The Evolution of FDA Regulatory Submissions in the PDUFA Era

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DISCLAIMER

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Prescription Drug User Fee Act (PDUFA) - 1992
PDUFA Bottom Line

Accelerate Life-Saving Therapies to Patients that Actually Need Them

• More than 100 initiatives
  • Standardized Study/Analysis Data initiative is just one of them...
What was actually happening in the 1980s?

• Section 505(d) of the Federal, Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C 355(d))
  – ... the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, ...

• FDA interprets this to mean **two adequate and well-controlled studies** based on a clinical endpoint (**i.e.**, survival and irreversible morbidity)
  – 21 CFR 314.126
  – Clinical endpoint should measure how a patient “Feels, Functions, or Survives”
What was actually happening in the 1980s?

- How about for diseases that take a long time to progress?
  - Taking may years to be able to assess survival/irreversible morbidity
- Who will pay for these long-term trials?
- What about *these* patients?!
PDUFA I

• Prescription Drug User Fee Act (PDUFA) was enacted on October 29, 1992
  – FDA revenue generated by “User Fees”

• In parallel, Accelerated Approval Pathway established (21 CFR 314 Subpart H for Drugs; 21 CFR 601 Subpart E for Biologics)
  – Rules Finalized on December 11, 1992
Accelerated Approval

• For **serious and life-threatening conditions** where there is an **unmet medical need**, approval is based on “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity” from **adequate and well-controlled studies**
Accelerated Approval

- Surrogate endpoint must be “verified” by post-marketing (“Phase 4”) adequate and well-controlled studies using endpoint(s) that measure how a patient “Feels, Functions, or Survives”
  - “Phase 4” verification studies (first ever post-marketing requirement [PMR]) should be ongoing at the time of accelerated approval
Third-Party Payer Access Granted!
PDUFA II

• Food and Drug Administration Modernization Act (FDAMA) was signed into law on November 21, 1997

• FDAMA authorized the second instance of PDUFA, i.e., PDUFA II
Other 1997 Events ...

• Electronic Records; Electronic Signatures Rule Finalized on March 20, 1997 (codified shortly thereafter under 21 CFR 11)

• Clinical Data Interchange Standards Consortium (CDISC) started to take root
21 CFR 11

My Opinion

Arguably the Most Underrated Rule/Regulation

Why?...
Federal Rule Making

- **Administrative Procedure Act (APA)** governs how US Federal Government Agencies propose and establish rules (that get ultimately codified into regulations)
  1. Advance Notice of Proposed Rulemaking (ANPR)
  2. Comment Period (usually 60-120 days)
  3. Proposed Rule (PR)
  4. Comment Period (usually 60-120 days)
  5. Final Rule (FR)

- This process is extended to Guidance
Federal Register (FR)

• Federal Register (FR) is the “official daily journal” of the US Federal Government

• Managed by the Office of the Federal Register (OFR)

• Daily announcements, known as “Notices”, across all US Federal Government Agencies pertaining to rulemaking, guidance, public meetings (e.g., Duke Margolis workshop on June 12, 2019!)
ANPR Electronic Records; Electronic Signatures – July 21, 1992 (2.5 pages)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration.

21 CFR Chapter I

[Docket No. 92N–0251]

Electronic Identification/Signatures; Electronic Records; Request For Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is announcing that it is considering whether the agency should propose regulations that would, under certain circumstances, accept electronic identification or electronic signatures in place of handwritten signatures where signatures are called for in Title 21 of the Code of Federal Regulations (CFR), and where the electronic form of the signature bearing record is allowable by the regulations. The decision on whether to propose such regulations will be based on information and comments submitted in response to this advance notice of

Royal Rd., Springfield, VA 22151-0493. Orders must reference NTIS order number PB 92–183193 and include payment of $50.00 (for paper copy; order number PB 92–183193 (A19)) or $19.00 (for microfiche; order number PB 92–183193 (A04)) for each copy of the document. Payment may be made by check, money order, charge card (American Express, VISA, or Mastercard), or billing arrangements made with NTIS. Charge card orders must include the charge card account number and expiration date. For telephone orders or further information on placing an order, call NTIS at 703–487–4650. The report is available for public examination in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:
Paul J. Motise, Center for Drug Evaluation and Research (HFD–323), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301–295–8089. Electronic mail address via MCI® Telecommunications Corp. (MCI®) Mail: Name: Paul J. Motise, EMS: FDA, MBX: MOTISE, MBX: A1, MBX: FDACD. (For help in addressing format contact the MCI® mail customer support line (1–800–444–6245)).

SUPPLEMENTARY INFORMATION: The agency is aware that automated systems are being used more extensively in the identification/signature, FDA found the issues to be complex, affecting regulations beyond the CGMP area. For example, a review of Title 21 of the CFR found references to signatures in 132 different sections; a listing of these sections is contained in the report identified below. These regulations typically address signatures in manufacturing production records, clinical investigation records, and formal submissions to the agency. Absent, however, is a codified definition of signature itself. The same preliminary examination took note of the agency’s own paperless electronic records which may contain electronic identifications/signatures.

To identify the issues and develop preliminary approaches on how FDA might accept signature alternatives in an agency-wide manner, the agency formed an FDA Task Force on Electronic Identification/Signatures. The task force created a subgroup, the Electronic Identification/Signature Working Group to address the issues in greater detail. A copy of the group’s initial report dated February 24, 1992, has been placed on file and is on display at the Dockets Management Branch (address above), for public examination; copies may be obtained from NTIS (address above). The report recommended publication of
PR Electronic Records; Electronic Signatures – August 31, 1994 (18 pages)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 11

[Docket No. 92N–0251]

Electronic Signatures; Electronic Records

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations that would, under certain circumstances, permit the agency to accept electronic records, electronic signatures, and handwritten signatures executed to electronic records as generally equivalent to paper records and handwritten signatures executed on paper. These proposed regulations would apply to records when submitted in electronic form that are called for in Title 21 of the Code of Federal Regulations (CFR). The use of electronic forms of recordkeeping and submissions to FDA remains voluntary. This proposed rule is a followup to the agency’s July 21, 1992, advance notice of proposed rulemaking (ANPRM). The e-mail message to DOC00009@FDACD.BITNET. The sole purpose of this electronic address is to automatically distribute the proposed rule by return e-mail. Therefore, no other correspondence should be sent to this electronic address, and there is no need to include text in the body or subject of the electronic request message. However, to permit any necessary followup, persons may include their names, postal addresses, and phone numbers in the body of the messages.

FOR FURTHER INFORMATION CONTACT:

E-mail address via MCI® Mail:
Name: Paul J. Motise, EMS: FDA, MBX: MOTISE, MBX: A1, MBX: FDACD.
(For help in addressing format contact the MCI® Mail Customer Support Line (1–800–444–6245)); or
Tom M. Chin, Division of Compliance Policy (HFC–230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1500.

computer systems developers, private organizations, a Federal agency, a university, and consumers. The comments generally support the ANPRM’s objectives. A number of the comments made suggestions. As appropriate, comments will be responded to in this document in the discussion of the proposed regulation set forth below.

II. Summary and Analysis of Comments to the ANPRM

A. Analysis of Comments

The agency received a total of 53 comments to the July 21, 1992, ANPRM. Comments came from a variety of sources including: 6 trade associations, 27 pharmaceutical manufacturers, 2 medical device manufacturers, 1 contract laboratory, 8 computer systems developers, 1 law firm on behalf of a computer systems developer, 1 law firm on behalf of a consortium of industrial research companies, 1 agency of the Federal Government, 1 drug sample distribution establishment, one medical center, 1 university food sciences unit, 1 express mail delivery service, and 2 individuals.

Comments generally supported the agency’s efforts relative to electronic signatures and electronic records. One
FR Electronic Records; Electronic Signatures – March 20, 1997 (37 pages)

I. Background

In 1991, members of the pharmaceutical industry met with the agency to determine how they could accommodate paperless record systems under the current good manufacturing practice (CGMP) regulations in parts 210 and 211 (21 CFR parts 210 and 211). FDA created a Task Force on Electronic Identification/Signatures to develop a uniform approach by which the agency could accept electronic signatures and records in all program areas. In a February 24, 1992, report, a task force subgroup, the Electronic Identification/Signature Working Group, recommended publication of an advance notice of proposed rulemaking (ANPRM) to obtain public comment on the issues involved.

In the Federal Register of July 21, 1992 (57 FR 32185), FDA published the ANPRM, which stated that the agency was considering the use of electronic identification/signatures, and requested comments on a number of related topics and concerns. FDA received 53 comments on the ANPRM. In the Federal Register of August 31, 1994 (59 FR 45160), the agency published a proposed rule that incorporated many of the comments to the ANPRM, and requested that comments on the other general signings required by agency regulations.

Section 11.2 provides that records may be maintained in electronic form and electronic signatures may be used in lieu of traditional signatures. Records and signatures submitted to the agency may be presented in an electronic form provided the requirements of part 11 are met and the records have been identified in a public docket as the type of submission the agency accepts in an electronic form. Unless records are identified in this docket as appropriate for electronic submission, only paper records will be regarded as official submissions.

Section 11.3 defines terms used in part 11, including the terms: Biometrics, closed system, open system, digital signature, electronic record, electronic signature, and handwritten signature.

Section 11.10 describes controls for closed systems, systems to which access is controlled by persons responsible for the content of electronic records on that system. These controls include measures designed to ensure the integrity of system operations and information stored in the system. Such measures include: (1) Validation; (2) the ability to generate accurate and complete copies of records; (3) archival protection of records; (4) use of
Why so many pages on the FR Notices???
- Rationale/Justification/Context

Part 11 established the ability for FDA to receive any electronic submissions
- Electronic submissions not required
- Any submission from a single cover letter to study datasets
- What’s a valid signature?
- Naturally extends to other things...and hence means different things to different people

You must read the FR Notices!
21 CFR 11
CDISC – The Early Years

Organization

1997
Volunteer CDISC Group Initiated

1998
Glossary Group Formed

1999
SDS and ODM Teams Formed

2000
ADaM Team Formed

2001
LAB Team Formed

Globalization

Non-profit Organization Incorporated

Teams and Alliances

CDISC Standards

SDS and ODM Initial Releases

ADaM Initial Models

ODM Production Release
CDISC – The Early Years
PDUFA III

- Public Health Security and Bioterrorism Preparedness Response Act was signed into law on June 12, 2002

- FDAMA authorized the third instance of PDUFA, i.e., PDUFA III
SDTM Happenings

• CDER SDTM Pilot in 2003

• In July 2004, FDA (CDER) announced that they recommend the use of Version 3.1 of the SDTMIG, a pivotal milestone in the recognition of CDISC as a major Standards Development Organization (SDO)
PDUFA IV

• Food and Drug Administration Amendments Act (FDAAA) was signed into law on September 27, 2007
• FDAAA authorized the fourth instance of PDUFA, i.e., PDUFA IV
• FDA received the explicit authority from FDAAA to require a Risk Evaluation and Mitigation Strategy (REMS) when necessary
What is a REMS?

• A REMS is a risk management plan that uses risk minimization strategies **beyond professional labeling**
  – Elements to Assure Safe Use (ETASU) – *usually linked to distribution!*
    • Prescriber Certification
    • Pharmacy Certification
    • Qualified Dispensing Center (e.g., infusion center, hospital)
    • Safe-Use Conditions (e.g., pregnancy test)
    • Patient Monitoring
    • Registry
  – Medication Guide
  – Communication Plan
What is a REMS?

• Potentially huge burden on healthcare delivery
  – Lesser of two evils: Third-Party Payer Access with REMS is better than no access at all

• FDA can require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks
  – Before approval
  – Post-approval if FDA becomes aware of new safety information

• REMS is/are enforceable
Thalidomide Tragedy
Thalidomide Tragedy
REMS

• In this context, so long as the benefits strongly outweigh the risks, a product that results in embryo-fetal developmental toxicities could still be approved with a REMS
  – ETASU: Safe-Use Conditions (would require a negative pregnancy test before every administration of the product)

• REMS continues to be assessed in a post-market setting
  – Similar “in spirit” to Accelerated Approval (but for Safety)
PDUFA V

- **Food and Drug Administration Safety and Innovation Act (FDASIA)** was signed into law on July 9, 2012

- FDASIA authorized the fifth instance of the Prescription Drug User Fee Act (PDUFA), i.e., PDUFA V

- **TITLE XI (‘OTHER PROVISIONS’)**, Subtitle C (‘Miscellaneous Provisions’), Section 1136 (‘Electronic submission of applications’) of FDASIA amended the Federal Food, Drug, and Cosmetic Act (FDCA) to include a new section, i.e., Section 745A
Regulation

Guidance
Regulation vs. Guidance

• Regulation
  – Interpretation of Statute
  – Enforceable (Binding)

• Guidance
  – Interpretation of Regulation
  – Not usually Enforceable (i.e., Not usually Binding)
  – Reflects Current Thinking
FD&C Act Section 745A

• Statutory electronic submission requirements
  – specifies format for submissions in binding guidance

• Section 745A(a) applies to all submissions made to CDER and all non-device submissions made to CBER

• Section 745A(b) applies to all submissions made to CDRH and all device submissions made to CBER
Binding Parent Guidance

• Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) for the Federal Food, Drug, and Cosmetic Act
  – Guidance finalized on December 17, 2014

• Establishes the overall requirement for all submissions specified under section 745A(a) to be electronic
  – Describes how FDA interprets and plans to implement (including general timelines) the requirements of section 745A(a)

• More or less presents the content directly from Section 745A(a) with additional Agency interpretation
Binding Parent Guidance

• INDs, NDAs, ANDAs, BLAs, DMFs all apply
  – Exemptions: **Pre-INDs (PINDs)**, Noncommercial INDs, i.e., Sponsor-Investigator INDs (Section 505(i)(1) of the FD&C Act) and Expanded Access INDs (Section 561 of the FD&C Act)

• Describes the process in which FDA will develop individual subject-specific binding guidances
  – **THESE** are the important guidances
  – Note: Criteria for any waivers will be discussed within these individual submission-specific binding guidance documents
Finalized Binding Individual Guidances

• Providing Regulatory Submissions in Electronic Format – Standardized Study Data
  – “eStudy Guidance” finalized on December 17, 2014

• Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications
  – eCTD Guidance finalized on May 5, 2015
Binding Individual Guidances in Development

• Guidance pertaining to Risk Evaluation and Mitigation Strategies (REMS) submitted using Structured Product Labeling (SPL) (Draft Guidance was issued in September 2017)

• Guidance pertaining to Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (Draft Guidance was issued in February 2018)

• Guidance from the Office of Prescription Drug Promotion (OPDP)

• Guidance from the Office of Pharmaceutical Quality (OPQ)
eCTD Guidance

• Provides further detail and implementation of the requirements with respect to *all* submission types in general
  – Requirement is that all submissions be electronic and CTD compliant

• **Timelines**
  – All NDA, ANDA, and non-device BLA submissions
    • For submissions made on or after 24 Months after the issuance of Final Guidance
      – 24 Months after May 5, 2015 = **May 5, 2017**
eCTD Guidance

- **Timelines** (continued)
  - All new master file (other than Type III DMFs) and IND submissions (previously noted exceptions aside)
    - For submissions made on or after 36 Months after the issuance of Final Guidance – 36 Months after May 5, 2015 = **May 5, 2018**
      - Type III DMFs – 60 Months after May 5, 2015 = **May 5, 2020**
  - There are *currently no* waivers for any of these
  - An eCTD Technical Conformance Guide has also been issued (and is a living document)
eCTD Guidance
eStudy Guidance – When Will Standards Be Required?

• Provides further detail and implementation of the requirements with respect to study dataset submissions

• Timelines
  – Datasets submitted in NDAs, ANDAs, and non-device BLAs
    • For studies **with study start dates** after 24 Months after the issuance of Final Guidance
      – After 24 Months after December 17, 2014 = **December 18, 2016**
  – Datasets submitted to INDs (previously noted exceptions aside)
    • For studies **with study start dates** after 36 Months after the issuance of Final Guidance
      – After 36 Months after December 17, 2014 = **December 18, 2017**
eStudy Guidance – When Will Standards Be Required?

Final Published: December 2014

24 Months*:

December 2016

Compliance:

Studies starting after MUST use the formally adopted study data standards

*36 months for INDs
eStudy Guidance – What Standards Will Be Required?

• Standards specified within the **Data Standards Catalog**, which is a list of all supported data standards that the Agency can currently process, review, and archive
  
  – **Exchange Format Standards**
    • Examples from the catalog include SAS XPT, extensible markup language (XML), portable document file (PDF)

  – **Study Data Standards**
    • Examples from the catalog include CDISC Study Data Tabulation Model (SDTM), Standard for Exchange of Nonclinical Data (SEND), and Analysis Data Model (ADaM)

  – **Controlled Terminology Standards**
    • Examples from the catalog include CDISC Controlled Terminology and Medical Dictionary for Regulatory Activities (MedDRA)
eStudy Guidance – What Standards Will Be Required?

Final Published December 2016

Study Data: SDTM, ADaM, SEND, Define.XML

Data Standards Catalog

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
eStudy Guidance – How Standards Will Be Required?

• The **Study Data Technical Conformance Guide** (i.e., **Tech Conformance Guide**) is a separate and detailed technical specifications document that supplements the requirements described in the eStudy guidance and is intended to assist sponsors and applicants in the electronic submission of standardized study data.

• This document replaces the archaic, and now retired, ‘**FDA Study Data Specifications’** and ‘**Common Issues’** documents in both CDER and CBER.

• Note that the **Data Standards Catalog** and **Tech Conformance Guide** are living documents in that each will be updated over time in order to reflect evolving study data needs.
eStudy Guidance – How Standards Will Be Required?

Technical Conformance Guide (non-binding)

Version 4.3 Published

Study Data Standardization Plan
Analysis Data Reviewer’s Guide
SDTM Exchange Formats
Domain SDTM General File
Specs Considerations Transport
SEND Domain Specs Efficacy, Safety,
Domain Specs Timing Variables
Controlled Terminologies
Therapeutic Area Standards
Data Validation & Traceability
Elect Sub Format

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
eStudy Guidance – Waivers

Unless it is for a previously supported version of a standard within the Data Standard Catalog, which has been retired/phased out
eStudy Guidance

Can FDA Refuse to File / Receive?

Yes.
Just FYI ...

- Boilerplate language on ‘Data Standards’, which is located on most, if not all, CDER OND communication templates that are managed by OND RPMs, has been updated.
  - If study data is currently supported by a standard within the Data Standards Catalog, then FDA cannot request (and sponsors/applicants cannot submit) this data in some other non-standardized/legacy format.
  - Formal Study Data Submission Requirements should foster much needed (and previously lacking) communication.
PDUFA VI

• FDA Reauthorization Act (FDARA) was signed into law on August 18, 2017

• FDASIA authorized the sixth instance of the Prescription Drug User Fee Act (PDUFA), i.e., PDUFA VI
Data Standards Governance at FDA

Office of the Chief Scientist

CBER Data Standards Committee

CDER Data Standards Program Board

Operations Committee

Validation Rules Group

Study Data Standards Group

Terminology Group

Conformance Guide Group

Data Standards Advisory Board

CDRH CFSAN CVM

Other Centers
Data Standards Strategy and Action Plan

Data Standards Strategy 2018-2020

Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Food and Drug Administration

Draft Version: 3.5
Document Date: April 17, 2019
IV. INFORMATION TECHNOLOGY GOALS

A. Objective
B. Improve The Predictability And Consistency Of PDUFA Electronic Submission Processes
C. Enhance Transparency And Accountability Of FDA Electronic Submission And Data Standards Activities

https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
Framework for FDA’s Real-World Evidence Program

Friday, March 15, 2019
1:00p.m. - 2:00p.m. (Eastern)

As part of the 21st Century Cures Act, the FDA released a framework for our Real-World Evidence (RWE) program. The goal for this webinar is to inform the public of FDA’s effort to understand the utility of real-world data (RWD) to generate evidence for regulatory decisions.

Speaker

Jacqueline Corrigan-Curay, J.D., M.D.
Director
Office of Medical Policy
Center for Drug Evaluation and Research
FDA

More Engagement from Clinical (they use ADaM!)
Remember my Disclaimer ...

Analysis Results Metadata (ARM)
Two words to help Ned Sharpless revolutionize clinical trials: data standards

By SAM VOLCHENBOUM / MAY 13, 2019

In the classic 1967 film “The Graduate,” young Benjamin Braddock was given one word of advice for his future: plastics. In that spirit, I’d like to offer Dr. Ned Sharpless, the new acting commissioner of the Food and Drug Administration,
Thank you for your attention!

• Questions?
• Special Thanks!
  – Charles (Chuck) Cooper
  – Sarada Golla
  – Wayne Kubick
  – Sandra Minjoe
  – Armando Oliva
  – Helena Sviglin
  – Stephen (Steve) Wilson