U.S. FOOD & DRUG ADMINISTRATION

A Medical Officer's Approach to NDA/BLA Review

SBIA REdI Spring 2019

Virginia Sheikh, M.D., M.H.S
Medical Officer
Division of Antiviral Products
FDA/CDER/Office of New Drugs

At the conclusion of this activity participants will be able to…

- Identify the major activities and milestones of the medical officer's NDA/BLA review.
- Recognize the importance of the submission's organization and completeness to the medical officer.
- Identify considerations included in the medical officer's benefit/risk assessment.
- Give examples of strategies a medical officer may recommend to mitigate the risk of adverse reactions.

Outline

Background

- Medical Officer's role in NDA/BLA Review
- Review Team
- Activities that precede NDA/BLA Submission

Review Activities

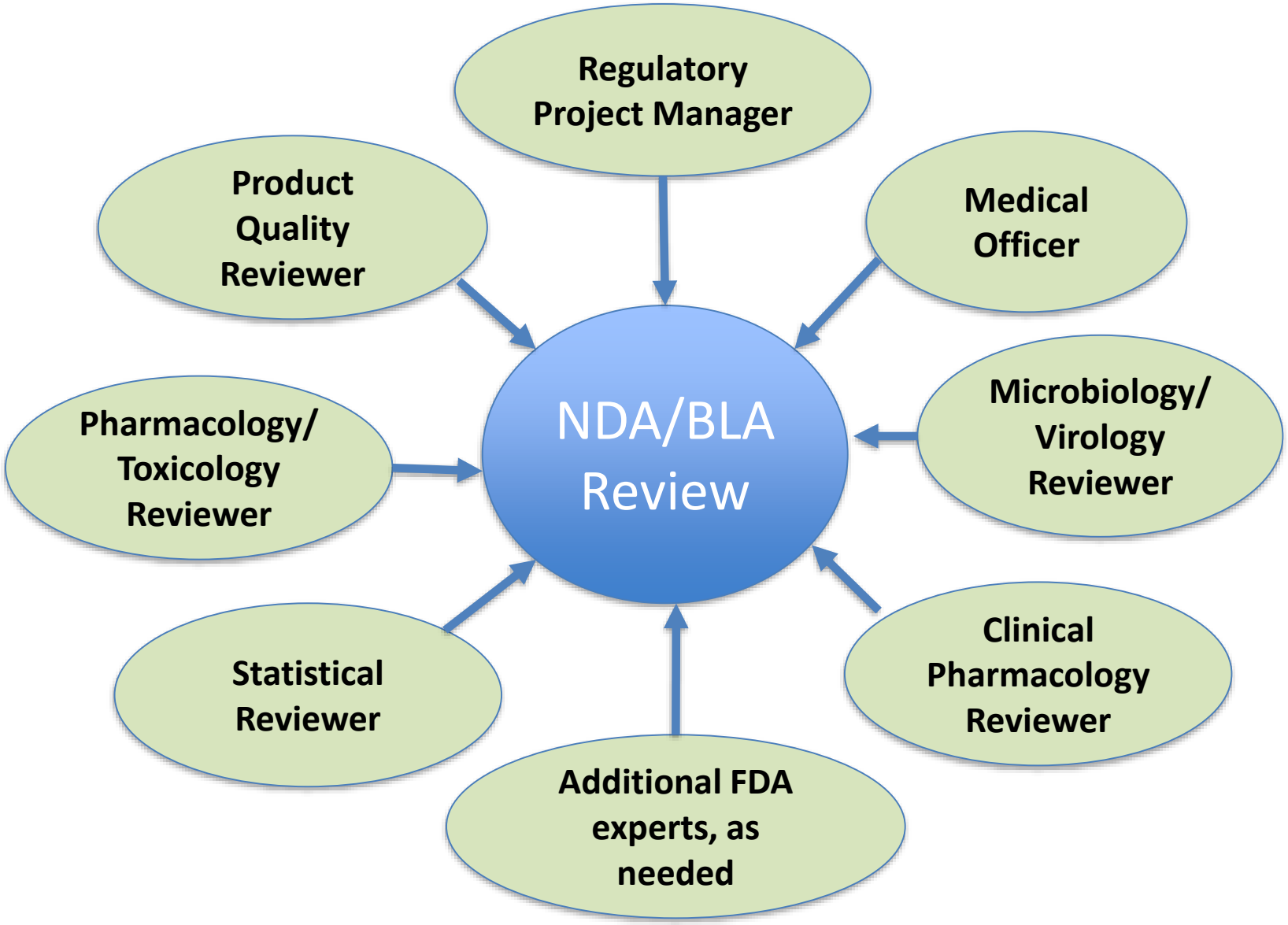
- NDA/BLA Filing and Planning
- Conducting the Review
- Wrap-Up Activities

Conclusions

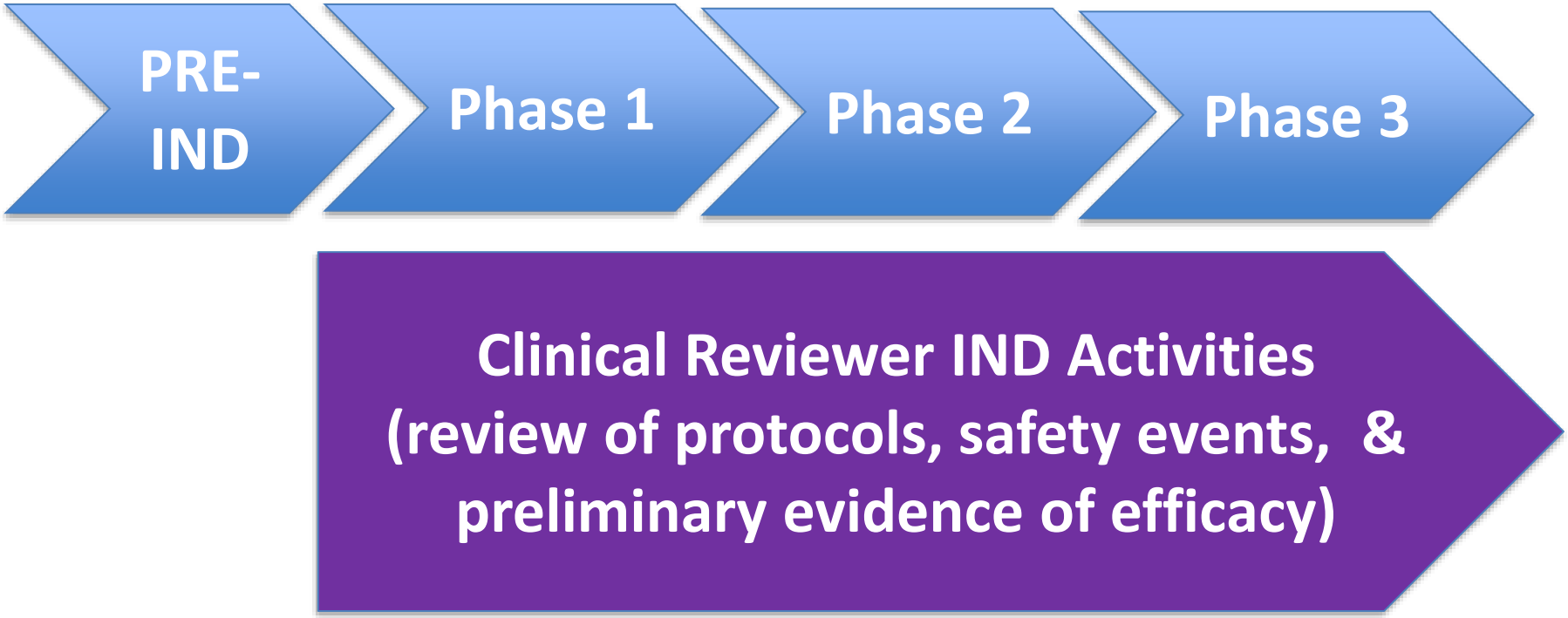
Medical Officer's role in NDA/BLA Review

- Reviews the evidence of efficacy and safety of a drug or biologic product from the clinical trials to conduct a benefit/risk analysis.
- Makes a recommendation about whether the product should be approved.
- If approved, makes recommendations for how the product should be labeled, potential post-marketing studies, and risk management plans.

NDA/BLA Primary Review Team



Prior to NDA/BLA Submission



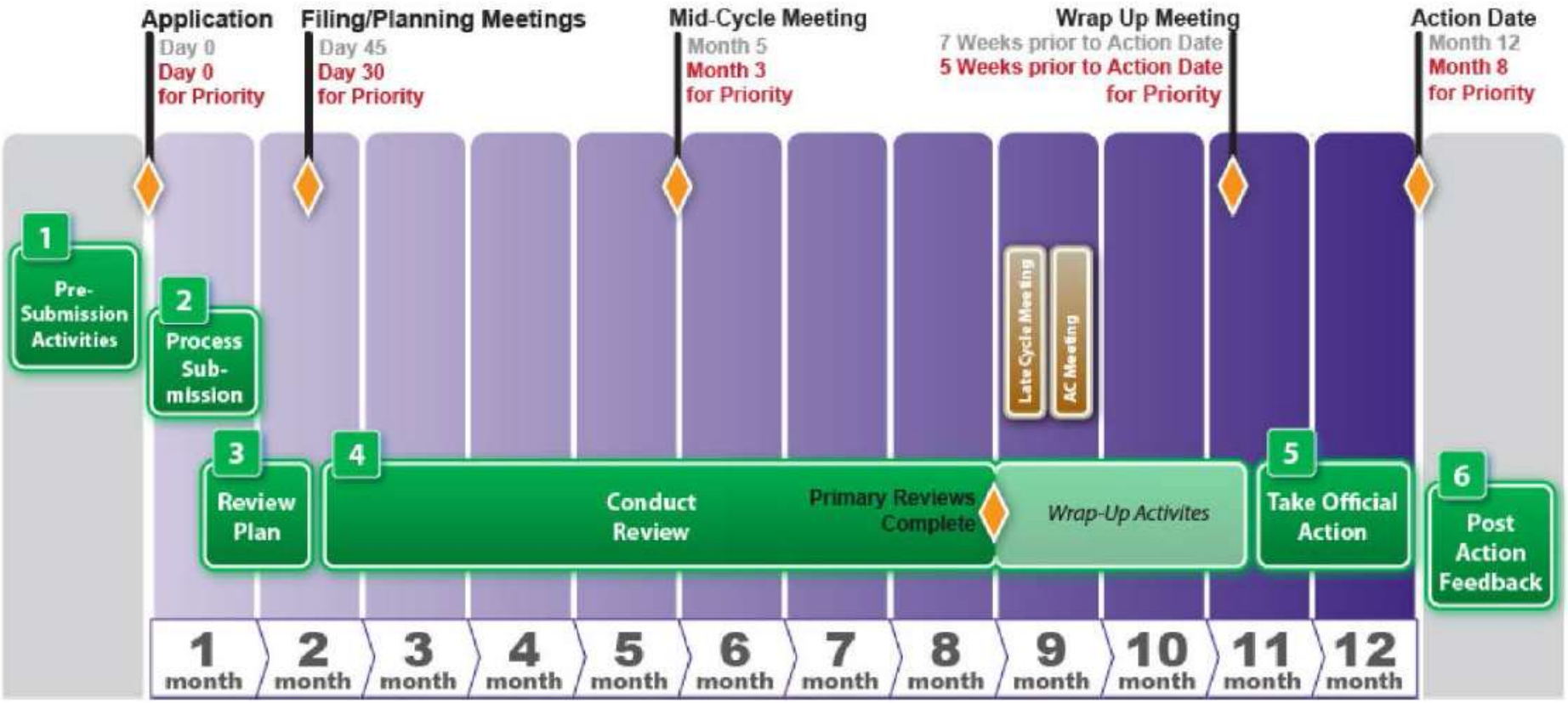
Pre-IND meeting (optional)

Type A, B, or C Meetings (as appropriate)

End of Phase 2 Meeting

Pre-NDA/BLA Meeting

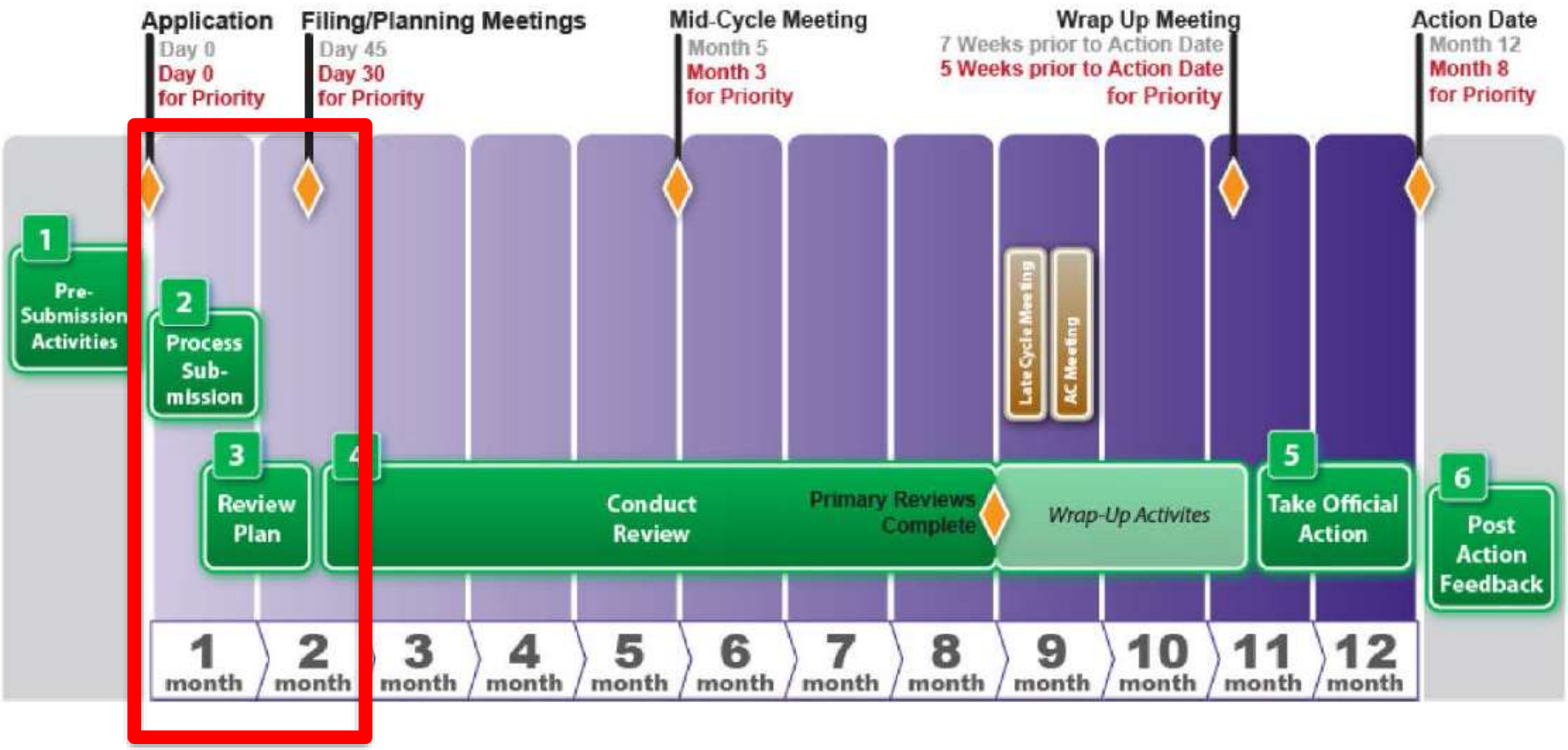
NDA/BLA Review Timeline



Standard Review: **12 months**

Priority Review: 8 months

NDA/BLA Filing & Planning



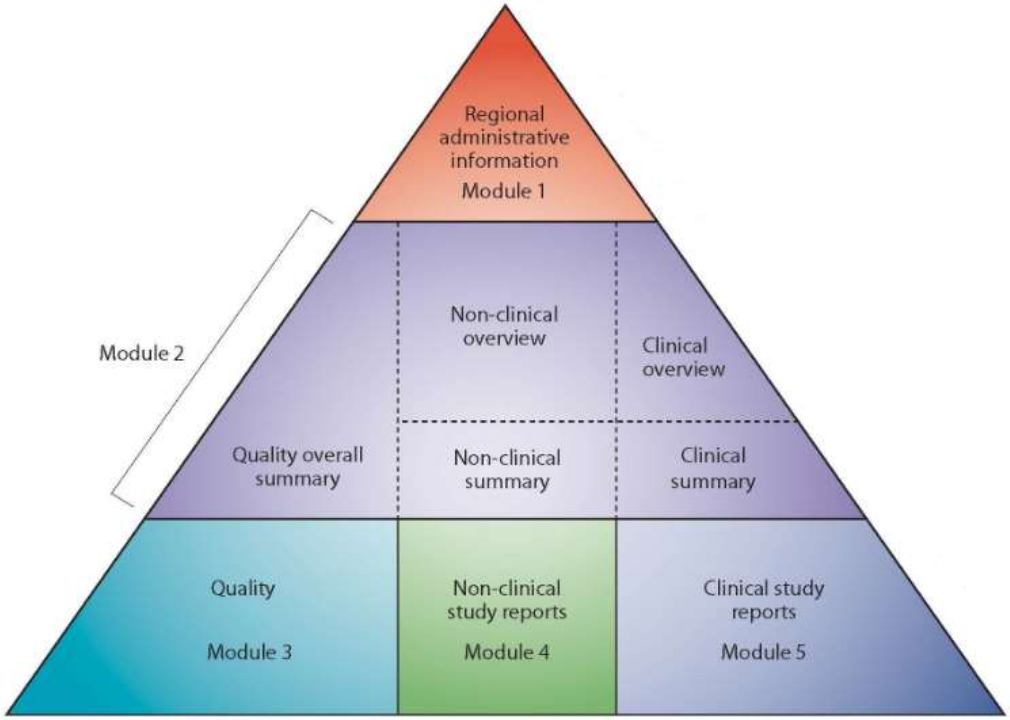
Graphic taken from FDA slide set created by Dr. Milena Lolic.

NDA/BLA Filing & Planning

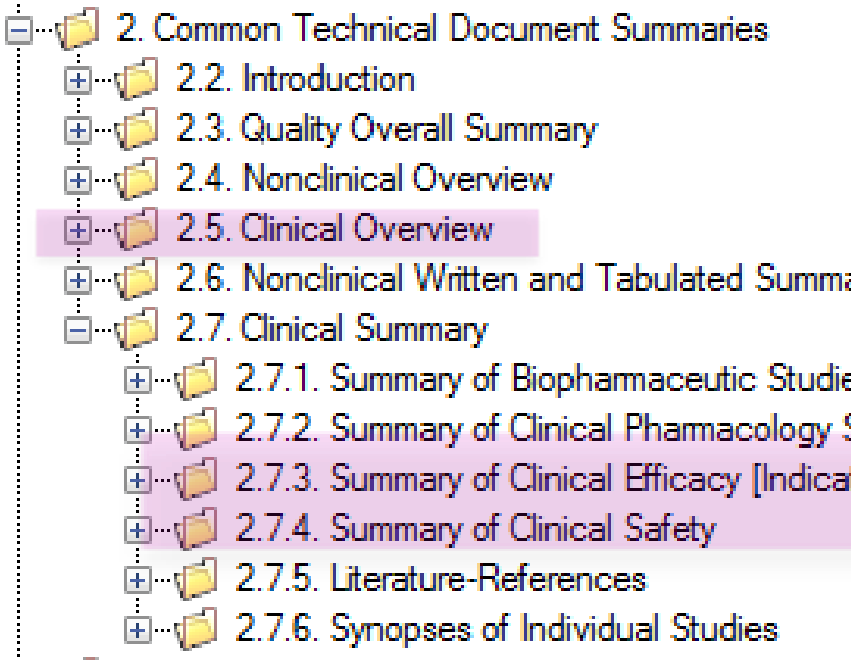
Milestones	Filing • Internal filing meeting • Filing Decision 74-Day Letter • Communicate any major problems or deficiencies to Applicant
Activities	Determining *Fileability:* Is the submission of sufficient quality & completeness to permit substantive review? Planning the NDA/BLA Review

Determining *Fileability*: Is the submission sufficiently organized?

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.



Determining *Fileability*: Are essential components included?

- 0000 (1) 11/05/2014 ORIG-1 /Multiple Categories/Subcategories
  - 1. Regional
    - 1.1. Forms
      - 1.1.2. Form FDA 356h: Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use
        - FDA Form 356h 2014-11-05
      - 1.1.3. Form FDA 3397: User Fee Cover Sheet
    - 1.2. Cover Letters
    - 1.3. Administrative Information
      - 1.3.1. Contact/Sponsor/Applicant Information
      - 1.3.3. Debarment Certification
      - 1.3.4. Financial Certification and Disclosure
      - 1.3.5. Patent and Exclusivity
    - 1.4. References
    - 1.6. Meetings
    - 1.7. Fast Track
    - 1.9. Pediatric Administrative Information
    - 1.11. Information Amendment: Information Not Covered Under Modules 2 to 5
    - 1.12. Other Correspondence
    - 1.14. Labeling
      - 1.14.1. Draft Labeling

Determining *Fileability*: Pivotal Clinical Trials

The following may be *review* issues or *filing* issues:

- Were the pivotal clinical trials adequate and well-controlled?
- Were the trial designs adequate to support the proposed indication?
- Did the trials adequately collect safety and effectiveness data?

In many cases, these issues will have been clearly communicated during IND development (End-of-Phase 2 and Pre-NDA meetings).

Determining *Fileability*: Electronic datasets

- Are define files and reviewer's guides present and usable?
- Can the submitted datasets be analyzed using FDA reviewer tools (e.g. JMP/JMP Clinical, JReview, MAED) ?

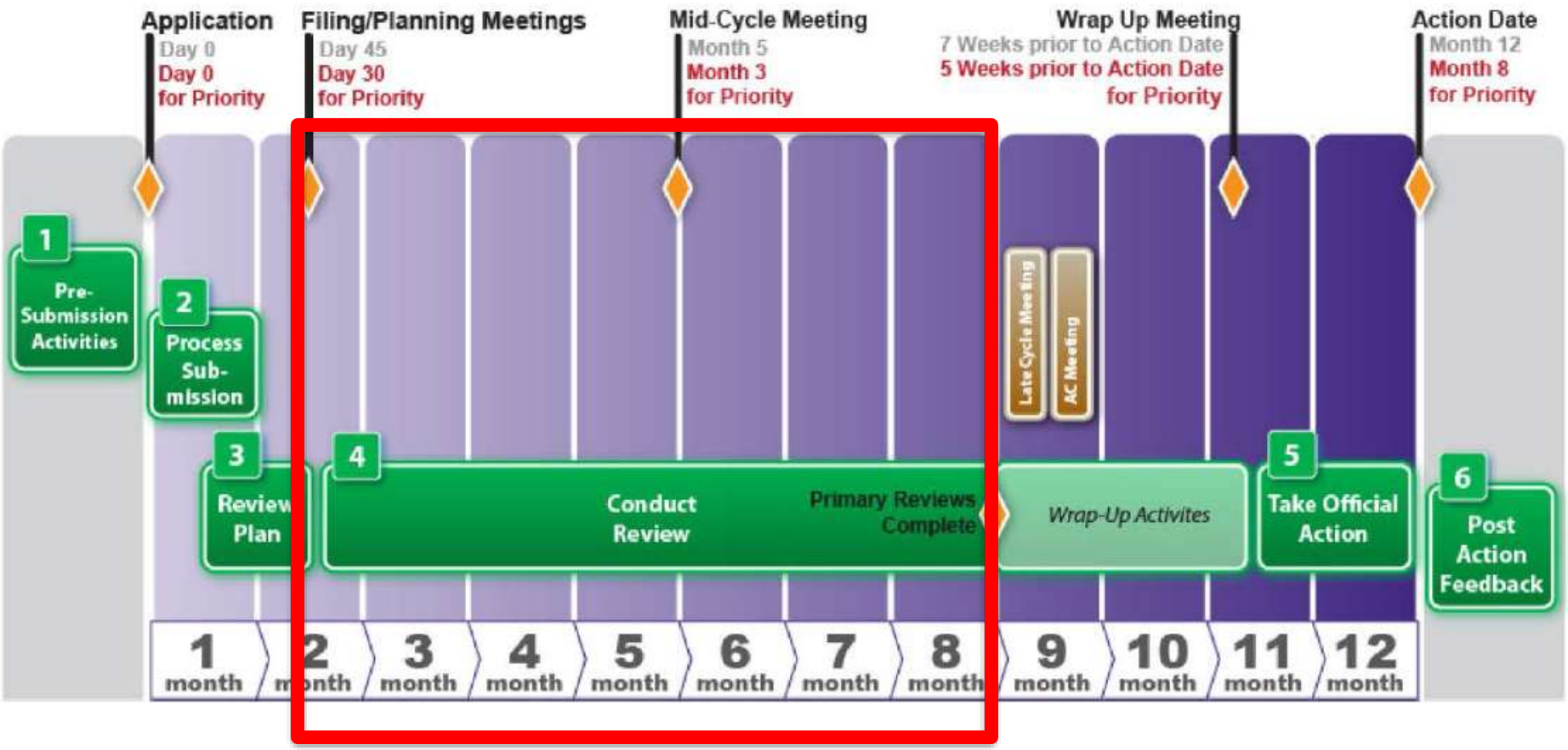
See **Providing Regulatory Submissions In Electronic Format — Standardized Study Data** Guidance for Industry. December 2014

NDA/BLA Planning

- What are the key review issues?
- Priority versus Standard Review Clock?
- Review strategy?
- Is additional FDA expertise needed?
- Is an Advisory Committee Meeting needed?
- Will the product need a Risk Evaluation and Mitigation Strategy (REMS)?
- Clinical and chemistry manufacturing inspection planning.

Photo by NORTHFOLK on Unsplash

Conducting The Review



Graphic taken from FDA slide set created by Dr. Milena Lolic.

Conducting the Review

Milestones	• Mid-cycle Meeting • Mid-cycle Communication • Primary Review Completion
Activities	• Efficacy and safety analyses • Identify & communicate major deficiencies • Benefit/risk assessment • Draft Labeling • Develop Risk Evaluation and Mitigation Strategy (REMS), if needed • Develop Post-Marketing Requirements (PMRs) and Commitments (PMCs)

Analysis of Efficacy

- Statistical analyses typically led by biostatisticians, but determination of clinical relevance led by MO
- Analysis of data integrity
- Review of study design, conduct, and limitations
- Analysis of primary endpoints: Do the results support the effectiveness of the product?
- Additional analyses:
  - Secondary endpoints
  - Demographic subpopulations analyses required
    - race, gender, age
  - Sub-group analyses, if needed (e.g. disease severity, dose groups, subjects on concomitant therapies)

Analysis of Safety MO Responsibility

- Identify potential safety review issues
- Assess whether the safety issue is real and related to the study drug
- Assess what the safety may mean to patients
- Recommends approaches to mitigate identified risks

Analysis of Safety Factors Considered

- Safety database and subpopulation representation
- Data integrity
- Adequacy of safety monitoring
- Deaths, serious adverse events (SAEs), and adverse events (AEs) leading to treatment discontinuation
- Treatment Emergent Adverse Events & Adverse Reactions
- Laboratory abnormalities, ECGs, vital signs
- Immunogenicity
- Safety analysis by demographic subgroup
- Sub-group analyses, if needed (e.g. disease severity, dose groups, subjects on concomitant therapies)

Benefit/Risk Assessment

- Seriousness of the condition
- Currently available therapies
- Strengths and limitations of pivotal clinical trials
- Clinical relevance of trial endpoints
- Magnitude and durability of the product's effects, including across subpopulations
- Safety database – size and subpopulations
- Adverse reaction – frequency and severity
- Risk management options (REMS, labeling)

Draft Labeling

- Labeling negotiations with the applicant typically occur in writing and are ongoing throughout the review process
- 21 CFR 201.56 and 201.57 are the regulations for prescribing information
- Numerous FDA Guidances have been published for labeling.
- Prior to approval, the entire label is reviewed by relevant disciplines, including experts in medication error prevention.

https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

Draft Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DELSTRIGO safely and effectively. See full prescribing information for DELSTRIGO.

DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: POSTTREATMENT ACUTE EXACERBATION OF HEPATITIS B
See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B (HBV) have been reported in patients coinfected with HIV-1 and HBV who have discontinued lamivudine or tenofovir disoproxil fumarate (TDF), two of the components of DELSTRIGO. Closely monitor hepatic function in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted. (5.1)

----------INDICATIONS AND USAGE----------

DELSTRIGO is a three-drug combination of doravirine (a non-nucleoside reverse transcriptase inhibitor [NNRTI]), lamivudine, and tenofovir disoproxil fumarate (both nucleoside analogue reverse transcriptase inhibitors) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Testing: Prior to or when initiating DELSTRIGO, test for HBV infection. Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage: One tablet taken orally once daily with or without food in adult patients. (2.2)
- Renal impairment: Not recommended in patients with estimated creatinine clearance below 50 mL per minute. (2.3)
- Dosage adjustment with rifabutin: Take one tablet of DELSTRIGO once daily, followed by one tablet of doravirine 100 mg (PIFELTRO) approximately 12 hours after the dose of DELSTRIGO. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate. (3)

----------CONTRAINDICATIONS----------

- DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO. (4)
- DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

---------- WARNINGS AND PRECAUTIONS ----------

- New onset or worsening renal impairment: Prior to or when initiating DELSTRIGO, and during treatment with DELSTRIGO, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. Avoid administering DELSTRIGO with concurrent or recent use of nephrotoxic drugs. (5.2)
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss. (5.4)
- Monitor for Immune Reconstitution Syndrome. (5.5)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Because DELSTRIGO is a complete regimen, co-administration with other antiretroviral medications for treatment of HIV-1 infection is not recommended. (7.1)
- Consult the full prescribing information prior to and during treatment for important potential drug-drug interactions. (4, 5.3, 7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2018

Risk Evaluation and Mitigation Strategy (REMS)

Designed to help reduce the occurrence and/or severity of certain serious risks, by informing and/or supporting the execution of the safe use conditions described in the medication's FDA-approved prescribing information.

WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

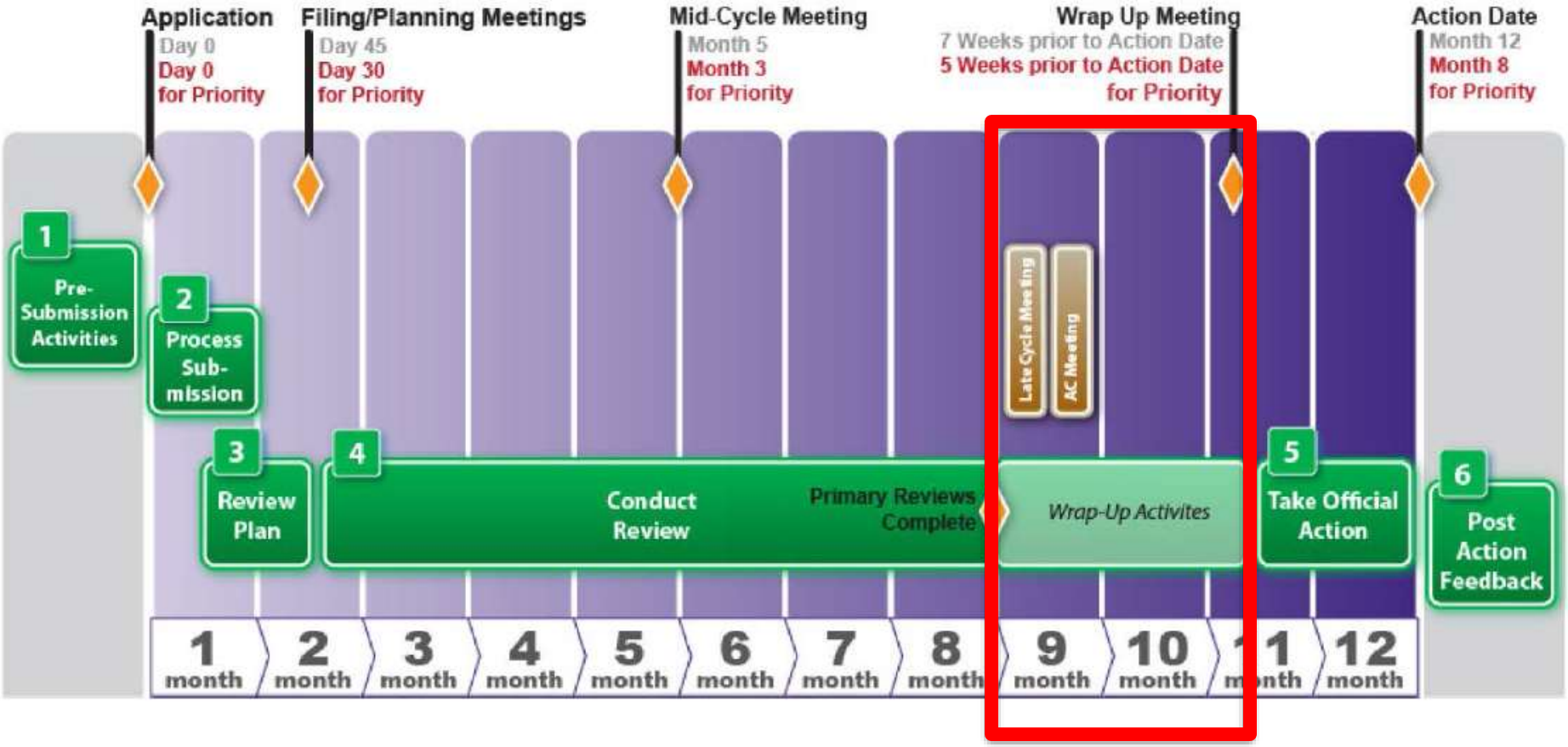
- **Patients are at risk for severe sedation (including coma) and/or delirium after each injection and must be observed for at least 3 hours in a registered facility with ready access to emergency response services. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment. (2.1, 5.1, 5.2, 10.2, 17.2)**
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis. (5.3, 5.16, 17.3)**

Post-Marketing Requirements (PMRs) & Post-Marketing Commitments (PMCs)

- FDAAA provides FDA with the authority to require drug manufacturers to conduct postmarket safety studies and clinical trials to assess possible serious risks associated with the drugs.
- Pediatric PMRs are often required under the Pediatric Research Equity Act (PREA)
- Other PMRs/PMCs may be product or disease specific

FDAAA = 2007 Food and Drug Administration Amendments Act (FDAAA)

Wrap-Up Activities



Graphic taken from FDA slide set created by Dr. Milena Lolic.

Wrap-Up Activities & Taking Action

Milestones	Late-Cycle Meeting Conduct Advisory Committee Meeting Wrap-up Meeting Senior Leadership concurrence
Activities	Advisory Committee activities, if needed Approvability Finalize label Develop final PMRs & PMCs, If needed Develop final REMS, if needed

Advisory Committee Meetings

- When independent professional expertise is needed to help inform regulatory decision-making, the FDA may host an Advisory Committee (AC) Meeting.
- The review team is responsible for the following:
  - Ensure AC panel has appropriate expertise.
  - Providing specific questions for the panel to discuss and answer by vote.
  - Presenting the FDA perspective to the panel.

https://www.fda.gov/advisory-committees

NDA/BLA Decision

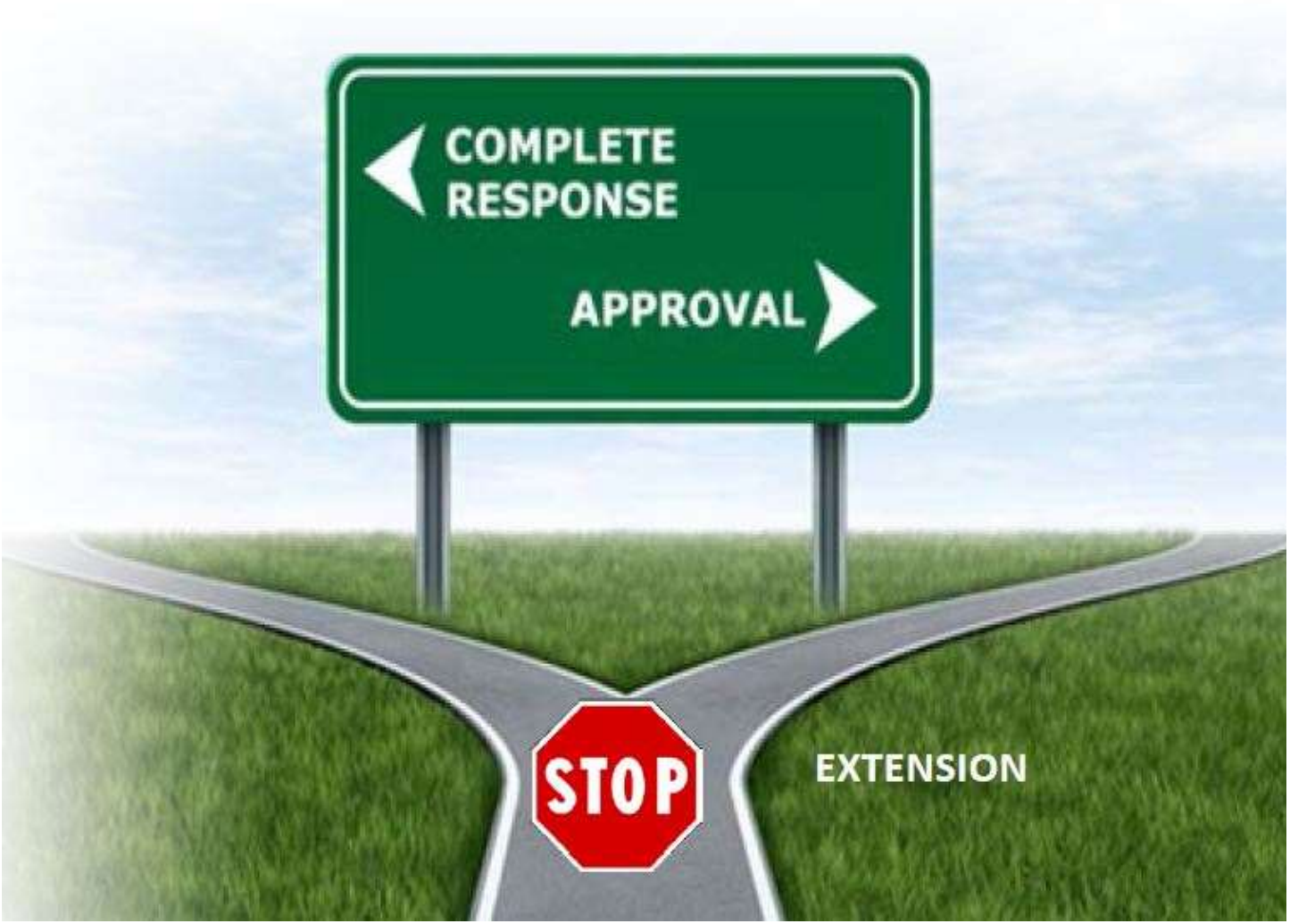


Image Credit: Hank Hoang, PharmD, MBA and Milena Lolic, MD, MS

Conclusions

- The MO is responsible for reviewing the evidence of efficacy and safety of a drug or biologic product from the clinical trials to conduct a benefit/risk analysis.
- The groundwork for the NDA/BLA Review takes place during the IND process.
- A well-organized (eCTD) and complete NDA/BLA submission allows the FDA review team to efficiently determine fileability and initiate the review.

Conclusions (continued)

- Well-organized and complete electronic data sets along with define files and reviewer guides enable reviewers to efficiently review the safety and efficacy data generated in the pivotal trials.
- The MO makes a recommendation about whether the product should be approved and how, if approved, the product should be labeled.

Challenge Question

Which of the following strategies may a medical officer recommend to mitigate the risk of an adverse reaction (AR) demonstrated in clinical trials?

A. Boxed warning
B. List AR in WARNINGS AND PRECAUTIONS
C. List AR in ADVERSE REACTIONS
D. REMS Program
E. Any of the above

Acknowledgements

CDER Reviewer Resources

DAVP
- Stephanie Troy, MD
- Prabha Viswanathan, MD
- Sarita Boyd, PharmD
- Stacey Min, PharmD
- Sarah Connelly, MD
- Adam Sherwat, MD
- Kim Struble, PharmD
- Debra Birnkrant, MD
- Jeff Murray, MD

Office of Antimicrobial Products
- John Farley, MD

REdI 2019 Speakers
- Swati Patwardhan, MS, RAC
- Jonathan Resnick
- Chao (Ethan) Chen

Resources

Drugs@FDA (labels, reviews) at:

https://www.accessdata.fda.gov/scripts/cder/daf/

FDA Guidance for Industry

https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry

Resources for drug labeling at:

https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

Questions?

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