Session 6 (PV): Regulatory Updates

Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Symposium
February 15, 2024 – 3:15 – 4:00 PM

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Combination Products PMSR Requirements

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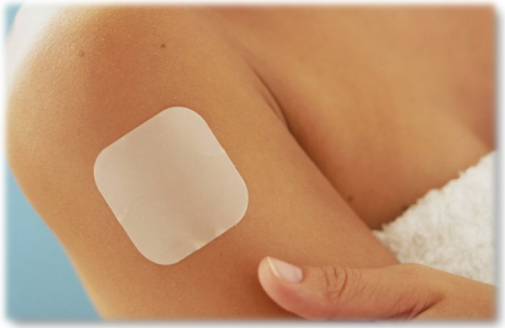
A Joint US-FDA | MHRA-UK | Health Canada Good Clinical Practice & Pharmacovigilance Compliance Workshop
February 15, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

Overview

- Combination Products
- Postmarketing Safety Reporting Requirements



Combination Products

Examples:
- Prefilled syringe
- Drug-eluting stent
- First aid kit with devices and drugs

- Combine two or more different medical product types
- **Constituent parts** are drugs, devices, biologics part of the CP
- Multiple **modes of action**
- Assigned to Lead Center based on **Primary Mode of Action (PMOA)**

Combination Product Examples

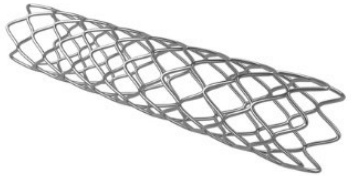
Example	Constituent Parts		PMOA	Center
Prefilled vaccine syringe	Vaccine *(Biologic)*	Syringe *(Device)*	Biologic	Assigned to **CBER**
Drug filled autoinjector	Drug *(Drug)*	Autoinjector *(Device)*	Drug	Assigned to **CDER**
Drug eluting stent	Stent *(Device)*	Drug Coating *(Drug)*	Device	Assigned to **CDRH**

Types of Combination Products

- **Single Entity:** Chemically or physically combined constituent parts
- **Co-packaged:** Constituent parts packaged together

- **Cross-labeled:** Packaged separately, but labeled and intended to be used specifically with one another to achieve the intended therapeutic effect

Postmarketing Safety Reporting (PMSR)



- Codified in 21 CFR Part 4, Subpart B
- Combination product applicants have **application-based reporting requirements** and **constituent part-based reporting requirements** (most common)
- Constituent part applicants (e.g., cross-labeled) have **application-based reporting requirements** only

PMSR Requirements

Appl-based Reporting Reqs	NDA, ANDA, BLA (includes device const. part)	BLA or device application* (includes drug const. part)	NDA or device application* (includes biological product const. part)
Const. Part-based Reporting Reqs [in addition to appl-based reporting reqs]	5-day (remedial action) reports (21 CFR 803.3, .53, .56)**	Field alert reports (FARs) (21 CFR 314.81)	Biological product deviation reports (BPDRs) (21 CFR 600.14, .171)
	Malfunction reports (21 CFR 803.50, .56)**	15-day (serious unexpected adverse event) reports (21 CFR 314.80) (with 30-day deadline if marketed under a device application)	15-day (serious unexpected adverse event) reports (21 CFR 600.80) (with 30-day deadline if marketed under a device application)
	Correction or removal reports and records (21 CFR 806.10, 806.20)		

*Device applications = PMA, 510(k), de novo, PDP, HDE (see 21 CFR 4.101)

**Must address 5-day and malfunction reports in periodic reports (21 CFR 314.80, 600.80)

How and Where to Submit ICSRs

- Lead Center procedural requirements apply for Individual Case Safety Reports (ICSRs) (e.g., CDER-led submitted to FAERS)
- Streamlining is available: Multiple ICSRs (e.g., Fifteen day and Malfunction submitted in one report), submitted by the shortest deadline

Constituent Part Information

Include constituent part information in ICSRs, regardless of whether the constituent part was implicated in the event

Examples of Fields

FAERS Device Constituent	eMDR Drug/Biologic Constituent
CP identifier Yes/No Procode Device brand name Device common name Device problem code Malfunction Yes/No	CP Identifier Yes/No Drug/Biologic product name Drug/Biologic dose Drug/Biologic route

Resources

- Combination Products (FDA)
- Postmarketing Safety Reporting for Combination Products
- 21 CFR 4, Subpart B. Postmarketing Safety Reporting for Combination Products
- Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff
- Links to Technical Information on Reporting Systems (FAERS, eMDR, VAERS)
- Device Product Codes (procodes) for Device Constituent Parts of ANDA/NDA/BLA Combination Products
- Coding Resources for Medical Device Reports
- International Medical Device Regulators Forum (IMDRF)
- Contact Office of Combination Products: Combination@fda.gov

Summary

- Is your product a combination product?
- What PMSR requirements apply to your product and where should reports be submitted?
- What constituent part information should be included in reports for your product?

Combination@fda.gov

Questions?

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FDA Adverse Event Reporting System (FAERS) Updates

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February 13, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

Overview

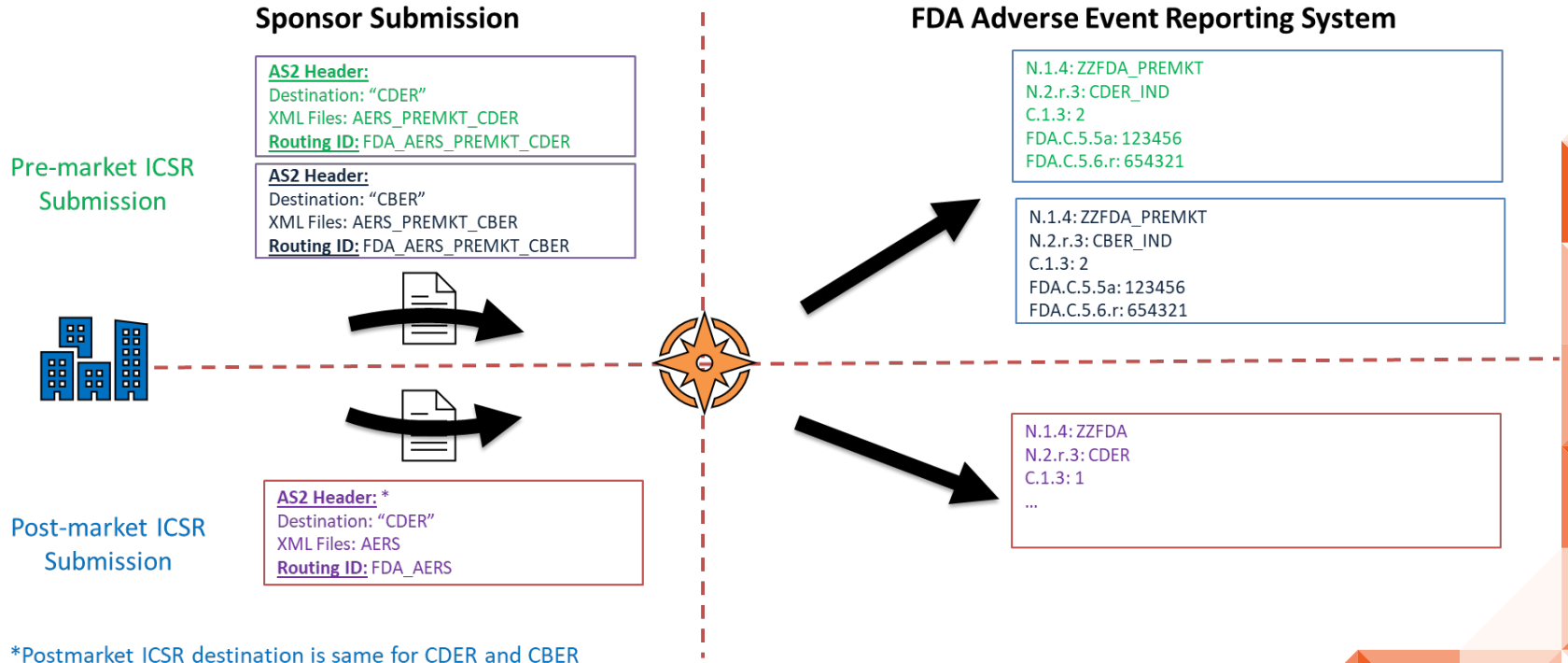
- Recognize that FDA will require reporting of premarket and postmarket safety reports in the ICH E2B(R3) format to FAERS
- Communicate implementation status, timelines and readiness
- FAERS case processing and analytics modules now accommodates product quality defect and complain reports

Recognize reporting in E2B(R3) format

- Implement electronic submission for both premarket and postmarket safety report using ICH E2B(R3) data standard
- Separate Submission Path and Business Rules for permarket and postmarket safety reports
- All Technical Specification documents posted on FAERS Electronic Submission* web page
- All communication via FAERS Electronic Submission* web page on FDA.gov

*https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions

Approach to Triage ICSRs via ESG



*Postmarket ICSR destination is same for CDER and CBER (excluding vaccine)

Separate Submission Path

- Section N.1: Transmission Identification
  - Batch Receiver Identifier (N.1.4) and Message Receiver Identifier (N.2.r.3)

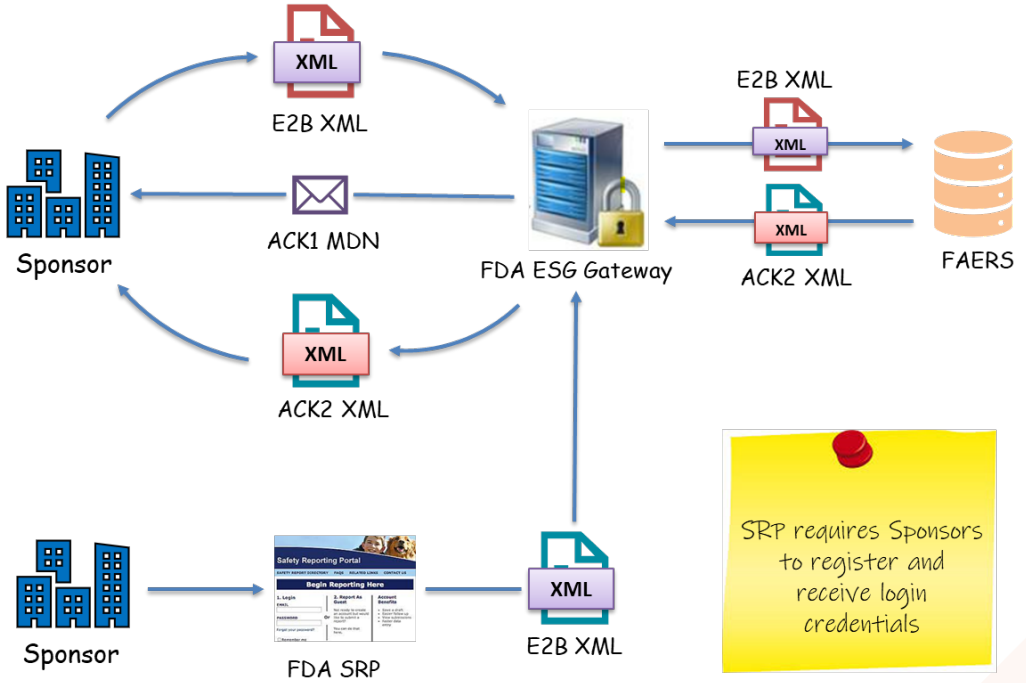
		AS2 Header	Routing ID	N.1.4 Value	N.2.r.3 Value
Premarket	CDER IND ICSR	Destination: “CDER” XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND
	CBER IND ICSR	Destination: “CBER” XML Files: AERS_PREMKT_CBER	XML Files: FDA_AERS_PREMKT_CBER	ZZFDA_PREMKT	CBER_IND
	CDER IND-exempt BA/BE ICSR	Destination: “CDER” XML Files: AERS_PREMKT_CDER	XML Files: FDA_AERS_PREMKT_CDER	ZZFDA_PREMKT	CDER_IND_EXEMPT_BA_BE
Postmarket	Postmarket ICSR	Destination: “CDER” XML Files: AERS	XML Files: FDA_AERS	ZZFDA	CDER

Submission Methods

Option A:
via Database-to-Database Transmission

OR

Option B:
via Safety Reporting Portal (SRP)



Safety Reporting Portal (SRP)

- **SRP Intended for**
  - Sponsors and CROs without infrastructure for direct ESG (gateway-to-gateway) submission
  - Individual reports only; no batch reporting via SRP
  - Can be used for both commercial and research INDs safety reporting
  - Not available for vaccine reporting
- **If CRO**
  - Separate account needed for each sponsor/license holder

Safety Reporting Portal (SRP)

- **Post-market and premarket reporting**
  - Maintained separately—select up front, can navigate between them
  - Complete an on-line form
  - Do not upload E2B R3 XML via SRP
  - Emails acknowledgement on submission – keep for records
- **“Free” (no added cost to use)**
- **Availability**
  - Both SRP and E2B R3 for premarket submission available at the same time
  - No additional action required by existing SRP users for postmarket reporting
- Contact FAERSESUB@fda.hhs.gov to request an SRP account

E2B (R3) FDA Implementation Package

Filename: FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products.pdf (August 2022)

Content:

- Purpose of this technical specifications document is to assist submitters transmitting electronic ICSRs with attachments to the (FAERS) database
- Describes FDA's technical approach for submitting ICSRs, for incorporating its regionally controlled terminology, and for implementing regional extensions that are not in ICH ICSR IG

Filename: FDA E2B(R3) Core and Regional Data Elements and Business Rules – Version 1.6.xlsx (January 2024)

Content:

- Provides a comprehensive list of core ICH and FDA regional data elements, data element attributes, conformance, business rules, XPaths and acknowledgement attributes
- Some of the regional data elements in this document are detailed in the FDA Regional Implementation Technical Specification for E2B(R3)
- Revision History describes all the updates

E2B (R3) FDA Implementation Package

Filename: FDA E2B(R3) Forward Compatible Rules.xlsx (April 2022)

Content:
- Assist reporters and recipients in implementing systems with special focus on the recommended rules for conversion of data from regional E2B R2 and regional E2B R3
- Applicable to postmarket safety reporting

Filename: FDA ICSR XML Instances.zip (September 2023)

Content:
- This document lists the scenarios provided as FDA ICSR XML Instance and acknowledgement examples based on FDA ICH E2B(R3) Technical Specifications Document
- The zip file has a Read Me.txt file describing the different scenarios

IND Safety Reports – Current and New Process

- Sponsors of clinical trials are required to submit IND safety reports as per 21 CFR 312.32

Current Process **PDFs in eCTD format**	**New Process** **ICH E2B XML files to FAERS**
▪ Inefficient and labor-intensive review ▪ Does not allow use of data visualization and analytics tools for review ▪ Lack of universal tracking system	▪ Allows for use of visualization and analytics tools for review and tracking ▪ In addition: • Leverages existing processes in use for postmarket safety reporting (ICH E2B data standards & FDA gateway) • Complies with existing federal regulations 21 CFR 312.32.(c)(1)(v)

Submission for Different Types of IND Safety Reports

- Not all IND safety reports will go to FAERS

Type of IND safety report	Submit to FAERS	Submit in eCTD format
A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (21 CFR 312.32(c)(1)(i)(A)	X	
One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug 21 CFR 312.32(c)(1)(i)(B)	X	
An aggregate analysis of specific events observed in a clinical trial (known consequences of the underlying disease or condition) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. (21 CFR 312.32(c)(1)(i)(C)	X	
Findings from other studies (21 CFR 312.32(c)(1)(ii))		X
Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))		X
Increased rate of occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv))		X

How will the new process benefit the Sponsors?

- No need to submit 1571 or cover letter for IND safety reports
- No separate submission for cross-reported IND
- Immediate acknowledgement of your ICSR submission
- Additional Benefits
  - Submit ICSR directly from your safety database
  - Eliminates need to send ICSRs to your Regulatory Affairs

IND-exempt BA/BE Safety Reporting

Options for submission:

1. Currently MedWatch form 3500A email to OGD-PremarketSafetyReports@fda.hhs.gov.

2. Once FAERS II enhancement for premarket is available:
   - E2B format is an acceptable form of notification to the FDA for an SAE(s) **required** under 21 CFR 320.31(d)(3).

   - Options for submitting IND-exempt BA/BE Safety Reports as ICSRs in E2B(R3) format
     - Electronic Submission Gateway (D2D Transmission)
     - Safety Reporting Portal

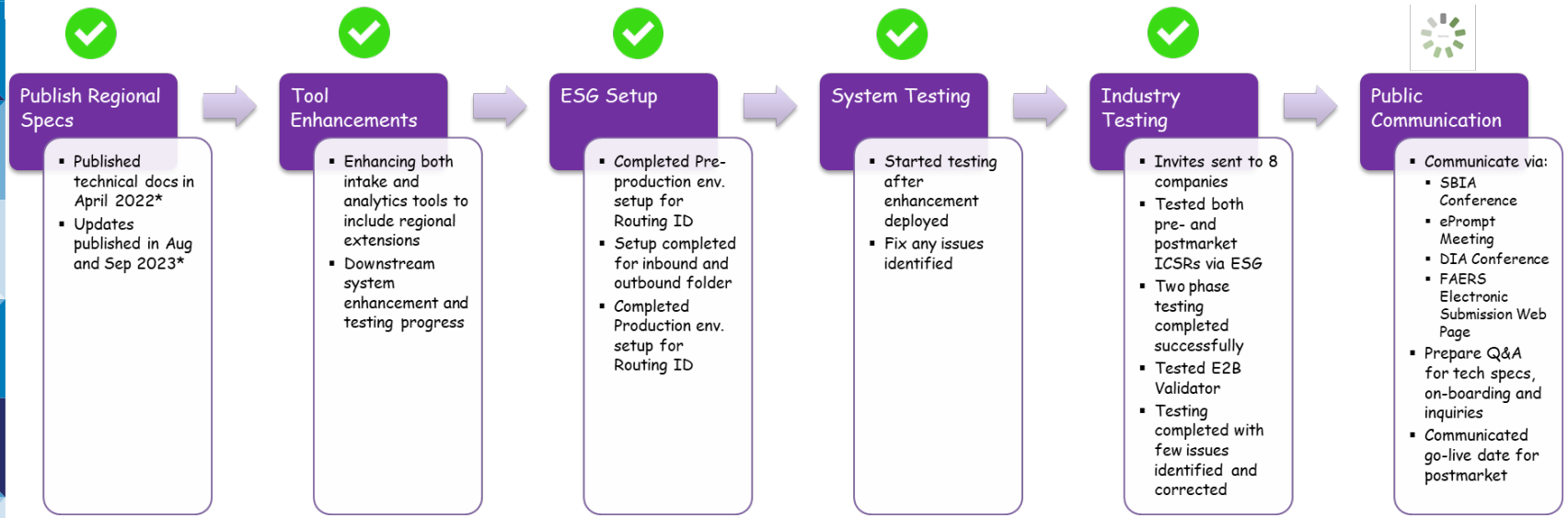
Voluntary Electronic Submission of IND-exempt BA/BE Safety Reports

- **Prepare IT system**
  - FAERS will accept **premarket ICSRs in E2B(R3) format.**
  - Learn the **specifications for preparing and submitting electronic submission** of ICSRs.
  - Need an ESG account to submit ICSRs electronically in E2B(R3) format.
  - Notify the FAERS electronic submission coordinator at faersesub@fda.hhs.gov to create an account, if submitting via SRP.

- **Obtain pre-assigned ANDA number ('Pre-ANDA')**[6,7]
  - Request using CDER NextGen Portal prior to:
    - Submitting an SAE(s) from the BA/BE study **or**
    - Starting subject recruitment for the BA/BE study

[6] Requesting a Pre-Assigned Application number (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number).
[7] CDER NextGen Portal (https://cdernextgenportal.fda.gov/Login_CDER?ec=302&startURL=%2Fs%2F).

Implementation Plan and Progress



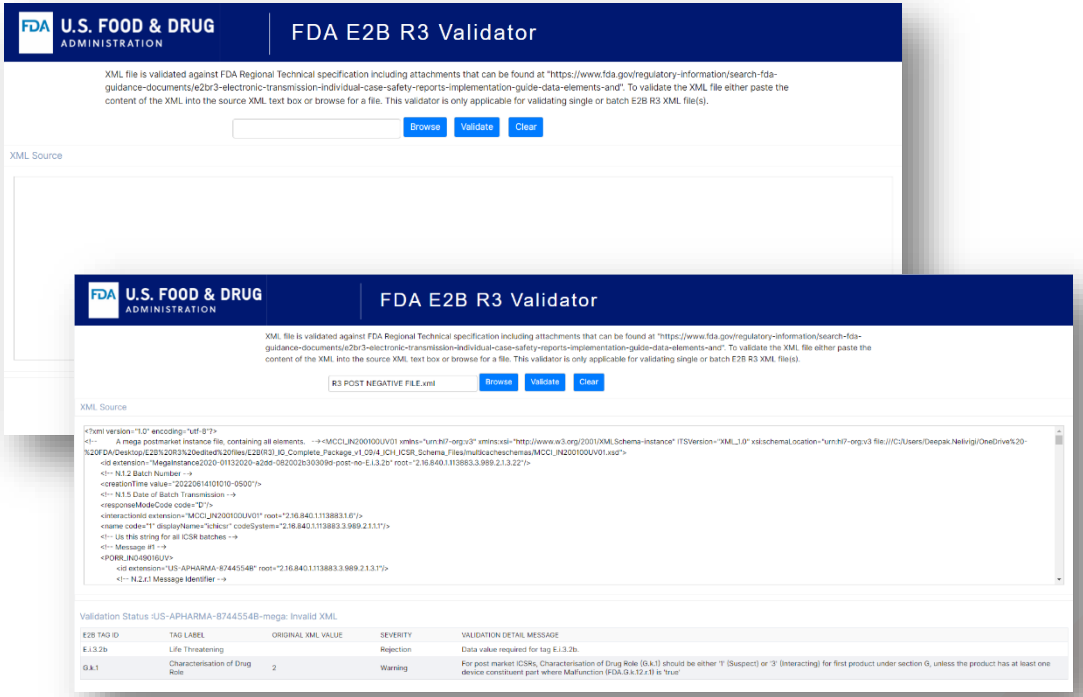
*FDA Adverse Event Reporting System (FAERS) Electronic Submissions | FDA

Completed In Progress

Sponsors should continue to submit premarket ICSRs in the eCTD format until FAERS is ready to accept E2B(R3). Starting Jan 16, 2024, FAERS started accepting postmarket safety reports in E2B(R3) format.

Mechanism to validate E2B(R3) XML files

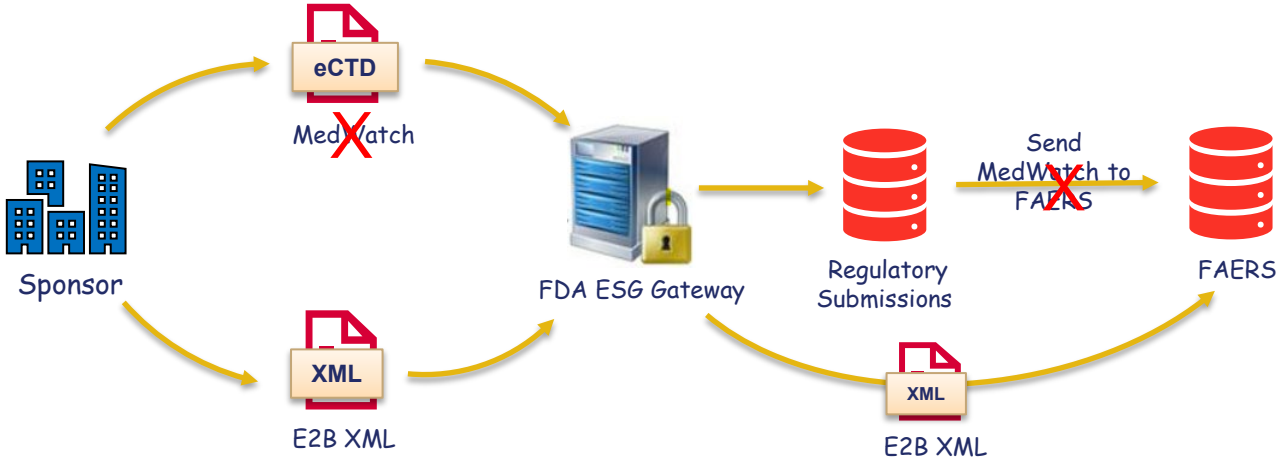
- FDA has provided the FDA E2B(R3) Validator* tool to facilitate validation of the E2B(R3) XML files generated from your safety database
- This validator has a web-based interface that enables submitter to select a E2B(R3) XML file and validate
- The validation status and results are displayed to the user



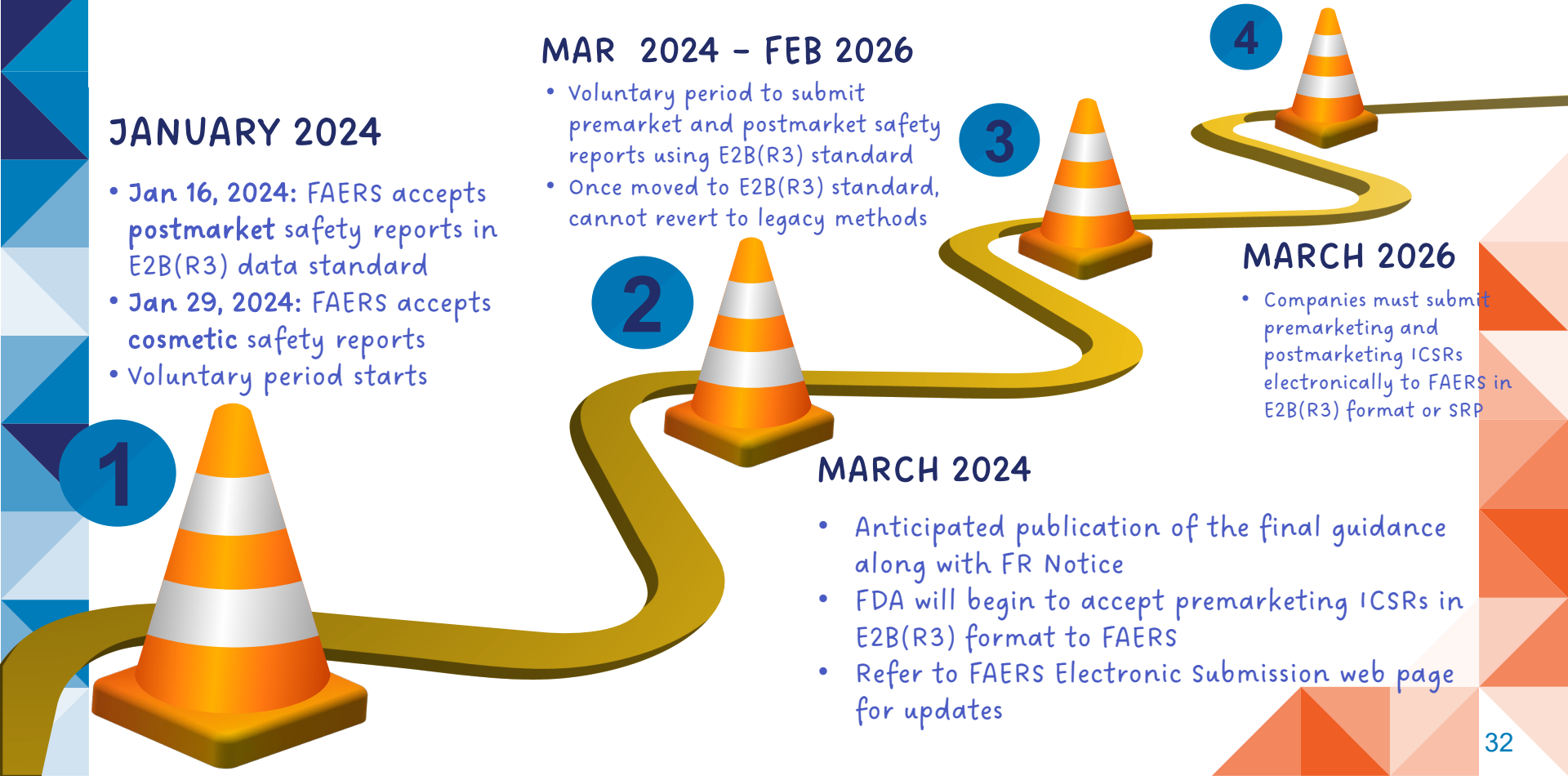
*https://faers2-validator.preprod.fda.gov/LSMV/Validator

E2B R3 Implementation Plan

- Data Submission Changes for IND safety reports



Proposed Implementation Timelines



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JANUARY 2024

- **Jan 16, 2024:** FAERS accepts **postmarket** safety reports in E2B(R3) data standard
- **Jan 29, 2024:** FAERS accepts **cosmetic** safety reports
- Voluntary period starts

2

MAR 2024 – FEB 2026

- Voluntary period to submit premarket and postmarket safety reports using E2B(R3) standard
- Once moved to E2B(R3) standard, cannot revert to legacy methods

3

MARCH 2024

- Anticipated publication of the final guidance along with FR Notice
- FDA will begin to accept premarketing ICSRs in E2B(R3) format to FAERS
- Refer to FAERS Electronic Submission web page for updates

4

MARCH 2026

- Companies must submit premarketing and postmarketing ICSRs electronically to FAERS in E2B(R3) format or SRP

FDA's Approach in Harmonize Surveillance for Safety and Quality Data

- Harmonized surveillance process for drugs and biologics “safety” and “quality” data with an “integrated database approach”
- Apply FAERS centralized coding process, validation, preparing the readiness to perform routine screening, review, and decision making in a structural form
- Maintaining the system of the records in one eco-system

Harmonize Surveillance for Safety and Quality Data

- Enhanced both case processing and analytics modules to accommodate Product quality defect and complaint reports for Office of Pharmaceutical Quality (OPQ).
  - Included end-to-end data processing of Biologic Product Deviation Report (BPDR), Field Alert Report (FARs), and MedWatch reports
- Aligned the Central Triage Unit (CTU) operation and OPQ personnel to process product quality defect and complaint reports along with adverse event reports using FAERS.

Harmonize Surveillance for Safety and Quality Data

- The analytics module now enables reviewers from both the safety and quality office to review a single source of truth
- The result turns to a significant gain in efficiencies and effectiveness in safety and quality reviews at FDA for both pre-market and post-market operations.
- By maintaining data integrity for new data and critical legacy data is determined to be appropriated for migrating to FAERS eco-system.

References

Document / Web Page	Accessible At
FDA Adverse Event Reporting System (FAERS) Electronic Submissions –Web page	https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions
FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products (Aug 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug
FDA E2B(R3) Core and Regional Data Elements and Business Rules v1.6 (Jan 2024)	https://www.fda.gov/media/157982/download
FDA E2B(R3) Forward Compatible Rules (Apr 2022)	https://www.fda.gov/media/157993/download
FDA ICSR XML Instances (Sep 2023)	https://www.fda.gov/media/157983/download
Electronic Submission of IND Safety Reports - Technical Conformance Guide (Apr 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide
Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry (Aug 2022)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-expedited-safety-reports-ind-exempt-babe-studies-guidance-industry

Summary

- Recognize FDA requiring submission of safety reports electronically
- Understand the submission methods and mechanisms of different report types
- Communicated implementation status, timelines and readiness
- Acknowledge FDA's approach in harmonize surveillance for safety and quality data

Questions?

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Regulatory Science Staff, Office of Surveillance and Epidemiology
CDER | US FDA

Closing Thought

FDA started accepting postmarket safety reports using ICH E2B(R3) data standards and will soon start accepting premarket safety repots electronically using ICH E2B(R3) data standards.

MHRA Update

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MHRA

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February 15, 2024

Medicines & Healthcare products Regulatory Agency

Health Canada Santé Canada

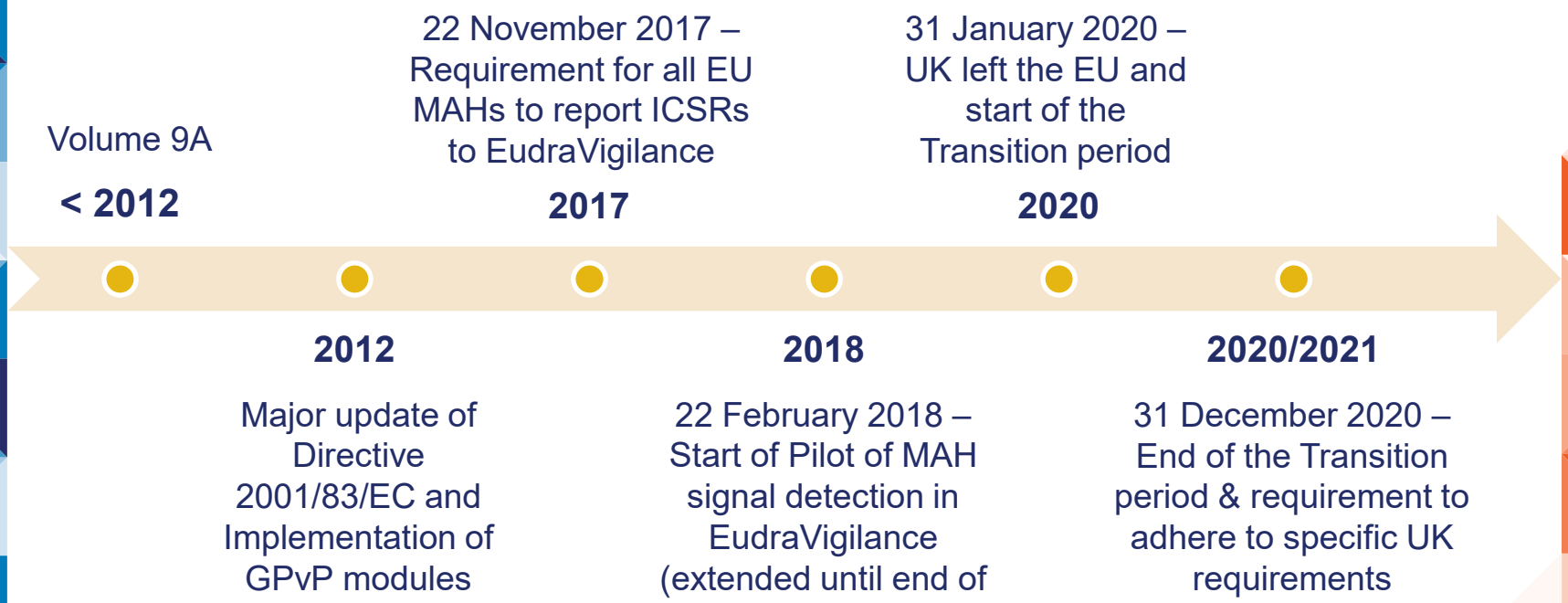
Agenda

History of UK regulation

MHRA Inspection Programme

Future Look

Major changes to PV requirements in UK



Pharmacovigilance Legislation

EU centrally authorised products

Regulation (EC) No 726/2004, Chapter 3

Directive 2001/83/EC, Title IX

Commission Implementing Regulation (EU) No 520/2012

UK nationally authorised products

The Human Medicines Regulations 2012, as amended, Part 11

Products in respect of NI

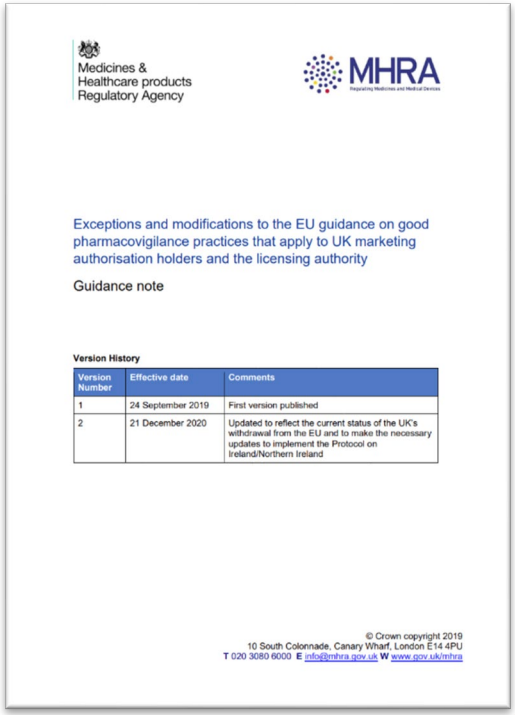
Commission Implementing Regulation (EU) No 520/2012

Products in respect of GB only

Schedule 12A of the Human Medicines Regulations 2012, as amended

Good pharmacovigilance practices

- Directive 2001/83/EC Article 108a requires the European Medicines Agency (EMA) to develop guidance on good pharmacovigilance practices (GVP). This guidance is therefore termed “statutory guidance”.
- GVP are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU.
- GVP apply to marketing authorisation holders, the EMA and medicines regulatory authorities in EU/EEA Member States.



Medicines & Healthcare products Regulatory Agency

MHRA

Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK marketing authorisation holders and the licensing authority

Guidance note

Version History

Version Number	Effective date	Comments
1	24 September 2019	First version published
2	21 December 2020	Updated to reflect the current status of the UK's withdrawal from the EU and to make the necessary updates to implement the Protocol on Ireland/Northern Ireland

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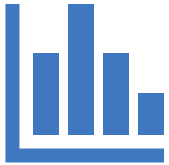
The Windsor Framework

Medicines provisions outlined in the Windsor Framework are expected to come into effect on 01 January 2025.

The implementation of the Windsor Framework will mean that the EU legislation relating to **new and innovative medicines**, will no longer apply to Northern Ireland and they will be governed by UK law.

Agenda



History of UK regulation

MHRA Inspection Programme

Future Look

Legal basis of MHRA GPvP inspections

UK SI 2012 No 1916: Regulation 327

(1) An inspector may inspect anything mentioned in paragraph (2)--

(a) in order to determine whether there has been a contravention of any provision of these Regulations which the enforcement authority must or may enforce by virtue of regulations 323 and 324; […]

(2) The things mentioned in paragraph (1) are--

(g) information and documents relating to the safety of medicinal products or active substances, including information and documents relating to compliance with--

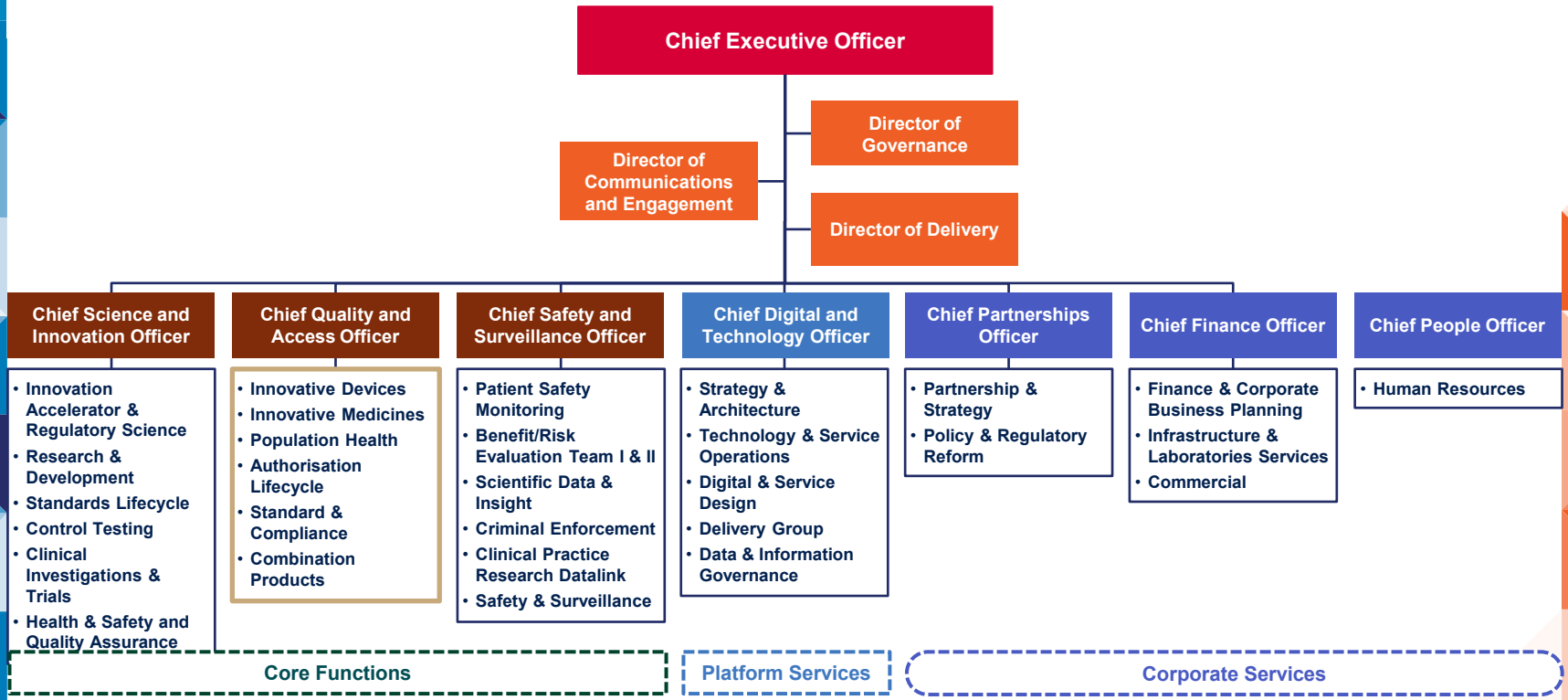
(i) conditions imposed under any of regulations 59, 60, 61 or 105,

(ii) the requirements of Part 11 (pharmacovigilance) or Schedule 12A,

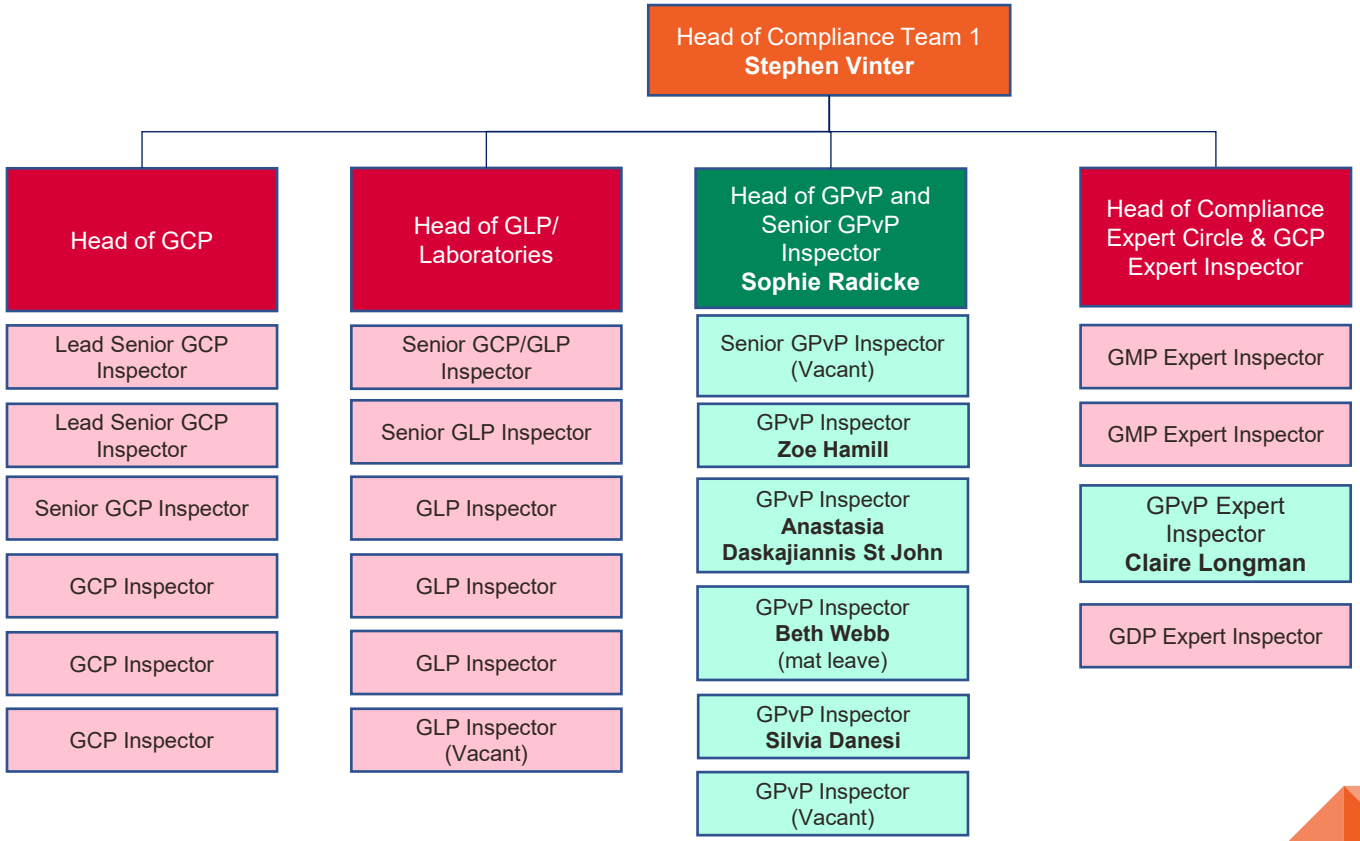
(iii) the requirements of Regulation 726/2004 and the Implementing Regulation, and

(iv) obligations under regulations 75 (obligation to provide information relating to safety) and 76 (obligation in relation to product information).

Our corporate structure



Compliance Team 1



MHRA Pharmacovigilance inspection programme

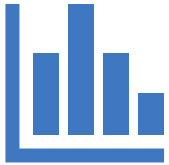
RISK

- Product
- MAH / Applicant
- PV System
- Compliance history

Inspections conducted under one of the four inspection arms:

- Routine pharmacovigilance activities
- Routine risk management and safety communication
- Additional risk minimisation measures (aRMMs)
- Non-interventional post authorisation safety studies (NI-PASS)

Agenda



History of UK regulation

MHRA Inspection Programme

Future Look

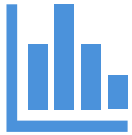
Regulatory updates:

International Recognition Procedure	• Came into effect 01 January 2024
The Early Access to medicines Scheme (EAMS)	• Statutory instrument laid in 2022
Point of Care	• Introduction of an innovative regulatory framework.
Windsor Framework	• To be implemented for medicines on 01 January 2025

Summary

- Current UK PV requirements
- Resource increased
- Risk based inspection model
- Legislative updates

Tools to promote compliance and education



Published inspection metrics

https://www.gov.uk/government/statistics/pharmacovigilance-inspection-metrics-2009-to-present

MHRA Inspectorate blog

https://mhrainspectorate.blog.gov.uk

Symposia, Conference & Stakeholder Engagement

Next Symposium 28th Feb 2024

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