

CBER (OVRR): Clinical Review Using Standardized Data

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PhUSE Computational Science Symposium
June 10, 2019

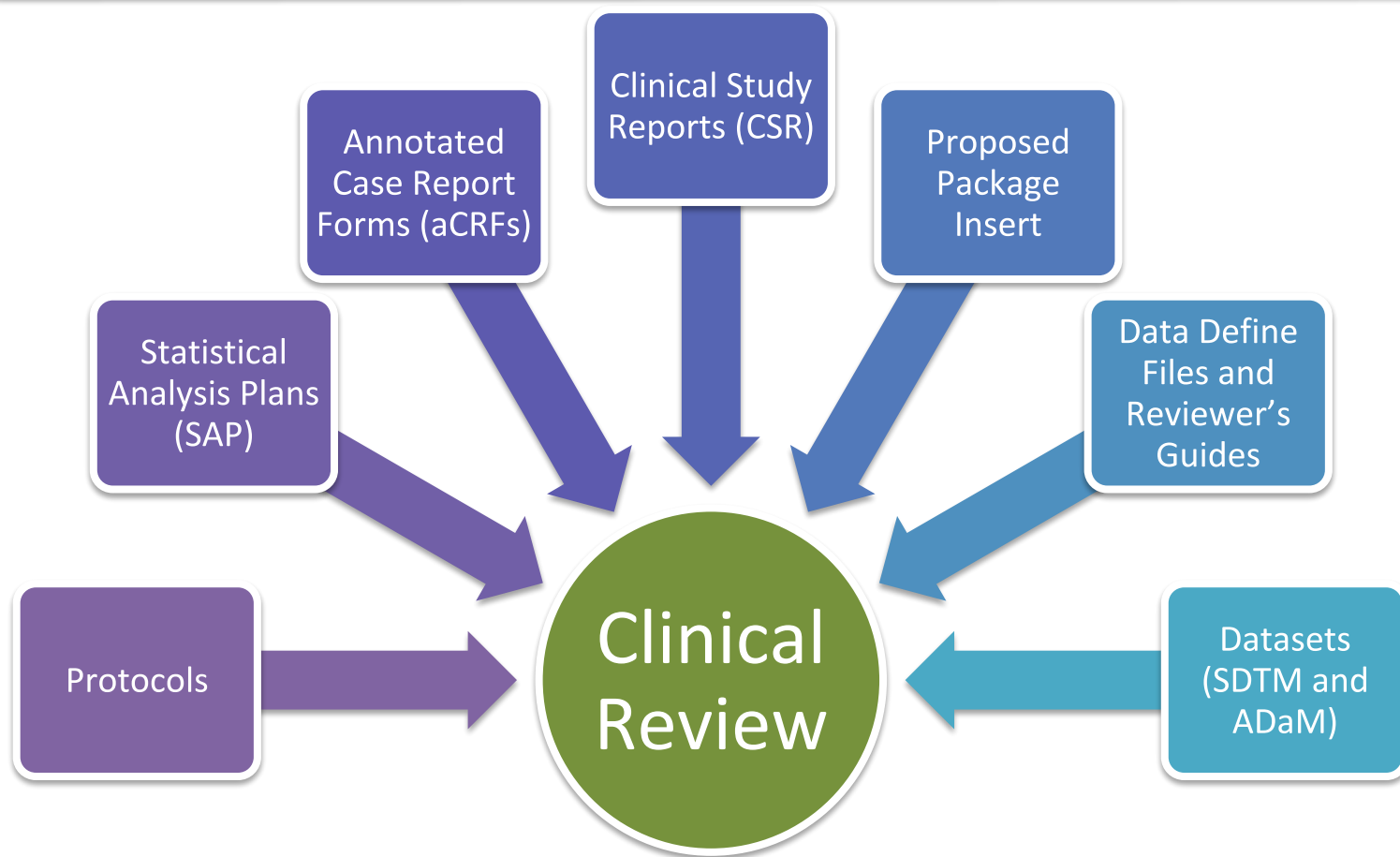
Disclaimer

This presentation is an informal communication and represents my own best judgment. These comments do not bind or obligate FDA.

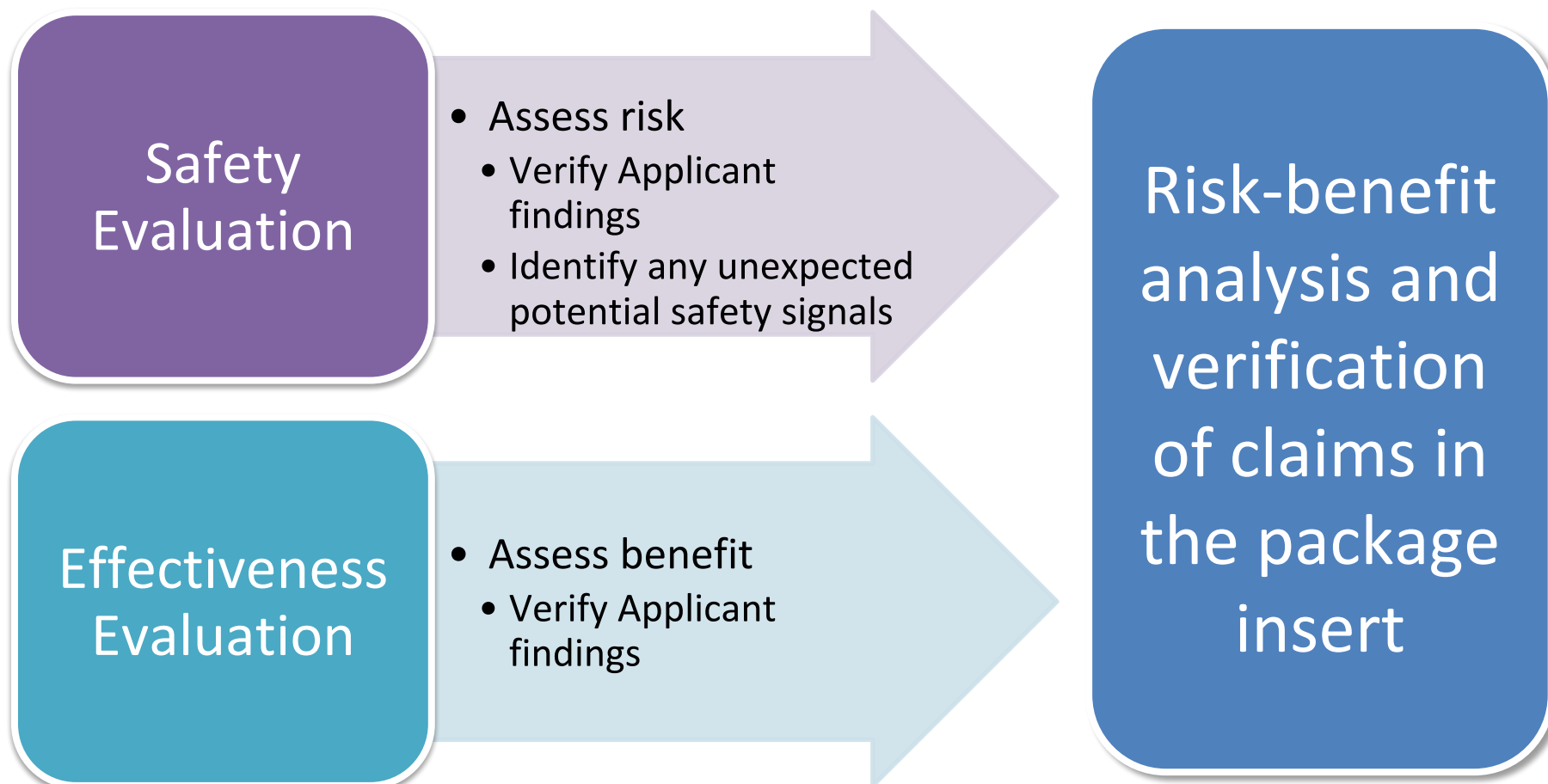
OVERR: Products Reviewed

- **Vaccines** for prevention or treatment of infectious disease indications
- **Allergenics** (PDUFA and non-PDUFA)
- **Other Biologics**
 - Fecal Microbiota for Transplantation (FMT)
 - Live Biotherapeutic Products
 - Bacteriophage

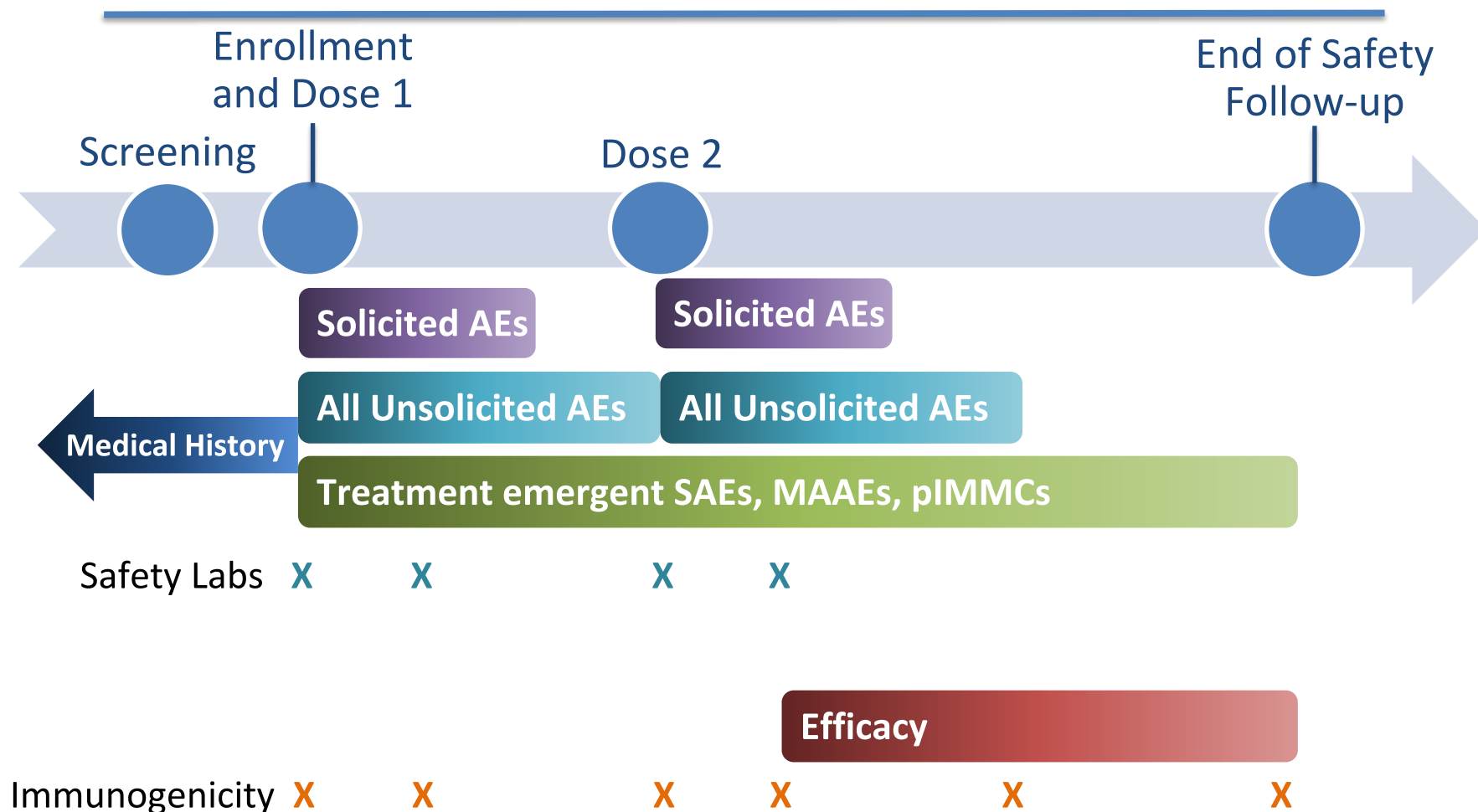
Approach to the Biologics License Application (BLA) Review: Documents



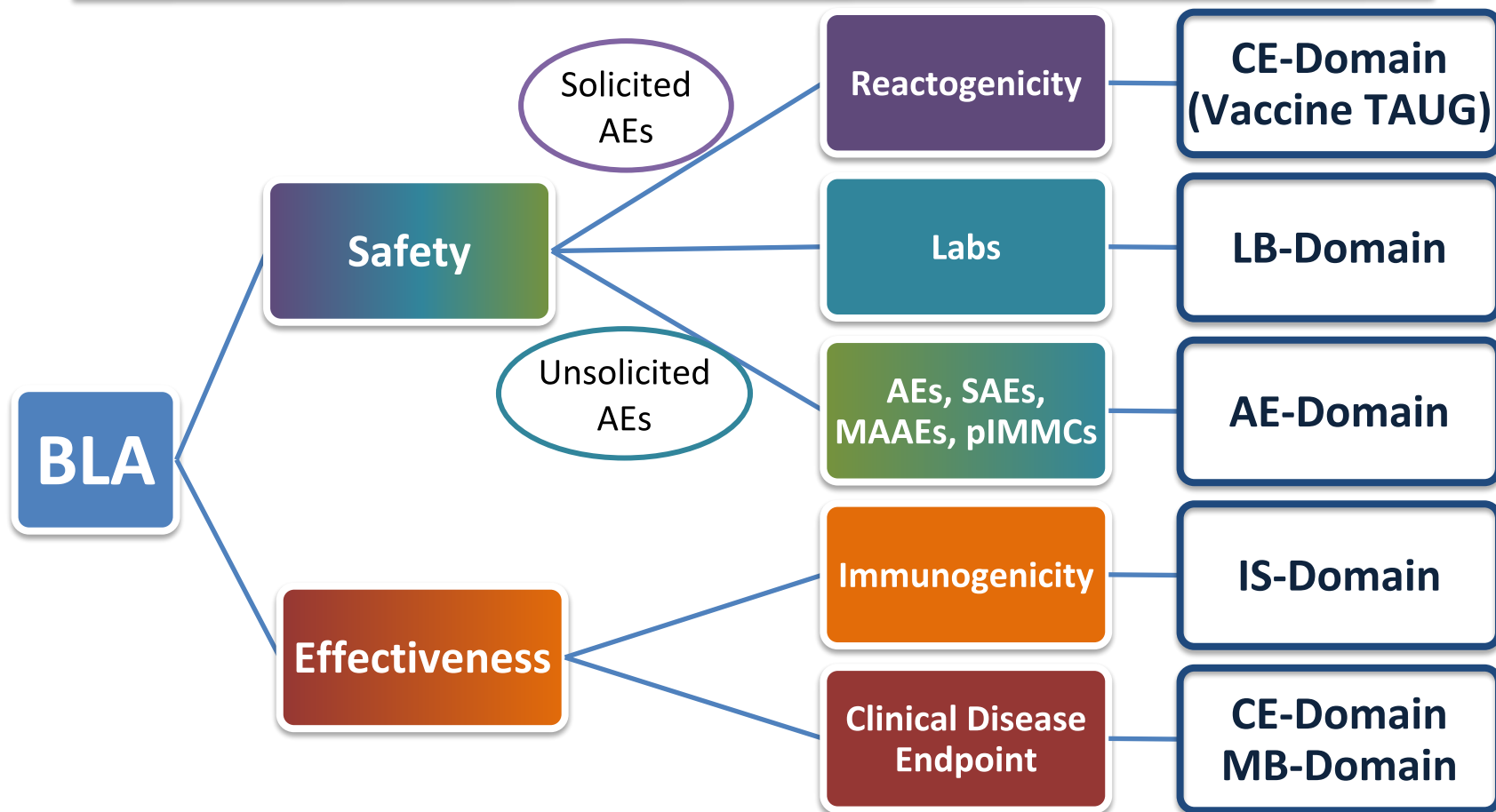
Approach to the BLA Review: General Principles



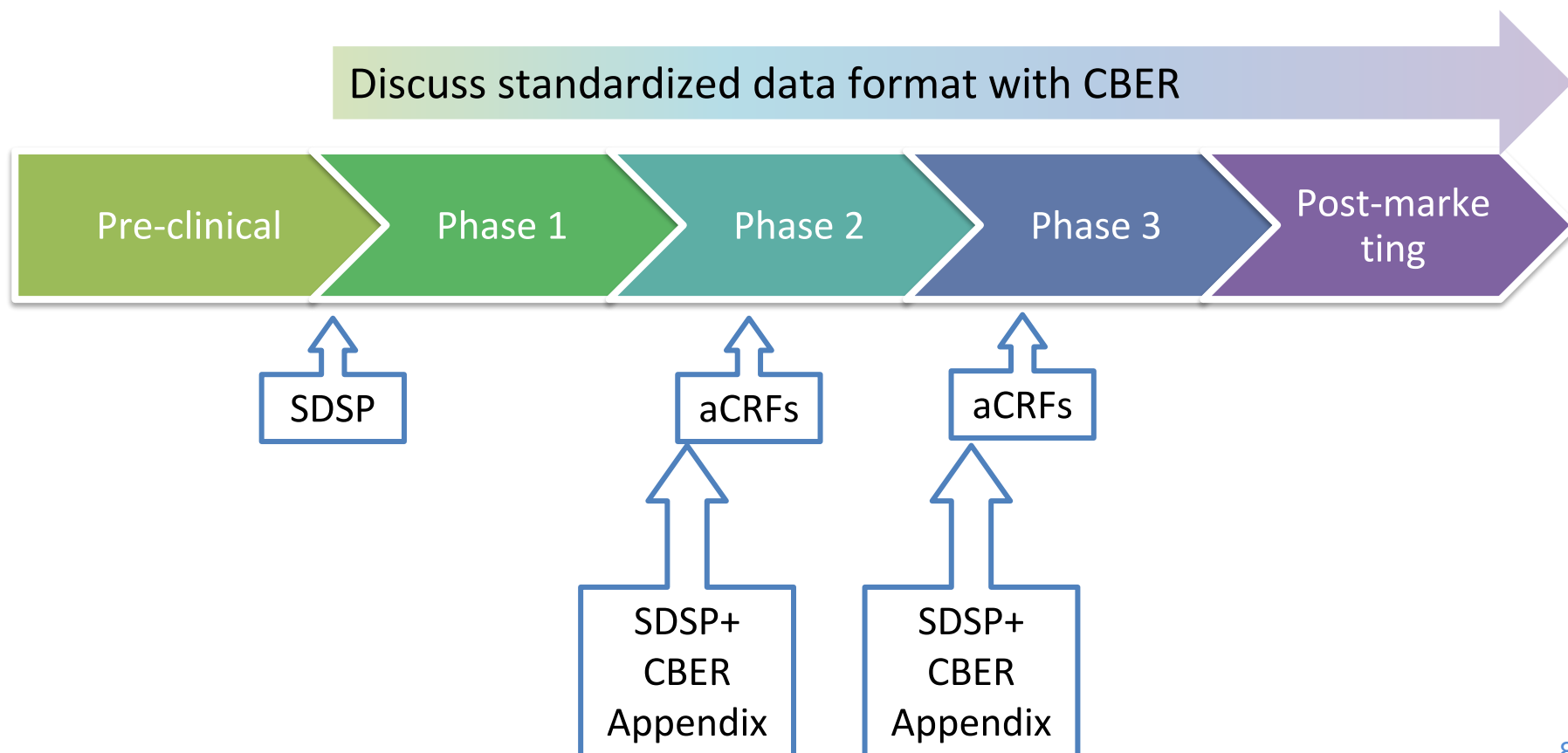
Elements of the BLA Review: Focus on Vaccines



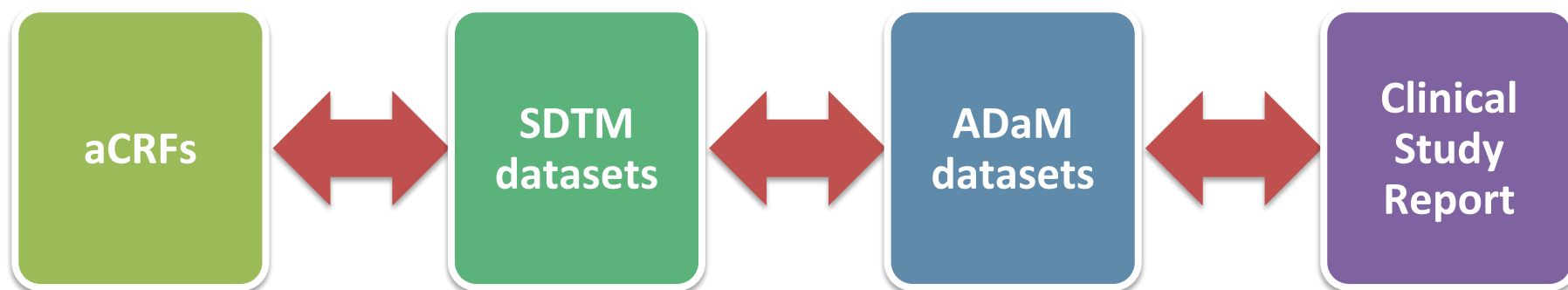
Elements of the BLA Review: Focus on Vaccines



Clinical Development and Data Standards



CBER Reviewer's Perspective: Traceability of Data



- If flags are used, they should be defined and include the method of derivation such that we could reconstruct the flag from raw data

CBER Reviewer's Perspective: STDM Format

Events			
	AE	☒	STUDYID DOMAIN USUBJID AESEQ AETERM AEDECOD AECAT AESCAT AEBODSYS AESEV AESER AEACNOTH AEREL AEOUT AESCONG AESDISAB AESDTH AESHOSP AESLIFE AESMIE AESTDTC AEENDTC AESTDY AEENRF AEENDY VISIT VISITNUM
	CE	☐	
	DS	☒	STUDYID DOMAIN USUBJID DSSEQ DSTERM DSDECOD DSCAT
	SR	☒	Solicited Reaction Data STUDYID DOMAIN USUBJID SRSEQ SRTESTCD SRDECOD SRTEST SRCAT SRMETHOD SRORRES SRORRESU SRSTRESU SRSTRESN SRSTRESC VISIT VISITNUM SRDOSE SRDC SRDTC SRLSTDTC SRSTDTC SRENDTC SRPRES SRACN SROG SRTERM
		☐	

- Reactogenicity should be reported in CE, not AE or custom.

CBER Reviewer's Perspective: SDTM Format

LB = Laboratory Tests

- Laboratory safety assessments
- Examples: Hematology, Chemistry, Urinalysis

IS = Immunogenicity

- Laboratory results to assess immunogenicity
- Example: Hemagglutination Inhibition titer

MB = Microbiology Specimens

- Test results to confirm the presence of the microbe of interest
- Examples: Viral culture and real-time RT-PCR (to confirm influenza-like-illness)

□ Safety lab data are in the LB-Domain. Effectiveness lab data are in the IS- or MB-Domains.

CBER Reviewer's Perspective: SDTM Format

The same AE is listed on more than one line.



AETERM	AELLT	AELLTCD	AEDECOD	AESOCOD	AESER	AESTDTC	AEENDTC	AESTDY	AEENDY
Sepsis	SEPSIS	10040047	SEPSIS	1002188	Y			241	242
Sepsis	SEPSIS	10040047	SEPSIS	1002188	N			240	240

- The structure of the AE domain is one record per adverse event per subject
 - “Collapse” the event to the highest level of severity, causality, seriousness and outcome.
 - Use the FA domain to provide additional details.

CBER Reviewer's Perspective: Dataset Validation

CT0001	Value for AEACN not found in (ACN) CT codelist	Error	66
CT0002	Value for AESEV not found in (AESEV) CT codelist	Error	23662
CT0027	Value for AEOUT not found in (OUT) CT codelist	Error	2515
SD1082	AEACNOTH variable length is too long for actual data	Error	1
SD1082	AEBODSYS variable length is too long for actual data	Error	1
SD1082	AEDECOD variable length is too long for actual data	Error	1
SD0063	SDTM/dataset variable label mismatch	Warning	26
SD0065	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	1357
SD0080	AE start date is after the latest Disposition date	Warning	360
SD0091	AEOUT is not 'FATAL', when AESDTH='Y'	Warning	50
SD1021	Unexpected character value in AETERM variable	Warning	126

□ Datasets should be validated prior to submission

CBER Reviewer's Perspective: Protocol-specified Analyses

AEDECOD	AESTDY	AESER
Meniscus injury	30	Y
Ventricular fibrillation	302	Y
Syncope	302	Y
Aortic valve stenosis	141	Y
Sciatica	94	Y
Device deposit issue	283	Y
Bile duct cancer	902	Y
Pelvic fracture	6	Y
Radius fracture	6	Y

This SAE occurred
 outside of the
 protocol-specified
 period for
 monitoring SAEs
 (through Day 426)

- Analyses in CSR should follow protocol and SAP pre-specified analyses

Take-home points

- Discuss data collection and dataset structure with CBER review team during the IND stage
- Ensure data quality prior to submitting your BLA
- Provide a clear, traceable pathway from the primary collection documents to the raw datasets to the analysis datasets.
- Think about me (the Clinical Reviewer)

Resources for CBER submissions

- Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review
<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm605147.pdf>
- Vaccine Therapeutic Area User Guide
<https://www.cdisc.org/standards/therapeutic-areas/vaccines>
- Study Data Technical Conformance Guide
<https://www.fda.gov/media/122913/download>
- FDA Data Standard Catalog
<https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm#Catalog>
- Study Data Standardization Plan with CBER Appendix
<https://www.phuse.eu/documents/sop/wp/phuse-tp001-study-data-standardization-plan-v1-8409.docx>
- SDSP Example Template Vaccine
<https://www.phuse.eu/documents/working-groups/version-control/sdsp-example-vaccine-final-v11-11737.docx>
- Clostridium Difficile Associated Diarrhea Therapeutic Area User Guide
<https://www.cdisc.org/standards/therapeutic-areas/cdad>

