

Discussion of Potential Mechanisms of Support for Non-product-specific Novel Technologies Considering Master File Submission in OTAT-regulated Therapeutic Product Manufacture

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Introduction

- Numerous product developers, at both preclinical and clinical stages of development, desire (and often require) the use of innovative tools, ancillary materials, manufacturing-enabling equipment, and/or platform technologies (herein referred to as “novel tech” for reference) in their OTAT-regulated product intended for the IND through BLA pathway
- These novel tech are not usually regulated as drugs, biologics, or medical devices, so their application in CMC/investigational medical product development are reviewed in the context of the product developer/sponsor IND
- Often these novel tech manufacturers are in the “unknown zone” between e.g., prototype and customer utilization in investigational medical product manufacture for a clinical trial under IND

These therapeutic products include but are not limited to:

- **Cell therapy**
 - MSC-based product
 - iPSC-derived product
- **Gene- or non-gene-modified or gene edited cell therapy**
 - CAR-T product
 - Product targeting gene augmented or gene corrected monogenic disease/condition
- **Tissue engineered cell-based combination product**
 - Bio fabricated or 3-D printed scaffold-containing cell-based product
- **In vivo gene therapy**
 - Product expressed via AAV vector

Scope of Novel Tech (1)

These novel tech as usually used in one or more major unit operations of the manufacturing process and include but are not limited to:

- Manufacturing-enabling equipment for cell isolation/manipulation meant for use in cGMP-compliant manufacture of a cell/gene therapy product **(non-medical device similar to a flow sorter)**
- A cell bank, such as iPSC or MSC banks, meant for further cGMP-compliant manufacture of a cell/gene therapy product **(Biological Starting Material for the product developer)**
- A culture media or reagent for specific cell types meant for further cGMP-compliant manufacture of a cell/gene therapy product **(Ancillary Material)**
- A media or reagent for specific cell types meant to be used as an excipient of a cell/gene therapy product **(Excipient)**

Scope of Novel Tech (2)

These novel tech as usually developed as platform technologies for use in the manufacturing process and include but are not limited to:

- A novel or next generation gene editing tool meant for further cGMP-compliant manufacture of a gene therapy product (**Genomic editing platform**)
- A next generation viral vector system meant for further cGMP-compliant manufacture for a gene therapy product (**for ex vivo and/or in vivo gene therapy, e.g. AAV platform**)
- A non-viral technology meant for further cGMP-compliant manufacture for a modified therapy product (**non-viral cell modification platform**)

Example - Manufacturing-enabling Equipment

As an example, a machine, often with buffer and disposables, compliant for use in a cGMP-process, that allows for a novel method to sort cells by size and/or label technology

- Can potentially be used to sort a specific cell type for further manufacture but is not a medical device
 - Better yield for selected cell phenotype
 - Less stress/activation potential for cells
 - Higher viability
 - Minimal or no residuals

Example – iPSC Biological Starting Material

As an example, a cell bank that consists of a homogeneous iPSC clone that were manufactured under cGTP- and cGMP-compliant processes, that have been comprehensively tested for safety, pluripotency, and differentiation capacity

- Can potentially be used for further manufacture of a differentiated cell-based product
- Proof of appropriate donor eligibility and informed consent for commercial use
- All upstream manufacturing process development can be leveraged

Example – Cell Culture Media Ancillary Material

As an example, a cell culture media manufactured under cGMP-compliant processes

- Can potentially be used for further manufacture of a cell-based product
- Animal component/xeno-free formulation
- Maintains cellular phenotype with rapid growth kinetics

Some Challenges for Novel Tech Manufacturer

For a novel tech manufacturer that does not have an internal R&D program of their own, the following occur:

- Don't understand what the FDA requires for their novel tech that product developers want to/will use in their cGMP-compliant drug product manufacturing process, including both IND and commercial stages of development
- Have proprietary technology that they can't/won't share with product developers for INTERACT, pre-IND and/or IND, or the public, in order to protect their IP (e.g., trade secret), that is assumed to be needed for IND review
- Have little experience with FDA regulatory filings
- Heard of the Master File process but don't know how it applies to their technology, or how to utilize the Master File process

Some Challenges for Product Developer/IND Sponsor

For a product developer/IND sponsor, the following occur:

- Use of novel tech benefits or is even required for their investigational medical product development to promote (more) favorable preclinical safety/bioactivity profile
- Wants more information from the novel tech manufacturer that manufacturer does not want to provide as info is considered confidential (e.g., trade secret)
- Does not want to include novel tech manufacturer in their INTERACT and/or pre-IND meeting(s) in order to protect their own IP (e.g., trade secret)

FDA Interactions with OTAT Prior to IND Submission -INTERACT

FDA interactions currently permitted:

- Product developer can request INTERACT meeting
 - From CBER INTERACT SOPP: *“Prior to requesting an INTERACT meeting, a sponsor needs to have selected a specific investigational product or a product-derivation strategy to evaluate in a clinical study.”*
 - Product developer CMC scope includes *“Innovative technologies for the qualification of new cell substrates; Product-manufacturing (e.g., cell sources, donor eligibility determination for allogenic cellular products and qualification of international donors); Product dependent and manufacturing process dependent reagents, starting materials and critical product components.”*
 - As previously stated, neither product developer nor novel tech manufacturer will want to share confidential information (e.g., trade secret)

FDA Interactions with OTAT Prior to IND Submission – pre-IND

FDA interactions currently permitted:

- Product developer can request a formal Type B pre-IND meeting
 - Draft FDA Guidance “*Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Product*”
 - Product and indication(s) need to be included
 - Specific Novel tech manufacturer Guidance not described

Currently Available, Directly Relevant Guidance

Currently relevant FDA Guidance includes:

- Novel platform technology manufacturer can submit Master File
 - No Guidance on if/when Master File should be submitted for a novel tech
 - No Guidance on format, which is very novel technology-specific
 - Draft FDA Guidance “*Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*”
 - Mentions Master File is required to be eCTD-compliant only
 - <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> “**May 5, 2018: Commercial Investigational New Drug Applications (INDs) and Master Files must be submitted using eCTD format**”

Currently Available eCTD Guidance

Currently available eCTD Guidance “Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications”

- Evolving quickly (Jan. 2019 Guidance above)
- <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> “Master files, such as DMFs, which are considered to be submissions to an IND, an NDA, an ANDA, or a BLA”
 - “All subsequent submissions to these types of applications, including amendments, supplements, and reports, even if the original submission was filed before the requirements went into effect”
- <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm> “If a DMF is in paper format with FDA, the same submission does not need to be resubmitted in eCTD format. However, starting May 5, 2018, any new submissions to the existing DMF must be done in eCTD format.”

Suggested Additional, Directly Relevant Master File Guidance – New Cell Isolation Equipment

- Request novel tech-specific Master File Guidance
 - For example, manufacturing-enabling equipment
 - Master File type?
 - Device Master File?
 - CTD structure?
 - Focus on 32A1 Facilities and Equipment?
 - Any 32S Sections where it may be utilized in the product developer's manufacturing process?

Suggested Additional, Directly Relevant Master File Guidance – iPSC Cell Bank

- For example, iPSC cell bank derived via single plasmid DNA technology
 - Biological Starting Material for product developer
 - One 32S Section “set” for plasmid?
 - One 32S Section “set” for iPSC Master Cell Bank?
 - Common 32A if Same manufacturing Facility?
 - Two 32A section “sets” if plasmid and cell bank manufactured in different cGMP-compliant Facilities?

Opportunities for Directly Relevant Guidance/Other

Potential suggestions for directly relevant FDA Guidance/other includes:

- Draft FDA Guidance “*Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*”
 - Incorporate into this Guidance?
- Develop separate Guidance that covers all in-scope novel tech?
- OTAT Learn session on novel tech-specific Master File structure
- Intent is to:
 - Help novel tech manufacturers
 - Help OTAT CMC reviewers know what to expect and chance to streamline more of submissions coming in to OTAT
 - Support confidence to product developer/IND sponsor that info required is included re: novel tech they utilized in their cell/gene therapy manufacturing process

Opportunities for Early FDA Interactions for Novel Tech Manufacturers

Potential suggestions for early FDA CMC interaction includes:

- Modify scope of INTERACT to include non-product-specific novel tech manufacturers
- Allow pre-Master File or “Novel Technology” interaction as an exclusive option outside of INTERACT but using a similar SOPP for CBER
- Allow novel tech manufacturers the opportunity to reach out to CBER OTAT via RPM Team to request CMC reviewer for very limited, informal advice, based on reviewer bandwidth and expertise
 - That staff member could be the intended assigned reviewer for the subsequent Master File

Conclusions

- ISCT requests FDA consider these discussion points based on the field progression
- ISCT wants to help ensure any Guidance, mechanism(s), etc. that may be utilized are least burdensome on FDA and industry
- ISCT is happy to further discuss FDA thoughts and proposals as they become available
- ***Thanks for listening!***

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