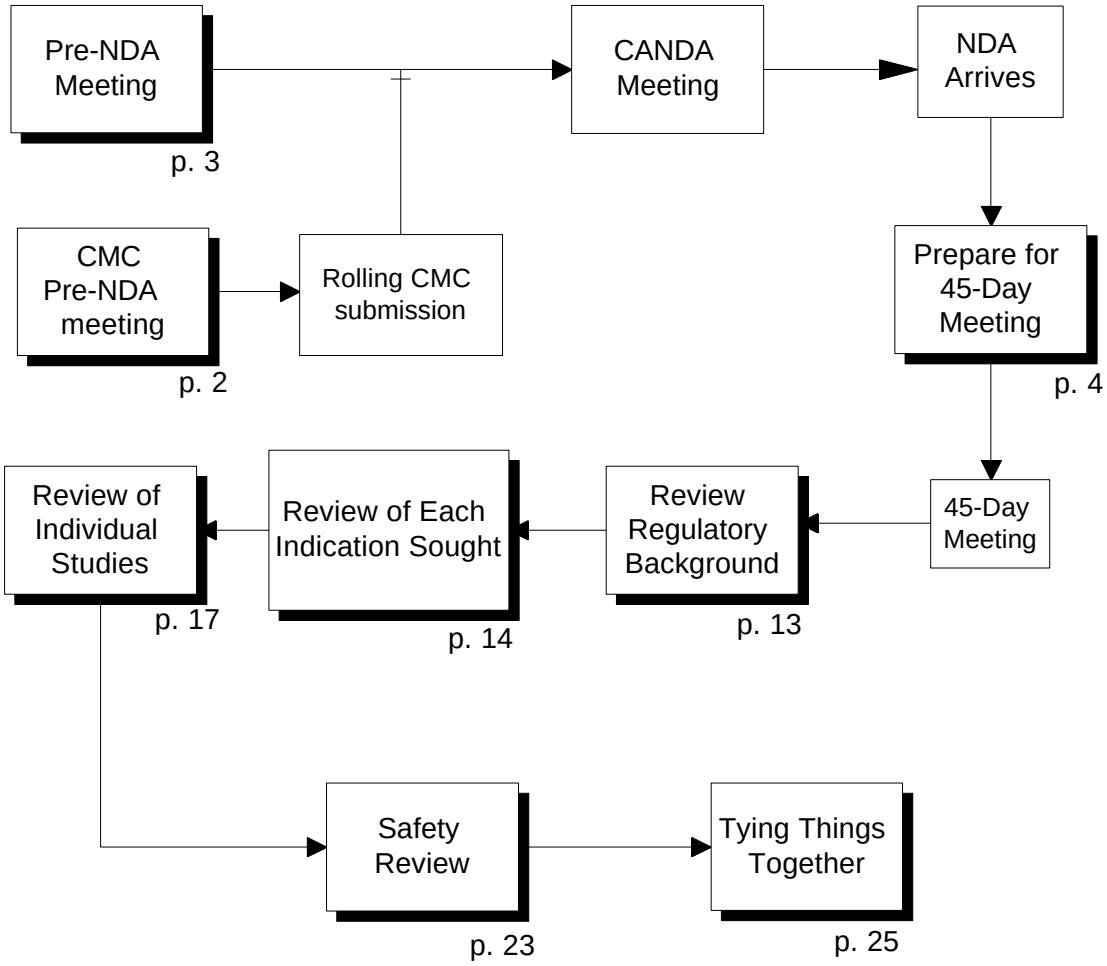
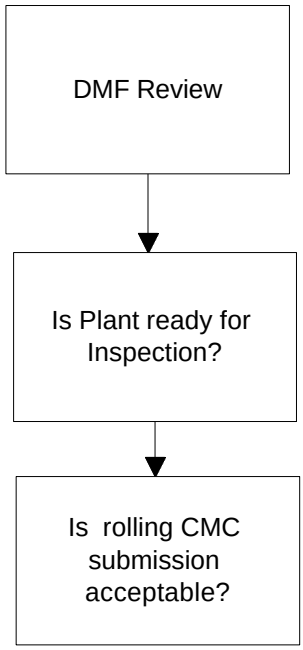
STEPS & ISSUES IN THE NDA REVIEW PROCESS

Nasim Moledina, Division of Anti-Infective Drug Products*

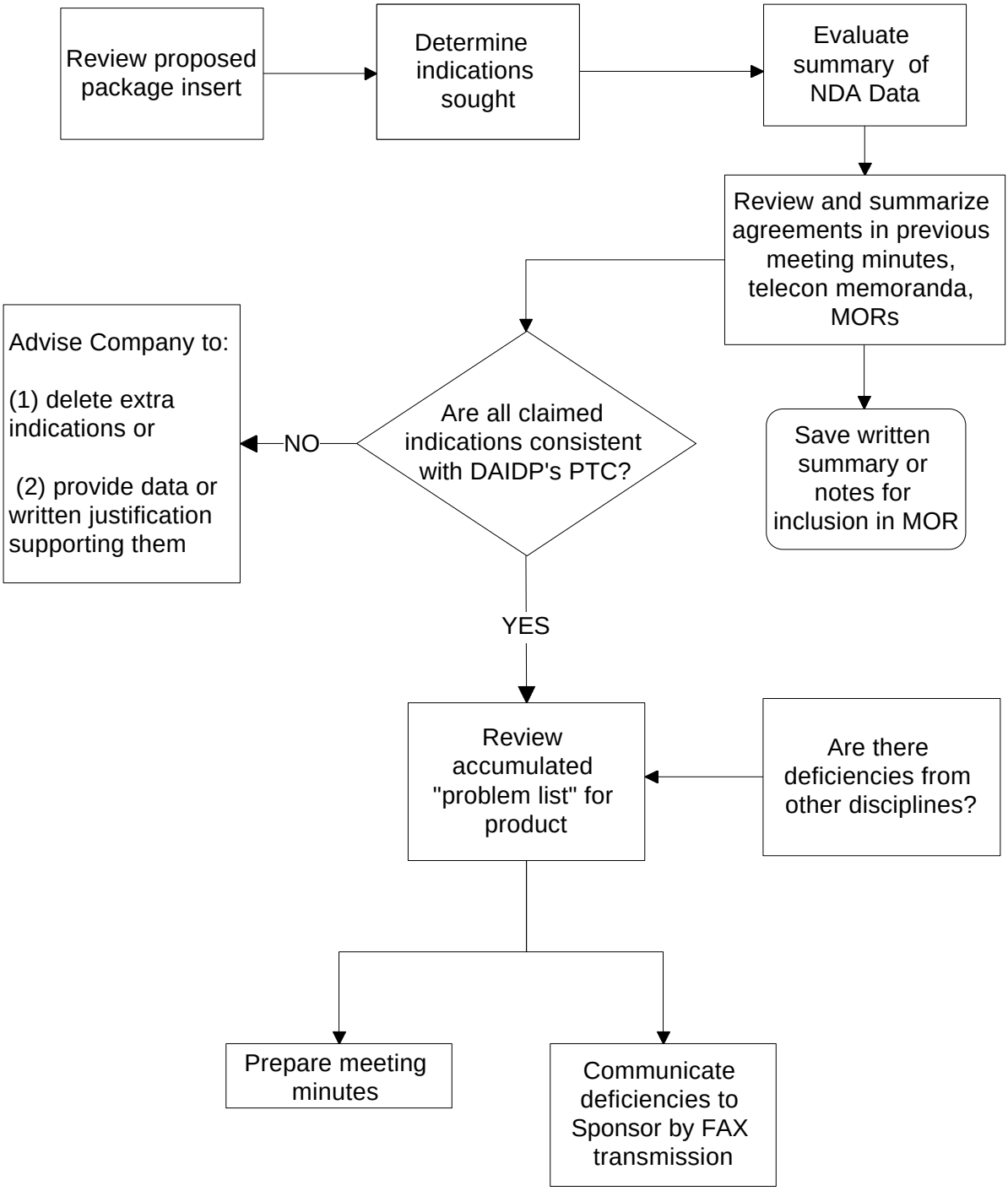


* Edited from a previous version created by Brad Leissa.

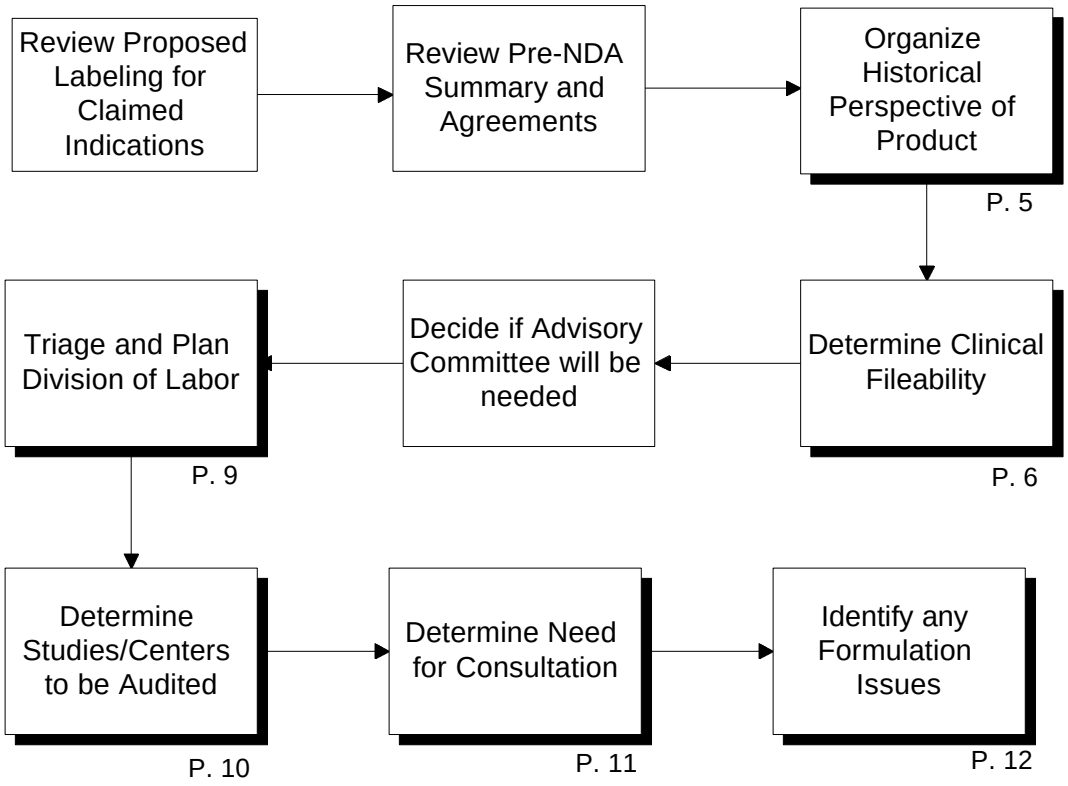
CMC PRE NDA MEETING



PRE-NDA MEETING



PREPARE FOR 45-DAY MEETING



C:\diagram\5.abc

Organize Historical Perspective of Product

ISSUES:

Are other formulations already approved?

If so, when and for which indications?

Were other drug formulations of this drug product submitted as NDAs but turned down?

Is this a resubmission based on a previous NA or AE action?

CLINICAL FILEABILITY

IS NDA ORGANIZATION ADEQUATE?

-Obtain Index and summary volumes

-For each study does the index list the location of Study Report, Protocol, Listings, and Investigators?

-Do summaries list for each indication the number of patients and the number clinically evaluable?

WERE AGREEMENTS KEPT?

-Using study summaries determine # of patients for each indication.

-Working with statistician calculate power for each indication.

-Compare to PreNDA agreements and to the cure rate needed.

-Are there enough studies for each indication?

Assess Quality of Data Submitted

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Evaluate Electronic Submission
-Is organization adequate?
-Can data be accessed with available software?
-Has Applicant submitted a written verification of the validity of the data in the CANDA?

Are Foreign studies evaluable?

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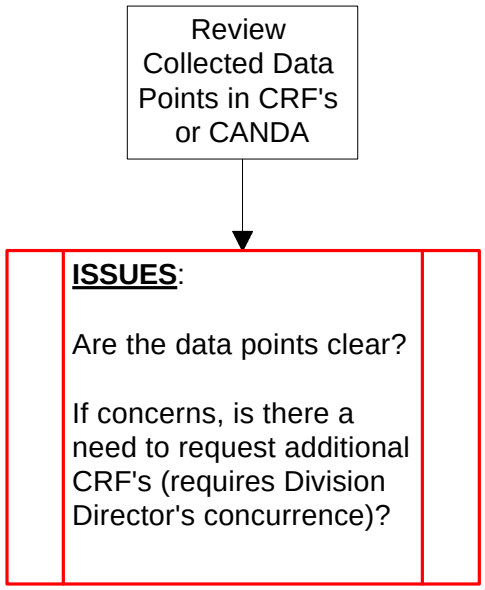
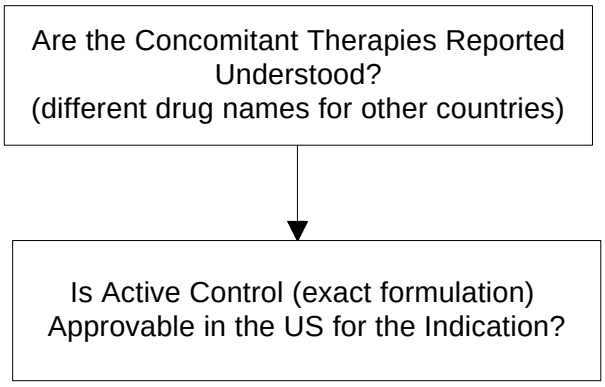
ASSESS QUALITY OF DATA SUBMITTED

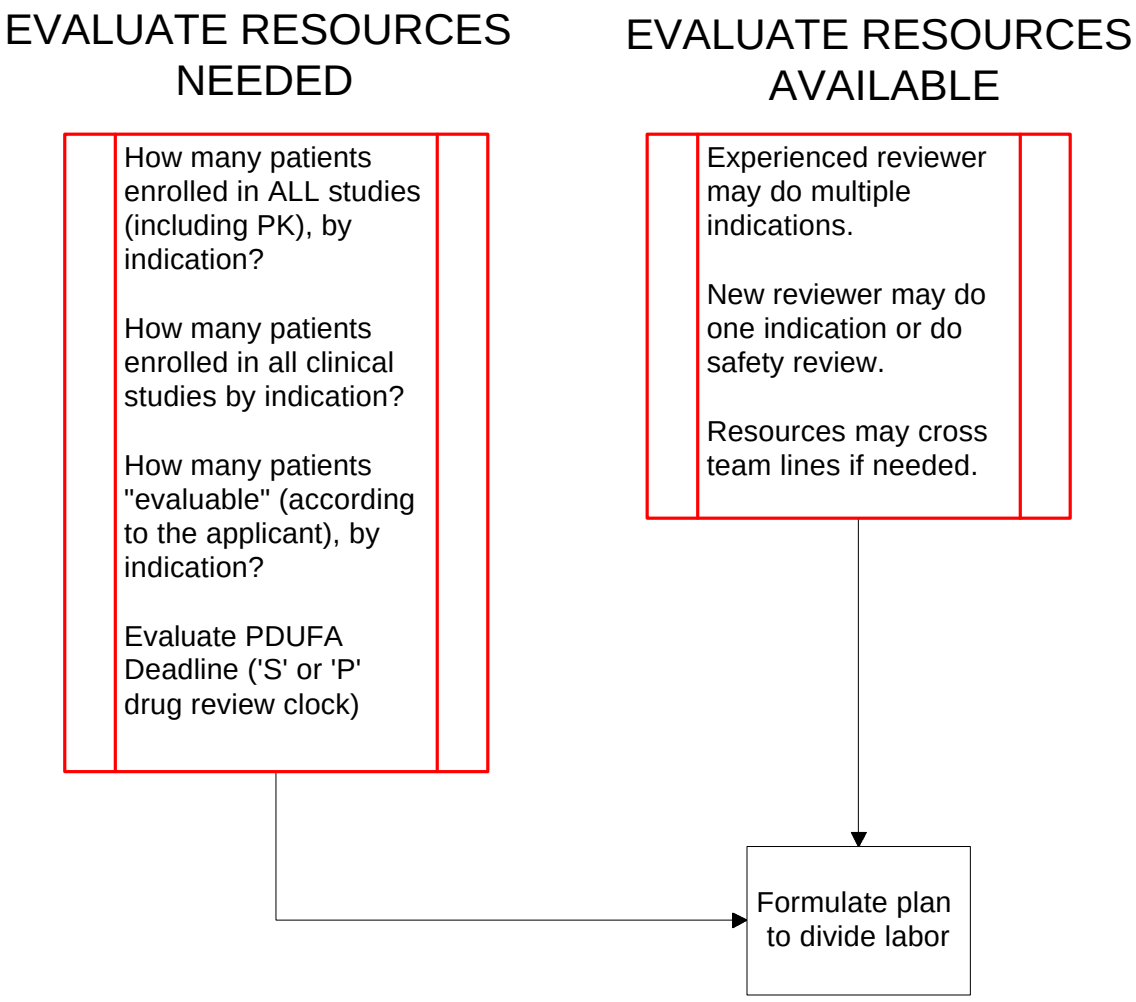


NOTE: In most large NDAs it may not be possible to evaluate data quality prior to the decision whether to file the NDA.

Foreign Studies



TRIAGE AND PLAN DIVISION OF LABOR



DETERMINE STUDIES/CENTERS TO BE AUDITED

ISSUES:

Is the study pivotal?

Are there concerns about the quality of the data?

DETERMINE NEED FOR CONSULTATION

ISSUES:

Do any organizations need to be consulted? Examples are:

CDER Review Divisions
- *DAVDP*
- *Reports Evaluation Branch*
- *Medical Imaging*
- *Gastrointestinal*

Other Centers
- *CBER*
- *CDRH*

General Counsel

Other Regulatory Authorities
- *CDC*
- *HPB*
- *WHO*

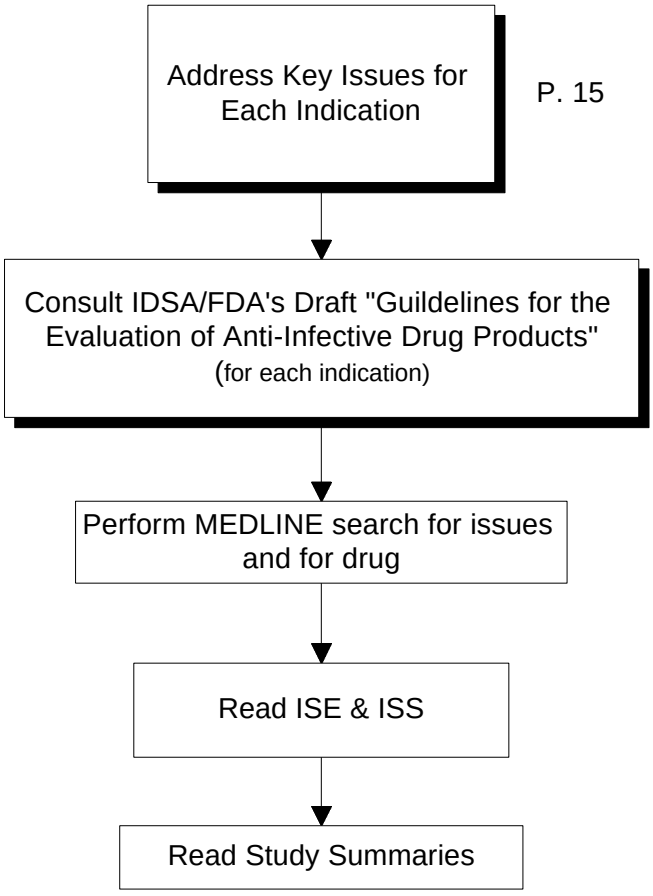
FORMULATION ISSUES

	1. Were the formulations used in clinical trials bioequivalent to the to-be-marketed formulation? 2. If more than one NDA submitted (two or more formulations of the same product), and clinical study done using only one formulation, are they bioequivalent?	

Review Regulatory Background

	<u>ISSUES</u>: Is the drug marketed in any other country? Is a dossier currently under review by another regulatory authority? Was an application submitted to another regulatory authority and rejected? If so, why?	

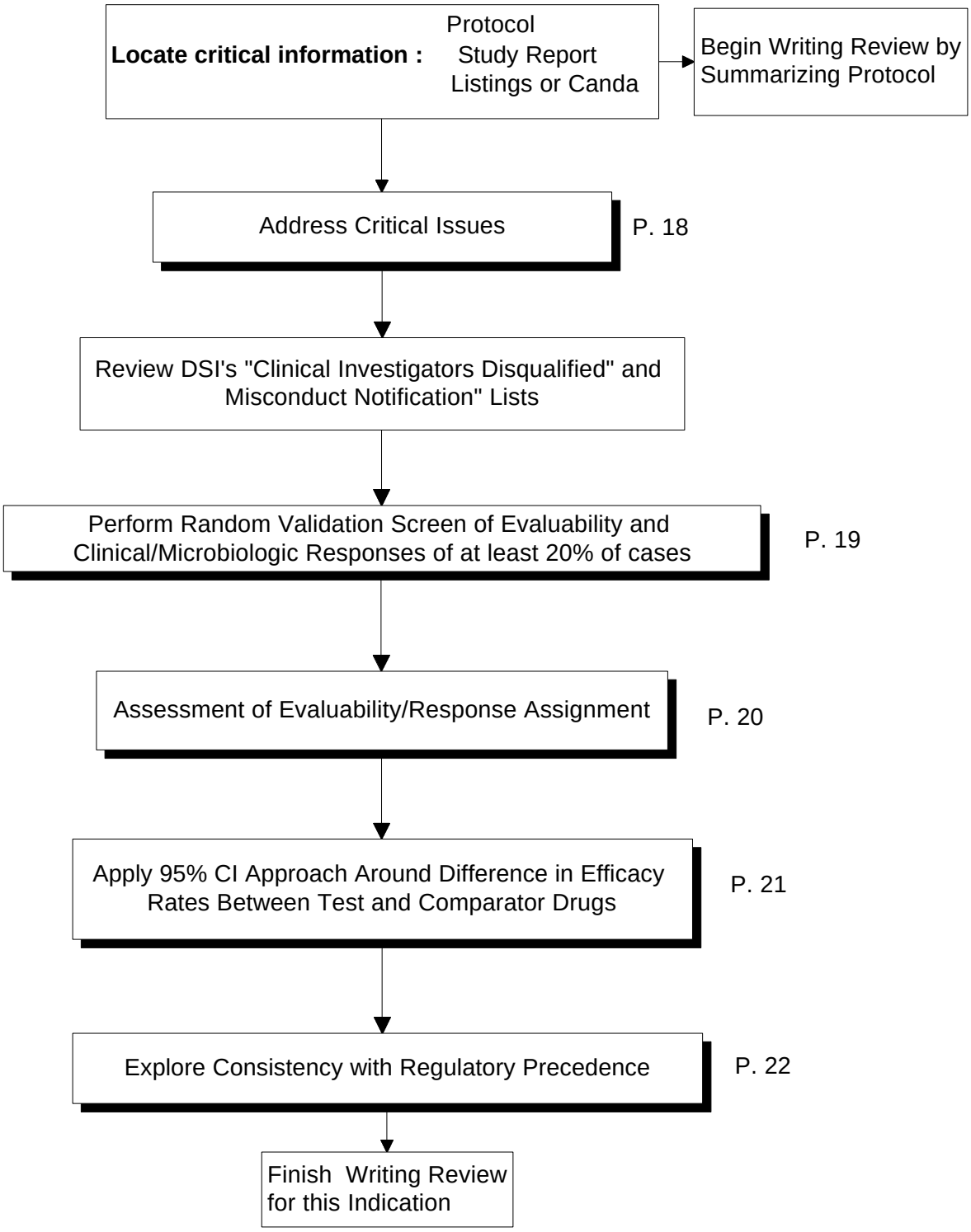
REVIEW OF EACH INDICATION SOUGHT



ADDRESS KEY ISSUES

	<u>ISSUES</u>: Were the studies conducted under an IND? If not conducted under an IND (foreign), findings may be considered supportive. Was informed consent (including verbal) obtained for all studies? If foreign studies were conducted, did they adhere to the Declaration of Helsinki? If not, it may invalidate the study. Did the applicant choose the appropriate test-of-cure visit in their analysis? Were the appropriate analytical points collected and scored by the study design? (Evaluate protocol design and data found in listings)	

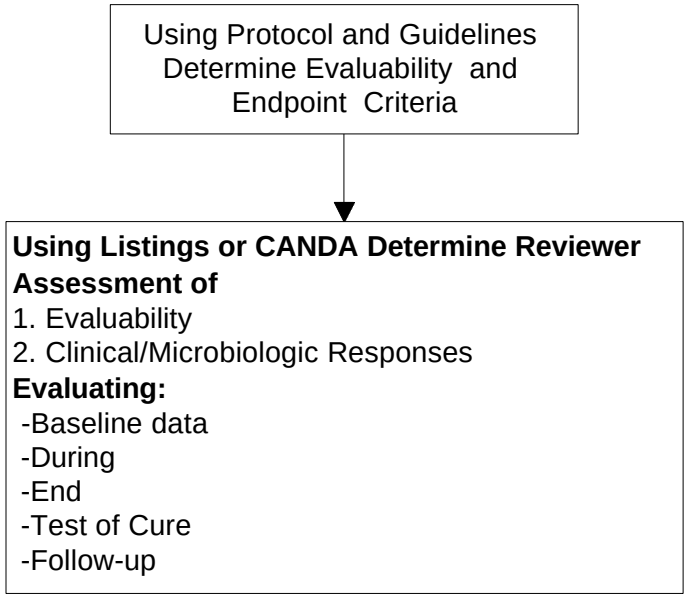
REVIEW OF INDIVIDUAL STUDIES



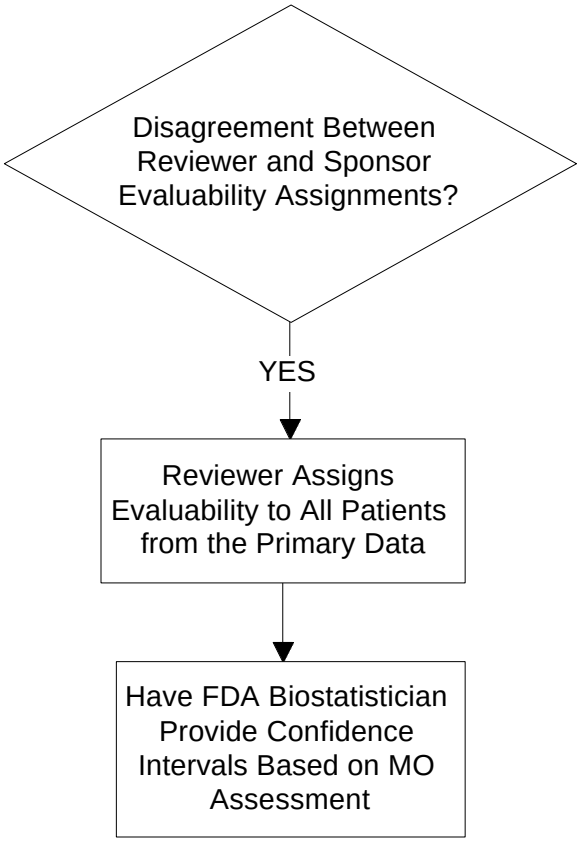
ADDRESS KEY ISSUES FOR EACH INDICATION

	ISSUES: Are there enough studies for each indication sought? Are the design of the studies for each indication consistent with the PTC?	

RANDOM VALIDATION SCREEN OF EVALUABILITY AND CLINICAL/MICROBIOLOGIC RESPONSES



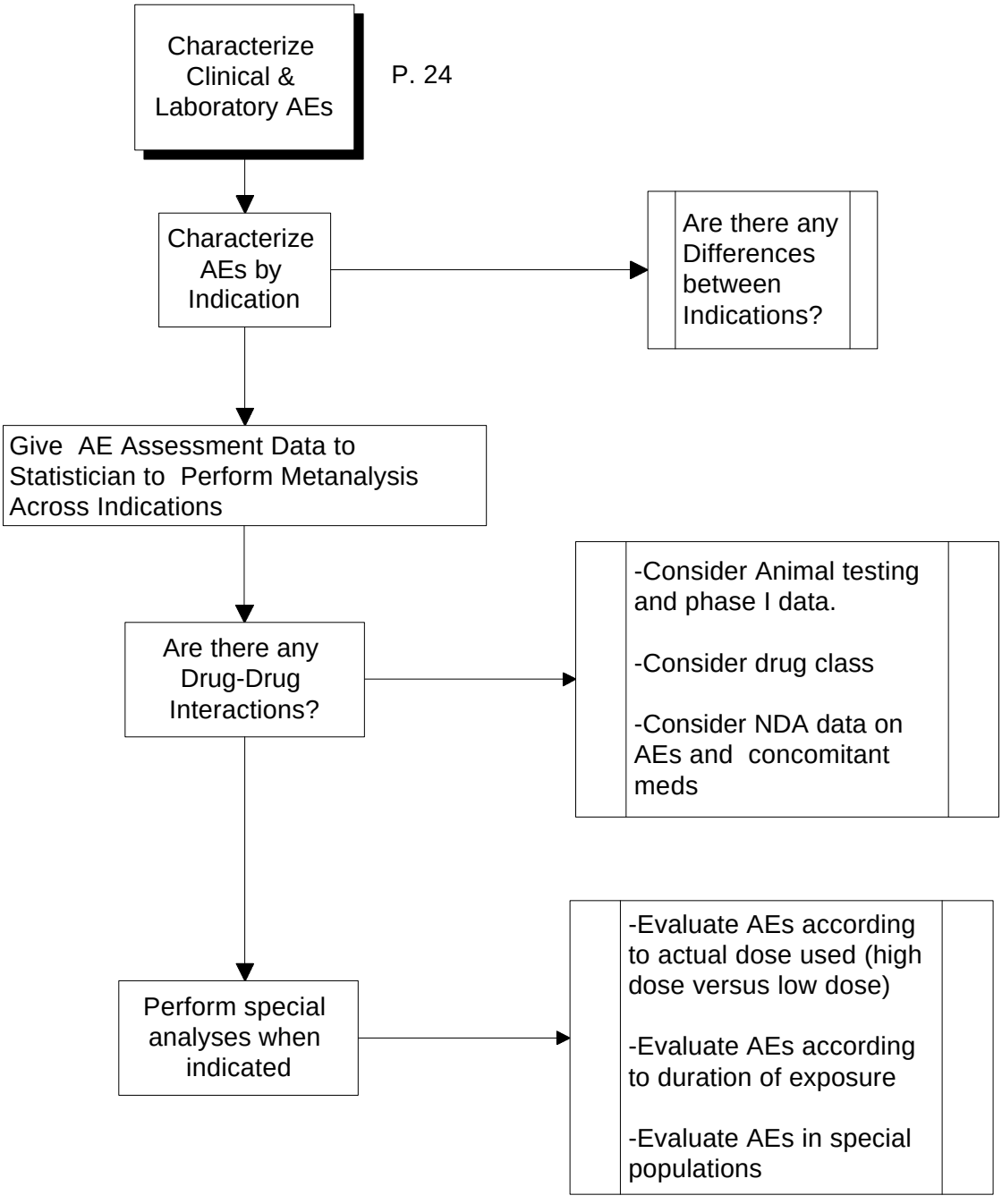
EVALUABILITY/RESPONSE ASSIGNMENT



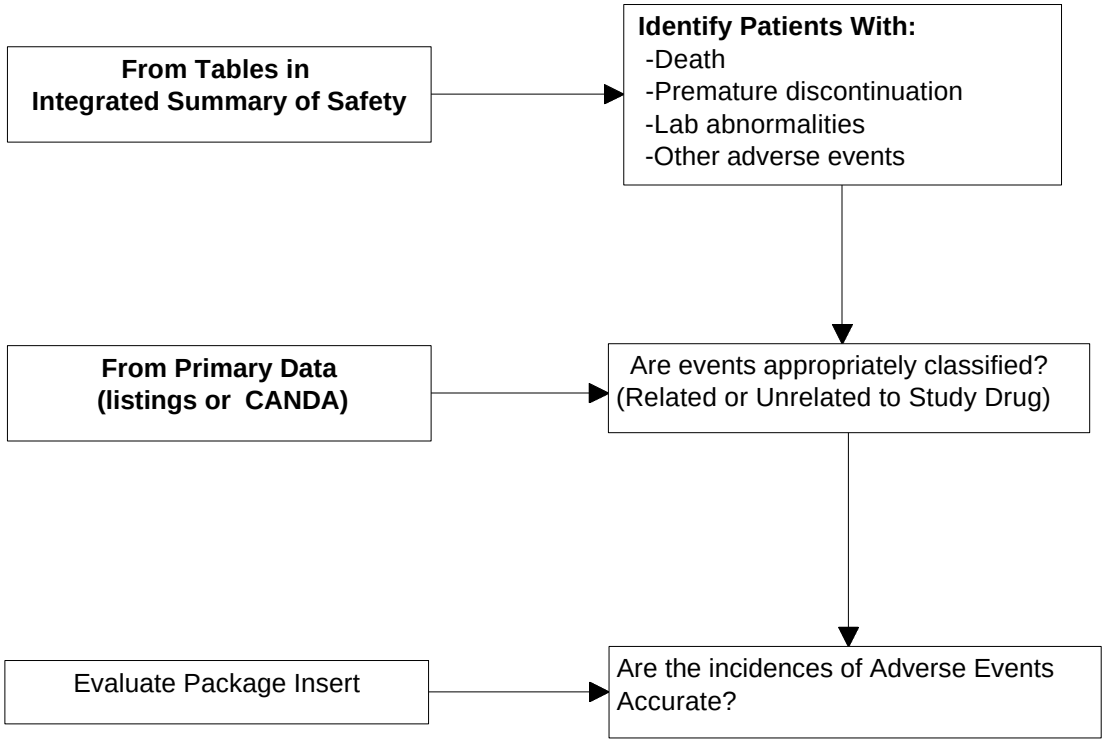
CONSISTENCY WITH REGULATORY PRECEDENCE

	ISSUES: How was the indication reviewed in recent applications? Have we set a "regulatory precedence" in previous regulatory decision-making? If so, this may influence the standard by which efficacy and safety are judged.	

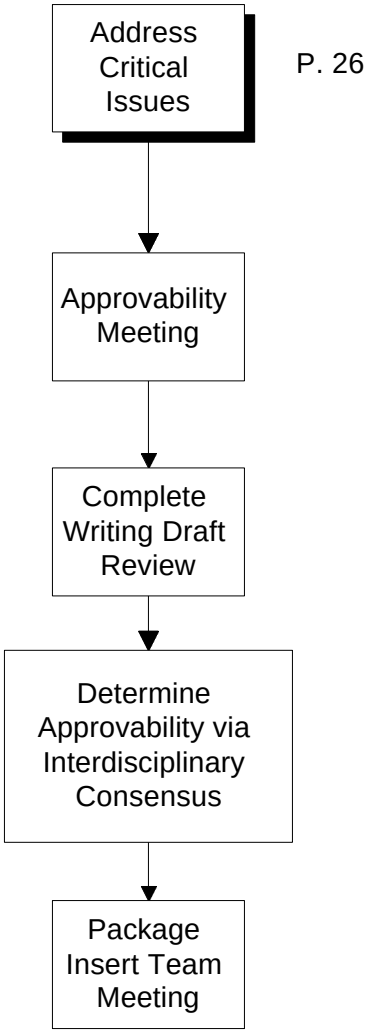
Safety Review



Characterize Clinical & Laboratory AEs



Tying Things Together



Critical Issues

	ISSUES: Can approvability of one treatment indication be used to support the approvability of another indication (e.g., intra-abdominal infections & GYN infections) Is this the first drug product available to treat this infection? This may infuence the standard by which efficacy and safety are judged. Although efficacy may not demonstrate equivalence, are there overriding patient drug compliance or safety benefit issues that weigh in favor of the new product?	