. |
| Relevant Requirement(s) | • On occasion, animal toxicity review involves the ability to do meta-analysis (e.g., review background incidence of certain tumors across studies).<br>• Need for Pharm Tox reviewer to access clinical (human) study data and other FDA reviews (Biostatistician and Medical Officers) for extrapolation of dose-response relationships from animals to humans. |

**Use case Data Requirements:**

- Study ID
- Animal ID
- Intervention – dosing or treatment – once daily dosing
- Findings – collected daily or weekly during course of study, or at time of sacrifice
  - Clinical signs (1x or 2x per day).
  - Body Weights (1x per week; measures drug affects: indicates state of health based on drug effects and food consumption); measured before / after treatment as well as weekly)
  - Plasma drug levels measured periodically over course of study
  - Macroscopic and microscopic findings (assessed at time of sacrifice and includes examination of fixed tissues by pathologist)
  - Clinical pathology: clinical chemistry (blood chemistry), hematology (blood cell components), urinalysis (usually measured weekly)
  - Food and water consumption (usually weekly)
- Time of measurement – relates temporal relationship of drug treatment to effect
  - Pre-dose
  - Periodically over the course of 28-day study
  - Day 28- terminal sacrifice
- Necropsy – day 28 - organ weights, macroscopic exam (visual assessment of any gross lesions), microscopic tissue exam (histopathology).

Data display: Useful for data to be viewed as any or all values by dose group, time point, gender, animal ID number, and specific tests or assessments. Tox Vision already designed to do this by clicking on/off desired characteristics and combinations.

- View all data for one animal through animal profile viewer to correlate all findings for an animal subject
- Also have ability to exclude outliers for calculation of means

Note: Always important to look at individual tabulated data because sponsor's summary data can be misleading if number of animals in a study is low (e.g., 5 or lower). It is also important to assess variability (i.e., standard deviation) between animals for drug-induced effects.