Case Study of a Recent Submission at ARIAD Pharmaceuticals

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Outline

- Background for NDA Submission
- Preparation of Submission-ready datasets
- NDA Review Period
- Lessons Learned

Background: ARIAD

- Oncology company (Cambridge HQ)
  ~300 employees currently
- Accelerated approval of first product by FDA in December 2012 for treatment of Chronic Myelogenous Leukemia
- First NDA filed July 2012

ARIAD Biostatistics/Stat Programming

- Biostatistics and statistical programming work generally done in-house
  - Fall 2011: 3 statistical programmers (SDTM expertise but not bandwidth)
  - Today: 6 statistical programmers
- Contracted Accenture (formerly Octagon Research, specialized in SDTM mapping) to provide mapping specifications, datasets, documentation
- Build on work provided by Accenture to bring capabilities in-house

Components of NDA for Accelerated Approval

- Phase 1 clinical trial* **(ARIAD)**
- Pivotal phase 2 clinical trial* **(ARIAD/Accenture)**
- Integrated Summary of Safety (ISS) **(ARIAD)**
- Clinical Pharmacology studies **(Completely outsourced)**

***Ongoing clinical trials**

What to submit to FDA? **(Addressed at pre-NDA Meeting)**

- Phase 1 clinical trial
  - "Raw" Tabulation datasets (define.pdf)
  - **Analysis datasets** (define.pdf)
  - Programs for efficacy endpoints/analyses
- Pivotal phase 2 clinical trial
  - SDTM datasets (define.xml)
  - **Analysis datasets** (define.pdf)
  - Reviewer's guide
  - Programs for efficacy endpoints/analyses
- Integrated Summary of Safety (ISS)
  - Pooled SDTM datasets for above 2 studies (define.xml)
  - Reviewer's guide

"Analysis Datasets": Approach

- Include all derivations for analysis of primary and secondary endpoints ("analysis ready")
  - Efficacy outcomes
  - Population flags
  - Prognostic factors
- For complex derivations, include "intermediate" datasets
- Thoroughly document derivations in data definition tables

ARIAD-Accenture Collaboration

- Resources not available to implement SDTM mapping at study initiation
- Analysis datasets and TLGs initially developed on “raw”/legacy data
- Engaged Accenture approximately 9 months prior to NDA submission for SDTM datasets for pivotal phase 2 trial

ARIAD-Accenture Collaboration

- Accenture contracted to provide mapping specifications, SDTMs, define.xml, Reviewer's guide, **SAS programs for creation of SDTM domains**
  - Pivotal trial ongoing, SDTMs to be updated with future data cuts (incl. full approval submission)
  - Transition to build all future work using SDTMs: analysis datasets, TLFs
- Use specifications from Accenture to map phase 1 data for ISS at ARIAD

ARIAD-Accenture Collaboration

- Accenture to develop draft domains starting with early data cut
- ARIAD to re-create domains by running Accenture programs in ARIAD environment
- ARIAD to re-create analysis datasets using SDTM domains

ARIAD-Accenture Collaboration

- Accenture developed draft mapping specifications based on protocol, SAP, eCRFs
- Thorough review of draft specifications by ARIAD
  - Vs. eCRF (ensure data points mapped)
    - Some changes requested w.r.t structure of datasets, additional variables to be mapped (i.e. indicator-type variables)
  - Vs. 3.1.2 Implementation Guide

Dress Rehearsal" with Accenture

- Draft domains, programs initially developed by Accenture on early data cut
- ARIAD sent Accenture raw datasets generated from "mature" data cut (~1 month prior to final database cut)

Dress Rehearsal" with Accenture

- Accenture provided SDTM domains, mature draft SAS programs
- ARIAD successfully re-created SDTM domains from Accenture programs
- Analysis datasets generated from SDTM domains, cross-checked with those based on raw datasets

“Showtime” with Accenture

- Final database cut taken at ARIAD on 27April2012 for pivotal trial
- Raw data sent to Accenture for preparation of final SDTMs, programs, publishing
- In parallel, ARIAD ran Accenture programs to generate SDTMs, analysis datasets, TLF package to facilitate writing of Clinical Study Report (CSR)

“Showtime” with Accenture

- Final package received from Accenture 20Jun2012:
  - SDTM domains, cross-checked with those produced by ARIAD
  - Define.xml
  - Reviewer’s guide
  - Final programs
- CSR finalized 13Jul2012

Submission-Ready Datasets: SDTM Compliance

- Use OpenCDISC to assess domains, identify errors to be fixed
- Define.xml
  - Identify missing values for Controlled Terminology (via OpenCDISC)
  - Check links working properly
- Split character fields that were originally > 200
- File sizes – trimmed variable lengths to satisfy 1 GB requirement (rather than split datasets)

Preparation of Submission-Ready Datasets: SDTM Compliance

- Reviewer's Guide
  - Explanation of remaining errors as identified by OpenCDISC
    - Anomalies due to ongoing data collection
    - CT not completely aligned with SDTM
  - Specify Implementation Guide, CT version

FDA Review Period: ~4 months

- Requests for revised/additional datasets
  - Analysis-like datasets for ISS (particularly AEs and laboratory data)
  - "Longitudinal" analysis datasets
    - Multiple records per patient (SDTM-like)
    - Flags/derivations for each record (analysis-like)
  - Customized analysis datasets
- Minor questions regarding navigation of SDTM domains
- No data points identified as missing

Lessons Learned

SDTM Datasets

- NDA post-action meeting with FDA: Submission of SDTM datasets helpful, facilitated review

- Implement SDTM mapping at trial initiation
  - Minimize steps between EDC extract and SDTM datasets
  - Check for SDTM compliance as early as possible

Lessons Learned

Analysis Datasets

- Provide additional “intermediate” analysis datasets
- Provide analysis datasets for ISS, in addition to tabulation datasets
- Align more closely with ADaM?

Thank you!

Questions?