

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2008-N-0428]

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Certifier A. Corbin

**Electronic Study Data Submission for Phase 3 Janus Operational Pilot;
Notice of Pilot Project**

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Center for Drug Evaluation and Research (CDER) is seeking sponsors interested in participating in a pilot project to test the submission and processing of clinical study data provided electronically in a standardized format. This pilot will test the data extract, validation, and load procedures developed to populate "Janus," the study data repository component of a common, standards-based infrastructure that is being developed jointly by the Food and Drug Administration (FDA) and the National Cancer Institute (NCI) to support the exchange of clinical research data. The pilot also will test a new XML (extensible markup language)-based submission format for standardized clinical study data. We anticipate that a successful pilot will enable CDER to routinely receive, process, and store all standardized clinical study data in a data warehouse environment that will enhance the center's capability to manage and review standardized study data.

DATES: Submit written or electronic requests to participate in the pilot project by *[insert date 90 days after date of publication in the Federal Register]*.

General comments on the Janus operational pilot project are welcome at any time.

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ADDRESSES: Submit written requests to participate and comments regarding this pilot project to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>.

FOR FURTHER INFORMATION CONTACT: Bobbie Witczak, Food and Drug Administration, 5600 Fishers Lane (HFD-070), Rockville, MD 20857, 301-796-4126.

For specific questions regarding Voluntary Genomic Data Submissions, please contact: Federico Goodsaid, Food and Drug Administration, 10903 New Hampshire Ave, Bldg. 51, rm. 2148 Silver Spring, MD 20903, 301-796-1535

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing an opportunity to participate in a pilot project that involves the ongoing development and testing of a repository for standardized clinical study data (the Janus study data warehouse). This pilot will test the electronic receipt, processing, and storage of standardized clinical study data, including the successful validation and loading of data into the Janus study repository and subsequent access of that data by reviewers using a combination of analytical and visualization tools. The Janus study data repository is the data warehouse component of a common, standards-based infrastructure that is being developed jointly by FDA and the NCI to support the exchange of clinical research data. Janus is designed to enhance the agency's capability to manage and review standardized study data.

CDER has been accepting voluntary electronic submissions of standardized clinical study data since July 2004.¹ Applicants wishing to provide clinical study data in standardized format are advised to follow the Study Data Tabulation Model (SDTM) defined by the Clinical Data Interchange Standards Consortium (CDISC). CDISC is an open, multidisciplinary, nonprofit organization that has established worldwide industry standards to support the electronic acquisition, exchange, submission, and archiving of clinical trial data and metadata for medical and biopharmaceutical product development (<http://www.cdisc.org>).

Under current regulations, applicants are required to provide case report tabulations (i.e., study data) for certain studies included in a marketing application (see 21 CFR 314.50). In guidance for industry titled “Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Application and Related Submissions Using the eCTD Specifications,” FDA makes recommendations about how to submit documents in electronic format for investigational new drug (IND) applications, biologic license applications (BLAs), and new drug applications (NDAs) using the electronic common technical document (eCTD) specifications. In Section III.E.4 of that guidance, FDA refers to the CDISC SDTM as the Study Data Specification for voluntary electronic submission of clinical study data.

In addition, FDA is planning to amend the regulations governing the format in which clinical study data and bioequivalence data are required to be submitted for NDAs, BLAs, and abbreviated new drug applications (ANDAs).² This proposal would revise FDA’s regulations to require that

¹ See <http://www.fda.gov/bbs/topics/news/2004/NEW01095.html>.

² See <http://www.reginfo.gov/public/do/eAgendaViewRule?ruleID=279292>. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

clinical data submitted for NDAs, BLAs, and ANDAs, and their supplements and amendments: (1) Be provided in electronic format and (2) use a standardized data structure, terminology, and code sets as referenced in FDA guidance to enable efficient and comprehensive data review.

The Janus study data repository is being developed by FDA and NCI through the Interagency Oncology Task Force (IOTF), which was established in 2003 to enable the two organizations to share knowledge and resources to facilitate the development of new cancer drugs and speed the development and their delivery to patients. As part of the IOTF agreement, FDA is working with NCI to build tools and an environment that facilitates and streamlines electronic interaction and collaboration among FDA and its stakeholders in the regulatory review process. The Janus initiative is part of a larger effort to implement a common, standards-based electronic infrastructure that supports the submission, validation, data warehousing, access, and analysis of structured scientific data to support regulatory review.

Phase 1 of the Janus implementation effort was a proof of concept pilot that successfully demonstrated the ability to load SDTM data into Janus, extract data from Janus using commercial-off-the-shelf (COTS) query tools, and produce data from Janus in SDTM format. Phase 2 of this initiative involved development of an operational pilot that includes a data import and validation facility, the integration of reviewer tools with the Janus repository, and provision of reviewer access to the data via selected analytical and visualization tools. Validation criteria for processing SDTM submissions were developed for use in that pilot based on the SDTM implementation guide and FDA business requirements. The SDTM validation specification for Janus established the business rules for error-checking functions that determine

whether SDTM submission data can be loaded successfully into the Janus repository.³

CDER has received a limited number of SDTM submissions since it began accepting these standardized datasets. Our experience with these submissions during the phase 2 pilot has shown that additional collaboration with sponsors will be needed on the preparation, submission, and analysis of SDTM datasets to facilitate a common understanding of the data quality requirements that are necessary to realize long-term benefits of an integrated clinical trials data repository.

As a result, FDA is now announcing the start of phase 3 of the Janus operational pilot, which will enable a wider stakeholder community to participate in the Janus development initiative. The goals of the phase 3 pilot are as follows:

- Transition the phase 2 pilot to operational production;
- Test the electronic processing of standardized clinical study data, including the successful validation and loading of data into the Janus study repository and subsequent access to that data by reviewers using a combination of analytical and visualization tools;
- Test a new XML-based submission format for CDISC content (CDISC–HL7 messages, see below) currently under development;
- Extend the Janus logical data model and service-oriented architecture to support submission of CDISC-HL7 messages;
- Integrate with NCI’s Enterprise Vocabulary Service (EVS);

³ See SDTM Validation Specification 1.0, Nov. 2007 at http://www.fda.gov/oc/datacouncil/janus_operational_pilot.html.

- Test the integration and analysis of clinical study data stored in Janus with pharmacogenomic data currently being received through the Voluntary Genomic Data Submissions (VGDS) program⁴.

A desired outcome of the phase 3 pilot is a production environment that supports the routine processing and management of all structured clinical study data provided in regulatory submissions.

The phase 3 operational pilot will also test a new submission format. Currently, SDTM datasets are provided in SAS transport format. FDA recognizes the limitations of the outdated SAS transport format and intends to transition towards a new, more robust XML-based submission format. FDA is currently sponsoring a project within HL7⁵ to develop a standard XML exchange format (called “messages”) for standardized clinical study data content as defined by CDISC. This “CDISC Content to HL7 Message Project” will enable the exchange of clinical study data in a standardized HL7–XML-based format. We believe this will facilitate loading study data into Janus and provide additional benefits. A successful phase 3 pilot will also enable FDA to routinely accept HL7–XML-based clinical study data submissions.

Concurrent with the phase 3 pilot, CDER also will be exploring ways to integrate related data standards initiatives with the Janus effort. These related initiatives include the enhancement of the current Janus logical model to incorporate preclinical and pharmacogenomics data and product safety data. Future efforts will continue to focus on business information requirements for managing product life-cycle data across all FDA regulated products.

⁴ See <http://www.fda.gov/cder/genomics/VGDS.htm>.

⁵ Health Level Seven in an American Standards Institute (ANSI)-accredited standards development organization operating in the health care arena. See <http://www.hl7.org>. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

II. Pilot Project Description

This pilot project is part of an ongoing effort to improve the efficiency of the review of study data within CDER. As we gain additional experience from this pilot, CDER expects to update its study data submission technical specifications as part of a continuing process to improve the quality of clinical study data provided electronically.

A. Approach

CDER is seeking applicants who have submitted or are planning to submit in the near future (i.e., within 6 months of publication of this notice) SDTM files in a regulatory submission in accordance with existing guidance and technical specifications. Our experience during phase 2 has shown that SDTM files routinely fail the Janus validation procedures and cannot be loaded into Janus automatically. Pilot participants should agree to work closely with Janus technical staff to review the validation errors, correct them, and resubmit the files. The ability to successfully load data into the Janus repository is an important pilot milestone. Experience gained as a result of working with participating sponsors during this pilot will help us improve the validation criteria, which subsequently will help improve the quality of future study data submissions. Pilot participants will also gain valuable experience in creating and submitting quality standardized data submissions. Of particular interest are pilot participants who are also able to provide pharmacogenomic data (i.e., VGDS) with the CDISC data. This will enable us to test the integration of clinical data stored in Janus with pharmacogenomic data. Although a VGDS is not required to participate in this pilot, it is a desirable component of the pilot and is encouraged whenever possible.

From this pool of pilot participants, we are also seeking five to eight companies willing to supply study data in the new HL7 XML format (in addition to SDTM datasets) for testing, processing, and loading into Janus. FDA will provide some technical support with the new HL7 XML format, such as help in understanding and interpreting the new specifications. Those who participate in this part of the pilot also will be provided secure access to their data in Janus so they can test the integrity of their data within the Janus environment. Although the SDTM files are part of a regulatory submission, all of the activities involved in this pilot will be conducted outside of a regulatory setting. That is, the SDTM datasets will be reviewed according to current review practices for any electronic dataset submission, and pilot activities will not impact the regulatory review clock, will not affect or delay reviewability assessments, filability decisions, or any regulatory actions.

B. How to Participate

Requests to participate in the pilot project should be submitted to the Division of Dockets Management (see **ADDRESSES**). Requests are to be identified with the docket number found in brackets in the heading of this document. The pilot enrollment period will last 6 months following publication of this notice. The pilot is expected to last approximately 1 year, but this duration will be subject to change as the pilot progresses. Updates to the pilot will be publicly posted on the FDA Janus Operational Pilot Web page.⁶

III. Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this pilot project. Submit a single copy of electronic comments or two paper copies of any mailed

⁶ See http://www.fda.gov/oc/datacouncil/janus_operational_pilot.html.

comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

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Dated: 8/8/08
August 8, 2008.



Jeffrey Shuren,
Associate Commissioner for Policy and Planning.

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