Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards

Meeting II of III

JULY 17, 2019

Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards

July 17, 2019

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Deputy Director
Regulatory Science Staff/OSE/CDER/FDA

Session 1: Synopsys from Meeting I

SUMMARY AND TIMELINE

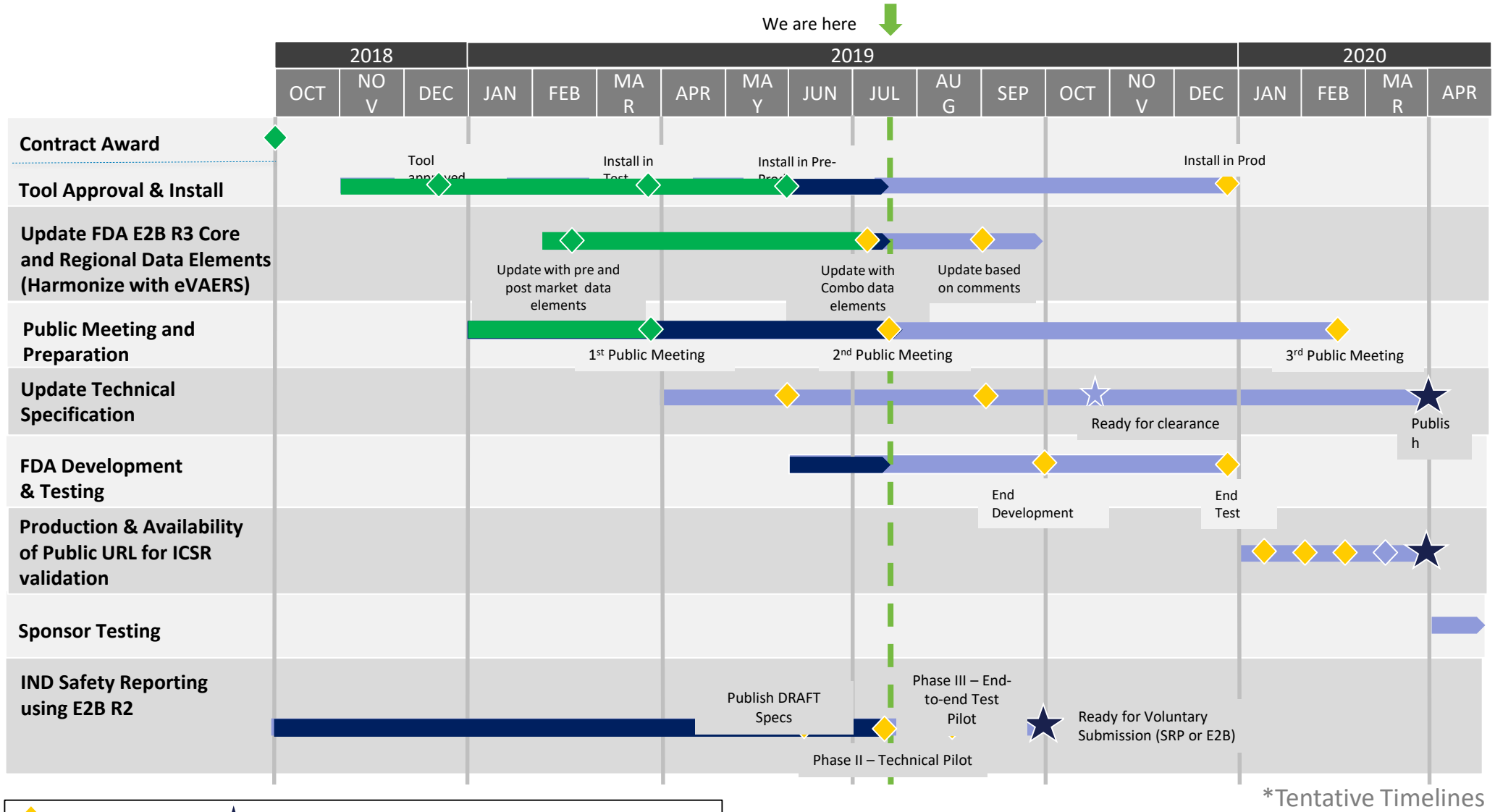
Meeting I Summary

- Session 1: FAERS II and E2B R3 Up Versioning Plans
  - Communicated FDA's plans on FAERS II and E2B R3 up versioning
  - FDA's current planned E2B R3 production date is March 2020
  - Currently no compliance timelines have set for E2B R3 by FDA
  - Discussed Testing Plan and Method
- Session 2: Electronic submission of IND safety reporting
  - Introduction to IND safety reporting to FAERS at the FDA
  - Provided information on the implementation plans, regional requirements using E2B R2 & R3, and use case examples
  - Discussed the regional data elements in R2 and R3 for IND safety reporting and IDMP
- Session 3: Electronic submission of Post-market safety reporting
  - Discussed the regional data elements in R3 for Post-market safety reporting
- Session 4: Updates on electronic submission routing mechanisms
  - Electronic submission routing mechanisms for pre-market and post-market
  - Mechanisms for industry to validate E2B R3 regional files

Next Steps after Meeting I

- Presentation posted on FDA meeting page
- No comments received via the docket since Meeting I
- Update schema with regional elements
- Prepare for the next meeting on July 17, 2019
  - Discuss data elements related to combination product and pre-market
- Contact: eprompt@fda.hhs.gov after the docket timeframe

FAERS II - E2B R3 Roadmap*



*Tentative Timelines

Session 2: E2B R3 Regional Requirements for Premarket Safety Reporting

REGIONAL DATA ELEMENTS

Regional Requirement

Section N.1: ICH ICSR Transmission Identification (batch wrapper)

a. N.1.4: Batch Receiver Identifier

- Identify premarket or postmarket report
- Used on the acknowledgement message
- For Premarket
  - Production: ZZFDA_PREMKT; Test: ZZFDATST_PREMKT
- For Postmarket
  - Production: ZZFDA; Test: ZZFDATST

Section N.2.R: ICH ICSR Message Header (message wrapper) (Repeat as necessary)

a. N.2.r.3: Message Receiver Identifier

- Identify the Center where the premarket has to be routed
- Can have one of the two values: CDER_PREMKT or CBER_PREMKT

Regional Requirement

ACK.B: ICH ICSR Message Acknowledgement

a. ACK.B.r.4: ICSR Message ACK Sender

- For Pre-market
  - Production: ZZFDA_PREMKT
  - Test: ZZFDATST_PREMKT
- Post-market
  - Production: ZZFDA
  - Test: ZZFDATST

Regional Requirement

Section C: Identification of the Case Safety Report

a. FDA.C.1.7.1: FDA Report Type

- Identifies the type of reports FDA classifies based on the reporting timelines
- Data length and Type: 1N
- Conformance: Mandatory
- Allowed Values
- New OID

Post-Market		IND		Combo	
CONFORMANCE	FAERS Business Rule	CONFORMANCE	IND Business Rule	CONFORMANCE	Combo Business Rule
Mandatory	1=15-Day 2=Periodic	Mandatory	1=15-Day 6=7-Day	Mandatory	1=15-Day 2=Periodic 4=5-Day 5=30-Day

Section C.2.r: Primary Source(s) of Information (repeat as necessary)

a. FDA.C.2.r.2.8: Reporter's Email

- Email address of the reporter
- Data length and Type: 100 AN
- Conformance: Optional
- Allowed Values: Free Text

Regional Requirement

Section C.5: Study Identification

a. FDA.C.5.5: IND or PANDA Number where AE Occurred

- Application number where the AE Occurred
- Supports routing of reports the reviewer
- Data Type: 15 AN
- Conformance: Mandatory only for Study report
- Business Rule: The format must be "123456" for IND or BA/BE safety report

b. FDA.C.5.r.6: IND number for other INDs with same suspect product

- Identifies the other application number with same suspect products
- Data Type: 15 AN
- Conformance: Mandatory only for Study report
- Business Rule: The format must be "123456" for IND safety report. Use nullFlavor=NA if there are no other INDs with same suspect product

Regional Requirement

Section D: Patient Characteristics

a. D.1: Patient (name or initials)

- Conformance: Conditional-Mandatory
- Business Rule: For Aggregate Report, the element value must be “AGGREGATE”

BREAK

Session 3: Generic Drugs – BA/BE trials safety reporting

Karen B. Feibus, MD
Acting Director
Clinical Safety Surveillance Staff
OGD/CDER/FDA

Topics

- Brief overview of generic drug pharmacovigilance
- Bioavailability/Bioequivalence (BA/BE) Trials and Safety Reporting Requirements
- Current process for receipt, tracking, and review of expedited reports from BA/BE studies for generic drugs
- Opportunities offered by electronic submission of expedited reports from BA/BE studies for generic drugs
- Important steps that will make electronic submission work

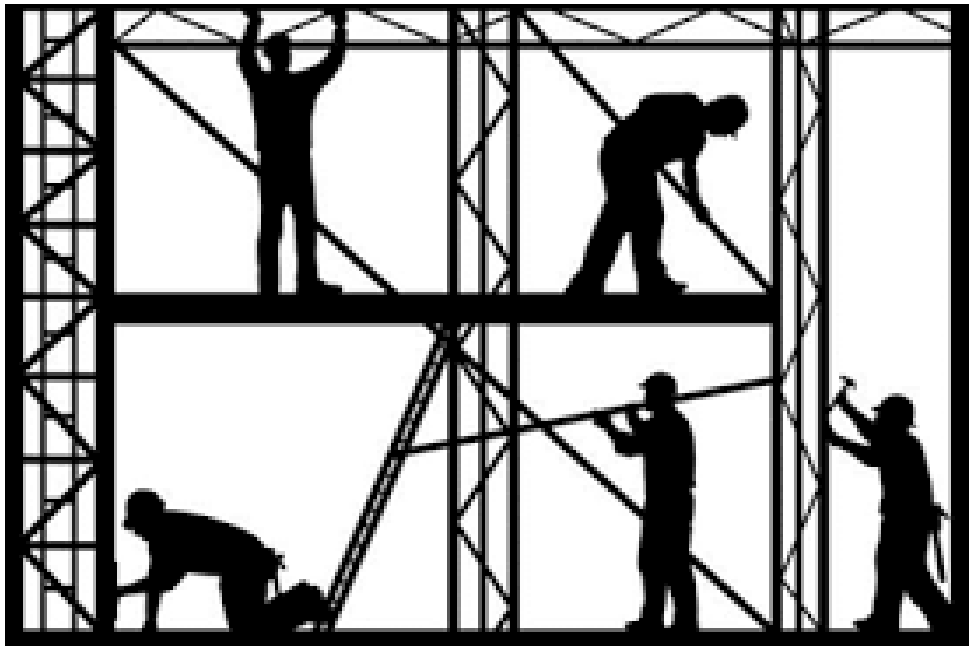
Generic Drug Pharmacovigilance – a Complex Process

Multiple CDER Offices:

- Office of Generic Drugs (OGD)
- Office of Surveillance and Epidemiology (OSE)
- Office of New Drugs (OND)
- Office of Pharmaceutical Quality (OPQ)

3 Time Periods

- Pre-ANDA
- ANDA review
- Post-approval



Multiple OGD Sub-offices

- Immediate Office
- Office of Bioequivalence
- Office of Research & Standards
- OGD Policy
- Office of Regulatory Operations/Division of Labeling

Foundation of "Sameness" to Brand

New Drug vs. Generic Drug Pharmacovigilance (PV)

NEW DRUG

Investigational New Drug (IND)

Define dose range/safety in healthy volunteers	Define therapeutic doses & evaluate safety/efficacy in patients

New Drug Application Review

Study data sufficient for NDA? Safety concerns? Benefit/Risk?	Develop prescribing information, Med Guide

Post-Approval

Monitor AE reporting for emerging safety signals related to active ingredient	Generics enter market. Monitor for emerging signals

GENERIC DRUG

Pre-Abbreviated NDA (ANDA)

Brand chosen. Formulation developed/tested	Product Specific Guidance guides bioequivalence (BE) study protocol

ANDA Review

Chemistry/BE reviews drive need for pharm tox/clinical consult	Potential safety concerns based on formulation/ features/BE data?

Post-Approval

Are generic drug AE profiles same as brand?	Evidence that a generic is not clinically substitutable?

AE = adverse event

Current Generic Drug Adverse Event (AE) Receipt, Review, Tracking

Post-market

- AEs submitted by drug companies electronically since 10 Jun 2015 via:
  - Database-to-Database Transmission (E2B) or
  - Safety Reporting Portal
- Archived in the FDA Adverse Event Reporting System (FAERS)
- OGD Clinical Safety Surveillance Staff access, review, and analyze through FAERS or Drug Quality Reporting System (DQRS)

Pre-market

- SAE sent by drug company or CRO to the OGD Pre-market email box
  - PDF of FDA form 3500A
  - PDF attachments (e.g., cover letter, protocol summary)
- Manually entered in project tracking system
- Follow-up reports manually linked to original
- When ANDA submitted, pre-market SAE reviews can't be linked to ANDA

SAE = serious adverse event; CRO = contract research organization

TODAY'S FOCUS:

Reporting Requirements for Serious Adverse Events from BA/BE Trials for Generic Drugs

...and opportunities for electronic submission

Generic Drugs & Pre-market AE Reporting

- Two Scenarios:
  - BA/BE Studies conducted **under IND**
    - Radioactively labeled drugs [21 CFR 320.31(a)(2)]
    - Cytotoxic drugs [21 CFR 320.31(a)(3)]
  - BA/BE Studies **NOT** conducted under IND
    - All other drugs not exempt from in vivo demonstration of bioequivalence

BE Study Reporting Requirements

Study conducted under IND

- Must meet safety reporting requirements described under 21 CFR 312.32
  - Submit an IND safety report for an event that meets 3 criteria: (1) it is serious, (2) it is unexpected (i.e., not listed in the investigator's brochure or reference safety information), and (3) there is **evidence to suggest a causal relationship** between the drug and the adverse event (i.e., it is a suspected adverse reaction)
- Includes individual case reporting and aggregate reporting

Study conducted without IND

- Meets conditions for IND exemption under 21 CFR 320.31
- Must meet expedited safety reporting requirements described under 21 CFR 320.31(d)(3):
  - The person conducting an IND exempt BA or BE study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event observed during conduct of the study, **regardless of whether the event is considered drug related**, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence.

Changing IND Reporting Requirements

(as presented at March public meeting)

- Required change in format of submitted Individual Case Safety Reports (ICSRs) under 745A(a) of the FD&C Act
  - December 2015: **Draft** Guidance for Industry: Safety Assessment for IND Safety
  - 24 months after **Final** Guidance publishes, sponsors of commercial INDs must submit specified IND safety reports to FAERS by one of two methods:
    - Electronic Submissions Gateway (Database-to-Database Transmission)
    - Safety Reporting Portal (SRP)
- **Goal:** Begin voluntary submissions in October 2019 – date to be published on FAERS website 30 days prior to launch

Safety Reporting for BA/BE Study Conducted without IND

- Regulatory requirement to submit 7- and 15-day expedited reports of adverse event from studies conducted in the United States
  - No regulatory requirement for electronic submission of adverse event reports
- For BA/BE studies conducted outside United States, no regulatory requirement for submission of adverse event reports prior to ANDA submission
- Current premarket process:
  - PDF version of FDA form 3500A submitted to OGD Pre-market mailbox
  - Manual processes used to track submitted adverse event reports and link initial and follow-up reports

Voluntary Electronic Submission of Non-IND BA/BE Study Safety Reports

Why do it?

- One submission method for all required generic drug safety reporting:
  - BA/BE studies conducted under IND
  - BA/BE studies conducted without IND
  - Post-market adverse event reporting
- All pre-market adverse event reports remain in a non-public space.
  - FAERS will use specific data fields to identify pre-market reports and sequester them from post-market reports that are summarized and included in the public portal.
- Automated confirmation of receipt.
  - Documentation that expedited reporting requirements were met on time.

Voluntary Electronic Submission of Non-IND BA/BE Study Safety Reports

How will it work?

- Request a pre-assigned ANDA number at: https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm114027.htm
  - Before submitting a serious adverse event from the BA/BE study or
  - Before starting subject recruitment for the BA/BE study
- Identify the serious adverse event submission using the following identifiers:
  - PANDA 123456 (123456 = your unique ANDA number)
  - Submit via E2B or SRP

Benefits to Pre-market Generic Drug Pharmacovigilance

- If pre-market safety reports submitted with a pre-submission ANDA (PANDA) number,
  - Initial and follow-up submissions for the same event can be linked in the Office of Generic Drug's work flow management and archival system
  - Reviews of serious adverse events prior to ANDA submission linked to ANDA
    - ANDA review team members can access this information quickly during their reviews
- Electronic submission supports:
  - Reducing errors and improving amount of information provided about events
  - Subject safety monitoring

A brief word about...

Post-Market Generic Drug Pharmacovigilance Enhancements

Enhancements of Generic Drug Surveillance: #1

MedWatch Form Updates

- Past improvements:
  - Increased prominence and clarity of manufacturer fields
    - Better identification of critical information
    - Steady decrease in the number of “no firm” MedWatch reports
- Future improvements:
  - Pre-ANDA checkbox (Section G, Form 3500A) to
    - Allow identification of pre-ANDA status
    - Seamlessly route pre-ANDA SAEs to OGD for review
    - Enable separation of pre-market and post-market adverse event reports

Enhancement of Generic Drug Surveillance: #2

FDA Adverse Event Reporting System (FAERS II) – Enhancing Every Aspect of Generic Pharmacovigilance

- OGD's Clinical Safety Surveillance Staff is engaged in needs assessment for new system
- Improved generic drug signal detection
  - Will use data from FAERS for routine pharmacovigilance rather than DQRS (more data)
  - Automated periodic reports specific to OGD needs - i.e., manufacturer/drug
- Improved generic drug data management
  - Tracking of generic drug signals over time within the software
  - Better visualization of generic drug data and automated report templates
- Enhanced generic drug analytics

Meeting our Missions

Electronic submission of pre-market and post-market adverse event reports for generic drugs advances efforts to meet our missions:

- OGD Mission: Make high quality, affordable medicines available to the public.
- AAM Mission: Improve access to safe, quality, effective medicine.

Acknowledgements

- Howard D. Chazin, M.D.
  - Acting Deputy Director, Office of Generic Products (OGD)

- Clinical Safety Surveillance Staff
  - James Osterhout, Ph,D., Data Team Leader
  - Glenn Mannheim, M.D., Acting Clinical Team Leader
  - Linda Forsyth, M.D., Medical Officer
  - Jung Lee, R.Ph., Data Analyst
  - Edward Kim, Data Analyst
  - Debra A. Catterson, R.Ph., Drug Safety Coordinator


Thank you!

LUNCH

Session 4: E2B R3 Regional Requirements for Combo Product safety reporting

BACKGROUND

FDA Final Rule and Draft Guidance on Postmarketing Safety Reporting for Combination Products

Electronic Submission of Adverse Event Reports to FAERS using ICH E2B(R3) Standards Meeting

July 17, 2019

Melissa Burns
Senior Program Manager

Office of Combination Products
US Food and Drug Administration

Overview

- Final rule
- Draft guidance highlights
- Next steps/key dates

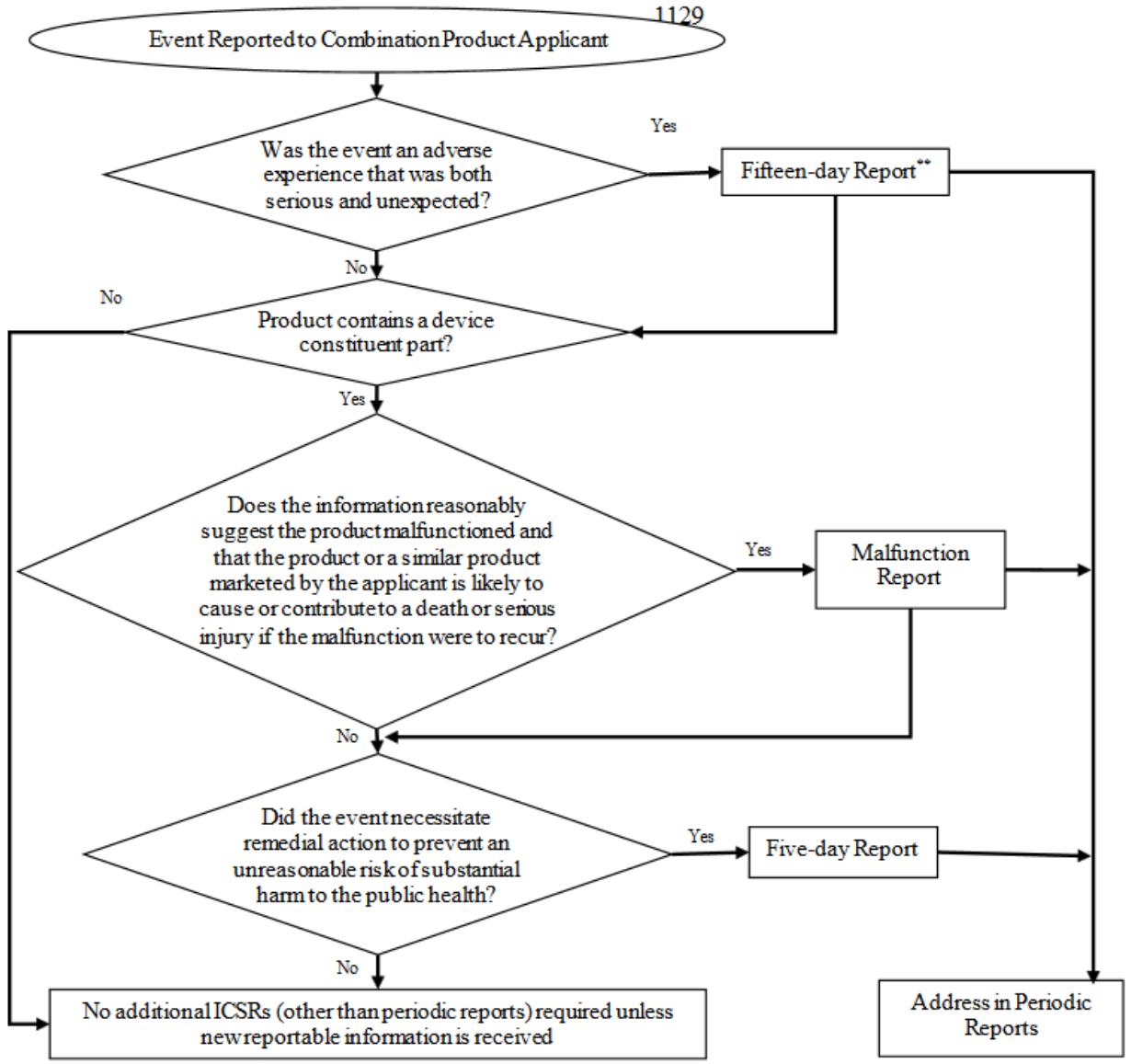
Combo Product PMSR Final Rule

- Scope: Applies to “combination product applicants” and “constituent part applicants”
- Reporting duties
  - Application-based reporting requirements (associated with application type, e.g., NDA, BLA, PMA, 510(k)) apply to “combination product applicants” and “constituent part applicants”
  - Specified, secondary “constituent part-based” reporting requirements apply to “combination product applicants”
  - Reporting duties apply to the applicant’s product
- Information-sharing requirements apply to “constituent part applicants”
  - To forward information re death, serious injury, adverse experiences
  - One-time per event
  - 5-day deadline

Constituent part-based PMSR Requirements

NDA, ANDA, BLA (if combination product includes a device constituent part)	BLA or device application* (if combination product includes a drug constituent part)	NDA or device application* (if combination product includes a biological product constituent part)
5-day (remedial action) reports (21 CFR 803.3, .53, .56)	Field alert reports (FARs) (21 CFR 341.81)	Biological product deviation reports (BPDRs) (21 CFR 600.14, .171)
Malfunction reports (21 CFR 803.50)	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)		
Other reports: - Combination product applicants marketing under an NDA, ANDA, and BLA applicants must address 5-day and malfunction reports in periodic reports (21 CFR 314.80, 600.80). - Combination product applicants marketing under a device application must provide additional reports only as required and specified in writing by FDA.		

ICSR Reporting for Combination Products Marketed Under NDA/ANDA/BLA



Combo Product PMSR Final rule, cont.

- Streamlining
  - Available for Individual case study report (ICSR) system reporting
  - Include all the information required for each report type and is submitted by the shortest deadline
- Reporting procedures:
  - ICSRs: Product's Center's procedural requirements apply for submitting reports
  - Non-ICSRs: Procedures in associated regulations/guidance
  - Technical instructions posted
- Record-keeping
  - Longest record-keeping term for either constituent part applies to combination product applicants
  - Product record-keeping requirements applies to constituent part applicants, with longest product record-keeping requirement applying for information sharing records

Highlights from Guidance – Who the Rule Applies To

- Clarification of “Constituent Part Applicant” meaning and purpose
  - You are only a constituent part applicant *if you hold an application under which a constituent part of a combination product is marketed.* Not for application holders for general use devices, for example.
  - If unsure of status, can check with OCP
  - Goal to promote information sharing among applicants who are marketing their products for combined use

Highlights from Guidance – Addressing Multiple Reporting Requirements in a Single Report/Stream

- Examples for streamlining Fifteen-day and malfunction report
  - Combined Death and serious injury and Fifteen-day report
  - Single Fifteen-day report for a drug/biological product combination product
- Use of follow-up reports to submit a different type of ICSR based on additional information received
- Address malfunction and 5-day reports in periodic reports by drug and biologic-led combination product applicants

Highlights from Guidance – What to Include in Combination Product ICSRs

- All information required for the report under applicable regulations and the following (if not already required under applicable regulations for the report type):
  - Combination Product Identifier
  - Report Type(s)
  - Patient Identifier (If no patient, enter “None”)
  - Reporter Identifier
  - Suspect Medical Device
  - Suspect Drug or Biological Product
  - Adverse Event Code (Device Application – Patient problem codes; NDA/ANDA/BLA – MedDRA)
  - Device Problem Code (If no device problem, enter “No Known Device Problem”

Highlights from Guidance – Data Fields for Electronic Reporting Systems

- Guidance presents ICSR scenarios and related information on electronic reporting
  - Data elements and how they align with eMDR and FAERS
  - Reporting Scenarios / Examples
  - Other situations – Multiple Entities (Combination Product Applicant, Constituent Part Manufacturer) and/or Multiple Lots, if available

Data Fields for Electronic Reporting Systems, cont.

- Reporting system technical specifications have been updated with combination product fields. See:
  - FDA Adverse Event Reporting System (FAERS) Electronic Submissions
  - eMDR – Electronic Medical Device Reporting
  - VAERS updates (proposed)
- FAERS and eMDR *can* accept combination product submissions now
  - Combination product applicants are encouraged to begin reporting combination product information when they are prepared to do so

Recurrent Themes in Stakeholder Comments

- Additional clarity on what information needs to be included in ICSRs and periodic reports
- What device constituent part information should be included in reports
- Reporting of foreign events - how “same or similar” applies for device constituent parts and the combination product

Next steps/Key Dates

- Compliance policy guidance delays enforcement for constituent part-based requirements and associated recordkeeping requirements until:
  - July 31, 2020, for Combination Product Applicants using the FDA Adverse Event Reporting System (FAERS) and Electronic Medical Device Reporting System (eMDR) to report ICSRs
  - January 31, 2021, for Combination Product Applicants using the Vaccine Adverse Event Reporting System (VAERS) to report ICSRs
- Working on finalizing draft guidance

Closing Remarks

- FDA is Actively Working on Final Guidance
- If you have Questions or Suggestions, CONTACT US!
  - Easier for FDA to address questions now in context of a specific fact-pattern for a given product and/or reporting issue
  - Welcome suggestions for additional information/resources for Industry stakeholders
  - Centers and OCP work collaboratively on inquiries
- PMSR materials (rule, guidance, dockets) posted on OCP webpage (https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products)

For additional information

combination@fda.gov

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www.fda.gov/CombinationProducts/default.htm

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Session 4: E2B R3 Regional Requirements for Combo Product safety reporting

REGIONAL DATA ELEMENTS

Regional Requirement

Section C.1: Identification of the Case Safety Report

a. FDA.C.1.12: Combination Product Flag

- Identifies if the ICSRs is for a combination product
- Data Type: Boolean
- Values Allowed: false, true, nullFlavor:NI
- Conformance: Mandatory
- Business Rule: YES: Indicate that the report is for a combination product. If not, then use NullFlavor

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
ICH	**G.k**	**G.k.2**	**Drug Identification**	**-**	**-**	**-**		
FDA	G.k	FDA.G.k.2.6	Expiration Date		Date/Time		Optional	UDI PI, the expiration date of a specific device
FDA	G.k	FDA.G.k.2.7	Product Available for Evaluation	1	N	1=Yes 2=No 3=Return	Optional	If product is available or was it returned. Suspect device only
FDA	G.k	FDA.G.k.2.8	Product Return Date		Date/Time		Optional	only populated if FDA.G.k.2.7 is 3 (return), Date When Product was Returned
FDA	G.k	FDA.G.k.2.9.r.1	Brand Name	80	AN	Free Text	Conditional-Mandatory	At least One of the 3 Must be Reported Brand Name or Common Device Name or Product Code for the Device Constituent Part
FDA	G.k	FDA.G.k.2.10.r.1	Common Device Name	80	AN	Free Text	Conditional-Mandatory	At least One of the 3 Must be Reported Brand Name or Common Device Name or Product Code for the Device Constituent Part
FDA	G.k	FDA.G.k.2.11.r.1	Product Code	3	AN	http://www.accessdata.fda.gov/premarket/ftparea/foiclass.zip	Conditional-Mandatory	At least One of the 3 Must be Reported Brand Name or Common Device Name or Product Code for the Device Constituent Part

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
ICH	**G.k**	**G.k.2**	**Drug Identification**	**-**	**-**	**-**		
FDA	G.k	FDA.G.k.2.12	Model Number	30	AN	Free Text	Optional	UDI DI, identifies the specific version or model of a device
FDA	G.k	FDA.G.k.2.13	Catalog Number	30	AN	Free Text	Optional	UDI DI, identifies the catalog number of a device
FDA	G.k	FDA.G.k.2.14	Serial Number	30	AN	Free Text	Optional	UDI PI, the serial number of a specific device
FDA	G.k	FDA.G.k.2.15	Unique Identifier UDI#	50	AN	Free Text	Optional	Manufacturer and distributor reports should include the DI only. Users facility reporters who can not parse the DI out of the complete UDI should include the whole human-readable UDI
FDA	G.k	FDA.G.k.2.16	Single Use Device		Boolean	false, true	Optional	Whether the device is a single-use device that was reprocessed and reused on a patient (Yes, No)?
FDA	G.k	FDA.G.k.2.17	Device Manufacture Date		Date/Time		Optional	UDI PI, the date a specific device was manufactured

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
ICH	**G.k**	**G.k.2**	**Drug Identification**	**-**	**-**	**-**		
FDA	**G.k**	**FDA.G.k.2.22**	**Manufacturer**	**-**	**-**	**-**		
FDA	G.k	FDA.G.k.2.22.1a	Device Manufacturer Name	100	AN	Free Text	Optional	UDI DI, identifies the labeler
FDA	G.k	FDA.G.k.2.22.1b	Manufacturer Address	100	AN	Free Text	Optional	
FDA	G.k	FDA.G.k.2.22.1c	Manufacturer City	35	AN	Free Text	Optional	
FDA	G.k	FDA.G.k.2.22.1d	Manufacturer State	40	AN	Free Text	Optional	
FDA	G.k	FDA.G.k.2.22.1e	Manufacturer Country	2	AN	ISO 3166-2	Optional	ISO 3166-2

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
ICH	**G.k**	**G.k.2**	**Drug Identification**	**-**	**-**	**-**		
FDA	**G.k**	**FDA.G.k.2.23**	**Remedial Action**					
FDA	G.k	FDA.G.k.2.23.r.1	Remedial Action	1	N	1=Recall 2=Repair 3=Replacement 4=Relabeling 5=Notification 6=Inspection 7=Patient Monitoring 8=Modification or Adjustment 9=Other	Optional	If 9 enter text in FDA.G.k.s.23.r.2
FDA	G.k	FDA.G.k.2.23.r.2	Other	250	AN	Free Text	Conditional	Required if FDA.G.k.2.23.r.1 = 9, different that the one(s) previously specified or mentioned.
FDA	G.k	FDA.G.k.2.24	Device Usage	1	N	1=Initial Use of Device 2=Reuse 3=Unknown	Optional	initial usage: Preceding all others in time or space or degree. Unknown: Not known, not observed, not recorded, or reused.
FDA	G.k	FDA.G.k.2.25	Device Lot Number	100	AN	Free Text	Optional	UDI PI, the lot or batch number within which a device was manufactured
FDA	G.k	FDA.G.k.2.26	Malfunction		Boolean	false, true	Optional	Type of reportable event, malfunction indicating that the report is serious injury.

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
FAERS	**G.k**	**FDA.G.k.2.27**	**Follow-Up Type**	**-**	**-**	**-**		
FAERS	G.k	FDA.G.k.2.r27	Follow-Up Type	1	N	1=correction, 2=additional information 3=response to FDA request 4=device evaluation	Optional	Classification of the type of follow-up ICSR. Use the same manufacturer control number (to ensure the report is not misidentified in FAERS as an initial report).
FAERS	**G.k**	**FDA.G.k.2.28**	**Device Problem and Evaluation Codes**	**-**	**-**	**-**		
FAERS	G.k	FDA.G.k.2.28.r.1a	Evaluation Type	2	AN	01=Device Problem 02=Method 03=Result 04=Conclusion	Optional	If type is populated, then valve FDA.G.k.2.28.1b with appropriate code.
FAERS	G.k	FDA.G.k.2.28.r.1b	Evaluation Value	6	N	MDR Adverse Event Codes	Conditional-Mandatory	The Value Depends on the Respective <evaluationtype> If <evaluationtype> = 01 --> https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/UCM584240.xlsx If <evaluationtype> = 02 --> https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/UCM584242.xlsx If <evaluationtype> = 03 --> https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/UCM584243.xlsx If <evaluationtype> = 04 --> https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/MDRAdverseEventCodes/UCM584245.xlsx

Regional Requirement

Field Identification				Field Type			Post-Market Combo	
SOURCE	HEADER ELEMENT	DATA ELEMENT NUMBER	DATA ELEMENT NAME	MAX LENGTH	DATA TYPE	VALUE ALLOWED	CONFORMANCE	Combo Business Rule
FAERS	G.k	FDA.G.k.2.29a	Operator of the Device	1	N	1= Health Professional 2= Lay User/Patient 3 = Other	Optional	Use '1' or '2' to describe the operator, If None Applicable, Then Specify value '3' and enter text in FDA.G.k.2.29b.
FAERS	G.k	FDA.G.k.2.29b	Other Operator of the Device	250	AN	Free text	Conditional	Required if FDA.G.k.2.29a = 3, different that the one(s) previously specified or mentioned.

BREAK

Session 5: CBER's Update on Electronic Safety reporting for Vaccine

VACCINE ADVERSE EVENT REPORTING

Vaccine Adverse Event Reporting System: Updates on Electronic Reporting for Vaccines

July 17, 2019

Craig Zinderman, MD, MPH
Associate Director for Product Safety, Division of Epidemiology
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research

Agenda

- VAERS Background
- Reasons for eVAERs Updates
- Status of Updates and where to find them
- What's New:
  - Revised format of Business Rules
  - Combination Product Data Elements
  - Selected Business Rule Changes

VAERS

- Vaccine Adverse Event Reporting System (VAERS)
  - A National Program for Monitoring Post-market Vaccine Safety
  - Established in 1990
  - Co-Managed by FDA and CDC

- Healthcare providers, parents, patients report via VAERS 2.0 Form
  - ➢ Online web reporting at vaers.hhs.gov
  - ➢ Fax, paper, phone

- **Manufacturers →→** Mandatory e-Submission to FDA **(eVAERS)**

eVAERS Background

- 2014: Electronic Safety Reporting Rule
  - “eSRR”
  - Must submit AEs for biologics (and drugs) electronically (21CFR600.80(h))
  - Prior to rule: Manufacturer reporting via paper VAERS Form

eVAERS Background

- 2015: eVAERs Launched
  - Paper forms →→ ICH E2B (R3)
  - Two Options for Reporting:
    - Direct database to database submissions (i.e., business to business)
    - eSubmitter Tool
  - Published a Technical Specification and Business Rules Document, available at: Vaccine ICSR Implementation Page*

*https://www.fda.gov/industry/about-esg/cber-vaccine-icsr-implementation

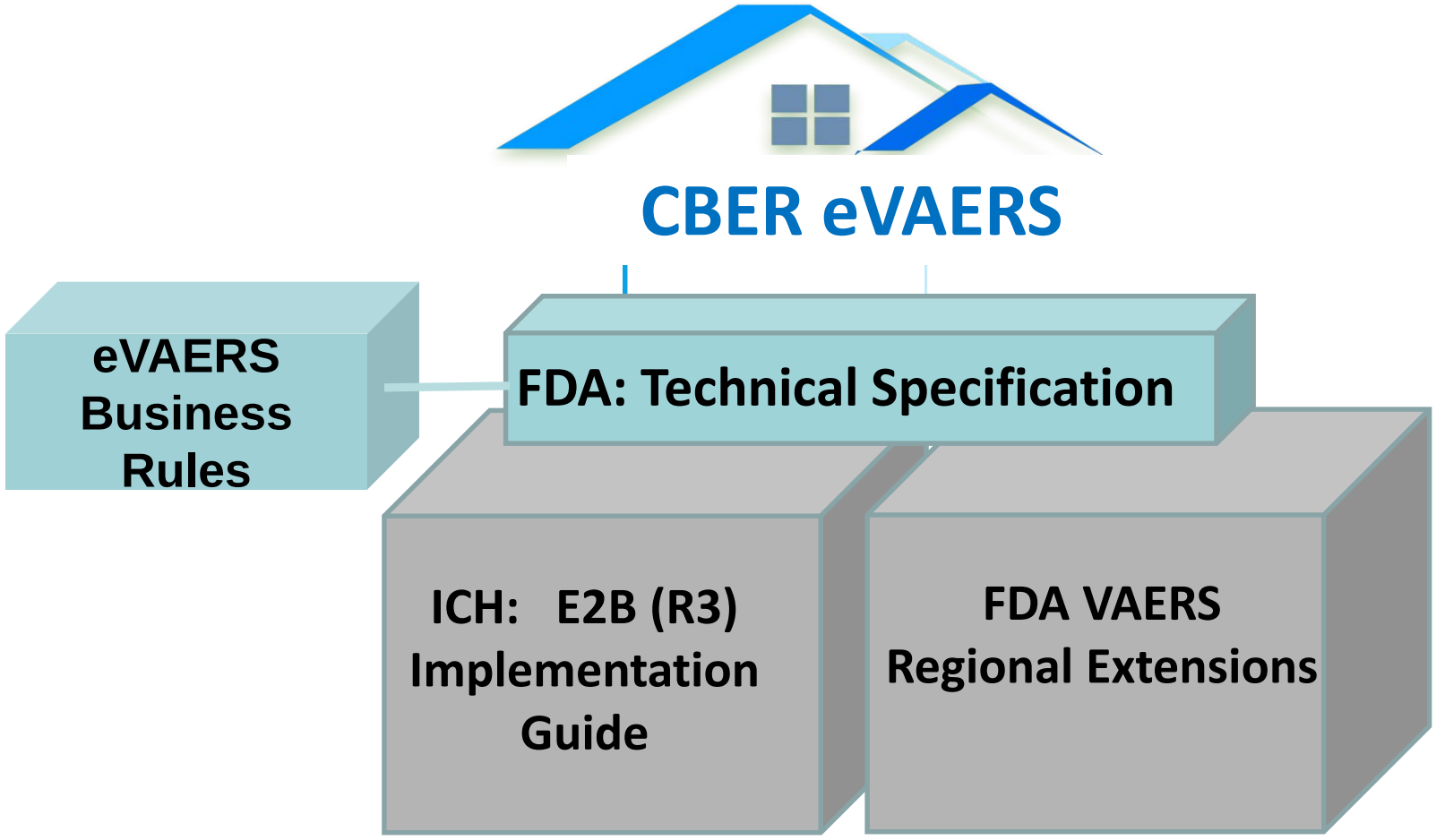
CBER Vaccine ICSR Implementation

CBER is implementing the updated International Conference on Harmonisation's (ICH) E2B(R3) Individual Case Safety Report (ICSR) specification to support electronic reporting of vaccine postmarketing safety reports as specified in the Electronic Safety Reporting Rule published June 10, 2014. Information about ICSR specifications supported by CBER is available at: http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/ucm174963.htm.

VAERS Electronic Reporting Resources:

- FDA E2B(R3) Guidance to Industry: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidanc
- Electronic Vaccine Adverse Event Reporting System (eVAERS) Guidance: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryI /Guidances/Vaccines/UCM458559.pdf
- FDA ICH E2B(R3) Regional Technical Specifications Document for Vaccine Reporting:

eVAERS Is Built on Standards, Specifications



https://www.fda.gov/industry/about-esg/cber-vaccine-icsr-implementation

VAERS Background

- ~50,000-60,000 reports received annually*
- ~40-50% from Manufacturers*
- Manufacturer electronic submissions increased from few hundred ICSRs in 2015 to all ICSRs in 2019

*Data from 2015-2018

eVAERS 2019 Updates

Purpose of Updates:

- Enable reporting required by the Combination Product Post-market Safety Rule, published in December 2016
  - Pre-filled syringes (some vaccines) = Combination Products
  - Malfunction reports and 5-day Reports required*
- Present Business Rules in ICH-prescribed format
- Incorporate various updates and clarifications of business rules since initial launch

*21CFR803.50

Status of Updates

- New Technical Specification and Business Rules posted:
  - http://wcms-internet.fda.gov/vaccines-blood-biologics/vaccines/cber-vaccine-icsr-proposed-updates
- Docket for submitting comments on Tech Specs
- Not implemented yet: anticipate production release 2020
  - Compliance Policy*: January, 2021
- FDA anticipates “Dual Reporting Options” available for limited time after implementation

*Combination Product Post-market Safety Reporting Rule: https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

What's New?

- Business Rules in ICH standard format

SOURCE	HEADER Element	DATA ELEMENT	FIELD NAME
ICH	C.2.r	C.2.r.2.4	Reporter's City
ICH	C.2.r	C.2.r.2.5	Reporter's State or Province
FDA	C.2.r	FDA.C.2.r.2.5.1	Reporter's County
ICH	C.2.r	C.2.r.2.6	Reporter's Postcode

- Source: Indicates if **ICH** or **Regional**
- Data Element Numbers for FDA Regional Elements

More on ICH Format

- Conformance Column
- IG Rules and FDA Rules Columns
- Type of Change Column: indicates difference from ICH

FIELD NAME	CONFORMANCE	IG Business Rules	FDA Business Rules	Type of Change
Device Problem Code	Conditional-Mandatory		This field is required when Malfunction = true. FDA will	New FDA regional data element
Device Brand Name	Conditional-Mandatory		~~At least one of the 5 must~~ be reported <brandname> or <commondevicename>	New FDA regional data element
Common Device Name	Conditional-Mandatory		~~At least one of the 5 must~~ be reported <brandname> or <commondevicename>	New FDA regional data element
Device Product Code	Conditional-Mandatory		~~At least one of the 5 must~~ be reported <brandname> or <commondevicename> or <productcode> for the device constituent part	New FDA regional data element

New Regional Data Elements: Combination Products

FDA.C.1.12	Combination Products Report
FDA.C.1.7.1	Local Criteria Report Type
FDA.G.k.12.r.1	Malfunction?

- Combination Product Report Flag (Y,N)
- Local Criteria Report Type
  - 15-day
  - Non-expedited AE
  - 5-day
  - Malfunction only/No AE
- Did a malfunction occur? (Y,N)

New Regional Data Elements: Device Data

FDA.G.k.12.r.2	If follow-up, what type?
FDA.G.k.12.r.3	Device Problem Code
FDA.G.k.12.r.4	Device Brand Name
FDA.G.k.12.r.5	Common Device Name
FDA.G.k.12.r.6	Device Product Code
FDA.G.k.12.r.7	Device Manufacturer Name
FDA.G.k.12.r.8	Device Manufacturer City
FDA.G.k.12.r.9	Device Manufacturer State
FDA.G.k.12.r.10	Device Manufacturer Country
FDA.G.k.12.r.11	Remedial Action Initiated

Other Data Element Changes I

- Rule changes for Malfunction events
  - May or may not involve a patient
  - Rules for certain patient-related fields revised accordingly; see Business Rules
  - Example: “None” for patient’s first/last name when no patient involved.

Other Data Element Changes II

- Added Pregnancy Data Element (FDA.D.13)
  - Consistent with VAERS Form 2.0 question

FDA.D.13	Pregnant at time of vaccination

- Deleted Fields
  - Parent Identifier Fields (i.e., Parent title, name, race, ethnicity)
  - Body Weight Unit

- Qualification (C.2.r.4)
  - Removed Null Flavor “OTH” (UNK Allowed)

Other Data Element Changes III

- Message Sender Identifier
  - N.2.r.2
  - Senders must receive FDA approval of their Sender Identifier.
  - Can be DUNS ID or other Identifier with FDA approval.
  - Once eVAERS updates are implemented, ICSRs with non-approved Sender IDs will be rejected.

Next Steps

- Proposed Updated Documents available
- Updated Technical Specifications and Business Rules anticipated end of 2019
- Programming Changes anticipated early 2020
- Reporting establishments must be compliant Jan 2021

Acknowledgements

- Judith Richardson, CBER/OD/ADRM/BSS
- Shifu Zhao, CBER/OD/ADRM/BSS

Contact info for questions:
Contact the CBER ICSR Submissions mailbox at
CBERICSRSUBMISSIONS@fda.hhs.gov

PMSR Requirements for Vaccine in pre-filled syringe:
Biologic with Device constituent part ()

Malfunction Reports (21 CFR 803.50)

- *information that reasonably suggests that a device has malfunctioned*

  AND
- *this device (or similar device that you market) would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.*

- Submit within 30 calendar days
- Submit malfunction reports the same way you submit AE reports

Malfunction:

- Malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

How-To-report

- Mfrs will submit malfunction reports via eVAERS
- May or may not be associated with 15-day AE report
- Streamlining: A single ICSR can serve as a 15-day AE report and a malfunction report if submitted within 15 days

More PMSR Requirements: Biologic with Device constituent part (Vaccine in pre-filled syringe)

5-day Reports (21 CFR 803.53, 803.56)

- You must submit a 5-day report when you become aware that:
  - (a) A medical device reportable event necessitates **remedial action** to prevent an unreasonable risk of substantial harm to the public health...

    OR
  - (b) FDA makes a written request for the submission of a 5-day report...

  - Submit within 5 working days
  - Submit 5-day report the same way you submit AE reports

More PMSR Requirements: Biologic with Device constituent part (Vaccine in pre-filled syringe)

Correction or Removal Reports (21 CFR 806.10, 806.20)

- Written report to FDA of any correction or removal of a device initiated by the manufacturer or importer
  - ➢ Initiated to reduce a risk to health posed by the device; or
  - ➢ To remedy a violation caused by the device which may present a risk to health...
  - ➢ Submit within 10 working days

Session 6: E2B R3 implementation – Industry experience with Regulators

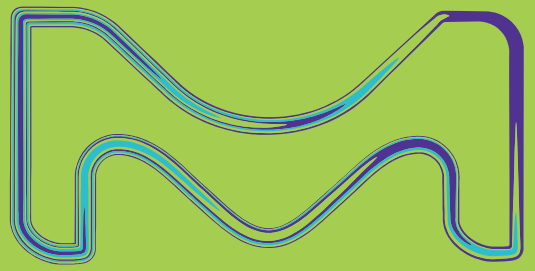
E2B R3 CHALLENGES

E2B(R3) Challenges

Experience from E2B(R3) Implementation for EMA (Europe) and PMDA (Japan)

Hans-Jörg Römming,
Head Global Patient Safety Operations

Merck KGaA, Darmstadt, Germany



EMD SERONO

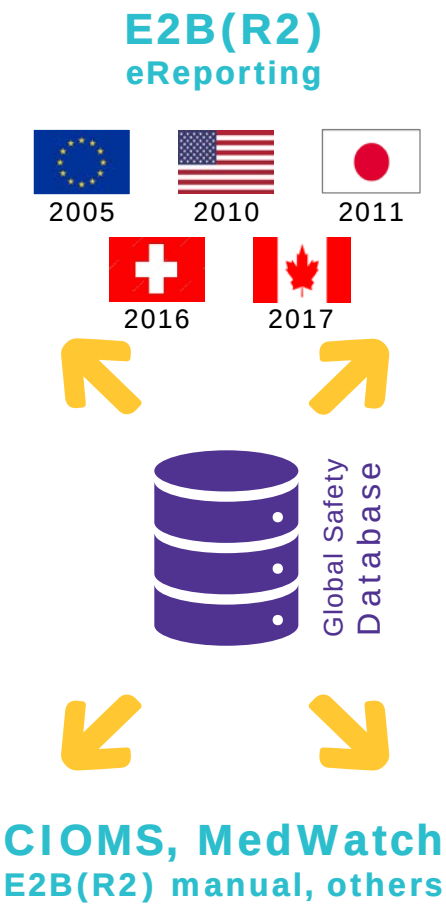
Content

1. Background
2. Implementation Strategy EMA & PMDA
3. Status Quo
4. Challenges EMA & PMDA
5. Upcoming Requirements
6. FDA Requirements
   - E2B(R3) PMS
   - Combination Products
   - E2B(R2/R3) IND
7. Summary and Proposed Next Steps

E2B(R3) Challenges
Background before our E2B(R3) reporting project

Merck KGaA, Darmstadt, Germany is running an integrated safety system for electronic reporting of ICSRs to FDA, EMA, PMDA and other Health Authorities from a single database.

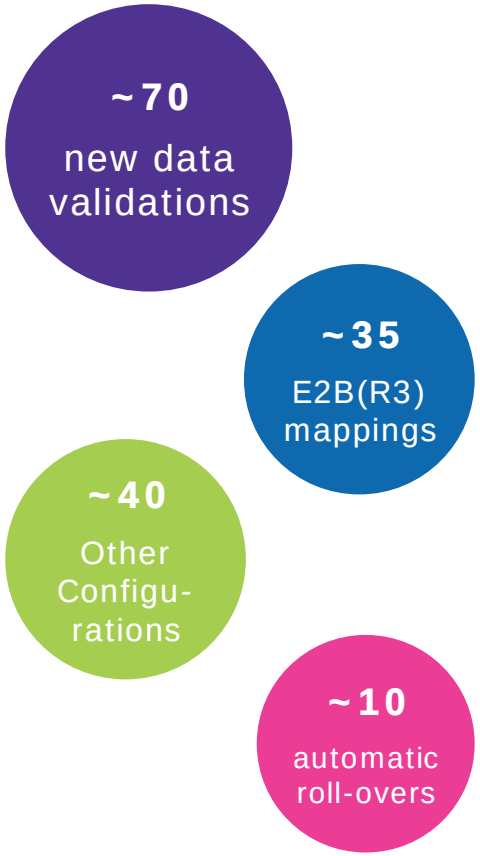
- The safety system had already been upgraded in 2017 for E2B(R3) import readiness to handle the ICSRs provided by EMA in E2B(R3) format (EVWEB)
- Since the E2B(R3) export had not yet been configured and tested, a separate project was initiated in 2018 to prepare for E2B(R3) export to EMA and PMDA
- Main driver for the project was the E2B(R3) deadline from PMDA at 01-Apr-2019



E2B(R3) Challenges
Project Implementation Strategy

Due to late availability of a compliant standard software release, we decided to implement parts of the E2B(R3) requirements as co-development with the software provider on the existing release branch to avoid any risks on project timelines

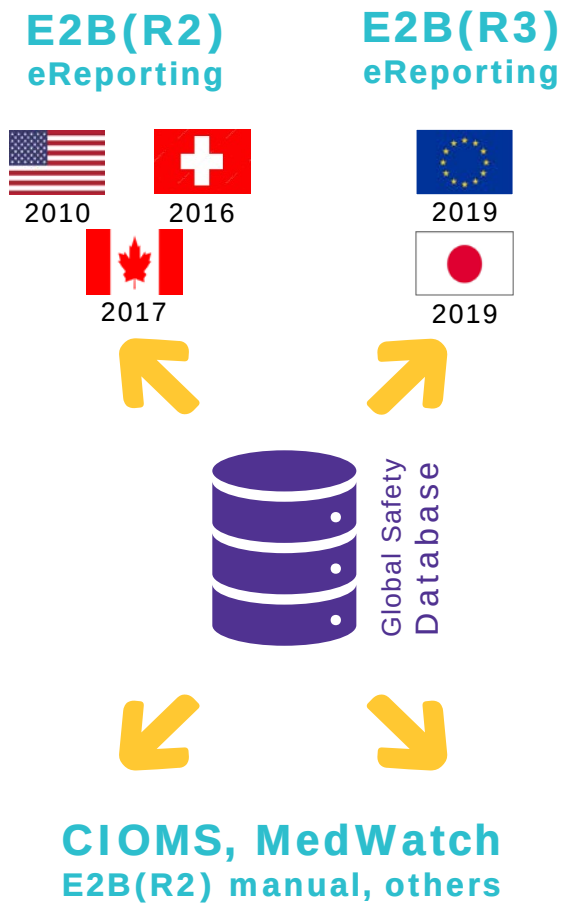
- To realize synergies, it was decided to include E2B(R3) export to EMA and PMDA into the project scope
- The system had to maintain E2B(R2) reporting capabilities as well as other formats (e.g. CIOMS, MedWatch) in addition to the new E2B(R3) functionalities
- To avoid negative impact on ICSR processing efficiency, double data entry (e.g. E2B(R3) fields and E2B(R2) fields) should have been avoided as much as possible
- The actual implementation project started begin Q2/2018 which allowed a planned project duration of ~10 months
- 2 months of buffer were included into the planning so that the E2B(R3) go-live was planned for end February 2019



E2B(R3) Challenges
Status Quo after project completion

We have implemented the project in time and are reporting in E2B(R3) standard to EMA and PMDA since begin of February 2019

- A well-planned transition made it possible to switch the reporting format without any negative impact on ICSR reporting compliance
- The experience since go-live shows that strict data validations during ICSR processing are crucial to handle the increased complexity and extended business rules introduced with E2B(R3)
- Error handling in case of negative Acknowledgements is much more complex and time consuming than before – e.g. > 800 business rules at EMA and > 300 business rules at PMDA to comply with
- Different rules for same ICH fields introduce a high complexity in necessary field mappings. Any change or correction in mapping definitions requires time consuming impact analysis



E2B(R3) Challenges
Challenges EMA & PMDA

Both Health Authorities, EMA and PMDA, have implemented regional concepts, and in addition deviate from the ICH standard which makes the implementation time consuming, complex and expensive

EMA
[examples]

- New NullFlavors for ICH fields (e.g. EMA has introduced NF for batch number G.k.4.r.7)
- Unaccepted NullFlavors against ICH definitions (e.g. EMA does not allow NF for reporter qualification C.2.r.4)
- Individual codelists for ICH fields (e.g. test result unit F.r.3.3 with a restricted list instead of full UCUM allowance)
- Old CodeSystemVersion (CSV) on field “Route of Admin” G.k.4.r.10.2a
- Regional fields with blocking business rules (e.g. EU Causality for CT SUSARs)

PMDA
[examples]

- Individual codelists for ICH fields (e.g. Pharmaceutical dose form G.k.4.r.9.1)
- For some date elements (e.g. date of creation C.1.2), JST time has to be used instead of making use of R3 field time zone component
- Reporter details not to be submitted (C.2.r.1x/C.2r.2x)
- Local language in ICH fields H.1, H.2 (Japan domestic cases) and H.4 (all cases) instead of making use of ICH multi-language field H.5.r (Rep. comment in native language)
- Regional fields with blocking business rules

E2B(R3) Challenges
Challenges EMA & PMDA – Examples

Field	Field Name	ICH	EMA	PMDA
C.1.2	Date of Creation 2019-05-29, 10:43am CEST	„20190529**1043+0200**“	See ICH or „20190529**1043**“ if senders time zone is max +/-12 UTC	„20190529**1743**“ (conversion to JST necessary)
C.2.r.1.x C.2.r.2.x	Reporter Title / Name Reporter Org/Address	Optional Fields	See ICH	Not allowed
C.2.r.4	Reporter Qualification	NullFlavor UNK	No NullFlavor allowed	See ICH
F.r.3.3	Test Result Unit	Unified Codes for Units of Measurement (UCUM)	UCUM restricted	UCUM
G.k.4.r.7	Batch/Lot number	Optional and no NullFlavor allowed	Mandatory with NullFlavor UNK, ASKU allowed	See ICH
G.k.4.r. 9.1	Pharmaceutical Dose Form Free Text	Free Text	See ICH	Controlled vocabulary (3-character code)
G.k.4.r. 10.2a	Route of Admin TermID CodeSystemVersion (CSV)	Latest CSV 2.2 (one term deprecated compared to CSV 2.1)	CSV 2.1	CSV 2.2
H.1 H.2	Case Narrative Reporter’s Comments	English	See ICH	Japanese (domestic cases)
H.4	Sender’s Comments	English	See ICH	Japanese (all cases)

E2B(R3) Challenges
Upcoming Requirements

With our E2B(R3) implementation for EMA and PMDA, we are well prepared for upcoming requirements:

- Many health authorities worldwide are in the planning phase or have already started to upgrade their database systems to E2B(R3)
- Some health authorities have already announced to make use of the E2B(R3) integrated regional concepts (e.g. China, Korea, USA)
- Integrated solutions for regional E2B(R3) concepts and especially deviations from ICH standards are causing significant efforts and costs for adaptation of the global safety database
- The best implementation approach has to be assessed and decided for each country individually (integrated global solution versus local solutions)

Further development of the local E2B(R3) requirements has to be monitored carefully

E2B(R3) Challenges
FDA Requirements – E2B(R3) PMS

Reference: FDA public meeting 2019/03/25

FDA has presented their plans for E2B(R3) implementation for PMS reporting

- No deviations from ICH standard have been communicated so far which is appreciated as it avoids negative impact or conflicting requirements with other Health Authorities
- Specification of regional fields is understood as it reflects the E2B(R3) concept. However, with respect to implementation timelines and costs, regional concepts have a significant impact to the industry
- Considering the currently known scope, a significant implementation time for the industry should be expected as regional implementation models usually go along with a necessary upgrade of the safety software solution
- An early availability of a final implementation guideline would allow reliable planning at software vendor and industry side

E2B(R3) Challenges
FDA Requirements – Combination Products

FDA has published a draft guidance document for combination product reporting in 2018 and has recently extended the timelines for implementation requirements

- The draft guidance is based on E2B(R2) reporting standard but specifies additional fields outside of ICH standard which would cause significant implementation effort at the industry
- In context of E2B(R3) plans, FDA also describes specifications for combination products as dedicated regional E2B(R3) fields
- The recently extended timelines do not specify whether E2B(R2) implementation is planned as an interim solution or if it will be replaced by the discussed E2B(R3) requirements
- The usage of existing E2B(R2) narrative field* would be a preferred interim solution for the industry until structured fields will be provided in FDA E2B(R3) regional fields

Clear guidance for industry is required to ensure that effort is spent in the right direction (extended E2B(R2) vs. integration into E2B(R3))

*) Data to be provided according to *"Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff"* (Draft, March 2018):

Combination product identifier, report type, product code, device problem code, cross-reference to other reports (could be added to ICSR narrative). Other elements are already part of structured E2B information (patient, reporter, drug, adverse event coding)

E2B(R3) Challenges

Reference: FDA public meeting 2019/03/25

FDA Requirements – E2B(R2/R3) IND Reporting

FDA has announced to start IND safety reporting using E2B(R2) by Q4/2019. The extended usage of E2B(R2) ICH values in specific fields* has major impact to the industry for fulfilling the requirements.

- Fields for additional values specified by FDA have to be implemented in the safety systems
- The mapping from database fields to the FDA E2B(R2) file has to be implemented
- Data validations have to be implemented to ensure correct data preventing negative Acknowledgements and effort intensive corrections
- Data entry rules and validations have to be setup and staff has to be trained accordingly
- The changes usually go along with an upgrade of the safety database system
- It should be clarified if IND eReporting can be started directly in E2B(R3) format at the time of the announced deadline

Significant effort and costs have to be spent for an extension of old E2B(R2) standard where at the same time E2B(R3) is getting implemented at FDA

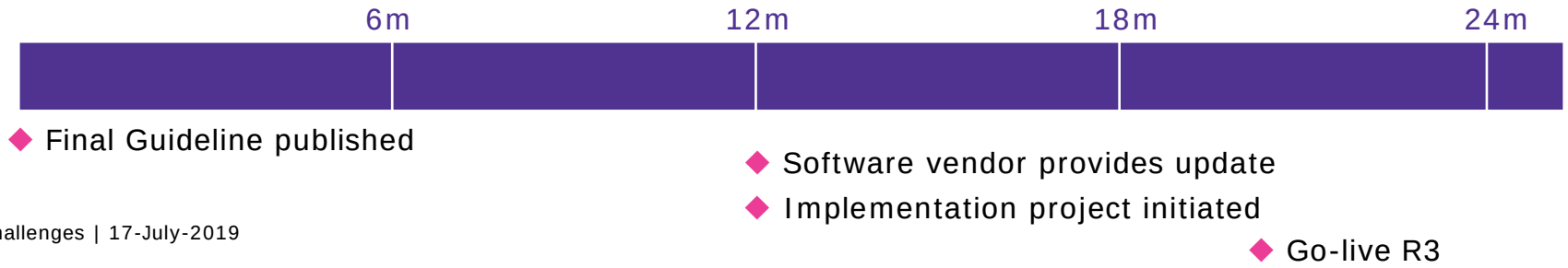
*) E.g. new values ”4” and “5” in A.2.3.3 (observestudytype), new values “4”, “5”, “6” for definition of report type in field A.1.9 (fulfillexpeditedcriteria)

E2B(R3) Challenges
Summary and Recommendations

- Clarity is required regarding combination product requirements (what is expected in 2020 and how does it fit to the E2B(R3) roadmap?) and IND reporting (is it possible to start directly with E2B(R3) at the time of the FDA deadline?)
- ICH standards should be used as specified by ICH. Otherwise risk of contradicting requirements.
- Controlled vocabularies should be ideally further standardized (see deviations by EMA and PMDA).
- Implementation E2B(R3) regional concepts causes significant effort at software vendors and industry. Sufficient time for implementation should be planned after publication of final implementation guides.

In order to make best use of resources, our preferred approach would be to address E2B(R3) requirements for PM reporting, combination products, and IND reporting in ONE project as soon as testing for E2B(R3) reporting can start.

Given the experience with EMA/PMDA, we expect a duration of ca. 20 months for implementation once all resources are made available by FDA (final guidance documents, test system etc).



THANK YOU!
Questions?

Summary & Closing Comments

- Session 1: Synopsys from previous meeting
  - Meeting I summary
  - Next Steps after Meeting I
  - Communicated E2B R3 Roadmap
- Session 2: E2B R3 Regional Requirement for Premarket Safety Reporting
  - Discussed the regional data elements
- Session 3: Generic Drugs – BA/BE trials safety reporting
  - Discussed the regional for safety reporting
- Session 4: E2B R3 Regional Requirements for Combo Product safety reporting
  - Discussed the background and rule
  - Discussed the regional data elements
- Session 5: CBER's Update on Electronic Safety reporting for Vaccine
  - Discussed the regional data elements
- Session 6: E2B R3 implementation – Industry experience with Regulators

Next Steps

- Today's presentation will be posted on FDA meeting page
- Invite comments via the docket on topics discussed in today's meeting by August 16, 2019
- Update schema with regional elements
- Update FDA Regional Implementation Specifications for ICH E2B(R3) Implementation
  - Incorporate comments received via the docket
- Prepare for the next meeting on Feb 19, 2020
- Prepare sample regional E2B R3 data files
- Contact: eprompt@fda.hhs.gov after the docket timeframe

Thank You!