U.S. FOOD & DRUG ADMINISTRATION

Major Deficiencies and Facility Issues in Type II DMF

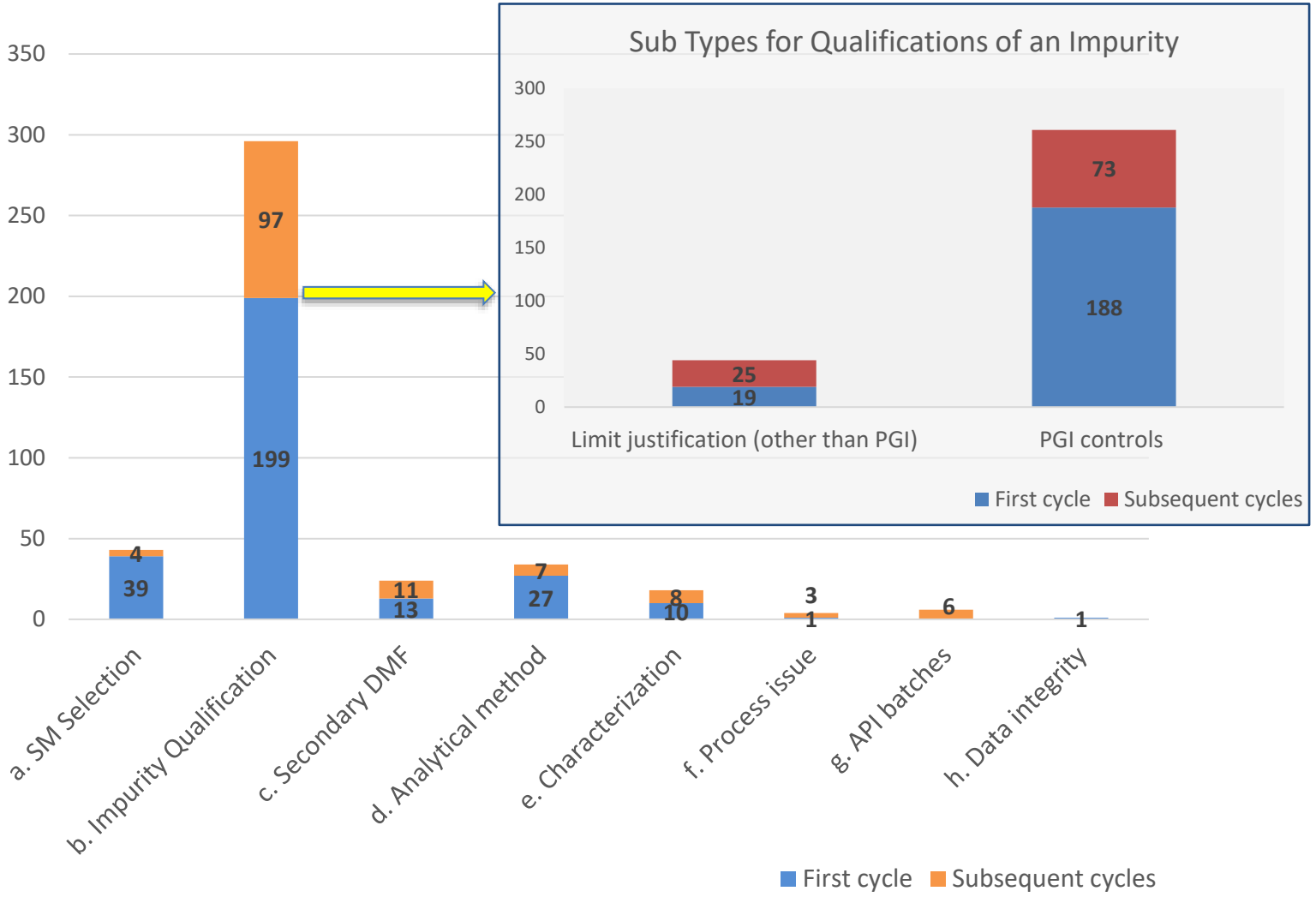
Wei Liu, Ph.D.
Division of Life Cycle API
Office of New Drug Products
Office of Pharmaceutical Quality
CDER/FDA

SBIA
July, 2020

DMF Major Deficiencies by Category

(Oct. 2017 ~ Jun. 2020)

- 234 first cycle DMFs have major deficiencies, which accounted for 25% first cycle DMF assessments .
- 83% of major deficiencies are "qualification of an impurity."



DMF Major Deficiencies

Qualifications of an impurity (83% of major deficiencies)

- ICH Q3A
- ICH M7
- Guidance for Industry ANDAs: Impurities in Drug Substances
- ICH Q3C

Impurity Qualifications in DMF Assessment

Impurity	Qualification Method	Assessment Timelines
Regular Impurity	Same limit in USP monograph	Immediate
	ICH Q3A Qualification Threshold	Immediate
	Side-by-side comparative analytical studies against RLD	Immediate
	Scientific literature and significant metabolites	Pharm/Tox consult, ~ 3 months
	Toxicity studies	Pharm/Tox consult, ~ 3 months
Genotoxic Impurity	General control options per ICH M7	Immediate
	(Q) SAR report	ComTox consult, 2 weeks
	ICH M7 Note 4 and Note 5	Pharm/Tox consult, ~ 3 months
	Ames report	Pharm/Tox consult, ~ 3 months
	Scientific literature	Pharm/Tox consult, ~ 3 months
Solvent	ICH Q3C limit	Immediate
	Scientific literature and Toxicity studies	Pharm/Tox consult, ~ 3 months

DMF Major Deficiencies (cont.)

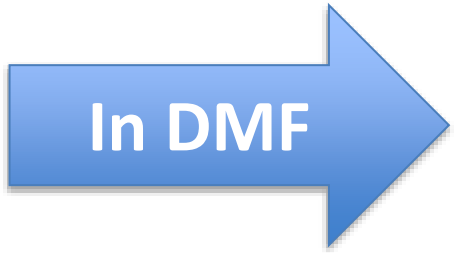
Selection of Regulatory Starting Material (12% of major deficiencies)

- ICH Q11 and Q&A represent the Agency's current thinking.
  - All general principles in section 5 should be considered. The presence of a "significant structural fragment" should not be the sole basis for justification.
- A starting material (SM) in ICH Q11 is same as an "API SM" in ICH Q7.
- Inappropriate selection of a regulatory SM resulting in reclassification of a proposed SM as a late stage intermediate, which is subject to the guidance on GMPs for APIs, i.e. ICH Q7.

DMF Facilities

ANDA Major Amendment:

Facilities: Any amendment that provides for a new facility that requires comprehensive evaluation



a. Inappropriate selection of regulatory SMs
b. Reference to a 2nd DMF whose product may be a critical intermediate
c. Outsourced API testing sites
d. Outsourced intermediate sites

…

DMF Facilities (cont.)

- The following facilities in DMF need to be included in NDA/ANDA 356h form:
  - Final drug substance manufacturing, micronization and testing sites (see slide 19) that are proposed to be involved in the disposition of commercial product.
  - Site for intermediates addressed by ICH Q7.
- The facilities that are in the DMF but do not appear on the NDA/ANDA 356h form are referred as hidden facilities.

GMP Requirement for API

ICH Q7 represents the Agency's current thinking on GMPs for APIs.

- Section 501(a)(2)(B) of the Act, requires all drugs to be manufactured in conformance with CGMP, including APIs.
- API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory GMP requirement.

ICH Q7: GMP Requirement for API

Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
"Classical" Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

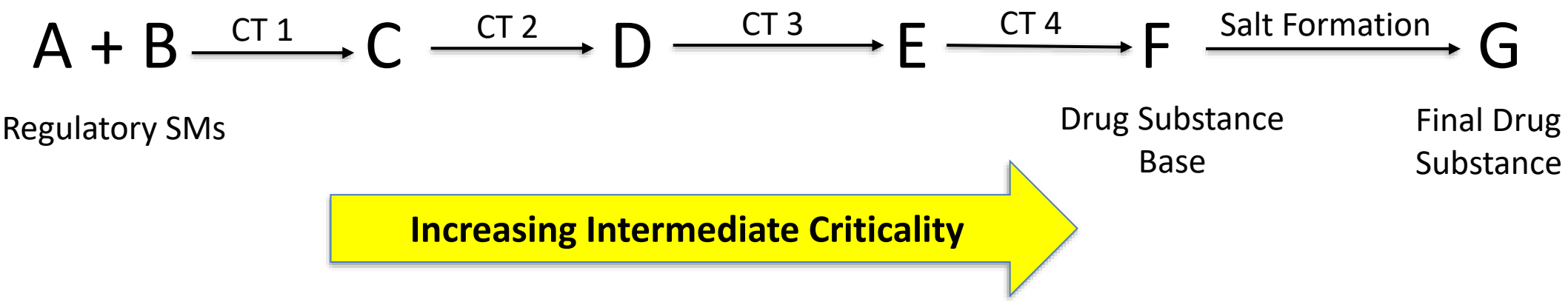
Increasing GMP requirements

- An **accepted** regulatory SM is the starting point of GMP.
- The manufacturing process of all intermediates is subject to GMP.

Critical Intermediate

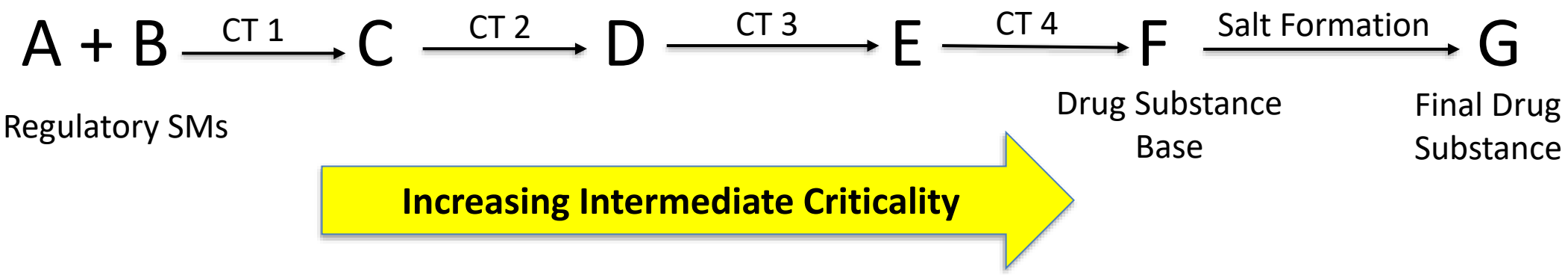
- Critical Intermediate is an intermediate whose manufacturing process is deemed so important to quality of the finished API that the manufacturing site needs to be part of the facility evaluation for the referencing application.
- Determination is made on a case-by-case basis using principles as outlined in ICH Q11 as well as the supporting data.
- DMF assessor makes the recommendation on intermediate criticality based on manufacturing process of API and the Office of Pharmaceutical Manufacturing Assessment makes the determination if an intermediate facility needs a comprehensive evaluation.

Critical Intermediate (Cont.)



- A & B: Acceptable regulatory SMs complying with the principles in ICH Q11.
- CT: Chemical transformation; Typically it involves C-X or C-C bond formation or breaking.

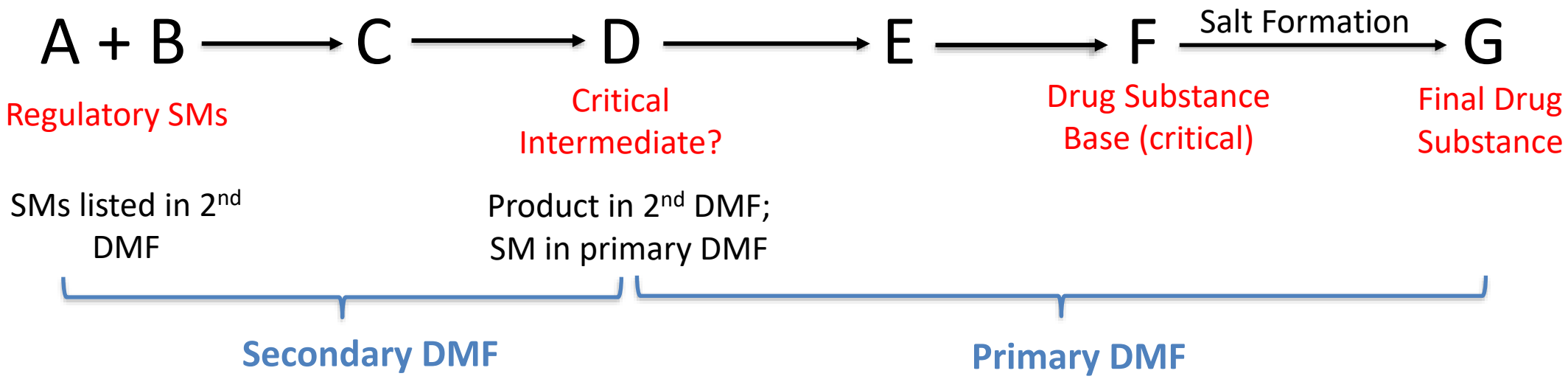
Critical Intermediate (Cont.)



- The considering factors includes (but may not limited to):
  - Overall synthetic scheme
  - Complexity of chemistry and final API
  - Understanding of impurity fates and supporting data
  - In-process controls and intermediate specifications
- Generally in-situ intermediate would not allow opportunities to remove impurities and thus not be considered as a separate CT step.

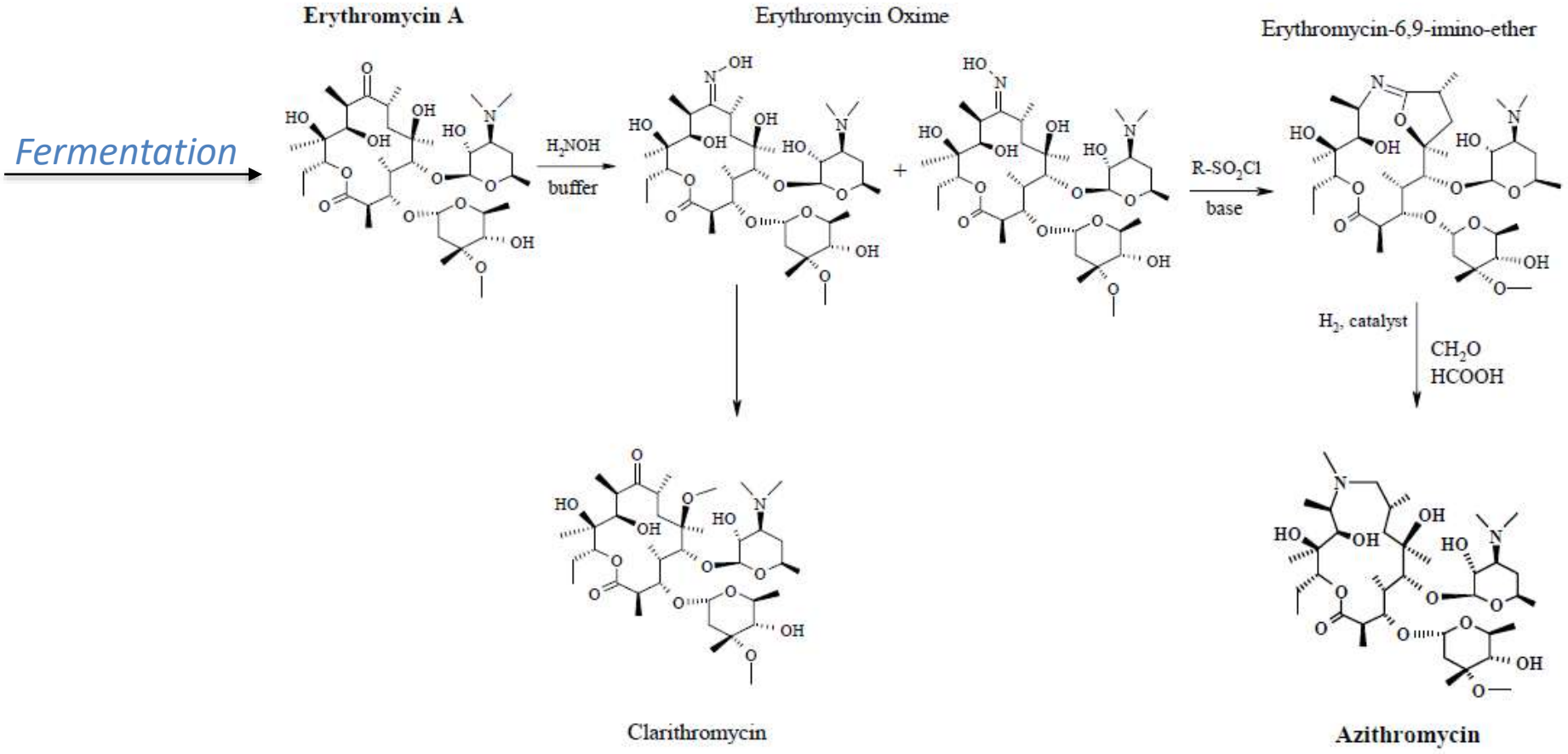
Critical Intermediate (Cont.)

- The determination of critical intermediate is based on complete manufacturing process from the regulatory SM to final API.
  - The regulatory SM may NOT be the "SM" listed in S.2.3 in your DMF when the secondary DMF is referenced.



Critical Intermediate (Cont.)

- The same intermediate which is “non-critical” in a process may be considered “critical” for a different manufacturer’s process.



Taken from ***Antibiotics*** 2016, 5, 29, “From Erythromycin to Azithromycin and New Potential Ribosome-Binding Antimicrobials”.

Current Hidden Facility Identification in DMF Assessment

Stage	Assessment
TCIR* for all original ANDA applications and resubmissions under GDUFA II	➢ Looking for facility discrepancies between what the applicant lists on their 356h form for API sites in ANDA and what the DMF lists for these facilities in the DMF. ➢ Issue comments to the applicant when there are discrepancies or ambiguities in the facility information.
DMF CMC Assessment for all NDA/ANDA applications	➢ Identify DMF facilities which are required to be listed in the applicant 356h form based on facility functions. ➢ Check if required facilities are listed in the applicant 356h form. ➢ Issue comments to DMF holder and/or applicant for any discrepancies or ambiguities.

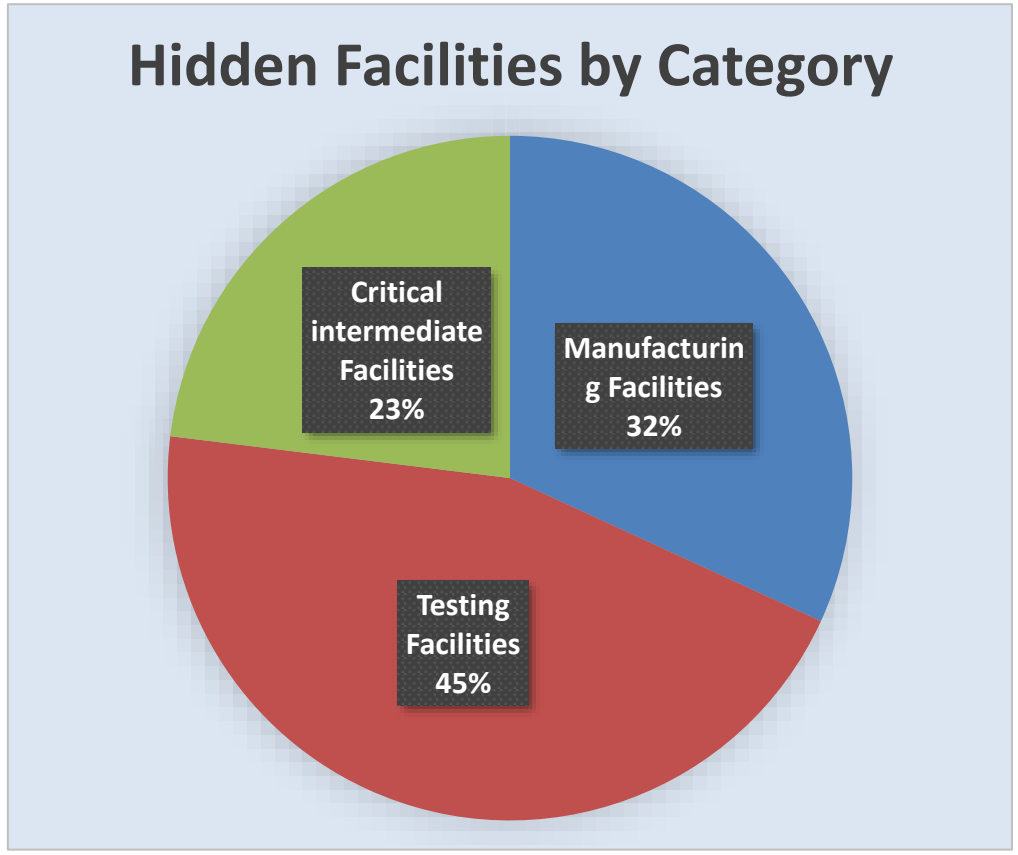
* TCIR: Timely Consults and Information Request

Timely Consults and Information Requests (TCIR) Process

- TCIR is one of the Agency's efforts to improve the opportunities for first cycle approvals.
- TCIR is implemented for all original ANDA applications and resubmissions under GDUFA II.
- Hidden facility identification (discrepancies) is one of the areas covered in TCIR process.
  - New facilities discovered late in the ANDA assessment cycle do not allow sufficient time for evaluation or inspection and may prevent an approval.

TCIR - Hidden Facilities

Description (Oct. 2017 ~ May 2020)	Number
Total number of unique ANDAs evaluated	2405
Number of applications with at least one hidden facility	363
Total number of hidden facilities identified	499
Overall percentage of ANDAs with a hidden facility issue	15.1%



- This high number is indicative of poor communication between applicants and DMF holders regarding the DMF related facilities that support their ANDAs.

How can industry improve?

- List all required facilities in S.2.1 in DMF:
  - Final API manufacturing and testing sites (see next slide)
  - Intermediate sites performing operations addressed by ICH Q7
- Clearly indicate the responsibilities of each facility in DMF.
- Communicate all required facilities and their responsibilities **early** to NDA/ANDA applicant(s).
  - The Agency considers all facilities that are listed in a DMF applicable to the referencing NDA/ANDA unless explicitly stated in the DMF LOA that only certain facilities will be used

Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers, Guidance for Industry, October 2019, Revision 1

How can industry improve? (cont.)

Required Facilities in DMF:

- Final API manufacturing and testing sites **(including alternates)**
  - API manufacturers
  - API routine commercial release/stability testing sites, including microbial testing
  - Facilities that micronize the API
  - Facilities that directly sterilize the API
  - Facilities used for storing or warehousing the API prior to a disposition decision, including that solely store the stability samples
  - For animal/plant-derived products, the facilities that perform crude extraction prior to purification of API

Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers, Guidance for Industry, October 2019, Revision 1

Summary

- Qualification of an impurity is the main reason for major deficiencies in DMFs. Following the relevant guidelines and choosing an appropriate qualification method may help to avoid the major deficiencies.
- DMF hidden facility identification is another potential barrier for application approval. List all required facilities and their responsibilities in Section S.2.1 of the DMF. Communicate **early** with drug product applicant to facilitate the application assessment and application approval.
- Determination on critical intermediate is made on case-by-case basis with risk assessment. Appropriate control strategy with supporting data may help to lower the risk.

Acknowledgement

- David Skanchy
- Ramnarayan Randad
- Barbara Scott
- Jayani Perera
- Hongbiao Liao
- Ying Zhang

Thank you

Please send comments to DMFOGD@fda.hhs.gov