

Drug Substance Facilities – Hidden and Critical Intermediate Sites

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Drug Substance Facilities

- The following facilities in DMF are recommended to be included in NDA/ANDA 356h form:
 - ❖ Final drug substance manufacturing, micronization, sterilization and testing sites (see slide 12) that are proposed to be involved in the disposition of commercial product.
 - ❖ Sites for intermediates addressed by ICH Q7.
 - ❖ Facilities used for storing or warehousing drug substance prior to a disposition decision, including that solely store the stability samples.
- The required facilities that are in the DMF but do not appear on the NDA/ANDA 356h form are referred as hidden facilities.

Hidden Facilities in DMF

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



- a. Inappropriate selection of regulatory starting material (SM).
- b. Reference to a 2nd DMF whose product may be a critical intermediate.
- c. Outsourced API testing sites.
- d. Outsourced intermediate sites.

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

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



Current Hidden Facility Identification in DMF Assessment

Stage	Assessment
TCIR* for all original ANDA applications and resubmissions under GDUFA II	<ul style="list-style-type: none">➤ 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.➤ Evaluate if the regulatory SM is acceptable for original DMFs and issue comment to DMF holder as necessary.
DMF CMC Assessment for all NDA/ANDA applications	<ul style="list-style-type: none">➤ 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

If a hidden facility is identified, the following comment will be sent to A/NDA applicant:

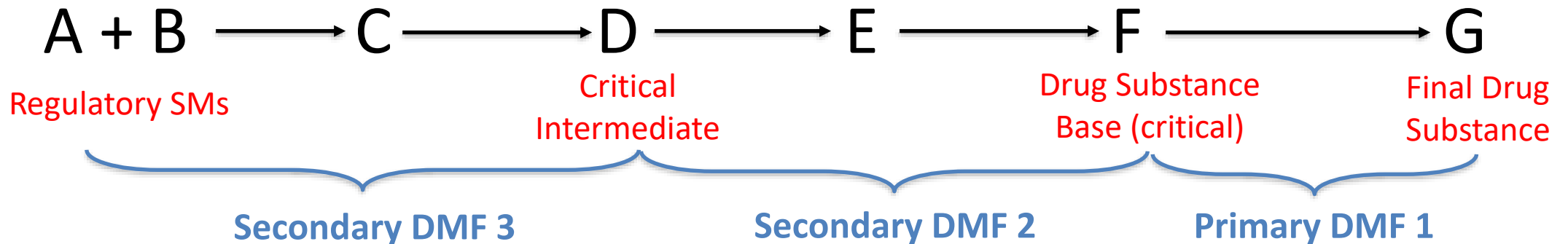


*There is a facility/are facilities (e.g. DS manufacturing, intermediate, or release/stability testing sites) that is/are included in DMF [primary DMF#] **OR** a DMF that is referenced by DMF [primary DMF#] for [API name] that was/were not listed in your application (i.e. Form FDA 356h and/or in Section 3.2.S.2.1). **Please note that the Agency cannot provide to you the status of facilities not listed in your application.** Please contact your DMF holder to identify and resolve any discrepancies and clarify which DMF related facilities support your application. We recommend that the DMF related facilities supporting your application be added to your Form FDA 356h and in Section 3.2.S.2.1. **If only a subset of the facilities in the DMF will be referenced by your application to support commercial manufacturing and/or testing, your LOA should specify those facilities.** Absent this specificity, the Agency intends to assume that all facilities listed in a DMF support your application. Note, there may be an extension of the performance goal date if any facilities have been added to the DMF since the last application assessment cycle. **For supplements only, a new supplement and revised 356h form will be required to add any new facilities to your application.***

If a hidden facility is identified, the following comment will be sent to A/NDA applicant (Cont.):

*There is a facility (e.g. DS manufacturing, intermediate, or release/stability testing sites) that is included in DMF XXX for API xxx (a DMF that is referenced by primary DMF xxx) that was not listed in your application (i.e. Form FDA 356h and/or in Section 3.2.S.2.1). **Please note that the Agency cannot provide to you the status of facilities not listed in your application.....***

- The LOA makes DMF as part of the referencing application, including the facilities in the DMF.
- When a secondary DMF is referenced, it includes the facilities in the secondary DMFs.



If a hidden facility is identified, the following comment will be sent to A/NDA applicant (cont.):



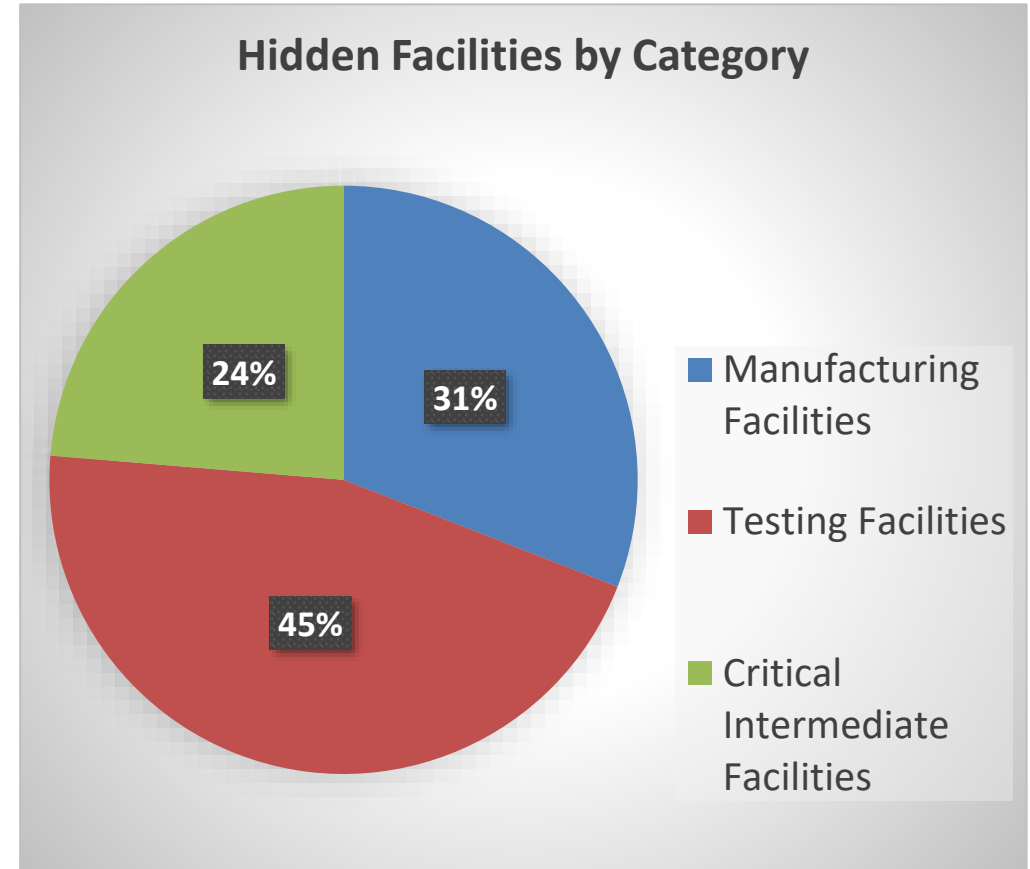
*There is a facility (e.g. DS manufacturing, intermediate, or release/stability testing sites) that..... Please note that the Agency cannot provide to you the status of facilities not listed in your application..... **If only a subset of the facilities in the DMF will be referenced by your application to support commercial manufacturing and/or testing, your LOA should specify those facilities.***

- Listing all required DMF facilities in A/NDA 356h form. This will facilitate:
 - ❖ The application assessment process.
 - ❖ The communication on application status between the Agency and the applicant.
- If only a subset of facilities in DMF will be referenced by the drug product application, specify those in the LOA.
- Whether or not a DMF facility is listed in the application will not change the determination whether a facility needs a comprehensive evaluation and/or may cause a potential barrier for application approval.

TCIR - Hidden Facilities

Description (Oct. 2017 ~ Dec. 2020)	Number
Total number of unique ANDAs evaluated	2739
Number of applications with at least one hidden facility	406
Total number of hidden facilities identified	553
Overall percentage of ANDAs with a hidden facility issue	14.8%

- 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.
 - ❖ Facilities used for storing or warehousing the API prior to a disposition decision, including that solely store the stability samples
- Clearly indicate the responsibilities of each facility in DMF:
 - ❖ If an intermediate site, indicate which intermediate.
 - ❖ If a testing site, indicate which test(s).
- 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.

How can industry improve? (cont.)

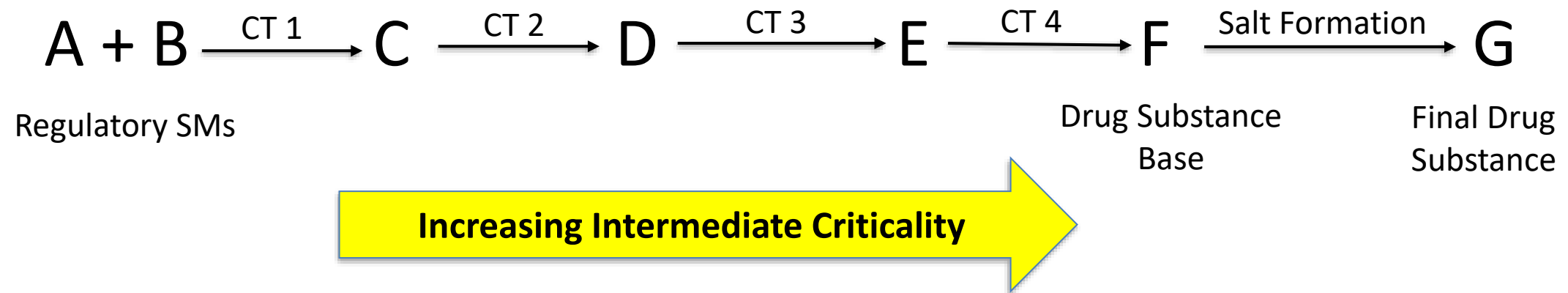
Required Facilities in DMF:

- 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
 - ❖ For animal/plant-derived products, the facilities that perform crude extraction prior to purification of API

Critical Intermediate

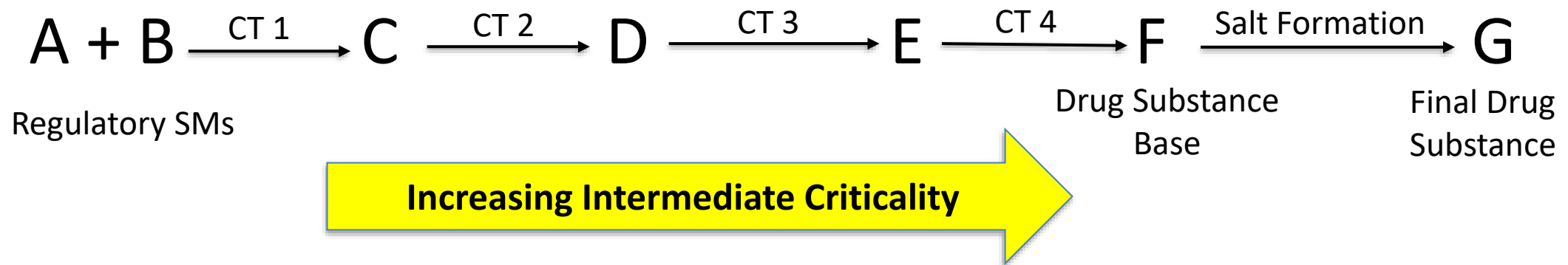
- Critical Intermediate is an intermediate whose manufacturing process is deemed so important to quality of the finished API that the manufacturing site needs to be part of the facility evaluation for the referencing application.
- Determination is made on a case-by-case basis using principles as outlined 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.

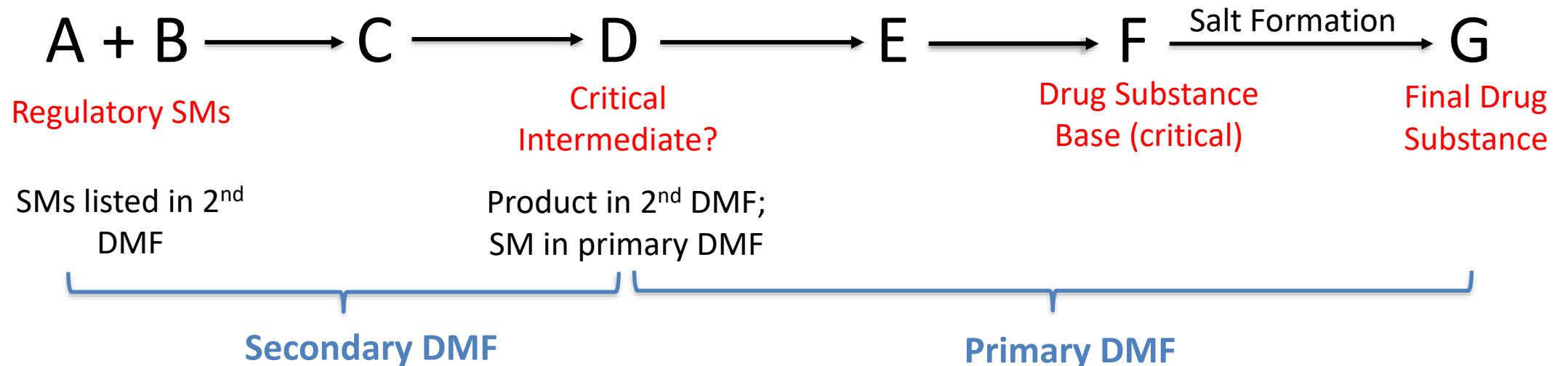
Critical Intermediate (Cont.)



- 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.

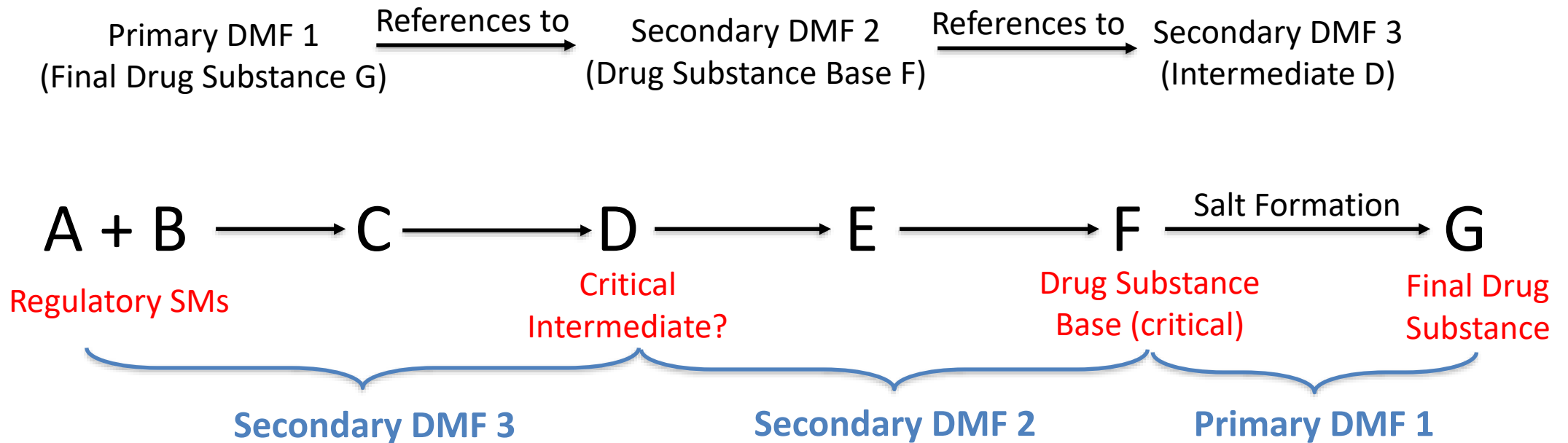
Critical Intermediate (Cont.)

- 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 a secondary DMF is referenced.



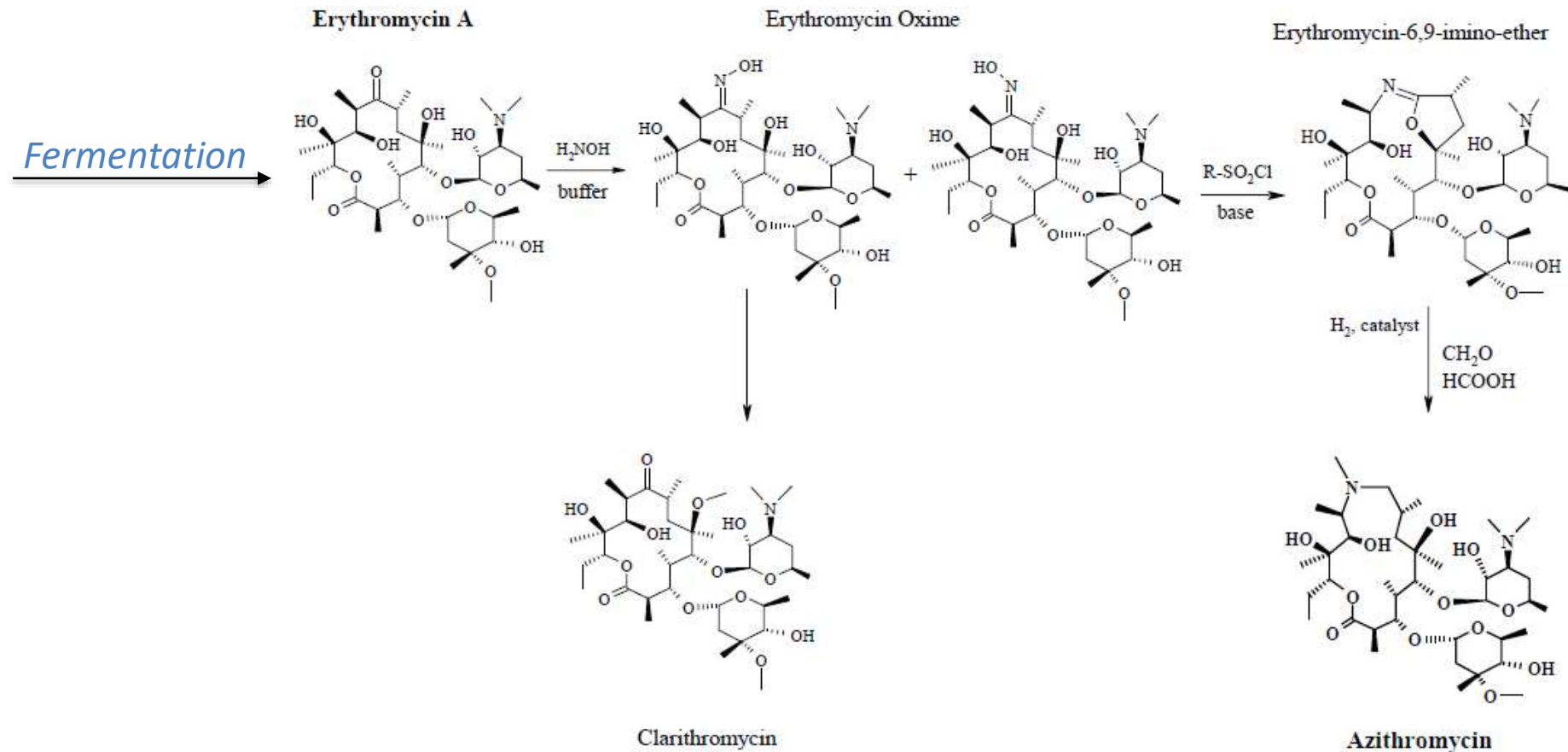
Critical Intermediate (Cont.)

- ❖ The regulatory SM may NOT be the “SM” listed in S.2.3 in your DMF when a secondary DMF is referenced – Can be extended to a chain of secondary DMFs



Critical Intermediate (Cont.)

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

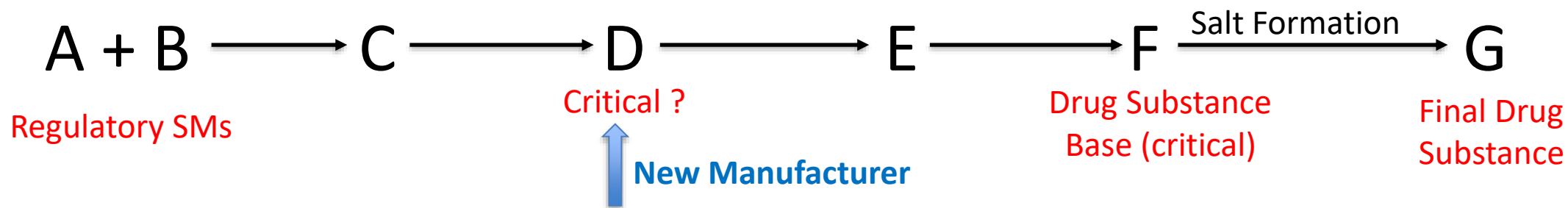


Taken from *Antibiotics* 2016, 5, 29, “From Erythromycin to Azithromycin and New Potential Ribosome-Binding Antimicrobials”.

Critical Intermediate (Cont.)



- Same principles also apply to post-approval changes
 - ❖ Post-approval submissions involving a new manufacturer for intermediate(s) should provide:
 - Name, address, FEI and DUNS for the new manufacturer
 - An evaluation of potential impact on impurity profile of intermediate and final API quality



- ❖ DMFs intended for reference in a generic drug submissions that are subject to the DMF fee under GDUFA may only contain a single drug substance process.

Summary

- DMF hidden facility identification is a 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

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Thank You!

- For questions regarding the content of this presentation, please type them into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.
- To submit questions on this presentation for inclusion in the follow-on webinar on April 9th, send them to: DMFWorkshop2021@fda.hhs.gov by March 19th.
- Please refer to the following presentations for additional information:
 - API Facility Inspections by Jay Jariwala
 - Starting Materials Selection ICH Q11 and Q&A by Anita Tiwari
 - Timely Consult and Early Information Request (TCIR) Process for Drug Master Files (DMFs) by Jayani Perera