full text of section 565A of the FD&C Act, go to *https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/21st-century-cures-act-mcm-related-cures-provisions#prv.* For further information about EYLEA HD (aflibercept), go to the ''Drugs@FDA'' website at *http://www.accessdata.fda.gov/scripts/cder/daf/.*

Dated: April 16, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2025–06969 Filed 4–22–25; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2025–N–0287]

Exploration of Health Level Seven Fast Healthcare Interoperability Resources for Use in Study Data Created From Real-World Data Sources for Submission to the Food and Drug Administration; Establishment of a Public Docket; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of a public docket; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is announcing the establishment of a docket for public comments exploring the Health Level Seven (HL7) Fast Healthcare Interoperability Resources (FHIR) for submission of data collected from real-world data (RWD) sources. In alignment with the new Department of Health and Human Services (HHS), Assistant Secretary for Technology Policy/Office of the National Coordinator for Health (ASTP/ONC) policy on health information technology (health IT), the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) are exploring approaches to optimize the submission of structured and standardized clinical study data collected from RWD sources. FDA is seeking public comment from interested parties on specific questions. Interested parties may include regulated industry, health IT vendors, academic medical centers, and electronic data capture vendors as well as other interested parties.

DATES: Either electronic or written comments on the notice must be submitted by June 23, 2025.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of June 23, 2025. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2025–N–0287 for ''Exploration of Health Level Seven Fast Healthcare Interoperability Resources for Use in Study Data Created From Real-World Data Sources for Submission to the Food and Drug Administration; Establishment of a Public Docket; Request for Comments.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Ethan Chen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993–0002, 301–796–7626, *ethan.chen@fda.hhs.gov,* or Hussein Ezzeldin, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903

New Hampshire Ave., Silver Spring, MD 20993–0002, 240–402–8629, *hussein.ezzeldin@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Sponsors are increasing their use of RWD to support claims of safety and effectiveness for FDA-regulated medical products. FDA defines RWD as ''data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status'' (Ref. 1).

As stated in FDA's guidance for industry entitled ''Data Standards for Drug and Biological Product Submissions Containing Real-World Data'' (Data Standards Guidance) (Ref. 2), the Agency recognizes challenges involved in standardizing clinical study data collected from RWD sources for inclusion in applicable submissions. The Agency is currently considering how data standards specific to data derived from RWD sources might help accurately and consistently represent data obtained from RWD sources when submitting study data to the Agency.

FDA will also consider the recently adopted HHS Health IT Alignment Policy (Ref. 3), which requests that all HHS operating and staff divisions (including FDA) align on health IT policy that is being developed and implemented by ASTP/ONC. ASTP/ONC defines health IT as ''hardware, software, integrated technologies or related licenses, intellectual property, upgrades, or packaged solutions sold as services that are designed for or support the use by health care entities or patients for the electronic creation, maintenance, access, or exchange of health information'' (Ref. 3). The policy asks for ''greater alignment of health IT-related activities in support of [HHS'] health IT and interoperability goals'' (Ref. 3) and, as such, creates an opportunity for FDA to explore such alignment with respect to clinical study data collected from RWD sources.

In 2020, the final rule entitled ''21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program'' (85 FR 25642; May 1, 2020) was published by ASTP/ONC, establishing the HL7 FHIR standard as a nationwide standard for access, exchange, and use of data for healthcare delivery organizations. The capabilities that the final rule requires from ONC-certified health IT will enable patients, clinicians, researchers, and other appropriate parties to access data from certified electronic health records (EHRs) and other certified health IT in a Representational State Transfer manner, utilizing application programming interface (API) technology. Beginning in 2022, more than 50 data elements in the United States Core Data for Interoperability (USCDI) are consistently and routinely available through certified health IT using FHIR (see *https://www.healthit.gov/isp/united-states-core-data-interoperability-uscdi#uscdi-v1*). The data elements contain a wide array of clinical concepts, including patient demographics, vital signs, laboratory tests, and unique identifiers for patient implantable devices.[1]

ASTP/ONC expanded the number of data elements available through the FHIR standard in the final rule entitled ''Health Data, Technology, and Interoperability: Certification Program Updates, Algorithm Transparency, and Information Sharing'' (HTI–1 final rule) published January 9, 2024 (89 FR 1192). The HTI–1 final rule establishes USCDI version 3, a data set of more than 80 data elements, as the new standard set of data classes and constituent data elements for nationwide, interoperable health information exchange. Additionally, ASTP/ONC has also created the Trusted Exchange Framework and Common Agreement (TEFCA), which operates in the United States as a nationwide framework for health information sharing.[2]

Although clinical study data submitted to FDA are not explicitly required to be collected or submitted using ONC-certified health IT, given the fact that some RWD sources (such as EHRs) are already adopting FHIR and support the USCDI standardized data elements, FDA will explore the possibility of receiving clinical study data that includes data collected from EHRs using HL7 FHIR (along with other data standards currently used in clinical research). The Agency has actively explored many exchange formats and data standards and terminologies that have gained maturity in the past decade for potential adoption. Current initiatives utilizing HL7 FHIR include:

- Structured Pharmaceutical Quality/Chemistry, Manufacturing, and Controls (PQ/CMC):[3] Aims to standardize electronic common technical document module 3 data elements, terminologies, and data structures by adopting HL7 FHIR standard to enhance the automation of exchange and analyses of PQ/CMC data.
- Structured Product Labeling (SPL) on FHIR:[4] Explores the potential approaches for transitioning from SPL submissions in HL7 version 3 to HL7 FHIR.
- CBER Biologics Effectiveness and Safety (BEST) Innovative Methods (IM) Platform (Ref. 4): A FHIR-based platform (see *https://build.fhir.org/ig/HL7/fhir-icsr-ae-reporting/*) which aims to improve CBER's postmarket surveillance capability through the validation, detection, and reporting of adverse events from EHRs. BEST IM Platform piloted two studies to evaluate the quality and timeliness of FHIR for public health use case (Ref. 5); and to explore using semi-automated detection of adverse events using interoperable computable phenotypes (Ref. 6).
- Application of HL7 FHIR to collect data directly from EHRs in a clinical trial:[5] Uses Substitutable Medical Applications Reusable Technologies on FHIR API to read discrete data from EHRs for a phase 2 breast cancer clinical trial. In addition, HL7 FHIR is being used as the exchange standard between health IT and clinical research systems.
- Common Data Model Harmonization (Refs. 7, 8): Builds a data infrastructure for conducting patient-centered outcomes research using RWD derived from routine clinical settings. This project aims to establish mappings between various common data models and currently supported data models, including harmonization with HL7 FHIR US Core.
- Risk Evaluation and Mitigation Strategies (REMS) Integration and Interoperability Initiative:[6][7] Explores

[1] An example of adoption of FHIR is the ''Centers for Medicare & Medicaid Services (CMS) Interoperability and Prior Authorization'' final rule published February 8, 2024 (89 FR 8758), furthering the implementation of FHIR across the Federal government for multiple use cases. See *https://www.cms.gov/newsroom/fact-sheets/cms-interoperability-and-prior-authorization-final-rule-cms-0057-f.*

[2] See *https://www.healthit.gov/topic/interoperability/policy/trusted-exchange-framework-and-common-agreement-tefca.*

[3] See FDA's PQ/CMC web page at *https://www.fda.gov/industry/fda-data-standards-advisory-board/pharmaceutical-qualitychemistry-manufacturing-controls-pqcmcandHL7PQ/CMC* project web page at *https://confluence.hl7.org/pages/viewpage.action?pageId=58656205.*

[4] See HL7 SPL–FHIR project web page at *https://confluence.hl7.org/display/BRR/SPL+V3+to+a+FHIR-based+submission.*

[5] See FDA's web page at *https://www.fda.gov/science-research/advancing-regulatory-science/source-data-capture-electronic-health-records-ehrs-using-standardized-clinical-research-data* and the Quantum Leap Healthcare Collaborative web page at *https://www.quantumleaphealth.org/partnerships/onesource/.*

[6] See HL7 CodeX REMS Integration and Interoperability Initiative Use Case project web page at *https://confluence.hl7.org/display/COD/Risk+Evaluation+and+Mitigation+Strategies+%28REMS%29+Integration.*

the use of standardized APIs, like the open source and freely available HL7 FHIR APIs, with pharmacy data standards, *i.e.,* National Council for Prescription Drug Programs SCRIPT, to integrate REMS into prescriber and pharmacy workflows. The use case ultimately aims to reduce REMS implementation burden, improve the quality of REMS data for feedback and evaluation, and optimize safe medication use and health outcomes.

These activities demonstrate FDA's commitment to information systems modernization as well as openness to using FHIR in general.

More generally, FDA is exploring approaches to modernize submissions of clinical study data collected from RWD sources to the Agency using FHIR, while ensuring alignment with other FDA policy regarding RWD and the work of ASTP/ONC. Given the ubiquity of FHIR-based data elements generated, exchanged, and used in healthcare organizations, and considering the overlap between healthcare data and the information required for clinical research from RWD sources, FDA seeks input from interested parties regarding the range of challenges to be addressed when considering the use of FHIR for submission of clinical study data collected from RWD sources. Additionally, the Agency is seeking feedback on possible approaches and challenges to structuring and standardizing study data submissions with RWD sources using FHIR while aligning with the data interoperability and exchange standards adopted by HHS through ASTP/ONC. Please use the questions in section II to frame your comments. Also, please specify which types of RWD source(s) are pertinent to your comment (for example, EHRs, insurance claims), if applicable.

II. Request for Comments

FDA is requesting public comment on the questions below. Given the context of the currently supported data standards and models, technical guides, terminologies, and exchange formats used for clinical and nonclinical study data submission to FDA, those used for RWD sources such as EHRs, and the need to align with ASTP/ONC health IT development as described above:

1. What challenges do you see for the pharmaceutical industry regarding the *current state* of submitting clinical study data collected from RWD sources to FDA?

2. What opportunities and/or challenges do you see for the pharmaceutical industry on reaching a future state of clinical study data submissions collected from RWD sources using HL7 FHIR (*e.g.,* business processes, technical considerations)?

3. What are your suggestions on how, from a data standards perspective, FDA might reach a future state of clinical study data submissions collected from RWD sources that aligns with ASTP/ONC health IT goals for HL7 FHIR-based exchange?

4. Does USCDI version 3 provide enough information for collecting RWD for research purposes? Is there information that USCDI version 3 does not sufficiently address?

5. Under TEFCA, a variety of ''Exchange Purposes'' are authorized. If ''Research'' was added as an ''Exchange Purpose,'' what role could TEFCA play with using RWD for clinical research? How could TEFCA support more efficient collection and exchange of RWD for clinical research purposes? What challenges might exist with this approach?

III. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. FDA, ''Real-World Evidence,'' web page, September 19, 2024. Available at: *https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.*
2. FDA, ''Data Standards for Drug and Biological Product Submissions Containing Real-World Data,'' guidance for industry, December 2023. Available at: *https://www.fda.gov/media/153341/download.*
3. HHS, ''HHS Health IT Alignment Policy,'' web page, September 16, 2024. Available at: *https://www.healthit.gov/topic/hhs-health-it-alignment-policy.*
4. FDA, ''CBER–CDER Data Standards Program Action Plan,'' August 2024. Available at: *https://www.fda.gov/media/180870/download?attachment.*
5. Deady, M., R. Duncan, L.D. Jones, et al. ''Data Quality and Timeliness Analysis for Post-Vaccination Adverse Event Cases Reported Through Healthcare Data Exchange to FDA BEST Pilot Platform,'' *Front. Public Health,* 12:1379973, 2024. Available at: *https://www.frontiersin.org/journals/public-health/articles/10.3389/fpubh.2024.1379973/full.*
6. Deady, M., R. Duncan, M. Sonesen, et al. ''A Computable Phenotype Algorithm for Post-Vaccination Myocarditis/Pericarditis Detection Using Real-World Data: Validation Study,'' *J Med Internet Res,* 26:e54597, doi: 10.2196/54597, 2024. Available at: *https://www.jmir.org/2024/1/e54597.*
7. FDA, National Institutes of Health, and ONC Health IT, ''Common Data Model Harmonization (CDMH) and Open Standards for Evidence Generation,'' final report, 2020. Available at: *https://aspe.hhs.gov/sites/default/files/private/pdf/259016/CDMH-Final-Report-14August2020.pdf.*
8. HHS Office of the Assistant Secretary for Planning and Evaluation, ''Code Map Services for Interoperability of Common Data Models and Data Standards,'' web page, accessed November 20, 2024. Available at: *https://aspe.hhs.gov/code-map-services-interoperability-common-data-models-0.*

Dated: April 16, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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[7] See U.S. Medication REMS FHIR IG web page at *https://build.fhir.org/ig/HL7/fhir-medication-rems-ig/.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2023–N–5706]

Voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing an opportunity for a limited number of drug manufacturing establishments to participate in the second year of the voluntary Quality Management Maturity Prototype Assessment Protocol Evaluation Program involving the use of a refined prototype assessment protocol to evaluate quality management maturity (QMM). The Center of Drug Evaluation and Research (CDER) implemented this voluntary program for manufacturers of CDER-regulated drug products to gain additional experience with, and further refine as necessary, the prototype assessment protocol and process, to help enable consistent and meaningful assessment of participating establishments' quality management practices, and to provide useful feedback to participants. This notice announces CDER's intent to continue the voluntary QMM Prototype Assessment Protocol Evaluation