

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: General Advice

Meeting Date and Time: Friday, October 31, 2014
Meeting Location: Teleconference

Application Number: pre-submission NDA 203652
Product Name: Gemcitabine Hydrochloride Injection, 10mg/mL
Proposed Indication:

- In combination with carboplatin for the treatment of (b) (4) advanced ovarian cancer
- In combination with paclitaxel for the first-line treatment of (b) (4) metastatic breast cancer
- In combination with cisplatin for the (b) (4) treatment of (b) (4) non-small cell lung cancer
- (b) (4)

Sponsor/Applicant Name: Sun Pharma Advanced Research Company Ltd. (SPARC)
[U.S. Agent: Salamandra, LLC.]

Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Missiratch Biable, M.S.

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2), OHOP

Patricia Keegan, M.D., Director

Steven Lemery, M.D., M.H.S., Clinical Team Leader

Shan Pradhan, M.D., Clinical Reviewer

Whitney Helms, Ph.D., Pharmacology/Toxicology Team Leader

Missiratch (Mimi) Biable, M.S., Regulatory Health Project Manager

Deveonne Hamilton-Stokes, RN, BSN, Regulatory Health Project Manager

Monica Hughes, M.S., CPMS

Office of Clinical Pharmacology, Division V

Jun Yang, Ph.D., Clinical Pharmacology Reviewer, DCPV

Office of New Drug Quality Assessment

Liang Zhou, Ph.D., Chemistry Team Leader, ONDQA
Danuta E Gromek-Woods, Ph.D., Chemistry Reviewer, ONDQA

Office of Surveillance and Epidemiology

Otto Townsend, Ph.D., DMEPA Reviewer
Frances Fahnbulleh, OSE RPM
Shaily Arora, PharmD., OSE/OPE/DPVII

SPONSOR ATTENDEES

Mr. Kirti Ganorkar, Senior Vice President (Business Development)
Dr. Subhas Bhowmick, Senior Vice President (Formulation Development)
Mr. Prashant Kane, Vice President (Formulation Development)
Mr. Samarth Kumar, Manager (Formulation Development)
Dr. Madhav Marathe, Vice President (Toxicology and Animal Resources)
Dr. Harry Ruan, Senior Director (Toxicology, Sun Pharma)
Dr. Henry Wolfe, Vice President (Research and Development, URL Pharma)
Dr. Shravanti Bhowmik, General Manager (Clinical Research)
Dr. Abhay Muthal, Senior General Manager (Regulatory Affairs)
Dr. Karin Kook Consultant, Managing Director (Salamandra, LLC)
Grace Shen, Vice President-Speciality Products, Marketing, SUN Pharma

BACKGROUND

On behalf of Sun Pharma Advanced Research Company (SPARC) Ltd., Salamandra, LLC requested a Type B, pre-NDA meeting on August 22, 2014 to confirm that their development plans are adequate to obtain the data necessary to support an NDA to be submitted under Section 505(b)(2) of the Federal FD&C Act. A Type B/Pre-NDA meeting was held with the FDA on December 16, 2011. The current meeting was granted as a Type C meeting on September 5, 2014.

SPARC plans to submit a New Drug Application (NDA) under the provisions of Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act, relying on FDA's prior findings of safety and efficacy for Gemzar® (gemcitabine for injection) for non-clinical, clinical pharmacology, and clinical information. SPARC will seek approval for the same indications for which Gemzar is approved:

- In combination with carboplatin for the treatment of (b) (4) advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy
- In combination with paclitaxel for the first-line treatment of (b) (4) metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated
- In combination with cisplatin for the (b) (4) treatment of (b) (4) non-small cell lung cancer

The recommended doses in the Gemzar package insert are 1000 mg/m² administered intravenously over 30 minutes (ovarian, non-small cell lung, and pancreatic cancers) and 1,250 mg/m² administered intravenously over 30 minutes (breast cancer indication), with different schedules depending upon the indication. SPARC stated their intent to “maintain the same dosing recommendations as for the reference product,” however proposed to seek approval for an alternative dose-banding approach to dosing rather than the body surface area (BSA)-based dosing recommended in the Gemzar label, as illustrated in tables on pages 13 and 14 of the briefing package. Tables 3:1 and 3:2 on pages 13 and 14 of the briefing package show the target dose, dose to be delivered using SPARC’s “ready to use” formulation, and the absolute differences between doses delivered using the proposed dose-banding approach and the recommended Gemzar dosing according to BSA. These tables show that the proposed formulation and dosing scheme appear to provide doses within 5% of the calculated target dose for all indications for patients with BSAs between 1.2 and 2.6 m².

SPARC’s proposed a “ready-to-infuse” formulation of gemcitabine hydrochloride, 10 mg/mL, will deliver gemcitabine at a concentration approved for Gemzar. Gemzar, the listed drug, is presented as a lyophilized powder available in single use vials containing either 200 mg or 1 g gemcitabine, to be reconstituted with 5 mL or 25 mL 0.9% sterile sodium chloride injection, respectively, producing a concentration of 38 mg/mL for infusion.

SPARC noted that the proposed drug product differs from that of the listed drug, Gemzar, in dosage form and in excipients. SPARC stated that the proposed formulation contains no mannitol and no sodium acetate, both of which are present in the listed product. SPARC proposed ten strengths/presentations (infusion bags) of the product, which SPARC stated will allow for the dosing of patients with body surface areas (BSAs) ranging from 1.2 to 2.6 m². The proposed strengths/ fill volumes are: 1200 mg (120 mL), 1300 mg (130 mL), 1400 mg (140 mL), 1500 mg (150 mg), 1600 mg (160 mL), 1700 mg (170 mL), 1800 mg (180 mL), 1900 mg (190 mL), 2000 mg (200 mL), and 2200 mg (220 mL). SPARC stated that the packaging for the product will have specially colored labeling to assist in identifying the dose in each bag.

A pre-NDA meeting was held on December 16, 2011. At that time DOP2 indicated that the proposed dosage and administration section for product labeling information would need to be provided in order for FDA to answer questions as to whether the proposed dosage and administration instructions were acceptable; FDA stated that the label would be evaluated at the time of NDA submission. SPARC was also advised that FDA would not commit to agreement on the practice of ‘dose-banding’ which may include rounding the calculated patient dose to the nearest ±5%. FDA stated that additional information, which may be requested for inclusion in a proposed NDA could include analyses of the potential for medication errors, accuracy of ability to deliver the intended dose based on BSA, and the potential impact on patient safety and efficacy of the proposed dose-banding scheme. FDA stated that additional clinical data may be necessary, however FDA did not believe additional clinical studies were needed.

Chemistry, Manufacturing, and Control (CMC)

Product Information:

SPARC's proposed "ready-to-infuse" solution contains gemcitabine hydrochloride drug substance manufactured by Sun Pharmaceutical Industries Limited (SPIL), a company affiliated with SPARC. SPARC stated that the drug substance manufacturer, SPIL, holds a drug master file (DMF # 19427) on file with FDA that also supports an approved ANDA and that Sun Pharma intends to reference this DMF in the planned NDA submission.

Physical Properties and Drug Substance

SPARC stated in their meeting briefing document that the drug substance batches will be manufactured at the SPIL facility in India. In support of the NDA, SPARC is proposing a reduced stability testing scheme whereby three registration batches of each of the four bracketing fill volume presentations (120, 160, 180, and 200 mL) and one registration batch of the five intermittent fills (130, 140, 150, 170, and 190 mL) are placed on stability. SPARC stated that at the time of NDA submission, a minimum of 6-month accelerated and 12-month long term stability results for three batches of each of the four bracketing fill volume presentations (120, 160, 180, and 200 mL) and one batch of the 140 mL fill volume presentation will be provided. Further, SPARC stated that at the time of NDA submission, 6-month accelerated and 9-month long term stability results for the fifth bracketing fill volume (220mL) presentation will be provided.

Nonclinical

SPARC has not conducted nonclinical studies with gemcitabine nor are any studies planned.

Biopharmaceutics / Clinical Pharmacology

SPARC has not conducted any biopharmaceutics or clinical pharmacology studies with their product nor are any studies planned. SPARC plans to request a waiver from the requirement to perform *in vivo* bioequivalence studies, as outlined in 21 CFR 320.22(b)(1). The basis for this waiver (per SPARC) is that the drug product is a parenteral solution that contains the same active ingredient and within in the range of concentrations that are approved for Gemzar, after dilution.

Clinical

According to the meeting briefing package, SPARC does not plan to conduct clinical trials with their product. SPARC proposed not to prepare an Integrated Summary of Efficacy (ISE), or a Summary of Clinical Efficacy (SCE). SPARC further stated that the safety of their formulation will be based upon safety data described in the Gemzar label, the published literature, and the Agency's prior findings of the safety and effectiveness of Gemzar. SPARC stated that this information will be summarized in an Integrated Summary of Safety (ISS).

Preliminary FDA responses were emailed to Salamandra, LLC (U.S. Agent for SPARC) on October 29, 2014. Salamandra, LLC (U.S. Agent for SPARC) submitted a response via email on October 30, 2014, and stated that they only wished to discuss FDA's responses to questions 9, 10, 11, and 12 during the teleconference.

SPONSOR QUESTIONS AND FDA RESPONSES

Chemistry, Manufacturing and Controls (CMC)

1. *Does the Division find acceptable the justifications presented to support the (b) (4) impurity limit in the drug substance and drug product specifications, respectively?*

FDA's Preliminary Response Sent on October 29, 2014:

In the absence of suitable test methods for (b) (4) impurity, FDA cannot evaluate or comment on the proposed limits. FDA noticed that the highest level of the impurity (b) (4) observed under accelerated stability conditions does not exceed (b) (4)%, which is less than the proposed limit of NMT (b) (4)%. Therefore based on the data provided by SPARC, the (b) (4) impurity should be (b) (4) and FDA recommends that the upper limit not exceed (b) (4)%.

Discussion during the meeting:

SPARC did not have any questions or comments.

2. *Is the planned extractables study adequate to sufficiently characterize potential extractables? Does the Division have any comments in this regard? Is it acceptable to be still monitoring and evaluating any potential leachables in parallel to FDA's review of the NDA?*

FDA's Preliminary Response Sent on October 29, 2014:

The extractable study plan appears to be acceptable and FDA has no comments on the study protocol.

The original NDA must contain the results of leachable studies that are at least 12 months in duration and SPARC must state their commitment to continue monitoring potential leachables until the proposed expiration dating period established based on adequate stability data.

Discussion during the meeting:

SPARC did not have any questions or comments.

3. *Is the planned ink migration study sufficient to justify the switch to colored printing inks from the black ink used in the proposed stability and migration studies?*

FDA's Preliminary Response Sent on October 29, 2014:

Although the overall proposed ink migration studies appear acceptable, FDA cannot provide a definitive response in the absence of information on the exact composition of printing inks. However, the acceptability of the proposed study to support use of colored printing inks will be determined during the NDA review. The NDA must either contain information on the composition and migration of all printing inks used for container

labeling or must provide a detailed reference including date of submission, volume, and page numbers to appropriate DMF containing this information.

Discussion during the meeting:

SPARC did not have any questions or comments.

4. *Is SPARC Ltd. 's NDA stability bracketing plan and number of batches to be tested acceptable?*

FDA's Preliminary Response Sent on October 29, 2014:

SPARC's proposed stability bracketing plan appears to be acceptable.

Discussion during the meeting:

SPARC did not have any questions or comments.

Pharmacology and Toxicology

5. *SPARC Ltd. seeks confirmation that no nonclinical studies are required for the NDA.*

FDA's Preliminary Response Sent on October 29, 2014:

The proposal to rely on the approved labeling of the listed drug appears acceptable. Additional nonclinical studies may be necessary if the safety of proposed (b) (4) % limit of (b) (4) is not adequately justified.

Discussion during the meeting:

SPARC did not have any questions or comments.

6. *Is the plan for preparation of the nonclinical sections of the NDA acceptable?*

FDA's Preliminary Response Sent on October 29, 2014:

The proposed plan appears acceptable.

Discussion during the meeting:

SPARC did not have any questions or comments.

Biopharmaceutics and Clinical Pharmacology

7. *Does the Division agree that no biopharmaceutics / clinical pharmacology studies are required for the NDA?*

FDA's Preliminary Response Sent on October 29, 2014:

Per the discussion at the December 16, 2011 meeting, SPARC's subsequent March 13, 2012 submission providing a rationale that supports the lack of effect of mannitol on the disposition of intravenously administered gemcitabine, and FDA's email communication of May 10, 2012, FDA confirms that SPARC's plan to request a waiver of in vivo BE studies between SPARC's proposed product and Gemzar appears acceptable. Include the

biowaiver request and the supporting data in in your NDA (i.e., a side-by-side comparison table with formulation, osmolarity, pH, labeling between the proposed drug product and the listed drug product. Also include the supportive information demonstrating that the difference in the inactive excipients between your proposed and the listed products do not affect the distribution and elimination of gemcitabine in vivo). Note that the final decision on the biowaiver request is a review issue under the NDA.

Discussion during the meeting:

SPARC did not have any questions or comments.

8. *Is the plan for not preparing the clinical sections of the NDA acceptable?*

FDA's Preliminary Response Sent on October 29, 2014:

The proposed plan for the biopharmaceutics section of the NDA is acceptable.

Discussion during the meeting:

SPARC did not have any questions or comments.

Clinical Safety and Efficacy

9. *Can the Division confirm that the plans for labeling the product are adequate to prevent medication errors?*

FDA's Preliminary Response Sent on October 29, 2014:

No. There is insufficient information to answer this question in the absence of the complete proposed labeling including instructions regarding the proposed scheme for dose-banding. Also refer to the discussion regarding question 9 contained in the minutes from the December 16, 2011 meeting between SPARC and DOP2, which stated that "additional information which may be requested could include analyses of the potential for medication errors, accuracy of ability to deliver the intended dose based on BSA, and the potential impact on safety and efficacy of the proposed scheme for dose banding."

SPARC's Response Received via E-mail Communication on October 30, 2014:

SPARC Ltd. recognizes that sufficient detail was not provided to allow the Division to fully address this question. In posing the question, SPARC Ltd. was hoping to ascertain that the general approach was reasonable.

SPARC Ltd has contracted [REDACTED] ^{(b) (4)} to undertake a risk assessment of the product and its container and container labels for potential medication errors that could arise from the use of "ready-to-infuse" bags. The goal of the risk assessment is to identify the potential use-related hazards and recommend strategies to mitigate those risks. Issues for evaluation may include but are not limited to: the distinctiveness of the different strengths, instructions for dosing and instructions for preparation of a given bag for dosing. A full report of the evaluation will be included in the upcoming NDA.

As noted in the Briefing Package, SPARC Ltd's intent is to claim the same indications and maintain the same dosing recommendations as for the reference product. The majority of the recommended doses can be achieved with a single infusion bag of the appropriate strength. PK modeling will be used to ensure that any deviation would not cause a significant change in safety and efficacy.

Should SPARC Ltd. conclude, either on the basis of the medication errors review (risk assessment) or the pharmacokinetic modeling, that Gemcitabine Hydrochloride Injection, 10 mg/mL cannot be safely and effectively given to individuals with a range of BSAs (primarily on the higher end) or indication (specifically, breast cancer), more restricted labeling will be proposed.

- Would it be acceptable to the Division that SPARC Ltd. request only the ovarian, non-small cell lung and pancreatic cancers indications and/or restrict the use of the product on the basis of BSA?
- If all indications and BSAs are requested but the Division determines that not all can be approved, will this have an effect on the overall approvability of the NDA?

Discussion during the meeting:

SPARC plans to conduct a risk assessment through a review of proposed labeling including carton and container labeling; this risk assessment will be included in the planned NDA. FDA noted that the dose-banding approach introduces greater complexity particularly through rounding to the nearest prescribed dose. FDA will consider this complexity in the review of the NDA, however in response to SPARC's question, FDA stated that the proposed NDA would not be refused for filing based solely on the proposed banded approach for dosing.

In response to SPARC's first new question (first bullet above), FDA stated that it would be acceptable for SPARC to request all, some, or only one of the indications held by the listed drug.

In response to SPARC's second new question (second bullet above), FDA stated that if the Division determines that not all requested indications can be approved, it will not affect approval of the NDA so long as at least one indication can be approved.

With regard to the pharmacokinetic (PK) modeling proposal described in SPARC's October 30, 2014 response, SPARC confirmed that this approach was not described in the meeting package. Therefore, FDA cannot provide comment on the acceptability of this approach to support approval of an NDA. FDA stated that the PK modeling approach can be submitted for FDA review and comment prior to the submission of an NDA.

10. *Does the Division agree with the strategy of dose banding with \pm 5% and/or using multiple infusion bags, based on the pharmacist's discretion, to cover the target population?*

FDA's Preliminary Response Sent on October 29, 2014:

As communicated in the discussion under question 9 in the December 16, 2011 meeting minutes (referenced above), FDA cannot commit to agreement on the dose-banding approach at this time based on the information provided. SPARC will need to provide a rationale as to why the proposed dose-banding strategy will not result in either increased toxicity or compromised efficacy as compared to the listed drug. SPARC should provide specific information and justification (refer to the response to question 9 above) regarding any proposal for the use of multiple infusion bags at a single time point, and for any proposal for withdrawal of a volume to achieve a specified dose. Additionally, SPARC should clarify the phrase in this question, “based on the pharmacist’s discretion.”

SPARC’s Response Received via E-mail Communication on October 30, 2014:

As noted above, SPARC Ltd. plans to evaluate the dosing instructions and provide a rationale for why the recommended doses will not result in either increased toxicity or compromised efficacy as compared to the listed drug.

The phrase “based on the pharmacist’s discretion” referred to the flexibility allowed a given pharmacist in choosing and preparing a dose in response to a prescription. This varies from institution to institution and is addressed in institution-specific Policy and/or Standard Operating Procedures. While this could include withdrawing an amount from an infusion bag or hanging more than one bag, SPARC Ltd. would not make any such recommendations. The labeling for the Gemcitabine Hydrochloride injection, 10 mg/mL would not recommend a dose other than that already approved.

Discussion during the meeting:

FDA stated that instructions should be provided for what to do when the prescribed dose is not one of the marketed strengths or achievable by infusion of multiple bags to achieve the prescribed total dose. SPARC’s consultant stated that the approach to be taken will depend on the results of the risk assessment. FDA acknowledged understanding.

11. *SPARC Ltd. is seeking confirmation that no clinical efficacy or safety studies will be required for the NDA.*

FDA’s Preliminary Response Sent on October 29, 2014:

There is insufficient information in the meeting briefing package to permit FDA to answer this question. FDA will determine whether additional clinical studies are needed based on the adequacy of the rationale, including supporting data (as requested in FDA’s response to question 10 above) regarding the clinical relevance of the differences between the delivered doses of SPARC’s formulation of gemcitabine and the recommended doses described in the Gemzar label.

SPARC’s Response Received via E-mail Communication on October 30, 2014:

Should an additional clinical trial be required for any indication, SPARC Ltd. would propose to drop that indication from the label.

Discussion during the meeting:

FDA acknowledged SPARC’s response.

12. Is the plan for preparation of the clinical sections in the NDA acceptable?

FDA's Preliminary Response Sent on October 29, 2014:

This question cannot be addressed until supportive data regarding the clinical relevance of the differences between delivered doses with the product as proposed and recommended doses as described in the Gemzar labeling has been submitted to the pre-submission and reviewed or when it is reviewed under the NDA. If the supportive data support a conclusion that there will be no clinically important differences, then the plan otherwise proposed for the clinical sections of the planned NDA is acceptable.

SPARC's Response Received via E-mail Communication on October 30, 2014:

SPARC Ltd. recognizes that additional information would be required in the clinical modules should clinical studies be performed.

SPARC Ltd. wishes to ascertain whether the approach to summarizing other safety information (other than as it pertains to achieving the target dose and exposure) is acceptable. Specifically:

- Is it acceptable to restrict the general literature search for new safety information to material published after the date of the current approved labeling for the Listed Drug (i.e., June 2014)?
- Should efficacy information be summarized (e.g., to support the possibility of "dose banding" that is up to -5%), is it acceptable to prepare only an ISE (without the need to repeat the same information in Module 2.7.3, Summary of Clinical Efficacy) or does the Division prefer that both documents be prepared?
- Is it acceptable to prepare only an ISS (without the need to repeat the same information in Module 2.7.4, Summary of Clinical Safety) or does the Division prefer that both documents be prepared?

Discussion during the meeting:

Regarding the first bullet, the proposal is acceptable when referencing the Gemzar package insert. However, additional information obtained from published literature as discussed in questions 9 and 10 may be required. Justification should be provided for the approach taken in identifying published literature sources.

Regarding the second bullet, FDA stated that SPARC should refer to the FDA Guidance that describes the correct locations for the integrated summaries of safety and effectiveness and the clinical summaries of safety and effectiveness. FDA stated that the SCE and ISE are required; however the ISE may reference the SCE in some cases, as described in the Guidance.

Post-Meeting Adendum:

The following Guidance document describes where to place the ISE and ISS documents within the structure of the CTD and provides a framework regarding which information can be placed in

Module 2 versus Module 5 of the NDA: Guidance for Industry: “Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document,” available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an end-of-phase 2 meeting, you should submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before the marketing application is submitted. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION

N/A

ACTION ITEMS

N/A

ATTACHMENTS AND HANDOUTS

N/A

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/s/

MISSIRATCH BIABLE
11/05/2014



Pre-NDA 203652

MEETING MINUTES

Sun Pharma Advanced Research Company Ltd.
Attention: Karin A. Kook, Ph.D.
Managing Director, U.S. Agent
Salamandra, LLC
One Bethesda Center
4800 Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Dear Dr. Kook:

Please refer to your Pre-New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gemcitabine Hydrochloride Injection, 10mg/mL, Ready to infuse.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2011. The purpose of the meeting was to confirm that the development plans are adequate to support an NDA under Section 505(b)(2) of the Federal FD&C act.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call me, Regulatory Project Manager at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Vaishali Jarral, M.S., M.B.A
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:

Meeting Minutes, DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications and Additional DOP2 CDISC Guidance

MEMORANDUM OF MEETING MINUTES

NDA Number: NDA 203652
Meeting Type: Type B
Meeting Category: Pre-NDA Meeting, 505(b)(2)
Meeting Date and Time: December 16, 2011; 10:00 AM to 11:00 AM (ET)
Product Name: Gemcitabine Hydrochloride Injection, 10mg/mL, Ready-to-Infuse.
Sponsor Name: Sun Pharma Advanced Research Company Ltd. [SPARC Ltd.]
U.S. Agent: Salamandra, LLC
Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Vaishali Jarral

LIST OF FDA ATTENDEES:

**Office of New Drugs
Office of Hematology and Oncology Products
Division of Oncology Products 2**

Patricia Keegan	Division Director
Steven Lemery	Clinical Team Leader
Michael Axelson	Clinical Reviewer
Vaishali Jarral	Regulatory Project Manager

Division of Clinical Pharmacology

Jun Yang	Clinical Pharmacology Reviewer
Hong Zhao	Clinical Pharmacology Team Leader

**Office of Pharmaceutical Sciences
Office of New Drug Quality Assessment**

Kareen Riviere	Biopharmaceutical Reviewer
Sue Ching Lin	Pharmaceutical Assessment Reviewer
Liang Zhou	Pharmaceutical Assessment Lead

**Office of Medication Error Prevention and Risk Management
Division of Medication Error Prevention and Analysis**

Zachary Oleszczuk	Team Leader
James Schlick	Safety Evaluator

LIST OF SPONSOR ATENDEES

Dr. Wattanaporn Abramowitz	Mr. Kirti Ganorkar
Mr. Narendra Lakkad	Dr. Shravanti Bhowmik
Mr. Samarth Kumar	Mr. Anil Gite
Dr. Alok Namdeo	Dr. Subhas Bhowmick
Dr. Karin Kook	Dr. Madhav Marathe
Ms. Kaylee White	Dr. Prashant Kan

BACKGROUND

On behalf of Sun Pharma Advanced Research Company (SPARC) Ltd., Salmandra, LLC had requested a Type B, pre-NDA meeting on October 19, 2011 to confirm that their development plans are adequate to support and NDA under Section 505(b)(2) of the Federal FD&C Act.

Gemcitabine is a nucleoside metabolic inhibitor that was first approved in 1996, under the trade name Gemzar (NDA 20-509). Gemzar is currently approved for the treatment of ovarian cancer in combination with carboplatin, the treatment of breast cancer in combination with paclitaxel, the treatment of non-small cell lung cancer in combination with cisplatin, and the treatment of pancreatic cancer as a single agent.

SPARC Ltd. proposes to seek marketing for a "ready-to-infuse" formulation of Gemcitabine Hydrochloride Injection, 10 mg/mL (b) (4) in 0.9% sodium chloride packaged in a (b) (4) infusion bag. SPARC Ltd. is planning to submit a New Drug Application (NDA) under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act rather than an Abbreviated NDA under Section 505(j) because the dosage form differs from the approved products. The reference product for the NDA will be Gemzar®, Gemcitabine Hydrochloride for injection (product form is a lyophilized powder).

SPARC Ltd. Intends to market Gemcitabine Hydrochloride Injection, 10 mg/mL in a ready-to-infuse infusion bag in four presentations:

- 1600 mg gemcitabine in 160 mL (b) (4)
- 1700 mg gemcitabine in 170 mL (b) (4)
- 1800 mg gemcitabine in 180 mL (b) (4)
- 2000 mg gemcitabine in 200 mL (b) (4)

SPARC claims that their Gemcitabine Hydrochloride Injection is expected to be associated with fewer errors in dose preparation and that this presentation will also prevent exposure to non-sterile conditions or contamination during reconstitution, as well as minimize exposure to the chemotoxic compound. As shown in the table from the meeting package, the developed formulation has the following compositions as compared to the two marketed gemcitabine products (of which Gemzar® will be the reference product).

**Marketed Gemcitabine Products versus SPARC Ltd.'s Product as Presented
 (Amounts per Container)**

	Gemzar® (RLD)		Gemcitabine Injection (Hospira), 38 mg/mL			SPARC Ltd.'s Gemcitabine Injection, 10 mg/mL ("Ready-to-Infuse" Infusion Bag)			
	200 mg / vial	1 g / vial	200 mg / 5.26 mL	1 g / 26.3 mL	2 g / 52.6 mL	1600 mg / 160 mL	1700 mg / 170 mL	1800 mg / 180 mL	2000 mg / 200 mL
Drug Product Composition									
Gemcitabine	200 mg	1000 mg	200 mg	1000 mg	2000 mg	1600 mg	1700 mg	1800 mg	2000 mg
Mannitol	200 mg	1000 mg	-	-	-	-	-	-	-
Sodium acetate	12.5 mg	(b) (4) mg	-	-	-	-	-	-	-
Sodium chloride	-	-	-	-	-	0.9%	0.9%	0.9%	0.9%
Hydrochloric acid	Used for pH adjustment								
Sodium hydroxide	Used for pH adjustment								

The gemcitabine hydrochloride drug substance is manufactured by Sun Pharmaceutical Industries Limited (SPIL), a company associated with SPARC Ltd. The drug substance manufacturer, SPIL, currently holds a DMF on file with FDA supporting an approved ANDA. SPARC Ltd. intends to reference this DMF in the upcoming NDA submission.

SPARC Ltd., proposes to support the NDA with a total of eight (8) manufactured registration batches as follows: three (3) batches for each of the lowest and highest fill-volumes, and one (1) batch of each of the two intermediate fill volumes. SPARC Ltd. also proposes a bracketing scheme in the stability protocol of the drug product to adequately represent the different fill-volumes and packaging presentations (see Section 4.2.8) with two (2) batches for each extreme fill-volume (1600 mg/160 mL and 2000 mg/200 mL). The briefing package indicates that the NDA submission will include 6-month ICH accelerated and 12-month room temperature stability data for the four (4) stability batches, with the 6-month ICH accelerated and the 9-month room-temperature data to be provided at time of submission and the remaining balance of data to be available at the time of the 120-day Safety Update.

Pharmacology and Toxicology

SPARC Ltd. is proposing to rely on FDA's prior judgment of the safety of Gemzar as described in the most current approved labeling for the reference product. SPARC Ltd. has not conducted any nonclinical studies with gemcitabine and no studies are planned. The briefing package indicates that the drug will be administered in the same dose (and concentration), route, and schedule as the RLD [Gemzar (NDA 20-509)]. SPARC Ltd. is asserting in the briefing package that with the exception of (b) (4) no impurity is present in either the drug substance or the drug product in amounts that require qualification and therefore no qualification studies are planned. SPARC Ltd. will however conduct a search of the literature relative to the most recent label of Gemzar® (dated 4 February 2011), a summary of which will be included in Section 2.4 Nonclinical Overview.

Biopharmaceutics/Clinical Pharmacology

SPARC, Ltd does not intend to conduct any biopharmaceutics or clinical pharmacologic studies with Gemcitabine Hydrochloride. Instead, the company is planning to apply for a waiver of the need to perform *in vivo* bioequivalence studies, as outlined in 21 CFR 320.22(b)(1), because the gemcitabine drug product is a parenteral solution that contains the same active ingredient within the range of concentrations and fewer inactive ingredients following preparation for administration for intravenous infusion as described in product labeling for the RLD.

Clinical Safety and Efficacy

SPARC Ltd. does not intend to conduct any clinical efficacy trials with Gemcitabine Hydrochloride Injection. Approval will be sought for the same indications and doses for which the reference product, Gemzar®, is currently marketed.

With respect to safety, SPARC Ltd. is proposing to review the published literature will for any new safety information (relative to the last revision to the Gemzar® label. SPARC Ltd. is not planning to conduct or sponsor any clinical trials.

General Comment: Based on the contents summarized in the pre-meeting package, please be aware that the proposed NDA will not be adequate to support promotional claims including but not limited to fewer errors in dose preparation as compared to referenced product.

Sponsor Submitted Questions and FDA Response:

Chemistry, Manufacturing and Controls (CMC)

1. **Sponsor Question #1:** Do the proposed tests and specifications for the drug substance satisfy FDA's regulatory requirements?

FDA Response: The proposed tests for the drug substance appear acceptable. The proposed acceptance criteria for the tests will be evaluated during NDA review based on the justification included in the NDA. In addition, provide justification for the proposed acceptance criterion for residual solvent (b) (4) in the NDA.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency's comments.*

2. **Sponsor Question #2:** Is the proposed overfill in the manufacture of the drug product adequately justified and acceptable?

FDA Response: The proposed overfill is not acceptable. The preparation of the infusion solution of the listed drug does not specify an overfill.

SPARC Ltd. Response: *SPARC Ltd.* (b) (4)
(b) (4)

(b) (4)

Discussion during the Meeting: The proposal for overfill of up to (b) (4)% is acceptable.

3. **Sponsor Question #3:** Do the proposed tests and specifications for release and stability of the drug product satisfy FDA's regulatory requirements?

FDA Response: The proposed tests for the drug product appear acceptable. The proposed acceptance criteria for the tests will be evaluated during NDA review based on the justification provided in the NDA.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency's comments.*

Discussion during the Meeting: There was no discussion during the meeting.

4. **Sponsor Question #4:** Regarding the infusion bags, is any additional extractables/leachables analysis required to support the NDA?

FDA Response: Yes, additional extractable and leachables studies are required. A complete extractable and leachables study report should be submitted in the NDA. Also include the following information:

- a. Perform extraction studies on each packaging component using appropriate solvents, including a stronger extracting solvent than the drug product, to obtain qualitative and quantitative extraction profiles. The profile of each extract should be evaluated both analytically and toxicologically.
- b. (b) (4) should be considered (b) (4) of the drug product.
- c. Study the potential migration of ink from the infusion bag to the drug product.
- d. If (b) (4) are used to seal the infusion bag during manufacturing, analyze the drug product for (b) (4).
- e. Validate the analytical methods for extractables/leachables to demonstrate the methods are suitable for their intended use.
- f. Analyze stability samples for leachables.

SPARC Ltd. Response: *SPARC Ltd will submit a proposal for the performance of the extractable and leachable studies; is the Division willing to review this prior to the submission of the NDA?*

Discussion during the Meeting: FDA will review the proposal as resources allow; however, it is unlikely that the proposal will be reviewed before SPARC Ltd. submits the NDA.

SPARC Ltd stated that they will conduct the standard assessments for identification and quantitation with qualification if necessary of leachables and extractables including the recommendations presented by the FDA in the original response to this item.

5. **Sponsor Question #5:** Are the proposed plans for NDA registration batches, stability batches, and stability bracketing scheme acceptable?

FDA Response: Conflicting information is provided in the briefing package. On page 31, it is stated that three registration batches of the highest and lowest fill volumes and one batch for each of the intermediate fill volumes will be included in the NDA. However, Table 4:15 shows that only two batches each of the 160 mL and 200 mL presentations are included in the per-approval stability protocol. Please clarify. Note that only the first option is acceptable.

It should be noted that, according to the Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. International Conference on Harmonization (ICH) Q1A (R2) states “long term testing should cover a minimum of 12 months’ duration on at least three primary batches at the time of submission.”

SPARC Ltd. Response: *At present eight batches are planned (the number of batches would be increased if additional fill volumes are to be proposed). Stability data will be submitted for three batches of the highest and lowest fill volumes and one batch of each intermediate fill volume.*

The Division indicated that a sufficient amount of data for at least “three primary batches” will be needed at the time of submission to support the shelf-life. Please clarify what is meant by primary batches; for example, can any combination of fill volumes be used? If SPARC Ltd is willing to accept a shelf-life shorter than 12 months (6 or 9 months), will it be acceptable to have a commensurate amount of data in support?

Discussion during the Meeting: FDA clarified that the primary stability batches referred to in the written response refers to the batches in the NDA to support the product expiration date. SPARC Ltd. may apply a bracketing strategy provided

that the sufficient justification (strength, container size and fill volumes) is included in the NDA. Bracketing assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

At time of NDA submission, SPARC Ltd must submit at least 12 months long term and 6 month accelerated stability data to be considered a complete application for the purpose of filing for this aspect of CMC information.

Pharmacology and Toxicology

6. **Sponsor Question #6:** SPARC Ltd. seeks confirmation that no nonclinical studies are required for the NDA.

FDA Response: The proposal to rely on the approved labeling of the reference listed drug appears acceptable. While nonclinical studies are generally not required, they may be necessary to qualify impurities [REDACTED] ^{(b) (4)} at levels exceeding the qualification thresholds specified in ICH Q3B(R2) or limits specified in ICH Q3C if adequate justification can not be provided. A final decision will be made following review of data submitted with the NDA.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency's comment.*

Discussion during the Meeting: There was no discussion during the meeting.

7. **Sponsor Question #7:** Is the plan for preparation of the nonclinical sections of the NDA acceptable?

FDA Response: The proposed plan appears acceptable.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency's comment.*

Discussion during the Meeting: There was no discussion during the meeting.

Biopharmaceutics and Clinical Pharmacology

8. **Sponsor Question #8:** Does the Division agree that the plan to request a waiver of *in vivo* studies is acceptable and that no additional biopharmaceutics / clinical studies are required for the NDA?

FDA Response: At this time, FDA does not have sufficient information/data to address this question. FDA is concerned about the differences on the inactive ingredients between Sun's and the RLD product, specifically the effect that the lack of mannitol may have on the disposition of the proposed product in relation to the RLD product. To address FDA's concerns, please provide information/justification supporting that the *in vivo* physiological disposition of

gemcitabine from the proposed product formulated without mannitol will not be different than that of the RLD product.

SPARC Ltd. Response: *There are two RLDs for gemcitabine: Gemzar® and Gemcitabine Injection. The latter product does not include mannitol in the formulation. As the approved dosing and administration information for the two products is identical, one can presume that the presence or absence of mannitol does not affect in vivo physiological disposition. Furthermore, no additional pharmacokinetic study is described in the approved labeling. Would this be a sufficient justification?*

Discussion during the Meeting: FDA stated that the scientific justification would need to be provided, supported by literature with or without additional data showing that the drug disposition is not affected by the presence or absence of mannitol, to support the proposed request for a waiver in the NDA. The data should be submitted with a request for teleconference to discuss the acceptability of this approach prior to the NDA submission.

Clinical Safety and Efficacy

9. **Sponsor Question #9:** SPARC Ltd. seeks confirmation from the Agency that the proposed dosage and administration instructions are acceptable for the product? If not, can the Agency provide any recommendations?

FDA Response: There is insufficient information to answer this question without viewing the actual proposed dosing and administration that the USPI will contain. In addition, this dosing form may not be appropriate for patients with breast cancer because the proposed presentation of the drug product only easily translates to body surface areas (BSA) of less than 1.7 m² when the recommended dose of the reference listed drug is 1,250 mg/m². Sun will need to develop additional product presentations to support a labeling that includes the treatment of patients with breast cancer, for whom the recommended dose of gemcitabine is 1,250 mg/m², and treatment of patients with a BSA of less than 1.6 m² or greater than 2.0 m² for indications where the recommended dose is 1,000 mg/m².

SPARC Ltd. Response: *The Agency indicated that the actual proposed dosing and administration information would need to be provided in order for this question to be answered. Will it be acceptable to submit a draft of this section of the labeling for review prior to NDA submission?*

SPARC Ltd proposes to also prepare a proposal for the presentations of the different product fill volumes for review to ascertain that they are sufficiently distinct; is this acceptable?

SPARC Ltd intends to include the breast cancer indication. While market research has shown that the use of doses higher than 2000 mg is not common, the

appropriate presentations will be manufactured such that the range of doses can be accomplished (with either one or two bags).

Discussion during the Meeting: FDA will evaluate SPARC Ltd. label at the time of the NDA submission. SPARC Ltd. requested to submit their proposed labeling and mock ups of the proposed container labeling prior to NDA submission for presubmission advice. FDA agreed to provide feedback as to potential problems and need for additional data to support specific labeling language in the Dosage and Administration section. FDA will not commit to agreement on the practice of “banding”, which may include rounding the calculated patient dose to the nearest $\pm 5\%$.

Additional information which may be requested could include analyses of the potential for medication errors, accuracy of ability to deliver the intended dose based on BSA, and the potential impact on patient safety and efficacy of the proposed scheme for dose banding. FDA noted that additional clinical data may be necessary.

10. **Sponsor Question #10:** Does the Division agree that no clinical studies are required?

FDA Response: At this time FDA does not believe that additional studies are needed.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency’s comment.*

Discussion during the Meeting: There was no discussion during the meeting.

11. **Sponsor Question #11:** Is the plan to limit the search of the published literature to the time period since the most recent version of the approved labeling for the RLD acceptable?

FDA Response: Yes.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency’s comment.*

Discussion during the Meeting: There was no discussion during the meeting.

12. **Sponsor Question #12:** SPARC Ltd. proposes to prepare only the Clinical Overview, summaries of biopharmaceutics and clinical pharmacology, and an ISS. Does the Division agree with the plan not to include an ISE, a Summary of Efficacy (Section 2.7.3), or a Summary of Safety (2.7.4)?

FDA Response: Yes.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency’s comment.*

Discussion during the Meeting: There was no discussion during the meeting.

ADDITIONAL COMMENTS

13. Sun should ensure that the different presentations of the product are adequately differentiated to minimize product selection errors.

SPARC Ltd. Response: *SPARC, Ltd. acknowledges the Agency's comment.*

Discussion during the Meeting: There was no discussion during the meeting

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOICAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--

TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARIABLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials⁽¹⁾. RECIST (Response Evaluation Criteria in Solid Tumors)⁽²⁾ has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification⁽³⁾ in the assessment lymphomas, or MacDonald Response⁽⁴⁾ in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:

--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

- (1) E.A. Eisenhauer,*, P. Therasse, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228-247
- (2) RECIST Criteria - <http://www.eortc.be/recist/>
- (3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007
- (4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology*, Vol 8, 1277-1280

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..x.x One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality / location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x.x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<p>1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting</p>	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<p>1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.</p>	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

- The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
- The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x.x One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRES	Target Response	
NTRGRES	Non-target Response	
OVRRES	Overall Response	
BESTRES	Best Response	
LESNRES	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. *TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.*
5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

In addition, the **CDER Data and Programs Standards checklist** is a separate document (appended to the end of OHOP's End-of-Phase 2 General Advice) that includes points to be considered for electronic submission, but it is not guidance. These recommendations represent our current advice to Sponsors. They do not create or confer any rights for or upon any person and are not binding on FDA or the public. An applicant can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Division. The purpose of the checklist and supporting documentation is to **highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant** regarding submission of CDISC data in support of an application for registration.

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval
<i>Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.</i>
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: <ul style="list-style-type: none">• Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').• A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an

application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.

- The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
- If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
- If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
- If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
- If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
 - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
 - Applicability of comparator treatment or of disease characteristics to U.S. population
- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials:

(www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

- If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB)

and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: <ul style="list-style-type: none"> a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) <u>Quantitative Safety Analysis Plan (QSAP):</u> The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components: <ul style="list-style-type: none"> a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

<ul style="list-style-type: none"> b) Safety endpoints for Adverse Events of Special Interest (AERI) c) Definition of Treatment Emergent Adverse Event (TEAE) d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter)) e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP) f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
<p>10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:</p> <ul style="list-style-type: none"> a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf) b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)
<p>11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.</p>
<p>12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application</p>
<p>13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.</p>
<p>14) <u>References:</u> There should be active links from lists of references to the referenced article.</p>
<p>Studies, Data And Analyses</p>
<p>15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).</p>
<p>16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:</p> <ul style="list-style-type: none"> a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
<p>17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07200)</p>

2.pdf).

- 18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
- a) subject age and gender
 - b) signs and symptoms related to the adverse event being discussed
 - c) an assessment of the relationship of exposure duration to the development of the adverse event
 - d) pertinent medical history
 - e) concomitant medications with start dates relative to the adverse event
 - f) pertinent physical exam findings
 - g) pertinent test results (for example: lab data, ECG data, biopsy data)
 - h) discussion of the diagnosis as supported by available clinical data
 - i) a list of the differential diagnoses, for events without a definitive diagnosis
 - j) treatment provided
 - k) re-challenge and de-challenge results (if performed)
 - l) outcomes and follow-up information
 - m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
- 19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.
- 20) Provide reports for any autopsies conducted on study.
- 21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
- 22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis
- 23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
 - b) Exposure-Response Relationships – important exposure-response assessments.
 - c) Less common adverse events (between 0.1% and 1%).
 - d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges

for the laboratory values.

- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.
- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions
 - i) Dosing considerations for important drug-drug interactions.
 - ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule	
Highlights	
1)	Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2)	The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3)	The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4)	The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5)	The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6)	For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7)	The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8)	Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9)	Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10)	A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11)	Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12)	The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13)	A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the

time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers (<i>not 8.2</i>) 8.4 Pediatric Use (<i>not 8.3</i>) 8.5 Geriatric Use (<i>not 8.4</i>)
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

<p>27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]</p>
<p>28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.</p>
<p>29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.</p>
<p>30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.</p>
<p>31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.</p>
<p>32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.</p>
<p>33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.</p>

CDER Data Standards Check-list (Version 1.0/April, 2010)

The purpose of this check-list and supporting documentation is to **facilitate discussion** between reviewers/review divisions and sponsors with regard to the submission of CDISC data in support of product approval.

This document will be **updated regularly** (every 6-12 months) based on division/reviewer feedback and experience. Therefore, it is important that reviewers refer to the CSC website to ensure that they are using the most up-to-date version. (<http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/ComputationalScienceCenter/ucm171013.htm>)

When a sponsor or review division is uncertain about a particular issue related to CDISC (Clinical Data Interchange Standards Consortium) standards implementation or submission, the review division should **request assistance from the CSC** at (CSCDataStandards@fda.hhs.gov)

(Each Bullet with link to Appendix for further details)

GENERAL CONSIDERATIONS

- Implementation of SDTM
- Follow SDTM (Study Data Tabulation Model) Implementations Guide (SDTM v. 3.1.2, www.cdisc.org)
- Follow ADaM (Analysis Data Model) Implementation Guide (ADaM v. 2.1, www.cdisc.org)
- Sponsor to discuss with review division and submit supporting documentation for non-Implementation Guide Decisions/Issues
- Define file
- SEND (Standard for Exchange of Non-Clinical Data) Data
- CDISC legacy conversion and analysis data

TERMINOLOGY

- Use of CDISC Controlled Terminology via NCI Enterprise Vocabulary Services (EVS) at (<http://www.cancer.gov/cancertopics/terminologyresources/page6>)
- Use of WHO DRUG terminology
- Use of Adverse Event Terminology (i.e., MedDRA, etc)
- Use of non-standard terminology
- Coded Variables
- Implementation of variable dictionaries

SDTM DOMAINS

- SUPPQUAL (Supplemental Qualifiers)
- DM domain (Demographics)
- EX domain (Exposure)
- DS domain (Disposition)
- AE domain (Adverse Events)
- Custom Domains
- LB domain (Laboratory)

ADaM DOMAINS

- Referral to CDER Analysis Data Submission Document and Data Specifications Document
- ADaM Implementation Guide
- Assessment of which domains to submit
- ADSL (Analysis Data Subject Level)
- ADAE (Analysis Data Adverse Events)

VARIABLES

- Required vs. Expected vs. Permissible
- Naming conventions and formats
- Dates
- USUBJID (unique subject identifier variable)
- Derived variables
- Imputed data variables

COMMON ERRORS

- Define.xml does not validate
- Invalid ISO8601 date format for SDTM datasets
- Begin date must be \leq to end date
- Required variable not found
- Inconsistent value for standard units
- Invalid value for preferred term
- If ARMCD equals "SCRNFAIL" then ARM must equal "Screen Failure"

Narratives

- pdf and non-pdf format

APPENDIX

GENERAL CONSIDERATIONS

The ideal time to **implement** SDTM standards is prior to the conduct of the study. Use of CDASH-designed case report forms allows for a simplified process for creation of SDTM domains. It is strongly encouraged that discussions with CDER divisions regarding use of SDTM data standards take place as early as possible in the review cycle, such as at end of phase 2, rather than pre-submission. If a sponsor decides to convert clinical trial data to SDTM that was originally collected in non-SDTM format, it is important to note that the resulting SDTM data should support the accompanying analysis data sets and sponsors' reports (study reports, etc.).

CDER has received numerous "CDISC-like" applications over the past several years in which sponsors have not followed the CDISC implementation guides.

The **SDTM Implementation Guide (SDTMIG)** should be followed carefully (CDISC.org). Section 3.2.2 of the SDTMIG provides general criteria conformance with the SDTM data model. These criteria should not be interpreted as the sole indication of the adequacy of submitted CDISC data, however, they should be followed unless otherwise indicated. If there is uncertainty with regards to implementation, the sponsor should discuss with the division.

For **analysis datasets**, sponsors should refer to the recently published ADaM Implementation Guide as well as the CDER Study Data Specifications Document and the CDER Analysis Data Request Document. It is expected that significant discussion between the sponsor and CDER clinical and statistical reviewers will be necessary to appropriately determine which analysis datasets as well as dataset content are needed to support application review.

It is understood that CDISC data standards are evolving and that there may be instances in which the current implementation guides do not provide specific instruction as to how certain clinical trial data should be represented. In this instance, sponsors should discuss their proposed solution with the review division and submit supporting documentation at the time of submission that describes these decisions/solutions.

CDER would prefer that sponsors submit the **define file** in both .pdf and .xml formats.

CDER is currently involved in pilot testing of the **SEND** standard for the submission of pre-clinical data. Sponsors who are interested in submitting SEND-compliant data should discuss with the toxicology reviewers from the appropriate review division.

CDISC legacy data conversion: It is strongly preferred that sponsors design their phase 3 trials using CDISC-defined data elements which allow for much easier SDTM domain creation (such as is possible with use of CDASH-specified CRFs). Conversion of non-CDISC data to CDISC format at the end of the drug development process is more challenging and if pursued, sponsors must ensure that converted SDTM datasets support key analyses contained in the sponsor's study/integrated reports. In addition, the accompanying analyses datasets should be derived from the SDTM data sets and also must support the analyses contained in the sponsors' reports.

TERMINOLOGY

Field entries for CDISC specified variables should use the **CDISC Controlled Terminology** which can be found at the NCI Enterprise Vocabulary Services (<http://www.cancer.gov/cancertopics/terminologyresources/page6>).

It is strongly preferred that the **WHO DRUG Dictionary** terminology be used for the concomitant medications domain. The generic WHO Drug term should be used for the CDISC standardized medication name variable. The SDTM medication class variable (CMCLAS) should be used to represent the WHO Drug level 3 ATC term (pharmacological subgroup) associated with the standardized medication name.

When using **MedDRA** for adverse events and past medical history terms, sponsors should exactly follow the spelling and case of the MedDRA terms. Sometimes clinical trials are conducted at different times during the development cycle which results in the use of different versions of MedDRA from one study to the next. It is expected that the Adverse Event data set for the Integrated Summary of Safety include MedDRA preferred terms from a single harmonized version of MedDRA.

For variables/field entries for which **no standard terminology exists**, the sponsor may propose their own terminology. Please provide supporting documentation that describes the non-standard terminology that is used.

No numerically **coded variables** should be submitted as part of the SDTM datasets.

It is expected that **common dictionaries** are used across all trials and throughout the submission for each the following: adverse events, concomitant medications, procedures, indications, study drug names, and medical history. Implementation of such dictionaries should be careful to exactly follow the spelling and case specified by the dictionary (for existing dictionaries such as MedDRA) or according to a single consistent sponsor specification if no pre-existing terminology exists.

SDTM DOMAINS

SUPQUAL is a dataset domain in SDTM. It is intended to include data variables that are not specified in SDTM. SUPQUAL datasets are often used as a “waste-basket” for data elements that the sponsor is not sure what to do with. Discussion needs to occur if the sponsor intends to include important variables (that support key analyses) in the SUPQUAL domains. One way to deal with this issue for important data elements that are likely to be needed to support review work, is to ensure that analysis datasets are prepared in a way that includes these and other relevant data elements.

In the **DM** domain (Demographics), if ARMCD (‘Planned Arm Code’) equals “SCRNFAIL” then ARM (‘Description of Planned Arm’) must equal “Screen Failure”. There is also terminology (NOTASSGN) for subjects who are not screen failures but, for other reasons, are never assigned to an arm. Uncertainty occurs in the situation that a subject was randomized, however, did not receive

treatment for other reasons. The recommended solution for this situation is to use the terminology of 'NOTTXD' for the ARMCD variable and 'Not Treated' for the ARM variable, and make a comment in the define.xml regarding the use of this terminology. For ARMCD, the arm entry is equal to the therapy the patient was randomized to, even if they mistakenly were treated under a different arm. However, there is no current variable included in the DM domain that denotes actual therapy received which can be used to determine the safety population. For example, if a subject is randomized to one arm, but then actually receives therapy in accordance with a different arm, there is no variable in the DM dataset that captures this. The recommended solution for this is to include in the DM dataset a variable called "ACTARM" with a label of "Actual Arm". Terminology for this variable should include the name of the arm that the patient was treated under (consistent with the terminology used for the ARM and ARMCD variables) and patients must have received at least one dose of drug in order to have a treatment arm entry for this variable.

The DM variable "RFENDTC" should correspond to the date/time of last exposure to study treatment. Also, the variable "RFSTDTC" should represent the start date/time of active study drug exposure (or placebo exposure for subjects who are receiving only placebo). There is also a need for a variable that represents the date/time for when the subject ended participation/follow-up in the trial. This variable should be called "RFTREDTC" with a label of "Reference Trial End Date." In the DM domain, each subject should have only one single record.

The EX domain. Exposure: Provide the exposure data in a consistent format across all the studies ("one record per dose per day").

DS domain: Deaths: The current SDTM version 3.1.2 does not address the need for a unique place for recording deaths. To simplify our safety analysis, for each patient who died there should be one record in the Disposition (DS) domain where DSCAT='DISPOSITION EVENT' and DSDECOD='DEATH'. When there is more than one disposition event the EPOCH variable should be used to distinguish between them so that if the death occurred during the treatment period EPOCH='TREATMENT' and if the death occurred during the follow-up period EPOCH='FOLLOW-UP'. Other values may be used for epoch depending upon the terminology used in the trial design model datasets.

AE domain (Adverse events): There is currently no variable in the AE domain that indicates if a variable was "treatment emergent." CDER would like the AE domain to include all adverse events recorded in any way in the patients' case report forms. An additional variable (called TREMR, label "Treatment emergent") should be added to the AE domain that indicates if the event was or was not treatment emergent. This variable should be a simple yes or no (Y/N) response. In addition, the AE domain does not include variables for levels of the MedDRA hierarchy other than the preferred term or system organ class levels. To address this issue, sponsors should include the following variables: LLT (Lower Level Term), HLT (High Level Term), and HLG (High Level Group Term). The field entries for these terms should exactly follow the MedDRA terminology. Also, please include an EPOCH variable in the AE domain. This will allow the reviewer to easily determine what phase of the trial the AE occurred during (i.e., screening, on-therapy, follow-up...). The SOC variable entry should represent the MedDRA-defined, primary mapped SOC. The SDTM Implementation Guide states that sponsors have the choice to use secondary mapped SOC in place of primary mapped SOC as they wish, however, CDER generally does not agree with this.

Custom Domains: The SDTM Implementation Guide does allow for the creation of custom domains if the data do not fit into an existing domain. Custom domains are highly discouraged. Prior to creating a custom domain, sponsors should confirm that the data do not fit an existing domain and also check the CDISC website for domains added after the most recent published implementation guide. If necessary, sponsors should follow the recommendations in the SDTM Implementation guide for how to create a custom domain (section 2.6).

LB Domain (Laboratory): The size of the LB domain is often quite large and can exceed the clinical reviewers' ability to open the file using standard-issue computers. This issue can be addressed by splitting the large LB dataset into smaller data sets according to lab type: chemistry (named "LBC"), hematology (named "LBH"), UA (LBU), serology (LBS), etc. Splitting it other ways (by subject or file size, etc) makes the data less useable. Sponsors should submit these smaller files **in addition to** the larger non-split standard LB domain file. File size of 400 megabytes is usually fine, however, it is recommended to confirm this with the review division.

ADaM DOMAINS (ANALYSIS DATASETS)

In determining how to create CDISC analysis datasets for submission to CDER, sponsors should refer to **three documents:** the ADaM Implementation Guide, the FDA Data Specifications Document, and the CDER Analysis Data Submission Document. Close adherence to the ADaMIG is expected and any specific questions that result from attempts to adhere to these documents should be discussed with the review division.

A careful assessment of **which analysis datasets** will be needed should occur. Sponsors must submit analysis datasets with their application to support key analyses. Additionally, it is important to remember that SDTM datasets do not have core variables (such as demographic and population variables) repeated across the different domains. The need for such duplication of core variables across various domains can be fulfilled through their inclusion in the corresponding analysis datasets. This need is sufficient for the purposes of justifying a request for analysis datasets. For example, the SDTM adverse event dataset does not allow for the inclusion of variables such as treatment arm, sex, age, or race. These and other variables may be included in an adverse event analysis dataset.

ADSL is the subject level analysis dataset for ADaM. CDER expects all CDISC submissions to include this ADaM-defined dataset along with the other supporting analysis datasets. In addition to the variables specified for ADSL in the ADaM Implementation Guide, it is expected that the sponsor will include multiple additional variables representing various important baseline patient characteristics. A few examples could include: disease severity scores such as APACHE scores or FINE scores; baseline organ function measurements such as calculated creatinine clearance or FEV1; range categories for continuous variables; numeric date variables in non-ISO format such as SAS or Oracle.

ADAE is the ADaM adverse events domain. As with the AE domain, it is preferred that the ADAE domain include variables for grouping-term levels of the MedDRA hierarchy. Also, sponsors should explain how they intend to represent events which were not treatment emergent or those terms which could represent efficacy endpoints.

VARIABLES

CDISC data standards categorize variables as being **Required, Expected, and Permissible**. Some sponsors have interpreted Permissible variables as being optional. However, for the purposes of submission of CDISC data to CDER, all permissible variables for which data were collected or for which derivations are possible should be submitted. **Examples** of some of the permissible variables that CDER expects to see include:

- Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic, Microbiology results
- EPOCH designators
- STDY variables in SE or other findings domains
- Exposure – total dose

Naming conventions (variable name and label) and variable **formats** should be followed as specified in the implementation guides.

Dates: Dates in SDTM domains should conform to the ISO8601 format. Examples of how to implement this are included in the SDTMIG. Because of the usefulness of numeric date formats in common software/systems used in CDER, it is expected that for the ADaM datasets, dates be also provided using numeric formats such as SAS and/or Oracle dates. Follow the same CDISC format for dates across all the trials and datasets. If no time measurements are available, the sponsor should truncate the format at the T instead of submitting dates with a T:00:00:00 attached to the end.

USUBJID: Each individual patient must be assigned a single unique identifier (USUBJID) across the entire submission. An individual subject should have the same unique identifier across all datasets including SDTM and ADaM. Do not add leading or trailing spaces in any dataset.

Derived variables: The sponsor should be encouraged to include in the SDTM domains derived variables which essentially represent derived extensions of existing variables (although not to the exclusion of those existing variables). An example would be the following: a creatinine clearance is derived from a patient's measured serum creatinine (and other variables). This could be represented in the LB data set with LABTEST equal to calculated creatinine clearance. Of course, supporting documentation must be provided to describe the methods of calculation and the original data elements, if collected, that were used to derive the variable should still be submitted.

Imputed data: SDTM should not include any imputed data. If there is a need for data imputation, this should occur in an analysis dataset and the relevant supporting documentation must be provided.

COMMON ERRORS

The **define.xml** does not validate. Please refer to www.cdisc.org/define-xml for instructions. Here sponsors can find the white paper for XML Schema Validation for Define.xml which provides

guidance on validating define.xml version 1.0 documents against the define.xml XML schemas. Prior to submission, a sponsor may submit their define.xml for testing to determine whether it validates. The submission of a define.xml is expected with all CDISC applications. If sponsors would like to also include a define.pdf document additionally, this would be ok.

Invalid ISO8601 date format. All dates in the SDTM domains must conform to the ISO8601 format. ADaM datasets can have numeric date formats such as SAS or ORACLE.

Begin date must be ≤ to end date. This is a common error. Examples include a concomitant medication or adverse event begin date that is after the end date.

Required variable not found. A Required variable is any variable that is basic to the identification of a data record (such as the unique subject identifier) or is necessary to make the record meaningful. Required variables must always be included in the dataset and cannot be null for any record.

Inconsistent value for standard units.

Invalid value for preferred term. This occurs when the sponsor has not accurately represented the MedDRA preferred term as it appears in the MedDRA terminology.

If ARMCD ('Planned Arm Code') equals "SCRNFAIL" then ARM ('Description of Planned Arm') must equal "Screen Failure". Uncertainty occurs in the situation that a subject was not a screen failure, however, did not receive treatment for other reasons. A recommended work-around for this situation is to use the 'SCRNFAIL' and 'Screen Failure' terminology for ARMCD and ARM variables respectively and make a comment in the define.xml that this is what was done.

Narratives:

In addition to narratives provided in .pdf format, CDER would strongly desire that narratives are also provided in a format that is a computer readable textual description of the patient's events and patient's care. The narrative text should integrate the information on all serious events, outcomes of serious adverse events, withdrawals, deaths, and Causes of Death, autopsy reports, concomitant conditions and procedures, etc. into a single narrative text. The narrative text should describe the patient's disease and event progression and patient's care.

File format: Narrative data should be submitted as plain ASCII text (txt) files. Each row of the file has two fields delimited by tab characters.

The first field is the unique subject ID (USUBJID) that is used in the submission. Because the USUBJID will be used to link the narratives to other data in the submission, the USUBJID should be *identical* to the USUBJID used in all other submission data sets, such as the SDTM datasets. The second field is the text of the narrative. The narrative must not contain TABS, HARD RETURNS, non-printing characters, or hidden "funny" or formatted characters.

Narrative Files

Naming narrative files: The file should be named narrative.txt.

It helps the process of preparation of the narrative text files, if these files are checked for the presence of only two fields: the first one with only the USUBJID (with the right character length), and the second one with only the “long” or “clob” field.

Narrative template format:

USUBJID	Narrative
01019929944	Patient made full recovery, and has no residual pain
01888777666	Patient is still hospitalized in ICU
Etc.	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VAISHALI JARRAL
12/20/2011