

Timely Consult and Early Information Request (TCIR) Process for Drug Master Files (DMFs)

Jayani Perera – Chemist

*Division of Lifecycle API
Office of New Drug Products
Office of Pharmaceutical Quality, FDA/CDER*

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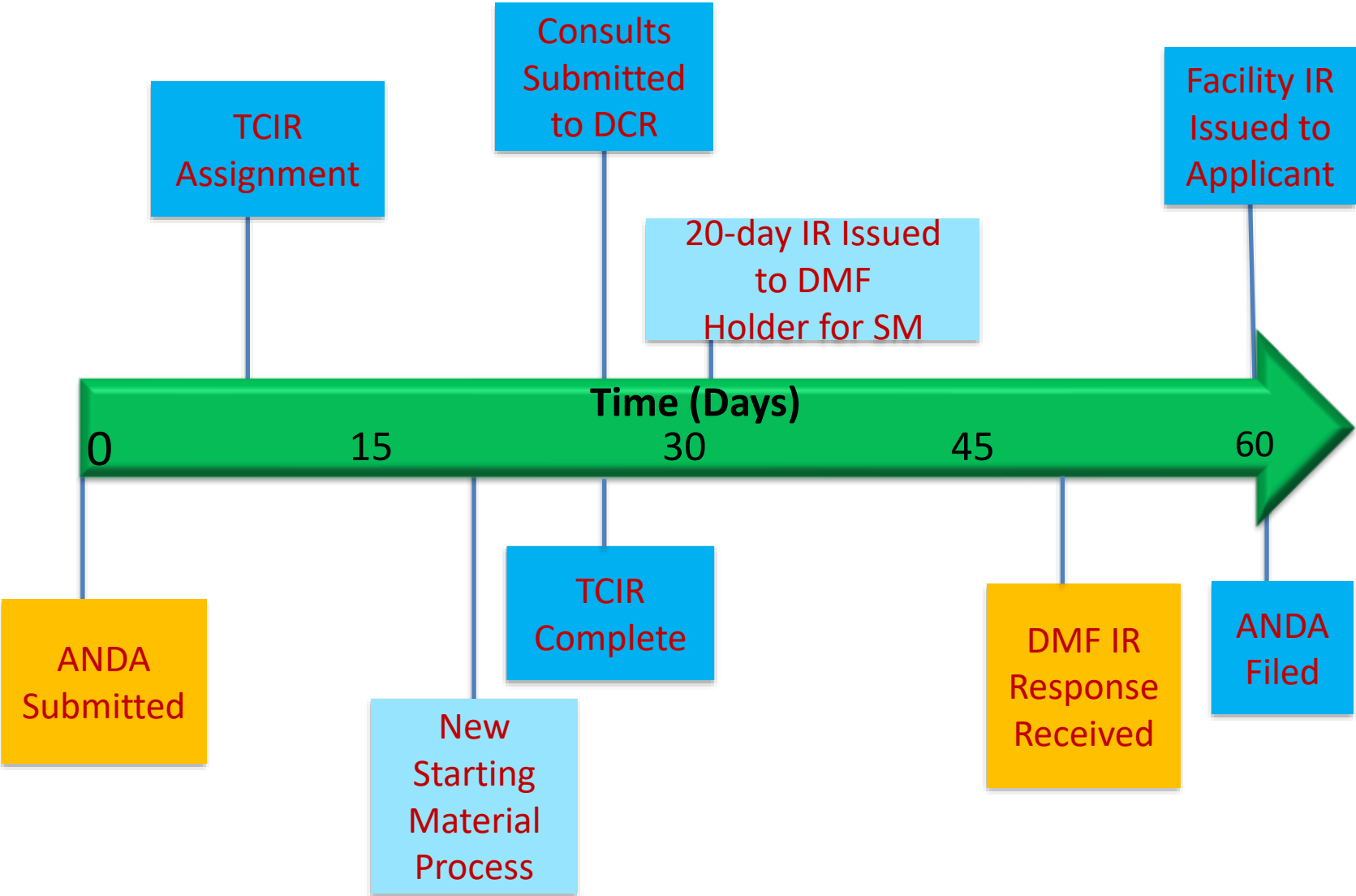
What is TCIR

- Process for early identification of ANDA review quality issues
- For all original ANDA applications
- Originally two focus areas:
 - Identification of facility discrepancies
 - Discovery of consultable information
- Designed prior to GDUFA II and implemented on October 1, 2018

TCIR Further Development

- Further developed in October of 2020 to identify critical intermediate facilities arising from inadequate starting material designation
 - Starting materials not acceptable as per ICH Q11, the DMF becomes an IQ-major
 - IQ-major has longer GDUFA goal dates
 - Redesignation of a starting material may generate a critical intermediate facility
 - Critical intermediates identified late can delay an approval

TCIR Timeline



TCIR-Starting Material Evaluation

- Applicable only for DMFs that have never been reviewed
- Inadequate SM designation may result a Information Request (IR) issued to the DMF holder
- Newly generated critical intermediate facility information is relayed to Office of Pharmaceutical Manufacturing Assessment (OPMA) for assessment
- If a late stage intermediate is used in the manufacturing process, DMF holder is advised to communicate with the applicant upfront

TCIR – Hidden Facilities

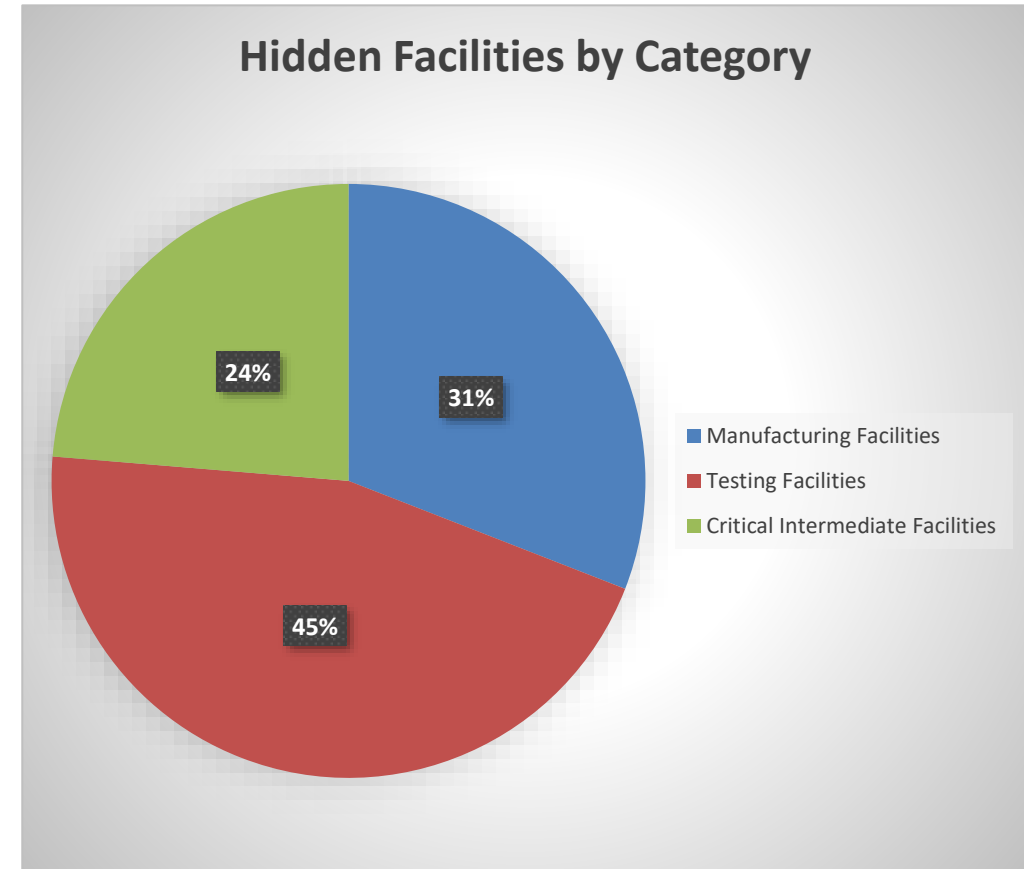
- Looking for discrepancies between ANDA 356h form and DMF facility section 3.2.S.2.1
 - Manufacturing facilities including micronization facilities
 - All release and stability testing facilities
 - Identifying and evaluating critical intermediate facilities
- Having correct facility information early in the application is critical for OPMA to perform timely evaluations

TCIR Progress-Hidden Facilities

- 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%

Hidden Facilities by Category

| Facility Type | Number |
|---|--------|
| Manufacturing (Non-sterile, Sterile, Non-sterile/sterile by fermentation, Plant/animal extraction purification) | 171 |
| Testing (Chemical/physical, microbiological sterile, microbiological non-sterile) | 251 |
| Critical Intermediate | 131 |



High number of hidden facilities is an indication of poor communication between applicant and DMF holder

TCIR – Timely Consults

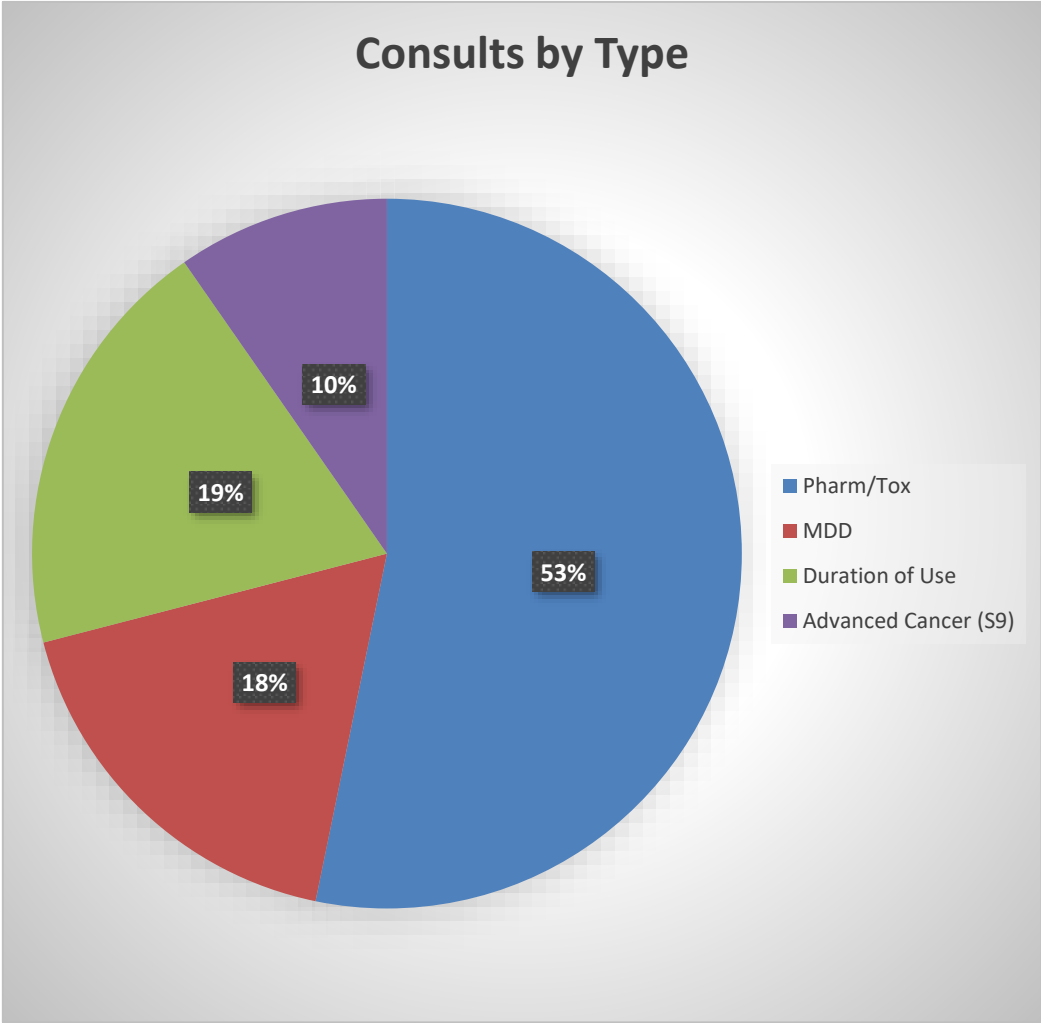
- Identify consultable information such as Pharm/Tox data, MDD, duration of use, advanced cancer indications
- Pharm/Tox data to qualify an impurity limit often takes a longer time
- Foundational consults related to the labelling, such as MDD, duration of use, etc. are also important to resolve early
- Helpful to OGD/Division of Clinical Review team to manage workload

TCIR Progress-Timely Consults

- Total number of unique ANDAs evaluated = **2739**
- Number of applications with at least one consult = **58**
- Total number of consults submitted= **62**
- Overall percentage of ANDAs with consults: **2.1%**
- Total number submitted during TCIR is about half of what we submit in a given year

Consults by Type

| Consult Type | Number |
|----------------------|--------|
| Pharm/Tox | 33 |
| MDD | 10 |
| Duration of Use | 12 |
| Advanced cancer (S9) | 6 |



TCIR-Communications

- Two types of Information requests (IR) are used in the TCIR process:
 - Hidden facility early IR comment to the ANDA applicant
 - Early IR comment to DMF holder regarding starting material designation issues.

Hidden Facility Early IR Comment

- Issued to the applicant at the time of ANDA filing

*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.*

Hidden Facility Early IR Comment Explained

*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).*

Hidden Facility Early IR Comment Explained *(Continued)*



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.

Hidden Facility Early IR Comment Explained *(Continued)*

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.

Early IR Comment to DMF Holder

- IR comment is related to the inadequacy of the SM designation
- Issued to the DMF holder as early as 30 days after the referencing application is submitted
- We request a response from the DMF holder within 20 days
- When a complete response is not possible, at least a partial response should be submitted

TCIR-SM IR Comment

The starting material that you have identified does not allow for adequate evaluation of the control of the process and/or the critical quality attributes of the drug substance and is thus not appropriate as regulatory starting material. Please do the following:

- i. Provide the [complete name, address, and contact information, including the name of the responsible on-site individual, FEI number, and DUNS number] for [name of the intermediate manufacturing facility].
- ii. Re-designate the regulatory starting materials from an earlier point in the manufacturing process and update your DMF with the complete information. Alternatively, you may reference that information to other DMF(s) with appropriate LOA(s).
- iii. Please update your cGMP statement to cover the process from the re-designated starting material since the cGMP compliance applies to the steps from the introduction of the re-designated regulatory starting materials.
- iv. Please commit to provide the information about the re-designation of starting material(s) and associated facility information to the ANDA applicant(s), who reference(s) this DMF, for compliance purpose.

What Can Industry do to Improve Facility Communications



- Clearly list all the facilities in the DMF section 3.2.S.2.1
 - Manufacturing facilities including micronization facilities
 - All the release and stability testing facilities
 - Critical intermediate manufacturing facilities
- Recommend clear communication between DMF holder and ANDA applicant regarding which DMF facility(ies) are listed in the ANDA 356h form
- Any DMF facility changes should be communicated to ANDA applicants in a timely manner

What Can Industry do to Improve Facility Communications *(Continued)*

- DMF holder should consider issuing a clear LOA to applicants specifying which facilities are being used to support the application
- The DMF holder should determine any facilities likely to be critical, communicate with the ANDA-do it up front
- If intermediates are purchased, make sure all the information is relayed to us, in 3.2.S.2.1

What Can Industry do to Improve Consult Process

- Include consultable information such as AMES data in section 3.2.S.3.2
- Clearly define Pharm/Tox studies vs analytical studies
- Section 3.2.S.3.2 impurity table: Clearly indicate how the impurity limits are qualified, e.g.,
 - Analytical approach
 - Based on QSAR
 - Based on AMES (complete data)
 - Based on literature (include all the information)
- If the information does not get caught early it will likely result a major CR for DMF and major CR for ANDA

Thank You!



- Send questions regarding this presentation to: DMFWorkshop2021@fda.hhs.gov by 3/19/2021 for inclusion in the follow-on webinar on April 9, 2021.
- Please refer to the following posters for cross-referenced material:
 - “Communications to holders and applicants throughout the DMF life-cycle” by Fatima Sequeira, et al.
- Please refer to the following presentations on March 3rd and 4th for additional information:
 - “Drug Substance Facilities – Hidden and Critical Intermediate” by Wei Liu
 - “Effective Communication Strategies For Drug Master Files (DMF)” by David Skanchy and Benjamin Danso
 - “Facility Inspections” by Jay Jariwala