Meeting Minutes

CDISC-HL7 Stage I-B
May 22, 2008
11:00 am – 12:00 pm (EST)

Attendees / Affiliation

Jay Levine/CDISC (Co-Chair)
Julie Evans/CDISC
Patty Garvey/FDA (Facilitator)
Scott Getzin/Eli Lilly
Wayne Kubick/Lincoln Technologies
Mary Lenzen/Octagon
Bill Rosen/Pfizer

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 is to finalize the Study Participation and Study Design storyboards.

Discussion

- The Study Participation and Study Design storyboards were reviewed and finalized. There were only minor grammar corrections made during the meeting.
- Scott will provide animal toxicity studies to add to Study Design storyboards.
- There will be a face-to-face meeting, to include webinar service, in Rockville, MD on June 12 - 13, 2008 to discuss project modeling for the study participation, study design and subject data.

Action Items:

1. Scott Getzin will provide animal toxicity studies to add to Study Design storyboards.

Attachment: DRAFT HL7 CDISC Message Project – Study Participation and Study Design Storyboards

Drafted: PGarvey/6-5-2008
Approved: 7-17-08

HL7 CDISC Message Project

The Business Case

The US Food and Drug Administration (FDA), as part of its mission to protect the public health[1], receives and processes vast amounts of information. A significant proportion of this information relates to the process of regulatory approval of drugs, biologics and medical devices and such information is currently received in a large number of disparate formats, both electronic and on paper, using a variety of formats and proprietary standards.

Significant steps have been taken to alleviate these issues with the development of standards that support electronic submissions in more consistent formats. Not all areas have been addressed and a significant proportion of that information is still paper-based. This situation makes it extremely difficult, if not impossible for example, to perform cross-study reviews or safety analyses throughout the entire life cycle, both pre and post approval, of a regulated product. Therefore the FDA wishes to receive, in regulatory submissions, standard clinical study information content in a standard exchange format. This approach is vital to the FDA strategic initiatives to integrate pre-marketing clinical trial data, post-marketing safety data, and product quality, manufacturing data to improve public health and patient safety.

Over the past few years, advances have been made in developing this standardised content through the development of the Biomedical Research Information Domain Group (BRIDG) model and the FDA feels the time is right to bring together many threads of work so as to take the next step and better integrate submitted information.

To meet this need the FDA wishes to combine CDISC content with the HL7 message exchange mechanisms.

The Clinical Data Interchange Standards Consortium (CDISC) is a global standards development organization with an open, consensus-based process and is the preferred semantic standard for medical research content. CDISC has liaison A Status with ISO Technical Committee 215 and a charter agreement with HL7 with a commitment to harmonize the CDISC standards with the HL7 RIM via the BRIDG model. The BRIDG model was initiated by CDISC in 2004 for this purpose.

CDISC has developed the Study Data Tabulation Model (SDTM) which defines a standard structure for study data tabulations that are to be submitted as part of a product application to a regulatory authority. The SDTM is the standard adopted by FDA as the mechanism for exchanging study data. CDISC is in the process of

[1] by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.
Source: FDA Strategic Action Plan, 2007

developing other standards using the BRIDG model for other areas such as medical research protocols and study designs.

Health Level 7 (HL7) is the preferred electronic exchange format for healthcare information. It is an ANSI-accredited standards development organization with liaison A status with ISO Technical Committee 215. The HL7 exchange format is already used for other FDA messages that will carry content to the JANUS warehouse including the Structured Product Label (SPL), the Integrated Case Safety Report (ICSR) and Regulated Product Submission (RPS) messages. HL7 is the preferred electronic exchange format for healthcare information, per the Department of Health and Human Services.

By bringing the CDISC content together with the HL7 exchange mechanisms via the BRIDG and RIM, the SDTM content will be combined with additional meta-data to meet the following needs:

- Overall improved Data Management in FDA
- Harmonize with HL7 standards for all structured regulated medical product information
- Prepare for eventual data integration with Electronic Health Records (EHRs) as they start being used for both Clinical Research and Surveillance

Improved Data Management in FDA

The current exchange standard for data content is the SAS Transport file (XPT). This method has limitations in that flat files do not inherently capture relationships between study data or between study data and study design as desired by FDA. Adding these relationships post-facto is invariably incomplete, done inconsistently, is time-consuming and inefficient. FDA would like to move away from the SAS Transport mechanism towards a more robust exchange standard for Clinical Observations that inherently relate clinical observations with each other (such as the HL7 ICSR) and with planned observations at the point of data collection so they can reliably and consistently be conveyed to FDA information systems. FDA recognizes that currently these important relationships are not often captured (or are captured inconsistently) at the point of data collection. However, as EHRs come into more widespread use, the opportunity to capture these relationships automatically at the point of collection will increase.

Harmonize with HL7 standards for all structured regulated medical product information

FDA is committed to harmonize all exchange standards for regulated product structured data with the HL7 RIM (using the Biomedical Research Integrated Domain Group (BRIDG) to achieve a more robust data model structured regulated product information.

Harmonizing study data exchange standard with the HL7 ICSR will provide a single data model for all pre- and post-marketing clinical observations. This will facilitate loading study data and post-marketing clinical observations into the JANUS data warehouse, which will in turn improve FDA's ability to analyze safety information throughout an entire medical product's life cycle.

Harmonization with the HL7 SPL standard provides a better way to associate clinical observations with medical product information. Although important for drugs, this will be particularly important for medical devices, biologics, and drug-

device combination products where model number, lot information, and other product information may be critically important to interpret causal relationships between specific medical products and the clinical observations associated with their use.

Prepare for eventual data integration with Electronic Health Records (EHRs) as they start being used for both Clinical Research and Surveillance

HL7 messages are the preferred exchange format for clinical observations captured within Electronic Health Record (EHR) systems. The Office of the National Coordinator for Health Information Technology (ONC-HIT), part of Health and Human Services, is facilitating a national effort to achieve EHRs for everyone in the U.S. by 2014. Efforts are also underway to enable the use of EHR systems to support data collection for clinical research (e.g. the Electronic Health Record – Clinical Research (EHR-CR) working group) as well as post-marketing surveillance. Having HL7 messages for both clinical research and post-marketing data will facilitate the use of EHRs for clinical research and surveillance purposes, which will in turn facilitate data exchange between EHR systems, third party clinical research and post-marketing surveillance databases, and FDA.

The CDISC-HL7 project and the resulting messages will also:

1. Enhance FDA regulatory decision making and address complex public health questions through improved data management to improve public health.
2. Standardize data exchange and terminology standards to facilitate data aggregation, analysis, data mining and signal detection.
3. Reduce the duplication of information received at the FDA especially when the data are received more than once in differing formats.
4. Allow reviewers to view the data that provides a better understanding of what happened to subjects and provide greater capability to analyze the data.
5. Improve access to aggregate data through the use of the JANUS data warehouse.
6. Support the FDA Critical Path Initiatives for the development of safer, more effective products.
7. Provide FDA with a mechanism to detect patterns (signal detection), determine the pace (problem scale) and know the place (specifically where) risks or emergencies are present.

FDA intends to update its progress towards meeting these goals through periodic updates to the Prescription Drug User Fee Act IV Information Technology 5-Year Plan.[2]

[2] http://www.fda.gov/ohrms/dockets/dockets/07d0481/07d0481.html

Study Participation

Summary of Requirement

The Study Participation message is intended to inform the agency about all experimental subjects, investigators, and other relevant entities that are involved in the conduct of an individual study. This information is often provided:

1. At the start of the study
2. As part of a subsequent update on that study
3. As part of the final study report

At each of the above time points the message could contain some or all of the following information:

1. The organizations involved within the study (e.g. sponsor, IND holders, CROs, central labs, safety monitoring boards, data management organizations etc.)
2. Subject demographics
3. Subject disposition information
4. Investigator participation

At the present time information on the organizations is passed to the agency in an ad hoc fashion at a variety of time points and encompassed within electronic free text documents such as PDF making the information difficult to access.

Information on subjects and investigators is currently contained within annual reports and protocol amendments[3]. These again are currently electronic PDF documents making access to the information difficult. Investigator information is also supplied as using Form 1572s. As such there is a desire to link to the clinical investigator information held within FIREBIRD.

It should be noted that this message deals with Study-level information. Investigational application level information (e.g. IND, IDE, INAD) is handled by the RPS message.

Storyboards

1. 1 Investigator Information

Acme Pharmaceuticals would like to submit investigator information for the principal investigator and investigator for three new sites for their 10-site multicenter trial – Study NCT99999999. The company does not require their investigators to use a centralized clinical investigator registry which FDA can access (e.g. FIREBIRD) so they submit the information directly to FDA. They will use the study participation message to provide the site information, investigator names and qualification information similar to what is currently captured in FDA Form 1572.

[3] See 21 CFR Part 312.30 Protocol Amendments and 312.33 IND Annual Reports

1.2 Updated Investigator Information

Acme Pharmaceuticals has identified the remaining seven site investigators for their study NCT99999999. Furthermore, the original investigator at site 3 has resigned and a new investigator has started at site 3 and investigator at site 5 has changed his address. Acme provides updated site investigator information using the study participation message.

1.3 Populate Clinical Investigator Registry

FDA has received and reviewed investigator qualification information for Acme Pharmaceutical Study NCT99999999. FDA will use the study participation message to update the centralized clinical investigator registry (FIREBIRD) with investigator qualification information.

1.4 Inspection Results

FDA has inspected investigator/site number 4 for study NCT99999999. FDA uses the study participation message to transmit inspection results to the centralized clinical investigator registry (FIREBIRD). Pertinent inspection results static elements include date of inspection. inspection type code, inspection outcome code, and one or more deficiency codes.[4]

1.5 Other Participating Organizations

Acme has contracted the services of several outside organizations to support the planned activities associated with Study NCT99999999. These include

- a contract research organization (CRO) to support data acquisition, storage, and analysis;
- a central laboratory vendor to process all laboratory samples;
- a central imaging vendor at a nearby academic institution to provide all interpretations of MRIs collected during the study
- site-specific Investigational Review Boards, including date of IRB approval, if available
- a central ECG vendor to interpret all electrocardiograms
- a Data Safety Monitoring Board to review blinded safety information in real time

Each participating organization is associated with a study participation start date, as well as an end date (if participation has ended). Acme sends the information to FDA using the study participation message. The message also supports updates to organization information (e.g. ending an organization's participation, adding a new organization).

(see Appendix 1 for a more complete list of roles and responsibilities of participants that are commonly associated with a study.)

1.6 Subject Protection Approval

The seven site investigators for Acme study NCT99999999 all obtain approval from a subject protection approving authority (e.g. Institutional Review Board

[4] See http://www.accessdata.fda.gov/scripts/cder/CLIIL/index.cfm?fuseaction=Search.Search

(IRB)). The three U.K. sites all receive central subject protection approval on 1/10/2008. The single site in France obtains approval from its subject protection approving authority on 2/1/2008, and the three U.S. sites from the U.S. central IRB on 2/15/2008. One U.S. site also requires approval from its local IRB. That approval is obtained on 2/28/08. This information along with the approval bodies' identifier is captured in the study participation message.

1.7 Institutional Review Board – withdrawal of approval

Following a protocol amendment to Acme study NCT99999999 that relaxes the safety monitoring, the local IRB for the one U.S. site withdraws approval on 3/15/2008. This information along with the approval bodies' identifier is captured in the study participation message and sent to FDA.

1.8 Updated IRB Approval – Change in an Investigator

The new investigator at site 3 for Acme study NCT99999999 (see 1.2) has requested IRB approval to continue conducting the study at that site. The change in investigator triggers IRB review, and the IRB approves the proposed investigator change. The updated IRB approval and date is captured in the study participation message.

1.9 Updated IRB Approval – Protocol Amendment

Acme Pharmaceuticals amends the protocol for study NCT99999999 to extend the duration of experimental treatment by an additional two months. The protocol amendment triggers a review by all the relevant subject protection approving authorities and each grants an updated approval. The updated approvals and respective dates are captured in the study participation message.

1.10 Study Subjects Progress Report

New Wave Pharmaceutical has committed to perform a phase 4 multi-center study (NCT88888888) 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 can use the study participation message to identify the subjects enrolled to date, including all relevant demographic information as currently defined by the DM Domain in the CDISC SDTM standard, the investigational site for each subject, and the status and disposition of the subject to date according to the CDISC DS domain, as well as the cutoff date used for the report. The message can contain either brand new subject information, or can update previously submitted subject information. The message can either append previously submitted information (update) or can replace all previously submitted subject information with new information (replace with a bulk load).

1.11 Final Study Subjects Disposition

New Wave Pharmaceutical's study NCT88888888 is now complete. They submit all final disposition information of all subjects with the final study report using the study participation message according to the CDISC SDTM DS domain. The message supports conveying that no additional study participation information is expected (i.e. message is 'closed').

1.12 Participation of a group of subject

Government Agency Aqua plans to study the effectiveness of a new immersion product, Drug A, administered at 100 mg/L for 15 minutes daily on alternative days to control mortality in two coolwater species of freshwater-reared finfish due to Disease X caused by bacteria *Fish pathogen*. [Study design details to be included in the study design storyboards] Six tanks of fish were studied, and the group of fish contained in each tank is the experimental unit of interest. Tank characteristics include tank dimensions, maximum total volume, and species of fish the tank contained. One tank was removed from the study because an unacceptable number of fish jumped out during the study (>15% by protocol). Another tank was removed because the drain pipe was accidentally left open after routine cleaning. The study participation message will carry tank participation information, and the relationship between the tank of fish (experimental unit) and the individual fish treated (organism of interest).

[CDISC/BRIDG Gap = characteristics of the tank – how to handle this?]

1.13. Participation of a part of a subject

Acme Pharmaceuticals studied 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 for treatment of sunburn in Study A1234 [design details to be provided in study design storyboard]. One hundred (100) subject were treated across 10 centers. Each subject treated three sunburned patches of skin, one each with each experimental treatment. Two dropped out due to local adverse events. Three dropped out due to systemic adverse events.

Two subjects only treated two sites and one subject only treated one site. Two were lost to follow-up. Subject participation and disposition information is provided in the subject participation message with the final study report, along with the relationships between subjects and actual treatment sites.

Map to SDTM

Data for the message maps to the existing SDTM DM and DS domains.

Note: A more detailed map would be useful to assist those working with SDTM today to see where things are going in the new messages. Will also allow for a cross check to see if all of SDTM is being carried by the combined set of 4 messages.

Domain Analysis Model etc

Note: Diane's information model and other supporting artifacts in here

Study Design

Summary of Requirement

Notes from previous document

*A **New Protocol** submission contains information about what will be done, including planned analyses, etc. The **study design** message will transport this information in a standardized format: study summary, trial design, eligibility criteria, and statistical analysis plan.*

1. *Study summary: The SDTM Trial Summary (TS) domain is structured in parameter/value format. CDISC has produced controlled terminology (parameters and valid value lists), but SDTM contains (in the not-yet-finalized SDTMIG 3.1.2) only a recommendation about which parameters should be submitted.*
2. *Trial design: The SDTM Trial Arms (TA) and Trial Elements (TE) domains contain information roughly equivalent to the study schema diagrams in common use. The SDTM Trial Visits domain contains information about planned visits. The TDM team has modeled the Schedule of Activities (what is to happen when) and harmonized with the BRIDG, but this information has not yet been implemented, other than the information in the SDTM Trial Visits domain. SDTM subject data domains make use of planned timepoints, but there are not currently trial-level SDTM domains for planned timepoints.*
3. *Eligibility criteria: The SDTM Trial Inclusion/Exclusion (TI) domain contains the text of eligibility criteria (actually, 200 characters of the text), along with a variable which indicates whether the criterion is an inclusion or an exclusion criterion. Work on structuring eligibility criteria is ongoing within the ASPIRE project, but is at a fairly early stage. The HL7 message will link to values for planned observations and subject chararacteristics that correspond to the eligibility criteria.]*
4. Statistical Analysis Plan (to be included in a future version): Some modeling work has been done in this area, but nothing is published, or is near implementation-ready.

Storyboards

2.1 New Protocol Submission – multiple arms, single treatment in arm, multi-center parallel design, drug

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 across 10 centers. 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.

2.2 New Protocol – single arm, single treatment in arm, device

Healthy Devices Inc. plans to study the effects of their new implantable defibrillator Arrythmatex-N200 in a Phase 4 open label trial in subjects with severe refractory ventricular arrhythmias with a history of successful resuscitation following sudden cardiac death. 200 eligible subjects among 40 centers will undergo device implantation and will be followed prospectively for two years. 48 hour continuous Holter monitoring will be done monthly. Outcome measures include frequency of ventricular arrhythmias, frequency of device defibrillation, overall mortality, cardiac mortality, device malfunction. The sponsor registers the trial on www.clinicaltrials.gov. Protocol information including the trial registry identifier (NCT number) is submitted to FDA using the study design message.

2.3 New Protocol – Single investigator, two treatments in arm, cross-over design

A clinical investigator at Palm State University plans to study the off-label use of a new anti-epileptic medication Eliptostatin on migraine prevention in 20 subjects with severe migraines as add-on therapy to their current regimen in a placebo controlled cross-over design. The investigator plans to use twice the maximum approved dose for epilepsy thereby requiring this protocol be submitted to FDA. After screening, subjects undergo a one month placebo run-in to determine the baseline monthly migraine frequency. Subjects are randomized to receive either Eliptostatin 100 mg daily (n=10) or placebo (n=10) for three months. After a two week washout, all subjects enter another one month placebo run-in followed by the other treatment for three months. A two week washout/observation period concludes the trial. Subjects record migraine headaches in a patient diary throughout the trial. The investigator, using a web-based, interactive protocol authoring tool provided by his University, generates a study design message and sends it to his IRB and to FDA as part of his IND submission.

2.4 New Protocol – repeated elements, conditional branching, assignment to study cell based on response, biologic

The National Cancer Institute is sponsoring a multi-center trial of a new promising monoclonal antibody antineoplastimab in metastatic breast cancer. Three hundred eligible women across 30 cancer centers are randomized in a 2:1 ratio, stratified by estrogen receptor status, to receive either standard of care + antineoplastinab vs. standard of care + placebo. After a week screening, subjects receive a 30 minute intravenous infusion of the experimental treatment. The treatment is repeated monthly until either disease progresses or they enter remission. Those that enter remission are treated with three more cycles and then enter follow-up. Those who progress are unblinded and offered open label antineoplastimab monthly if they previously received placebo. They are maintained on monthly antineoplastimab until disease progresses further or for three cycles past a remission, should one occur. Those who progress following double-blind or open label treatment with antineoplastimab are dropped out of the study as treatment failures. The protocol information is captured in the study design message and submitted.

Gap: randomization is not described – need to cover randomization characteristics

2.5 New Protocol – Oncology Drug + Radiation +/- Surgery

NCI-sponsored Study RTOG 93-09[5] is a randomized, unblinded, multicenter, two-arm parallel design study comparing Chemotherapy + Radiation Therapy (CT+RT) vs. Chemotherapy + Radiation Therapy + Surgery (CT+RT+S) for the treatment of Stage IIIa non-small cell lung cancer. Planned sample size is 510 subjects. Following screening, eligible subjects are identified (see full Eligibility Criteria in Appendix 2) and are randomized to receive either CT+RT or CT+RT+S. After randomization, all subjects initially receive induction CT+RT (Cisplatin 50 mg/m2 IV days 1,8,29, 36 and VP-16 50 mg/m2 IV, on days 1-5, 29-33, plus 45 Gy RT (1.8 Gy per weekday over 5 weeks)).

Those in the surgical arm are evaluated 2-4 weeks after completion of induction for tumor progression. Those who progress are taken off protocol treatment and undergo follow-up. The remaining are considered for surgery. Those who refuse surgery or are medically unfit to undergo surgery receive two cycles of chemotherapy and then undergo follow-up. The remaining undergo surgical resection of the tumor followed by two cycles of chemotherapy beginning 3-5 weeks after surgery.

Those in the medical arm are evaluated 7 days before completion of induction. Those who progress are taken off protocol treatment and undergo follow-up. The remaining receive an additional two cycles of chemotherapy plus additional radiation therapy, and then enter follow-up.

Progression free, median, 2 and 5 years survivals are compared between the two groups.

These study design details are captured and transmitted using the study design message.

2.6 New Protocol – adaptive trial desing

Acme Pharmaceuticals plans to study the effects of two new drugs in study NCT777777 on survival and neurological outcome in subjects following severe traumatic closed head injury. Four hundred eligible subjects across 10 centers are randomized to receive either Placebo, Drug A, or Drug B 10mg, or Drug B 50 mg daily for three months. A planned interim analysis will be performed for futility when 100 have completed the study, in which case that arm will be dropped. It will also test power calculation assumptions and increase the sample size if necessary. These study design features are captured in the study design message and submitted.

2.7 Protocol Amendment – planned change in study design following an interim analysis

The planned futility analysis performed in study NCT7777777 (see 2.6) indicates the Drug A arm is futile and this arm is dropped from the study. The analysis also advises increasing the sample size by 30 subjects.

[5] Protocol publicly available at: http://www.rtog.org/members/protocols/93-09/93-09.pdf

These changes to the protocol are captured in the study design message and submitted with the protocol amendment.

2.8 Protocol Amendment – planned change in study design following Safety Monitoring Board recommendation

Partway during the trial, the safety monitoring board for study NCT7777777 has determined that the Drug B 50 mg dose is unsafe and recommends that arm be dropped. The protocol is amended, the change is captured in the study design message and submitted with the amendment.

2.9 Protocol Amendment – unplanned change in eligibility criteria

Recruitment for trial NCT7777777 is slower than expected. The sponsor decides to relax the eligibility criteria by expanding the upper and lower age limits permitted for enrollment. This change in study design is captured in the study design message and submitted with the protocol amendment.

2.10 Food Animal Study #1

ACME Animal Health plans to study the effect of a drug given in feed on growth performance (weight gain) and feed efficiency (weight gain per feed consumed) in male and female finishing swine on a 5-site study. The company seeks approval for a dose range: 5 to 10 ppm of drug in feed. They wish to evaluate two treatment durations: 14 and 28 days. Animals will be housed in pens to simulate standard industry housing practices. Eight (8) animals will be randomly assigned to each pen. The medicated feed will be administered, and intake recorded, on a pen basis, not by individual animal. Individual animals are ID'ed and weights of pigs will be recorded on an individual basis.

Three doses will be tested: 5 ppm, 7.5 ppm, and 10 ppm, and the durations of the treatments will be 14 days and 28 days. Based on statistical power needed to detect a significant difference between control and treatment groups, it is estimated that the study should include 10 pens for each dose, treatment duration, and study location. Thus, the total number of pens will be 600 (10 pens X 3 doses X 2 durations X 5 sites X 2 genders). Treatments (dose X duration) will be randomly assigned to pen within a location. A total of 4800 animals will be enrolled in the study (8 animals X 600 pens). The study design message captures and conveys this information.

[deleted as unnecessary, as all key design features are already captured in 2.10]2.11 Aquaculture Study – multiple species, derived baseline population size

Government Agency Aqua plans to study the effectiveness of a new immersion product, Drug A, administered at 100 mg/L for 15 minutes daily on alternative days to control mortality in two coolwater species of freshwater-reared finfish due to Disease X caused by bacteria *Fish pathogen*. The drug is 100% active and will be administered as a static bath in flow-through tanks. Study animals will be from a reference population that is experiencing increased mortality due to the disease as confirmed by gill biopsies. Completely randomized design procedures will be used to allocate fish to experimental units and treatments to experimental units. There will be a total of nine experimental units, three treated for species A, three

treated for species B, and three control (placebo). Each unit will contain approximately 700 fish at a density of 30 g/L, a density similar to the reference population. An experimental unit will be removed from the study if a standpipe is left out resulting in drainage of the water in experimental unit that unduly stressed test fish or an unacceptable number of fish jump out of the experimental unit (15%). Percent cumulative mortality between treatment groups will be compared; analysis will be conducted using the tank the experimental unit. Sample counts will be used to determine the number of live fish present in an experimental unit at the end of the study. Baseline fish count per tank (for mortality calculations) will be calculated based on total weight of live fish at the end of the study divided by the average weight per fish based on sample counts at the end of the study, plus the number of fish lost during the study. Fish appetite and behavior during the study will also be recorded using an objective scale. Water quality parameters will be measured and the dose of the drug verified. The drug will be considered effective if the mean percent mortality in untreated tanks is greater than that in control tanks with a p value less than 0.05. The study design message captures and conveys this information.

2.12 *In vitro* Toxicology Assay – Ames Test

To test the potential genetic toxicology of Product X, each of five strains of bacteria (four strains of *S. typhimurium* and one strain of *E.coli*) will be exposed to a range of concentrations (500, 1000, 2500, 5000 µg/plate) of Product X, both in the absence and presence of metabolic activation. All plates will be incubated at 37º C for 48-72 hours; triplicate plating will be used at each dose level. Negative (solvent) and positive controls (single concentration) will be included for all tester strains, both in the absence and presence of metabolic activation. Pertinent observations include the number of revertant colonies per plate. The study design message is used to convey this information.

2.13 Embryo-Fetal Development Study – parent-child relationships

To test adverse effects on embryo-fetal development, Product X will be administered orally to pregnant rats (20 animals/group) from implantation to closure of the hard palate (i.e., from Day 6-7 to Day 15-18 of gestation). Animals will receive either vehicle (control group) or Product X at one of three dose levels, with the high dose producing some evidence of maternal toxicity (i.e., a maximum tolerated dose). Dams will be examined for clinical signs, body weight, food consumption, and upon sacrifice (approximately one day prior to parturition) will be examined for effects on reproductive parameters (including corpora lutea, numbers of live and dead implantations). All fetuses will be examined for viability and external abnormalities. Of the total number of fetuses, one-half will be examined for skeletal abnormalities and the other half will be examined for visceral abnormalities. The study design message is used to convey this information.

2.14 Multigenerational Study

To test multigenerational effects of low dose estrogens on tumors in rats, 50 F_0 female rats per dose group in were exposed to 5, 100, or 500 mg/kg of the estrogen analog, genistein, daily beginning shortly after weaning. The feed did not contain alfa or soy, which are known to contain naturally occurring estrogenic compounds. They were bred and subsequently sacrificed at two years and evaluated for evidence of tumors. The F_1 and F_2 female rats were similarly exposed to the same dose as the parent, bred, and assessed for tumors at 2

years. The F_4 generation was not exposed following weaning, followed for 2 years and assessed for tumors. The incidence of tumors are compared across the 5 generations to assess the cumulative effects of low dose estrogen exposure across generations. This design is captured in the study design message.

2.15 Stability Study

Acme Pharmaceuticals is testing the stability of their new drug Decarol 100 mg capsules (Lot #123) to support a 60 month expiry, Lot #123 is a 500 kg batch. Capsules from a specific lot and pre-identified drug substance lots are kept in 30cc plastic bottles. 20 bottles are tested in real time (25 ±2 C / 60 ±5% RH (relative humidity) Upright), with testing at 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months; 20 bottles are stored in intermediate storage conditions (30 ±2 C / 60 ±5% RH Upright), with testing every 3 months; and 20 bottles are stored under accelerated storage conditions (40 ±2 C / 75 ±5% RH Upright), with testing at 0, 1, 2, 3, and 6 months. Three capsules from once container are sampled for each test. Tests include measures for container/closure seal, appearance and print, capsule odor, capsule integrity, disintegration, dissolution, microbial limits, capsule fill, strength (assay), and BHA (butyl hydroxyanosole). Results are compared with established specifications, which are documented in the protocol. The study design message captures these design details.

2.16 Device Performance Study

Acme Pharmaceuticals is developing a new drug for the treatment of migraine that will be delivered intranasally. They have hired Healthy Devices, Inc. to manufacture a new aerosol spray drug delivery device. The new device promises to have improved performance characteristics compared to existing drug-deliver device. The company will perform a study on ten devices. Each is activated 10 times and the spray patterns are recorded and compared with established performance standards for similar devices. Examples of data to be recorded include droplet size, dispersion pattern, angular spread, spray intensity. In the second phase of the study, each device is activated repeatedly until the performance degrades below an established lower limit for prespecified parameters and the number activations to reach device failure are measured.

2.17 Observational (Cohort) Study

Because of rare post-marketing reports of retinal degeneration and blindness associated with long term use of their anti-epileptic drug Eliptostatin, Acme Pharmaceuticals decides to conduct a cohort study. Three thousand patients already being treated with Eliptostatin for chronic epilepsy are recruited across 30 multinational sites. Three thousand matched controls treated with other antiepileptic medications (matched for age, sex, body mass index, duration of epilepsy, duration of treatment) are similarly selected. Both cohorts are followed for five years and undergo eye examinations every six months, to include visual field testing. The incidence of retinal degeneration and visual loss at six month intervals are calculated and compared. The protocol is submitted to FDA with the goal of including the results in labeling at the conclusion of the study. These design features are captured in the study design message.

Map to SDTM

Domain Analysis Model etc

Subject Data

Summary of Requirement

Notes from previous document

*A **Study Report** submission (interim or final) contains the results. The **Study Participation** and the **Subject Data** messages will transport this information, including collected study data and derived data for analysis.*

1. *Study Participation information as described above.*
2. *Study Data*
   a. *Study data will need to be submitted in a form consistent with the HL7v3 ICSR. The message will need to contain all of the data contained in the following existing CDISC standards*
      i. *Case Report Tabulations: The subject data domains of the SDTM contain all the collected data, as well as coded and standardized versions of the collected data (e.g., MedDRA codes, numeric results converted to standard units, scores of questionnaire data), and some particularly useful derived data (e.g, timing converted from date to study day format, flagging of baseline values, which analysis populations a subject belongs to).*
      ii. *Analysis Datasets (to be included in a future version): These are the ADaM datasets that were used to produce the key results of the analysis. "Key" is defined by negotiation between sponsor and FDA. There is at least one analysis dataset, the ADSL dataset which contains one record per subject. ADaM datasets contain a mixture of collected and derived data, including a number of flags and other features that are helpful to FDA statistical reviewers in reproducing results and exploring their sensitivity and robustness.*
      iii. *Dataset Definition Tables: The CRT-DDS (more commonly known as the define.xml) contains metadata about the SDTM and ADaM datasets, links from the dataset to precursor information (annotated CRF pages for SDTM, other datasets for ADaM), and derivation information. Analysis Results metadata was demonstrated in the SDTM/ADaM pilot, and is being incorporated into the define.xml standard.*
   b. *The harmonization of the ICSR and the proposed study data message may require changes to the ICSR.*

Storyboards

Map to SDTM

Domain Analysis Model etc

HL7 ICSR

1. HL7 ICSR
2. An **Expedited Adverse Event Report** contains information about an adverse event that must be reported shortly after it is observed. The HL7 ICSR will transport this information.

Gaps in BRIDG

The gaps that need to be filled in BRIDG. Summary of the information held above

Recommendations

1. 5th Message to cover the Study Completion (study status) use case

Appendix 1 – Study Roles and Responsibilities for Organizations

Title	Description
Sponsor	The individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
IND Owner	The organization that submitted the IND (investigational new drug) application to the FDA.
Central Lab vendor	The responsible party for providing central laboratory services (routine clinical pathology, special diagnostic biomarkers, cytology, histopathology, histomorphometry, genotyping and genomics/sample storage). These responsibilities include acquisition, analysis, data management and results delivery.
Central ECG vendor	The responsible party for providing central ECG services (resting, continuous 12-lead). These responsibilities include acquisition, analysis, data management and results delivery.
Central Imaging vendor	The responsible party for providing central imaging services (CT scan, MRI, bone mineral density, routine X-rays, ultrasound, mammography, total body composition, echocardiography). These responsibilities include acquisition, analysis, data management and results delivery.
Central Diagnostic vendor (other)	The responsible party for providing other central diagnostic services. These responsibilities include acquisition, analysis, data management and results delivery.
Electronic Data Capture Hosting	The vendor responsible for providing the electronic data capture computer hosting service.
ePRO Vendor	The vendor responsible for providing the electronic patient-reported outcome (ePRO) service for the sponsor.
Pharmacology (PK – ADME)	The responsible party for providing the Pharmacokinetics or ADME (Absorption, Distribution, Metabolism and Excretion) analysis.
Protocol Preparation	The responsible party for preparing or reviewing protocol documents (i.e. protocol synopsis, protocol, protocol amendments, and protocol addenda)
Informed Consent Document	The responsible party for preparing or reviewing study-specific inform consent documents (ICDs), site-specific ICDs; amendments and supplementals – using

	content from the protocol, the risk profile and the country-specific ICD requirements.
CRF Development and CRF Instruction Guide	The responsible party for the review, design, draft, and/or development of study CRFs and the CRF instructions.
Translations of Protocol, ICD, CRF	The responsible party for performing the translations for the protocol, ICDs, IBs, CRFs, CRF instructions and potentially other study specific documents.
Printing, Binding, and Shipping (Non-Study Drug Supplies)	The responsible party for printing, binding, and shipping of the protocol, CRFs, regulatory packages (e.g. IB, 1572 forms, ICD, etc.) and other study-related documents to sites.
Site Qualifications	The responsible party for developing a list of potential sites and the subsequent screening and qualifying of the selected sites
Site Contracts and Budgets	The responsible party for obtaining site confidentiality agreements, negotiating site budgets, preparing, negotiating and executing site letter of agreements, and paying investigator sites per initial budget.
Site Regulatory Documents	The responsible party for the preparation, collection, and submission of site regulatory documents. This includes the tracking the submissions of the document versions and approval.
Institutional Review Board (IRB)	The responsible party or parties acting as an independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a study.
Investigator Meeting and Adjunct Clinical Training	The responsible party for the investigator meetings or adjunct clinical training.
Site Initiation Visits	The responsible party for conducting site initiation visits.
Site Monitoring	The responsible party for routine site monitoring visits including (but not limited to) the review, verification of the following: visit data; drug accountability, reconciliation, and return; informed consent documents; and running records (e.g. adverse events, concomitant medication).
Site Communication / Management	The responsible party for routine site communication / management. This will include the supervision and monitoring the progress of the study as well as the participation of the investigators to ascertain and verify the compliance of the investigators with the protocol, maintenance of the investigator documents, proper drug accountability / reconciliation and regulatory requirements.
Adverse Experience Reporting	The responsible party for collection of serious adverse events (SAEs) and regulatory reporting. This includes site compliance,

	safety mailing, patient narratives, trial level safety review, periodic reports and blinding and unblinding subject treatment.
Project Management	The responsible party for general project management of the study
Quality Assurance Audits of Investigator Sites	The responsible party for QA audits of the investigator sites.
Close-out Visits	The responsible party for close out visits including preparation and report completion.
Study Drug Management	The responsible party for Clinical Trial materials and related services. This includes: material planning, inventory management, study drug packaging, labeling, shipments, returns, destruction and monitoring / reconciliation of unblinding envelopes.
Interactive Voice Response System (IVRS)	The responsible party for developing and maintaining the IVRS system for usage in study enrollment, randomization and treatment assignments.
Data Management	The responsible party for data management (DM) activities. This includes the building and validating of the data entry and edit system; entry of CRF pages; data validation; coding terms; SAE review / reconciliation; database quality review; database lock; ancillary data integration and dataset delivery.
Statistical Analysis - Tables, Listings and Figures	The responsible party for statistical analyses and may include the preparation of the statistical analysis plan, and/or creating tables, figures and listings.
Clinical Study Reports and Manuscripts	The responsible party for preparing clinical study reports and/or manuscripts.
Investigator Brochure (IB)	The responsible party for preparing investigator brochures (IBs).
Clinical Endpoint Committee ("CEC")	The responsible party for providing services to support the Clinical Endpoint Committee (CEC) in making clinical endpoint determinations for the study.
Data Monitoring Committee	The responsible party for providing services to support the Data Monitoring Committee (DMC) for the study.

Appendix 2 – Eligibility Criteria for Study 93-09

Protocol	Logic Equivalent
General Requirements 1. Single, newly diagnosed, primary lung parenchymal lesion of stage IIIA *(T1, 2 or 3)* with ipsilateral positive mediastinal nodes *(N2)* 2. Either measureable or evaluable disease by chest xray and/or contrast CT scan is allowed 3. A contrast CT scan of the thorax is required to complete the T and N staging 4. Histologic *(biopsy)* or cytologic *(needle aspiration or sputum)* proof of non-small cell histology must be obtained and satisfy both of the following: a. Adenocarcinoma, large cell carcinoma, squamous carcinoma or non-lobar and non-diffuse bronchoalveolar cell carcinoma b. Documentation of non-small cell carcinoma may originate from the mediastinal node biopsy or needle aspiration only if a distinct lung primary separate from the nodes is clearly evident on the CT scan.	1. [Lung Parenchymal Lesion Num = 1] AND [Lung Parenchymal Lesion status = new] AND [Lung Parenchymal Lesion Origin= Primary] AND [Stage = IIIA] AND [Mediastinal nodes = Present] AND [Lung Parenchymal Lesion Side = Mediastinal Node Side] 2. {[CXR = Measurable Disease] OR [CXR = Evaluable Disease]} OR {[CCT = Measurable Disease] OR [CCT = Evaluable Disease]} 3. [CCT Thorax Status] = Done 4. {[Diagnosis = adenocarcinoma] or [Diagnosis = large cell carcinoma] OR [Diagnosis = squamous cell carcinoma] OR [Diagnosis = non-lobar and non-difuse broncoalveolar cell carcinoma]} AND {[Diagnosis Procedure = Biopsy] OR [Diagnosis Procedure = Needle Aspiration] OR [Diagnosis Test = Sputum Cytology]} AND {[Diagnosis Location = Lung

Protocol	Logic Equivalent
	Parenchymal Lesion] OR ([Diagnosis Location = Mediastinal Node] AND [CCT = Lung Primary separate from the nodes])}
Primary Tumor Stage (T Stage) Requirements 1. T1, T2, or T3 only according to International Lung Cancer Staging System in Appendix II 2. Lesion must clearly arise from the bronchus 3. If a pleural effusion is present, 1 of the 2 following criteria must also be met to exclude T4 disease: a. When the pleural fluid is present either before or after prestudy mediastinoscopy or exploratory thoracotomy, a thoracentesis with negative cytology must be performed, OR, b. When pleural fluid is present only on the CT scan and not the chest xray, but is deemed too small to tap safely under either CT or ultrasound guidance, the patient is eligible and this must be clearly documented on the I1 form.	
Nodal Stage (N stage) Requirements on the Ipsilateral *(same as primary)* Side 1. Positive ipsilateral mediastinal node or nodes *(nodal stage N2)*, with or without positive ipsilateral hilar *(N1)* nodes 2. N2 nodes must be separate from primary tumor by either CT scan or surgical exploration *3.* Proof of N2 disease may be either histologic *(biopsy)* or cytologic *(needle aspiration)* 4. Diagnostic methods acceptable for N2 documentation include: thoracotomy, mediastinoscopy, mediastinotomy, Chamberlain procedure, Wang needle or fine needle aspiration under bronchoscopic or CT guidance 5. The only exception to 3.3.4 is a special circumstance in	

Protocol	Logic Equivalent
which if all of the following are true, a nodal biopsy or aspiration can be omitted: a. Paralyzed left true vocal cord documented by bronchoscopy or indirect laryngoscopy b. Nodes visible in the AP *(Level 5)* region on CT scan c. Distinct primary separate from the nodes is visible on CT scan 6. Regardless of method of documentation of N2 disease, the following must be true: a. From the Operative and Pathology reports, all mediastinal nodes shown to be both positive and negative must be designated on the I1 form according to the Lymph Node Map in Appendix III b. If the procedures to document N2 eligibility were done at a non-member facility, the patient is still eligible if the study institution PI reviews the outside pathology slides and report with the study institution's pathologist in conjunction with the outside operative report, and generates a report that verifies the original diagnosis and lymph node mapping, as consistent with the staging requirements of the protocol	
Nodal Status in the Contralateral *(opposite)* Mediastinum and Neck must be Negative 1. Nodes may not be present in the supraclavicular areas or higher in the neck unless they are proven to be benign on excisional biopsy 2. The negative status of the contralateral mediastinal nodes must be established by any one of the following ways: a. Mediastinoscopy, mediastinotomy, Chamberlain	

Protocol	Logic Equivalent
procedure, or thoracotomy must be done if lymph nodes larger than 1 cm are visible on the contrast CT scan of the chest on the side opposite the primary. b. If there are either no nodes or if nodes less than or equal to 1.0 cm are visible on the contrast CT scan of the chest on the side opposite the primary tumor, a surgical procedure as in 2a is not required 3. If criteria in 3.4.2.1 are met, using the Pathology and Operative reports, the lymph node station *(level)* designations should be used to label the negative contralateral nodes according to Appendix III on the I1 form.	
Evaluation to Exclude Distant Metastases *(M stage M0)* 1. Lymphadenopathy may be present on physical examination only if there is biopsy-proof of a benign cause 2. The serum SGOT or SGPT and bilirubin must be less than or equal to 1.5 times the upper institutional limit of normal unless benign cause is documented 3. Hepatomegaly or splenomegaly on physical examination or CT scan of the upper abdomen must have a benign cause documented 4. No evidence of distant metastases on contrast CT or MRI of the brain, bone scan, CT of the lungs to exclude other ipsilateral or contralateral parenchymal lesions, and on contrast CT of the upper abdomen including ENTIRE liver and adrenals 5. Abnormal findings in the abdomen should be further assessed by MRI or ultrasound. a. If clearly benign on further imaging, invasive assessment by biopsy is not required.	

Protocol	Logic Equivalent
b. If indeterminate on further assessment, biopsy is required unless in clinical judgement area is inaccessible 6. Bone scan abnormalities with normal plain radiographs are considered metastatic unless they are either: a. Clearly caused by degenerative joint disease, traumatic fracture or other benign entity, OR b. Are proven to be benign by additional tests such as MRI, CT or biopsy	
Multidisciplinary Pretreatment Assessment 1. The surgeon who would potentially perform the thoracotomy, the treating medical oncologist and the treating radiation oncologist must all assess patient before registration and their names provided on the on-study form. a. They must agree on the staging designations in 3.2, 3.3, 3.4 and 3.5 above b. They must agree that the patient is potentially operable and resectable after induction chemotherapy and radiation	
Other Laboratory and Function Studies Requirements *Performance Status Evaluation* 1. Apply Karnofsky *(KPS)* system found in Section 11.4 during pretreatment history and physical examination 2. Eligible if 90 or 100%, OR, 3. If 70 or 80%, the albumin must be at least .85 x lower institutional normal and weight loss within 3 months prior to diagnosis must be less than or equal to 10%	
Hematology Requirements	

Protocol	Logic Equivalent
1. Hemoglobin less than 8.5 must be investigated by bone marrow to rule out metastatic tumor; if marrrow is negative, patient is eligible. 2. Hemoglobin levels of 10.0 or greater are strongly recommended just prior to treatment via transfusion, if necessary, to insure better tolerance of chemoRT 3. White blood cell count at least 4000; if less, granulocytes at least 2000 4. Platelets at least institution lower limit of normal	
Renal Requirements 1. The creatinine clearance must be at least 50 ml/min 2. This may be measured or calculated according to the following formula: *(140-age) x (body weight in kg)* 72 x serum creatinine *Multiply this number by 0.85 if the patient is female.*	
Pulmonary Function Requirements 1. FEV1 greater than or equal to 2.0 liters; if less than 2.0 liters, the predicted postresection FEV1 must be at least 800cc based on the following formula using the quantitative V/Q scan: a. If a pneumonectomy will be necessary or is a strong possibility, *predicted post-resection FEV1 = FEV1 x % perfusion to uninvolved lung from quantitative lung V/Q scan report.* b. If only a lobectomy will be required,	

Protocol	Logic Equivalent
predicted post-resection FEV1 = FEV1 x % perfusion to uninvolved lung plus the FEV1 x estimated % perfusion to uninvolved ipsilateral lobe(s).	
Ineligibility Criteria 1. Small cell carcinoma and lobar or diffuse bronchoalveolar cell carcinoma 2. Two or more parenchymal lung lesions 3. Previous diagnosis of lung cancer 4. Previous surgical resection of the current primary lesion 5. Prior radiotherapy or chemotherapy for lung cancer 6. Pericardial effusion 7. Superior vena cava syndrome 8. Significant hearing loss and patient unwilling to accept potential for further hearing loss 9. Symptomatic peripheral neuropathy 10. Currently receiving chemotherapy for another condition (such as arthritis) 11. Medical illness not controllable by appropriate medical therapy including but not limited to myocardial infarction within previous 3 months, active angina, unstable heart rhythms, congestive heart failure and peptic ulcer disease under active treatment 12. Pregnant or lactating women may not participate. Women/men of reproductive age or potential may not participate unless they use effective contraception. 13. Prior or concurrent malignancy other than adequately treated basal or squamous cell skin cancer, in situ cervical cancer, and either ductal or lobular carcinoma in situ of the breast. Any other prior malignancy	

Protocol	Logic Equivalent
EXCEPT lung cancer is allowed if a 5-year disease-free interval has elapsed since last treatment.	