Session 5 (PV): Future of Inspections

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 15, 2024 – 2:00 – 3:00 PM

Moderator: **Carolyn Volpe, PharmD, MS**
Regulatory Officer | DEPS | OSI | OC | CDER | FDA

Ginneh Stowe, MS
Health Scientist | Oncology Center of Excellence (OCE) | FDA

Peter Diak, PharmD, MPH
CAPT | *USPHS* | *Branch Chief* | Postmarketing Safety Branch (PSB) | DEPS
OSI | OC | CDER | FDA

Chrissy Cochran, PhD
Director | OBIMO | OMPTO | ORA | FDA

Robert Ball, MD, MPH, ScM
Deputy Director | Office of Surveillance and Epidemiology (OSE)
CDER | FDA

Remote Regulatory Assessments for FDA's Postmarketing Safety Compliance Programs

Ginneh Stowe, MS
CAPT Peter Diak, PharmD, MPH

Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations, Office of Compliance
CDER | US FDA

A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 15, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

Overview

FDA's experience with piloting the use of Remote Regulatory Assessments (RRAs) to inform inspection planning for Postmarketing Safety Programs

- Postmarketing Adverse Drug Experience (PADE) Compliance Program
- Risk Evaluation and Mitigation Strategies (REMS) Compliance Program

Overview

Lessons learned from pilot project and the future of RRAs

PADE Compliance Program

Compliance Program 7353.001: Postmarketing Adverse Drug Experience Reporting Inspections

- Foreign and domestic inspections
- Number of inspection assignments varies each fiscal year depending on available resources
- Routine surveillance or For-cause
- Available compliance actions: Untitled Letter, Warning Letter, Seizure, Injunction

Public website: Postmarketing Adverse Event Reporting Compliance Program

PADE Compliance Program: Scope

Application holders of NDA, ANDA, BLA and certain non-applicants named on product labels

Approved prescription drugs and therapeutic biologics, Marketed unapproved prescription drugs, and OTC monograph drugs

Inspection sites where PV activities are conducted or coordinated (corporate headquarters, US regulatory agent, US affiliate, etc.)

Assignments are issued by PVC team and conducted by ORA-BIMO investigators

Assessment of PV activities

- ✓ **Past** performance and data verification
- ✓ **Current** processes, written procedures, and electronic systems
- ✓ Processes and systems in place that may impact **future** activities and submissions

REMS Compliance Program

Compliance Program 7353.001c: REMS Data Reporting Inspections

- REMS are required if FDA determines it is necessary to ensure benefits of a drug outweigh risks
- REMS inspections monitor industry compliance and conduct risk assessments

Public website: REMS Compliance Program

REMS Components

RRA Background

During the COVID-19 pandemic, FDA determined that RRAs are a valuable tool to:

Conduct oversight, mitigate risk, meet critical public health needs

Help maximize compliance with applicable FDA requirements

Provide information about deficient practices leading to regulatory actions, inspections, and future inspection planning

Use agency resources more efficiently

Draft Guidances for Industry (July 2022, October 2023)

Expands use of RRAs beyond the COVID-19 pandemic

Describes how FDA intends RRAs to be incorporated consistently

Describes how RRAs help determine compliance with applicable FDA requirements, inform regulatory decisions and verify information

Possible RRA benefits

Helps advance FDA's public health mission and provide the robust oversight needed to protect patients and consumers

Allows FDA to remotely evaluate compliance

May identify issues that lead establishments to promptly make corrective actions, which may enhance preparedness for the next inspection

Efficient and effective use of inspectional resources
- RRA preceding an inspection could reduce and/or optimize inspection time
- RRA information may be incorporated into a risk-based inspection schedule

Remote Regulatory Assessments

Business operations

Demonstration of electronic systems

Verification of data in regulatory submissions

Compliance management activities

Collection, evaluation, management, reporting of adverse events

Documents supporting communications related to PV activities

Personnel / staffing (e.g., qualifications, training)

Data integrity

Alternate Compliance Tool- PADE/REMS RRA Pilot Background

What are RRAs?

- Examinations of an FDA-regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements
- An additional regulatory tool that can be used in advance of or (RRAs are not inspections)
- RRA is an umbrella term (includes Remote Interactive Evaluations and Remote Record Reviews)

RRAs in the PADE / REMS Pilot

- Voluntary- an establishment can decline or withdraw their participation at any time
- Conducted to inform planning for PADE and REMS inspections
- Focused on requesting and reviewing records and documents similar to what FDA would request during an inspection

RRA Conclusions

- Information and documentation from the RRA may be used to determine:
  - Whether an establishment is in compliance with applicable laws and regulatory requirements
  - The priority and focus for subsequent inspection

Pilot Experience

Initiated in 2023-Q2 and is ongoing

Participation

- Voluntary participation
- Considered firm's willingness and ability to support RRA (e.g., technology, personnel)
  - Most firms contacted were willing and able to participate
- Required PADE and REMS Teams resources and planning

Conduct

1. PADE / REMS Team sent participating firms a request for documents related to the PADE / REMS compliance programs
2. Firms submitted documents to PADE / REMS Team via box.com
3. PADE / REMS Team reviewed information provided to inform risk-based inspection planning
4. PADE / REMS Team notified firms of RRA completion

Voluntary Feedback

<u>Firms</u>

- Positive experience
- Sufficient time to respond
- Technology was user-friendly
- Clear instructions and communications

<u>PADE and REMS team reviewers</u>

- Generally satisfied with quality of information received
- Helpful when submissions were organized, and each request addressed (even if there were no supporting documents)

Opportunities

Resources

Compliance Programs
PADE 7353.001: Postmarketing Adverse Drug Experience Inspections
REMS 7353.001c**:** REMS Data Reporting Inspections

Public websites
Postmarketing Adverse Event Reporting Compliance Program
REMS Compliance Program

FDA Guidance Documents
Postmarketing Adverse Event Reporting for Medical Products and Dietary Supplements During a Pandemic (May 2020): https://www.fda.gov/media/72498/download
Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers (August 2020): https://www.fda.gov/media/141312/download
Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency, Guidance for Industry (April 2021): https://www.fda.gov/media/147582/download
Conducting Remote Regulatory Assessments Questions and Answers (July 2022): https://www.fda.gov/media/160173/download
Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities (October 2023): https://www.fda.gov/media/173286/download

Reports
Resiliency Roadmap for FDA Inspectional Oversight (May 2021): https://www.fda.gov/media/148197/download

Closing Thoughts

Post market safety modernization efforts strengthen and streamline FDA's ability to monitor industry compliance and inform risk-based inspection planning.

We will continue evaluating the benefits, limitations, and utility of RRAs as a compliance tool in advance of planned PADE and REMS surveillance inspections.

Questions?

PADE Compliance Program:

cder-osi-ade@fda.hhs.gov

REMS Compliance Program:

cder-osi-rems@fda.hhs.gov

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Carolyn Volpe

U.S. FOOD & DRUG ADMINISTRATION

The Future of FDA PhV Inspections

Chrissy J. Cochran, PhD
Director
Office of Bioresearch Monitoring Operations
ORA | US FDA

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Overview

- FDA BIMO Overview
- Application Holder Responsibilities
- Future of Inspections

FDA BIMO Overview

Robert Califf, M.D.
Commissioner of FDA

- Center for Biologics Evaluation and Research
- Center for Drug Evaluation and Research
- Center for Devices and Radiological Health
- Center for Food Safety and Applied Nutrition
- Center for Tobacco Products
- Center for Veterinary Medicine

Office of Regulatory Affairs

Associate Commissioner for Regulatory Affairs (ACRA)

Assistant Commissioner for Import Operations

Assistant Commissioner for Medical Products & Tobacco Operations

Acting Assistant Commissioner for Human & Animal Food Operations

Assistant Commissioner for Criminal Investigations

OBIMO

OBPO

OMDRHO

OPQO

TOS

HAF-E

HAF-W

BIMO Program Objectives

- To protect the rights, safety, and welfare of human and animal research participants
- To ensure the quality, reliability, and integrity of data collected
- To maintain the integrity of the FDA review process by ensuring that FDA-regulated research is conducted in compliance with applicable regulations

Office of Bioresearch Monitoring Operations

Inspection Workflow

Contact Information

- Form FDA 483 response/correspondence
  - ORABIMOE.Correspondence@fda.hhs.gov (Division 1 - East)
  - ORABIMOW.Correspondence@fda.hhs.gov (Division 2 - West)
- Inspection issues
  - BIMO East (Div 1):
    - PDD Anne.Johnson@fda.hhs.gov
    - DIB Christine.Smith@fda.hhs.gov
  - BIMO West (Div 2):
    - PDD Eric.Pittman@fda.hhs.gov
    - DIB Audrey.Vigil@fda.hhs.gov
  - Foreign Inspections
    - SCSO Barbara.Wright@fda.hhs.gov
    - SCSO Jennifer.Adams@fda.hhs.gov

Recruitment and training

- Hiring
- Basic training
- Advanced training
- Resources
  - IOM
  - PADE (PhV) CP

PROGRAM 7353.001

CHAPTER 53 – Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products

SUBJECT:	IMPLEMENTATION DATE:
POSTMARKETING ADVERSE DRUG EXPERIENCE (PADE) INSPECTIONS COMPLIANCE PROGRAM FOR HUMAN DRUG AND THERAPEUTIC BIOLOGICAL PRODUCTS	10/18/2022

DATA REPORTING	
PRODUCT CODES	PRODUCT ASSIGNMENT CODES
eNSpect does not require product codes for Postmarketing Adverse Drug Experience (PADE) reporting inspections	53001A Adv Drug Experience Rptg Reqs Center Initiated

Application Holder Responsibilities

Application Holder Responsibilities

- Control and oversight
  - Written procedures
  - Access
    - Subcontractors
    - FDA investigators
- FDORA – must provide FDA with access to electronic systems

Reporting to FDA

Application Holder Responsibilities

- Safety reports must be in electronic format
  - 21 CFR 314.80
  - Electronic Submission of IND Safety Reports
  - Providing Submissions in Electronic Format

Future of PhV Inspections

Future of Inspections

- RRA Pilot
- Inspection access
  - Electronic
  - Box.com
  - Teams
- Inspection readiness

Summary

- ORA works closely with CDER
- Application Holders are responsible for electronic ADE submissions
- Inspections are evolving

Questions?

Chrissy J. Cochran, PhD
Director
Office of Bioresearch Monitoring Operations
ORA | US FDA

Email: Chrissy.Cochran@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Artificial Intelligence (AI) in Pharmacovigilance (PV)

Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
January 30, 2024

U.S. FOOD & DRUG ADMINISTRATION

The opinions expressed in this lecture are those of the presenter, and do not necessarily represent the views of the US Food and Drug Administration or the US Government

Robert Ball is an author on US Patent 9,075,796, “Text mining for large medical text datasets and corresponding medical text classification using informative feature selection”

Outline

- What is “Artificial Intelligence (AI)”?
- How might AI apply to pharmacovigilance (PV)?
- A framework for readiness for AI in PV
- Regulatory and Consensus Development Activities for AI in PV
- Summary

What is “AI”?

- “Artificial Intelligence has been broadly defined as the **science and engineering of making intelligent machines**, especially intelligent computer programs” (1)
- Many technologies have been placed under the “AI” umbrella
  - **machine learning (ML) and natural language processing (NLP)** are two of the most common being applied to ICSR processing and assessment
  - ML is defined as a “… technique that can be used to design and train software algorithms to learn from and act on data...” (2)
  - NLP is defined as “the application of computational techniques to the analysis and synthesis of natural language and speech” (3)

1. McCarthy, J. (2007). What Is Artificial Intelligence? Stanford University, Stanford, CA. Retrieved from https://hai.stanford.edu/sites/default/files/2020-09/AI-Definitions-HAI.pdf
2. US FDA. Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device. Accessed 20 Oct 2023.
3. "Definition of natural language processing“, Oxford University Press. Lexico.com. https://www.lexico.com/definition/natural_language_processing.

What is “AI”?

CLASSICAL MACHINE LEARNING
Data is pre-categorized or numerical
Data is not labeled in any way
SUPERVISED
UNSUPERVISED
Predict a category
Predict a number
Divide by similarity
Identify sequences
CLASSIFICATION
«Divide the socks by color»
REGRESSION
«Divide the ties by length»
CLUSTERING
«Split up similar clothing into stacks»
Find hidden dependencies
ASSOCIATION
«Find what clothes I often wear together»
DIMENSION REDUCTION (generalization)
«Make the best outfits from the given clothes»

Deep Learning
Learned Rules
Transparent and Explainable Rules
Human Review and Update
Production

AI
ML
NLP
DL
L
L
M
Artificial intelligence
Machine learning
Language Processing
Deep learning

Key Concepts about LLMs (>10B parameters)

- Pre-Training of the Foundation Model
  - The model learns to **predict the next word** in a sentence
  - Uses a massive corpus of internet text (100B-TBs)
  - 100s to 1000s of GPU cards for several months
  - Clearly not something that can be easily done

- Fine-Tuning of an LLM
  - Task specific datasets for instruction tuning or **human feedback** for alignment tuning
  - 1 to 10s of GPU cards for few days. SMEs for preparing the datasets or feedback; AI engineers for model fine-tuning

- Prompt engineering
  - In-context learning and Chain-of-Thought prompts
  - **SMEs and AI scientists** work together to **design and refine prompts** (including the examples for in-context learning)

Slide courtesy of Joshua Xu and Leihong Wu, NCTR, FDA

An Explosion of Large Language Models (LLM) Presents Opportunities

Fig. 2: A timeline of existing large language models (having a size larger than 10B) in recent years. The timeline was

Zhao, et al. A Survey of Large Language Models (http://arxiv.org/abs/2303.18223)

Slide courtesy of Joshua Xu and Leihong Wu, NCTR, FDA

Why focus on AI for ICSRs?

- ICSRs have a **long, proven track record** of identifying new safety issues and remain the source of important new safety information
- ICSRs will likely **continue to play an important role** as an early warning system of drug safety signals, especially for rare events
- **Increasing number and variety of data sources** to be assessed for safety information
  - a **growing volume of ICSRs** that are processed and assessed for safety signals
- Submission of ICSRs is required by regulators globally and **harmonization** of approaches improves efficiencies and promotes standardization

FDA Adverse Event Reporting System (FAERS)

Ball R, Dal Pan G. “Artificial Intelligence” for Pharmacovigilance: Ready for Prime Time? Drug Safety 45:429–438, 2022.

ICSR Processing

- Case processing has been described as having four activities including **intake, evaluation, follow-up, and distribution**, with many subprocesses for each activity (4)
- Intake of cases includes **identification of the four minimum elements** of an ICSR
  - “an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect product” (5)
  - ICSRs must also include all relevant information when such information is available
- Additional steps involve **determination of important regulatory categories** (6), e.g.
  - seriousness of the adverse event
  - expectedness - whether the adverse event is already in the prescribing information for the product
  - for adverse events from a study, likelihood of a causal association

Figure 1. Case processing deliverables.

Image Schmider J, Kumar K, LaForest C, Swankoski B, Naim K, Caubel PM. Innovation in Pharmacovigilance: Use of Artificial Intelligence in Adverse Event Case Processing. Clin Pharmacol Ther. 2019;105:954-961.

ICSR Causality Assessment

- Case causality assessment is the determination of whether the **drug is likely to have caused** the reported **adverse event**
- Assessment of ICSRs for causality still relies primarily on **expert judgment** and global introspection
- Assessment of ICSRs for causality relies on **information internal and external** to the report
- A complete **computable "cognitive framework"** for ICSR causality assessment **has not been developed**

Elements of Cognitive Framework for ICSR Causality Assessment

Ball R, Dal Pan G. "Artificial Intelligence" for Pharmacovigilance: Ready for Prime Time? Drug Safety 45:429–438, 2022.

Framework for considering readiness of AI for ICSR processing and assessment

- **Algorithm performance**, documentation, transparency, explainability, **quality control**, and algorithm change control
- If an AI algorithm doesn't achieve performance levels required for full automation, the key **challenge** of including a "human-in-the-loop" is to **ensure quality without reducing the efficiency gained from the AI algorithm**

Ball R, Dal Pan G. "Artificial Intelligence" for Pharmacovigilance: Ready for Prime Time? Drug Safety 45:429–438, 2022.

Quality assurance of “human-in-the-loop” AI systems General Considerations

- Characteristics of quality assurance that might be applied to a human-in-the-loop approach to an imperfect AI system include:
  - a **risk-based** approach in which effort is proportional to the implications of misclassification on the overall evaluation goals
  - incorporation of the **reliability of the AI algorithm's performance** through carefully applied principles of algorithm development or formal confidence metrics
  - selection of **quality assurance** techniques such as sampling, simultaneous independent algorithm application, and incorporating the AI algorithm in a general evaluation process that includes other means of quality assurance

Ball R, Dal Pan G. “Artificial Intelligence” for Pharmacovigilance: Ready for Prime Time? Drug Safety 45:429–438, 2022.

Select Regulatory and Consensus Development Activities for AI in PV

- **FDA Discussion Paper** on AI in Drug Development, including Pharmacovigilance
- **EMA Reflection Paper on** AI in the lifecycle of Medicines
- **FDA-EMA PV cluster working group on AI** formed fall 2023 with Health Canada and PMDA joining as observers in 2024
- **CIOMS XIV WG for AI in PV** is comprised of regulators, industry, and academia developing a scientific consensus document on AI in PV
- **Pharmaceutical Inspection Co-operation Scheme (PIC/S)** is a non-binding, informal co-operative arrangement between Regulatory Authorities that aims at harmonizing inspection procedures worldwide by developing common standards and providing training opportunities to Inspectors
  - In the field of Good Pharmacovigilance Practices (GPV), PIC/S is exploring establishing an Expert Circle focused on inspecting emerging technologies like AI-ML

Goal is to promote mutual learning around three main core issues:

- Human-led governance, accountability, and transparency
- Quality, reliability, and representativeness of data
- Model development, performance, monitoring, and validation

Slide courtesy of Tala Fakhouri

Next steps for AI in Drug Development

- Continue collaboration and mutual learning
- Continue tracking of AI/ML uses in the development of drugs
- Advance and support the development and dissemination of demonstration projects
- Identify best practices
- Develop a **risk-based** framework for **credibility assessment**, building on the Agency's longstanding commitment to support innovative work in this area

Slide courtesy of Tala Fakhouri

Unanticipated challenge? Social Loafing and AI

Cymek DH, Truckenbrodt A and Onnasch L (2023), Lean back or lean in? Exploring social loafing in human–robot teams. *Front. Robot. AI* 10:1249252. doi: 10.3389/frobt.2023.1249252

Summary

- "Classic" AI systems are being used for ICSR processing and analysis, but **uncertainty** remains about **best approaches to monitoring quality**
- Including **"humans in the loop"** for quality assurance will likely not only be necessary, but desirable, for the foreseeable future but not a panacea
- **LLMs** are extremely powerful and have changed the AI landscape, but **introduce even more uncertainty**
  - Technical considerations
    - Public vs private
    - Number of parameters
    - Cost
    - Need for domain specific tuning
  - Policy considerations
    - Need for transparency of training data and models?
    - Is there an increased risk of false report generation?
    - Is "explainability" possible?
    - Will same approaches to quality assurance for classic AI work for LLMs?
- FDA is building a **regulatory approach** for AI in drug development, including pharmacovigilance, based on a **risk-based** framework for **credibility assessment**

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