Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products

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Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), Center for Biologics Evaluation and Research, Food and Drug Administration or by calling 1-800-835-4709 or 240-402-8010, or email industry.biologics@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Frequently Asked Questions — Developing Potential Cellular and Gene Therapy Products[1]

Guidance for Industry

This represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to provide industry with answers to frequently asked questions (FAQs) and commonly faced issues that arise during the development of cellular and gene therapy (CGT) products and is intended to help facilitate the development of safe, effective, and high-quality CGT products. The FAQs represent common questions directed to the Agency and span multiple disciplines, including regulatory review, chemistry, manufacturing, and controls (CMC), pharmacology/toxicology (PT), clinical, and clinical pharmacology.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On September 30, 2022, the FDA User Fee Reauthorization Act of 2022 was signed into law. The Act includes the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA), *PDUFA VII: Fiscal Years 2023 – 2027 FDA,*[2] which provides FDA with resources to help maintain a predictable and efficient review process for human drug and biological products.

This guidance was created as part of FDA's response to the PDUFA VII commitment to increase efficiency in the development of CGT products. CGT-related research and development in the United States continues to grow at a fast rate, with a number of products already approved and many more advancing in clinical development. This guidance is intended to support the

[1] This guidance has been prepared by the Office of Therapeutic Products in the Center for Biologics Evaluation and Research at the Food and Drug Administration.
[2] See www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.

development of CGT products by providing a repository of common questions posed to the Office of Therapeutic Products (OTP) in the Center for Biologics Evaluation and Research (CBER) by sponsors and other key stakeholders. To develop this guidance, the Agency compiled FAQs received from a variety of sources, including FDA interactions with sponsors in development programs, questions received following public presentations by FDA staff, questions received from public stakeholders via CBER's Industry.Biologics@fda.hhs.gov email address, and OTP's virtual events series. For example, OTP hosted a series of virtual town hall meetings in a question-and-answer format to engage with product development stakeholders and discuss topics related to OTP-regulated products with the goal of providing regulatory information to advance drug development.[3] As such, the guidance covers relevant, current, and timely topics related to the development of CGT products. FDA may update this guidance in the future to include additional FAQs as appropriate. Sponsors are encouraged to visit the Cellular & Gene Therapy Guidances webpage on the FDA website for a full list of finalized as well as draft guidances relevant to the development of CGT products.[4]

III. SUBMISSIONS AND FDA REVIEW[5]

A. IND Submission and Quality

Q1. What should sponsors know about electronic submission of an Investigational New Drug application?

Sponsors of Investigational New Drug applications (IND), other than noncommercial INDs, are generally required to submit an IND through FDA's Electronic Submission Gateway (ESG) in electronic common technical document (eCTD) format, whereas the eCTD format is optional for sponsors of noncommercial INDs (also commonly referred to as research INDs).[6] FDA's document titled "Instructions for Filling Out Form FDA 1571" discusses when "Research" versus "Commercial" should be selected, which correlates to when eCTD requirements apply for an IND application.[7]

A commercial IND is generally one for which the sponsor (usually a corporate entity) intends to commercialize the product by eventually submitting a marketing

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[3] FDA town hall meetings can be found at https://www.fda.gov/news-events/otp-events-meetings-and-workshops.
[4] A list of relevant guidances can be found at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.
[5] For additional information, see Interactions with Office of Therapeutic Products | FDA.
[6] See section 745A of the FD&C Act and FDA Guidance, *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (Feb. 2020) ("Submissions in Electronic Format Guidance") at 2. Section 745A(a)(2) of the FD&C Act allows FDA to establish exemptions from the electronic submission requirements; FDA has established limited exemptions, including for submissions to noncommercial INDs. https://www.fda.gov/media/156718/download?attachment.
[7] See FDA, Instructions for Filling out Form 1571available at https://www.fda.gov/media/77596/download. The instructions describe how certain INDs, including expanded access INDs and protocols, should be marked as "Research" and are exempt from eCTD requirements.

application. In this case, the sponsor should select "Commercial IND" on FDA Form 1571 Field 7B. FDA may also designate an IND as commercial if it is clear that the sponsor intends for the product to be commercialized at a later date.

In comparison, a noncommercial IND is an IND for a product that is not intended for commercial distribution and includes research and investigator-sponsored INDs.[8] The sponsor of a noncommercial IND may generally be an individual investigator, academic institution, or non-profit entity. The studies proposed in these INDs are generally for research, and may result in publications in peer-reviewed journals.

One difference between the submission of a commercial versus a noncommercial IND is that commercial INDs must be submitted consistent with the eCTD requirements under section 745A(a)(2) of the FD&C Act, whereas noncommercial INDs are encouraged but not required to be submitted in eCTD format.[9] However, when a sponsor of a research IND submits either a Phase 2 or Phase 3 clinical protocol, the sponsor should select "Commercial" or otherwise submit a justification, along with a protocol, explaining why their Phase 2 or Phase 3 protocol is still solely for research. If the Phase 2 or Phase 3 IND is not considered to be a noncommercial IND, eCTD requirements would apply.[10]

FDA recommends that noncommercial IND sponsors submit their applications in common technical document (CTD) format previously described in FDA's guidance entitled "M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use: Guidance for Industry," October 2017, [Ref. 1] if they cannot submit their application in eCTD format. In the CTD format, each module should be submitted as a separate PDF file, named after the CTD module name or number, with a dedicated table of contents with hyperlinks to content as noted in FDA's guidance entitled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications: Guidance for Industry," February 2020 [Ref. 2] (hereinafter referred to as "Submissions in Electronic Format Guidance"). Also see "SOPP 8110: Submission of Regulatory Applications – Exempt from eCTD Requirements," [Ref. 3].

[8] See Submissions in Electronic Format Guidance, at 2.
[9] See section 745A(a)(2) of the FD&C Act and Submissions in Electronic Format Guidance, at 2.
[10] See section 745A(a)(2) of the FD&C Act and Submissions in Electronic Format Guidance, at 2.

Q2. What must be included in an original IND submission?[11]

In addition to the required[12] Form FDA 1571,[13] a cover letter should be included. The cover letter can be addressed to OTP without a specific name. The letter should identify in bold font that the submission is an original IND application and should provide a brief explanation of the study, product name (company monikers (e.g., PMN 201, BS648, S103A26) are discouraged), brief product description, and mode of action. The title of the protocol and the proposed indication should also be included. We highly encourage sponsors to include a list of all authorized contacts for the IND if individuals other than authorized representatives (those identified in Form FDA 1571) are allowed to communicate with the FDA regarding the IND. If an **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **CBER/C**DER Produc**T**s (INTERACT) and/or a pre-IND meeting was held prior to IND submission, then that/those meeting(s) should be referenced in the cover letter.

For INDs cross-referencing other INDs or information submitted in other applications, sponsors must include a Letter of Authorization (LOA) from the sponsor of the cross-referenced IND or file (e.g., Master File (MF)) in the IND submission.[14] This gives FDA permission to review the relevant information for the new IND. In the LOA, sponsors or MF holders allowing cross-reference must describe the incorporated material by name; reference number (e.g., IND, MF, or other number (e.g., Biologics License Application (BLA)); and location and nature of the information authorized for cross reference.[15] The LOA should also include information such as the name of sponsor being authorized; reference number incorporating the information; and name or description of the product using the supportive information, when available. The LOA should also be submitted as an amendment to the originating IND or MF.

Please note that both active and inactive files may be cross-referenced, but sponsors must always cross-reference the original source of information.[16] This means that if a sponsor chooses to cross-reference an IND where the information being referenced is located in another submission, the sponsor must include LOAs

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[11] See 21 CFR 312.23. See also SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications, available at https://www.fda.gov/media/156718/download?attachment, at 5.
[12] See FDA guidance, *Frequently Asked Questions – Statement of Investigator (Form FDA 1572)*, question 6: "Although the sponsor is required to collect the 1572 from the investigator, FDA does not require the form to be submitted to the agency. Many sponsors submit the 1572 to FDA, however, because it collects, in one place, information about the investigators that must be submitted to FDA under 21 CFR 312.23(a)(6)(iii)(b)."
[13] See 21 CFR 312.23(a)(1) (stating that "A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.")
[14] See 21 CFR 312.23(b).
[15] See 21 CFR 312.23(b).
[16] See 21 CFR 312.23(b).

from both the cross-referenced IND and the IND or MF containing the original source of information.[17]

Other information required in IND submissions[18] includes: a general investigational plan; Investigator's Brochure (IB) for sponsors other than sponsor-investigators; investigational drug labeling; and environmental assessment or a claim of categorical exclusion.[19] If applicable, IND submissions should also include cross-reference to previously submitted information from the same sponsor and previous correspondence (e.g., relevant pre-IND or INTERACT meeting correspondences).

Please also note that the IND submission must be in the English language.[20] Per 21 CFR 312.23(c), a sponsor must submit an accurate and complete English translation of each part of the IND that is not in English. The sponsor must also submit a copy of each original literature publication for which an English translation is submitted.[21]

For additional considerations related to information to include in original IND submissions, refer to Submissions in Electronic Format Guidance [Ref. 2] and INDs by Sponsor-Investigators Guidance [Ref. 4].

CMC

Please include detailed, complete information on drug substance (DS) and drug product (DP) manufacture and testing in Module 3 of the IND, as referenced in FDA's guidance entitled "M4Q: The CTD — Quality: Guidance for Industry," August 2001 [Ref. 6]. The amount and type of CMC information required to support the clinical study outlined in the IND may vary depending on the phase of the study.[22] Instructions on how to receive, handle, prepare, and administer the investigational product at the clinical site (e.g. Pharmacy Manual, Instructions for Use, Investigator's Brochure) should be provided in Module 5 and hyperlinked to the quality section in Module 2 of the IND.

For additional information on CMC information in INDs for CGTs, refer to FDA's guidances "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs): Guidance for Industry," January 2020 [Ref. 7] (hereinafter referred to as "CMC GT INDs Guidance") and "Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational

[17] See 21 CFR 312.23(b).
[18] See 21 CFR 312.23. See also SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications, available at https://www.fda.gov/media/156718/download?attachment at 5.
[19] 21 CFR 312.23.
[20] See 21 CFR 312.23(c).
[21] See 21 CFR 312.23(c).
[22] See also 21 CFR 312.23(a)(7).

New Drug Applications (INDs): Guidance for Industry," April 2008 (hereinafter referred to as "CMC CT INDs Guidance") [Ref. 8]. Additional product-specific resources for CGT CMC are located on the CGT guidances website.[23]

Pharmacology/Toxicology

Please include PT information in Module 4, and summaries in Modules 2.4 and 2.6, as applicable. PT studies of the CGT product involving laboratory animals or in vitro studies must provide a scientific basis to ensure reasonable safety of the product in the proposed clinical investigation.[24] The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.[25] Animal studies in a relevant animal species and model of disease/injury should mimic the proposed clinical trial design as closely as possible, including route of administration (ROA). Studies should be performed using the final clinical product, to the extent feasible, or you should provide a comparison of the final clinical product to the product used in the nonclinical studies. For each nonclinical toxicology study subject to Good Laboratory Practice (GLP) regulations, a statement that the study was conducted in compliance with GLP must be submitted; otherwise, if the study was not conducted in compliance with GLP, a brief statement of the reason for noncompliance must be submitted.[26] If technical limitations do not allow for GLP compliance, it is acceptable to perform the study as a non-GLP study with Quality Assurance (QA) oversight, following GLP practices, to the extent feasible. The QA unit/personnel must be independent of the personnel responsible for conducting the study to ensure quality and integrity of the data. [27]

Data from nonclinical studies should support all elements of the clinical study design. Rationale and supporting information for each animal model, test system, and calculation for dose-level extrapolation from animal to human should be submitted. For applicable nonclinical studies initiated after March 15, 2023, standardized datasets in the Standard for the Exchange of Nonclinical Data (SEND) format are required as discussed in FDA's guidance "Study Data Technical Conformance Guide [Ref. 9]."

Nonclinical data should be submitted to support starting dose level, dose regimen, and ROA. Additionally, information should be provided on nonclinical product lots, animal model/species selection, rationale for nonclinical study designs, and safety and activity information.

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[23] https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.
[24] See 21 CFR 312.23(a)(8).
[25] See 21 CFR 312.23(a)(8).
[26] See 21 CFR 312.23(a)(8)(iii).
[27] See 21 CFR 58.35

An IB must be included in the IND if the sponsor is not a sponsor-investigator.[28] The IB must include a brief description of the DS and formulation, as well as the following information:[29]

(1) A summary of the PT effects of the product in animals and humans, if known
(2) A summary of pharmacokinetics and biological disposition, and/or pharmacodynamics in animals and humans, where applicable
(3) A summary of information relating to safety and effectiveness in humans obtained from prior studies.

For additional information regarding PT for CGT products, refer to FDA's guidance "Preclinical Assessment of Investigational Cellular and Gene Therapy Products: Guidance for Industry," November 2013 (hereinafter referred to as "Preclinical Assessment CGT Guidance") [Ref. 10].

Clinical

Please include clinical information in Module 5. Sponsors must provide a brief summary of previous human experience with the investigational product, including referencing prior clinical investigations and marketing history outside the United States, if relevant.[30] A complete protocol for each planned study must be submitted and must include:[31]

(1) Study objectives and design
(2) Appropriate inclusion/exclusion criteria
(3) Product administration and dosing plan
(4) Observations and measurements made to fulfill the objectives of the study
(5) Monitoring plan

For Phase 2 and Phase 3 protocols, the study design should be adequate to evaluate both safety and efficacy.

The protocol submission should also include a statistical analyses plan. The requirements regarding the content of the protocol submission will depend on the stage of product development.[32]

[28] See 21 CFR 312.23(a)(5); 21 CFR 312.55.
[29] See 21 CFR 312.23(a)(5).
[30] See 21 CFR 312.23(a)(3)(ii).
[31] See 21 CFR 312.23(a)(6).
[32] See 21 CFR 312.23(a)(6)(i)-(ii).

Q3. What regulatory forms are included in original INDs and IND amendments?[33]

Form FDA 1571 is required for a sponsor submitting an IND submission.[34] This form contains a sponsor's commitment to conduct the investigation in accordance with all applicable regulatory requirements and must be signed by the sponsor or authorized representative.[35] Please note that for sponsors who do not reside or have a place of business within in the United States, the IND is required to contain an additional signature from an attorney, agent, or authorized official who resides or maintains a place of business in the U.S.[36] Form 1571 also provides an overview of the contents of the submission and is used by CBER's document control center staff and regulatory project managers (RPMs) to route submissions to the appropriate office and review team.

Please include administrative documents, such as Form FDA 1571, as well as cover letters, reviewer guides, cross-reference authorization letters, claims of categorical exclusion, and labeling information, in Module 1 of the CTD submissions. The cover letter for the sponsor's submission should include a brief explanation of the submission and its contents. When amendments are submitted to the IND for manufacturing changes, the cover letter should clearly describe the purpose of the amendment and highlight proposed changes. For IND amendments containing numerous or significant changes (e.g., manufacturing process, assays for critical quality attributes (CQAs), new manufacturing site, or manufacturer, etc.), the Agency recommends that the sponsor include a "Reviewer's Guide," as described in FDA's eCTD Technical Conformance Guide: Technical Specifications Document,[37] or a document with all changes tracked, and that the sponsor allows sufficient lead time (e.g., 30 days) for FDA review before release of a new lot of clinical trial material as discussed in the CMC GT INDs Guidance [Ref. 7]. A signed copy of Form FDA 3674,[38] which contains a certification that the sponsor has complied with the requirements related to clinical trial registration under section 402(j) of the Public Health Service Act (PHS Act), to the extent applicable, must be submitted and contain the appropriate National Clinical Trial control numbers.[39]

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[33] See FDA Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: *Frequently Asked Questions – Statement of Investigator (Form FDA 1572) May 2010,* for additional information regarding Form 1572, at 11.
[34] See 21 CFR 312.23(a)(1).
[35] See 21 CFR 312.23(a)(1).
[36] See 21 CFR 312.23(a)(1)(ix).
[37] eCTD Technical Conformance Guide: Technical Specifications Document, December 2019. https://www.fda.gov/media/93818/download.
[38] Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA). See also Form FDA 3674, available at https://www.fda.gov/media/134964/download, and FDA guidance, Form FDA 3674 – Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions (June 2017), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions.
[39] Section 402(j)(5)(B) of the PHS Act.

Q4. What is the general process for evaluating original INDs for CGT investigational products?[40]

Stage 1 of the 30-day IND review process begins when FDA receives the IND. The document control center processes the submission and sends a submission notice to OTP who then confirms the submission is in the correct office. An RPM is then assigned to the IND and performs an administrative review to ensure the submission appears to be complete. The RPM then verifies that the sponsor's authorized representative has a secure email and emails an acknowledgement letter to the authorized representative.[41]

IND review Stage 2 includes assigning reviewers from each discipline, including CMC, PT, and clinical. Additional experts are assigned as needed (e.g., biostatistics, bioinformatics, clinical outcome assessment). This stage is also known as the IND interactive review period and includes safety reviews conducted by discipline reviewers. Consults are requested as needed, which can be internal (within CBER) or external to CBER (e.g., Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), etc.). If the review team or a specific discipline identifies missing information or requires clarification of any information in the IND, the RPM emails information requests to the sponsor and may also request informal meetings.

In Stage 3, INDs are generally determined as safe to proceed or placed on clinical hold. Internal meetings may be held to discuss these decisions, and discipline supervisors review and concur on the IND decision. The RPM then notifies the authorized contact whether the IND is deemed safe to proceed or FDA places an IND on clinical hold by issuing an order to the sponsor via phone call, voicemail, or email. An IND goes into effect 30 calendar days after FDA receives the IND, unless FDA notifies the sponsor that the trials described in the IND are subject to a clinical hold, or on earlier notification by FDA that the trials may proceed.[42]

If an IND is placed on clinical hold[43], the RPM informs the sponsor via phone call, voicemail, or email. After this notification, the review team provides specific comments for the clinical hold letter, which will explain the basis for the hold[44], such as the specific deficiencies causing the IND to be placed on clinical

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[40] Further information can be found in the webcast "Original IND Applications — Behind the Scenes," https://fda.yorkcast.com/webcast/Play/0fb4cbfbbcaa4746917bdc836b2372cd1D. See also SOPP 8217: Administrative Processing and Review Management Procedures for Investigational New Drug Applications, available at https://www.fda.gov/media/156718/download?attachment.

[41] For a description of how CBER uses email for regulatory communications, see SOPP 8119: Use of Email for Regulatory Communications, available at https://www.fda.gov/media/108992/download

[42] 21 CFR 312.40(b).

[43] 21 CFR 312.42. See also SOPP 8201: Administrative Processing of Clinical Holds for Investigational New Drug Applications, available at https://www.fda.gov/media/88774/download.

[44] 21 CFR 312.42(d).

hold and what actions the sponsor needs to take to remove the hold. The comments are sent for supervisory review and concurrence, with internal meetings held as necessary. The RPM sends a letter to the authorized representative within 30 days of the hold decision date.[45]

On the other hand, if an IND is safe to proceed, the RPM typically sends an email communicating that information, which can be used by sponsors as official correspondence that might be needed by other entities, such as Institutional Review Boards (IRBs). Non-hold comments are sent in a separate communication. CBER does not send letters to sponsors when INDs are allowed to proceed.

Q5. What should sponsors know about submission tracking numbers for applications submitted through the Electronic Submission Gateway?

Sponsors of applications subject to the electronic submission requirements of section 745A(a) of the FD&C Act must submit their applications in eCTD format, in the electronic format required under the statute.[46] Most submissions are sent electronically through FDA's ESG, which is an Agency-wide solution for accepting electronic regulatory submissions. The FDA ESG enables the secure submission of premarket and postmarket regulatory information for review and is the central transmission point for sending information electronically to the FDA.

A tracking number is pre-assigned by CBER prior to receiving an eCTD-submitted original submission (e.g., IND or BLA) to automate receipt and processing of the submission. The tracking number is included within the electronic submission's XML backbone and on FDA's fillable-PDF version of Form FDA 356h or Form FDA 1571 for electronic BLAs and electronic IND submissions. When requested, CBER will issue the tracking number to a sponsor/applicant no earlier than 8 weeks in advance of the target receipt date for the electronic submission. When a sponsor/applicant requests a pre-submission (PS) number for an INTERACT or pre-IND meeting, or for a Type D meeting with no associated IND, CBER's Regulatory Information Branch (RIB) within the Division of Informatics, Office of Regulatory Operations, should provide the number within 2 business days of the request.

Sponsor/applicant requests for preassigned numbers should be made by email to cberrib@fda.hhs.gov. The request should include the sponsor/applicant name and address; primary point of contact name and phone number; the biological product name (company monikers (e.g., PMN 201, BS648, S103A26 are discouraged)) and indication; and the anticipated submission date.

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[45] 21 CFR 312.42(d).
[46] See section 745A(a) of the FD&C Act and the Submissions in Electronic Format Guidance.

Sponsors should include the tracking number on:

(1) The cover page of the submission
(2) The XML backbone for a submission in the eCTD format
(3) The PDF Form FDA 356h or Form FDA 1571
(4) All future correspondence and submissions

Please note that in CBER, PS numbers (for a pre-IND meeting) and IND numbers (for an IND submission) are separate. Sponsors who are preparing their IND submission should not reuse their PS number but should request an IND number by contacting the RIB at cberrib@fda.hhs.gov. More information about PS numbers can be found in FDA's "SOPP 8117: Issuing Tracking Numbers in Advance of Electronic Submissions in eCTD Format," (hereinafter referred to as "SOPP 8117") [Ref. 12].

B. Meeting Types[47]

Q6. What are the differences between INTERACT and pre-IND meetings?

INTERACT is a meeting at a specific time early in product development. This meeting type is intended for novel products and development programs that present unique challenges in early development. The appropriate timing for an INTERACT meeting generally should be when a sponsor has identified the investigational product to be evaluated in a clinical study and conducted some preliminary preclinical proof-of-concept (POC) studies with the intended investigational product but has not yet designed and conducted definitive nonclinical studies.

Considerations for whether the status of product development is premature or too advanced for an INTERACT meeting for CGTs are discussed on FDA's webpage.[48] For additional details on a development program's qualification for INTERACT, how to request an INTERACT meeting, and where to send the meeting request, see FDA's "SOPP 8101: Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products," (hereinafter referred to as "SOPP 8101") [Ref. 13].[49] Additionally, sponsors may email meeting requests to cberdcc_emailsub@fda.hhs.gov, with OTPRPMS@fda.hhs.gov in the cc line for Regulatory Management Staff awareness.

The primary purpose of a pre-IND meeting is for sponsors to receive feedback on their product development program before submitting an IND. A pre-IND meeting is an opportunity to obtain feedback on the design of nonclinical studies, the design of the initial clinical study, and product manufacturing and quality

[47] For additional information see Interactions with Office of Therapeutic Products | FDA.
[48] See https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meeting.
[49] See https://www.fda.gov/media/84040/download.

controls needed to initiate human studies. The meeting may also provide an opportunity to discuss the plans for studying the product in pediatric populations, strategize the target product profile, identify the design and results of any natural history studies, and discuss the best approach for presentation and formatting of data in the IND, among other possible relevant topics.

Examples of when a pre-IND meeting would be appropriate include when:

(1) The sponsor has defined the manufacturing process to be used for the clinical studies and has developed assays and preliminary lot-release criteria
(2) The sponsor has completed POC and possibly some preliminary nonclinical safety/toxicology studies and desires to move to the definitive toxicology studies
(3) The sponsor's questions involve IND-enabling CMC, PT, and/or clinical trial design issues

For additional information on meeting types and procedures, refer to FDA's draft guidance "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products: Draft Guidance for Industry," September 2023 (hereinafter referred to as "PDUFA Formal Meetings Draft Guidance") [Ref. 14].[50]

Q7. How should sponsors prepare briefing packages for and request INTERACT and pre-IND meetings?

INTERACT

INTERACT meeting requests and briefing packages should be submitted through FDA's ESG or by email to cberdcc_emailsub@fda.hhs.gov.

OTP does not send an acknowledgement email or letter following receipt of the request. If the meeting request is granted, OTP intends to send confirmation of the meeting within 21 days and schedule the meeting within 75 days of FDA receipt of the request. INTERACT meetings are typically scheduled as teleconferences. Similarly, OTP intends to communicate meeting denials within 21 days with a rationale for denial.

INTERACT briefing packages should be submitted with the meeting request and not exceed 50 pages in length (excluding appendices). The package should include the summary information pertinent to the product, relevant questions the sponsor needs advice on,[51] and sufficient background for the questions included

[50] When final, this guidance will represent FDA's current thinking on this topic. See https://www.fda.gov/media/172311/download.

[51] For more information regarding CMC, pharmacology/toxicology, and clinical information in an INTERACT briefing package, see https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meeting.

in the package. The package should contain a high-level description of the manufacturing process, characterization, and proposed lot release for CMC. For the nonclinical section, sponsors should include detailed summaries of animal studies conducted with the investigational product and discussions on any additional planned POC studies, including protocol outlines for the intended patient population. Clinical sections should include a description of the proposed indication, target patient population, available treatments, summary of natural history data, and a brief outline of the first-in-human (FIH) study protocol. Additional information about an INTERACT meeting can be found in SOPP 8101 [Ref. 13].[52]

A pre-assigned PS number is not required for an INTERACT meeting request. If you do not have a pre-assigned PS number, one will be automatically assigned to you upon submission of your INTERACT meeting request. Additional information on requesting a PS number or submission tracking numbers for electronic INDs can be found in SOPP 8117 [Ref. 12].

Pre-IND

Pre-IND meeting requests and briefing packages should be submitted through FDA's ESG or by email to cberdcc_emailsub@fda.hhs.gov.[53, 54] The meeting request should include a list of specific meeting objectives and draft questions grouped by disciplines (e.g., CMC, PT, etc.).

OTP does not send an acknowledgement email or letter following receipt of the pre-IND meeting request. If the meeting request is granted, the RPM intends to send confirmation of the meeting within 21 days and schedule the meeting within 60 days of FDA receipt of the request. Similarly, meeting denials are also communicated within 21 days with a rationale for denial.

Please note pre-IND meeting requests should not be submitted under an IND number. All pre-IND meeting requests should be submitted under a PS number. Sponsors who want a pre-assigned PS number should contact the RIB at cberrib@fda.hhs.gov. Additional information on requesting a PS number or submission tracking numbers for electronic INDs can be found in SOPP 8117 [Ref. 12].

Pre-IND briefing packages should be submitted no later than 30 days before the scheduled date of the pre-IND meeting or written response only. Pre-IND briefing packages are typically 50 to 100 pages in length (excluding appendices)

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[52] See https://www.fda.gov/media/84040/download.
[53] Cited email addresses are current as of publication of this draft guidance. Please see FDA website below for up-to-date information.
[54] For additional ways to submit to CBER, please see https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper-format-cber-regulated-products.

and should include a maximum of 10 targeted questions (inclusive of sub-questions) that directly address concerns about the product development programs.[55] A cover letter should be included in the briefing package with the inclusion of the assigned PS number.

For additional information on meeting types and procedures, refer to the PDUFA Formal Meetings Draft Guidance [Ref. 14].

Q8. What is a Type D meeting and how do sponsors request one?

A Type D meeting is a meeting focused on a narrow set of issues (limited to no more than two focused topics) and should not require input from more than three disciplines or divisions. Type D meetings should be requested at critical junctures of development where decisions regarding critical questions for the development program are needed.

Consistent with the PDUFA Formal Meetings Draft Guidance [Ref. 14], examples of when a Type D meeting would be appropriate include:

(1) A follow-up question that raises a new issue after a formal meeting (i.e., more than just a clarifying question about an FDA response from a prior meeting)
(2) A narrow issue on which the sponsor is seeking Agency input with only a few (e.g., three to five total) associated questions
(3) A general question about an innovative development approach that does not require extensive, detailed advice

Type D meeting requests and accompanying briefing packages should be submitted through FDA's ESG or by email to cberdcc_emailsub@fda.hhs.gov. If the meeting request is granted, OTP intends to send confirmation of the meeting within 14 days and schedule the meeting within 50 days of FDA receipt of the request.

In the briefing package, sponsors should include summary information pertinent to the product or issue, with an adequate background section for the questions posed in the package, and a list of questions (limited to no more than three to five questions including sub-questions regarding the one to two focused topics).

Type D meetings may be converted to Type B or C meetings if the scope of the meeting is broad or includes complex questions or issues that require input from more than three disciplines or divisions. FDA will inform the sponsor that the Agency will be converting the Type D meeting to the appropriate meeting type,

[55] For additional information, please see the webpage "Interactions with Office of Therapeutic Products" at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-therapeutic-products.

and the sponsor can withdraw their initial request or accept the FDA's meeting conversion without submitting a new request.

Q9. Does FDA recommend a pre-BLA meeting, and what should be included in the briefing package if sponsors choose to request one?

In an effort to mitigate review delays, the Agency strongly recommends sponsors schedule a pre-BLA meeting with their review team in OTP to help ensure all information, data, and analyses necessary to support review are included in the BLA submission. FDA has found that delays associated with the initial review of a marketing application may be reduced by exchange of information about a proposed marketing application.[56] The primary purpose of this kind of exchange is to uncover any major unresolved problems; identify those studies that the sponsor is relying on as adequate and well-controlled to establish the product's effectiveness; identify the status of ongoing or needed studies to assess pediatric safety and effectiveness; acquaint FDA reviewers with the general information to be submitted in the marketing application (topline study results and technical information should be included in the pre-BLA briefing document); discuss appropriate methods for statistical analysis of the data; discuss the best approach for presenting and formatting data in the marketing application; and discuss inspection and facility related information.[57, 58]

Only one 60-minute pre-BLA meeting will typically be granted for a specific product or indication planned for the submission of an original marketing application. Pre-BLA meetings should be multi-disciplinary; discipline-specific CMC or clinical pre-BLA meetings will generally not be granted.

Meeting Request

The sponsor should submit the meeting request as an amendment to the existing IND. The meeting request should include a list of the specific objectives of the meeting and a list of questions grouped by discipline. The meeting request should include adequate information for the FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss proposed agenda items.

The meeting request should be submitted at least 4 months before the anticipated BLA submission. Upon receipt of the request, OTP will determine if the request is appropriate for a pre-BLA meeting (i.e., if the sponsor is ready for a pre-BLA meeting) as described in more detail in the PDUFA Formal Meetings Draft Guidance [Ref. 14]. If the meeting request is granted, the RPM intends to send confirmation of the meeting within 21 days and schedule the meeting within 60

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[56] 21 CFR 312.47(b)(2).
[57] See 21 CFR 312.47(b)(2).
[58] Also see https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-pre-bla-meetings (for more information about pre-BLA meetings).

days of FDA receipt of the request. Confirmation will include meeting date, time, and briefing package due date. If the meeting is denied, a rationale for the denial will be provided.

Briefing Package

Sponsors should submit briefing packages at least 30 days before the scheduled meeting. Based on experience, to facilitate a productive meeting, we recommend that no more than 10 questions or sub-questions are included in the briefing package. It is important to provide background information sufficient to support the questions in the package.

OTP will not commit to reviewing packages greater than 250 pages or answering questions that require review of large volumes of material. The briefing package contents should include all elements detailed in the PDUFA Formal Meetings Draft Guidance [Ref. 14].

C. IND Amendments

Q10. What is FDA's timeline for feedback on new or revised information submitted to an active IND?

Sponsors submit amendments to alert FDA about changes to their development program on a regular basis. The CMC information in an IND describes a sponsor's commitment to perform manufacturing and testing of the investigational product as stated in the IND or in a cross-referenced IND or MF. If a manufacturing change could affect product quality, the Agency considers the manufacturing change essential information that must be submitted in an information amendment to the IND (21 CFR 312.31(a)(1)). The sponsor should submit such amendments for FDA review prior to use of the changed product in clinical investigations. Please also see the answer to question 3.

A new or revised clinical protocol may be implemented provided the sponsor has submitted the change to FDA for its review, and the change has been approved by the IRB responsible for review and approval of the study.[59] The sponsor may comply with these two conditions in any order.[60] With a few exceptions[61], amendments with new or revised protocols submitted to an active IND do not have a review clock associated with them; provided the requirements in 21 CFR 312.30 are met, sponsors can implement the protocols without waiting for FDA to finish its review.[62]

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[59] 21 CFR 312.30(a)-(b).
[60] 21 CFR 312.30(a)-(b).
[61] See e.g., 21 CFR 312.305(d)(2) regarding expanded access protocols.
[62] For details, please see 21 CFR 312.30.

If the sponsor desires FDA to comment on the submission, including before the sponsor initiates the protocol or implements a manufacturing change, a request for such comment should be made in the cover letter with the specific questions the sponsor wishes FDA to address. The cover letter should also indicate when the sponsor intends to initiate the new protocol or implement a change. Although OTP strives to provide prompt feedback, the ability to provide input within a specific timeframe may depend on several factors, including complexity of the requested feedback and/or competing priorities. Therefore, sponsors should ensure that if such feedback is desired, that they submit the new or revised information well in advance of when they plan to implement the change, such as a protocol or manufacturing change. More detailed information regarding communication timing can be found in Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance [Ref. 15].

D. Expedited Programs

Refer to Expedited Programs for Serious Conditions – Drugs and Biologics; Guidance for Industry [Ref. 16] and Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry [Ref. 17] for additional details.

Q11. When does rolling review begin for qualifying BLAs and what is the timing of module submission?

Rolling review means that FDA may consider reviewing portions of a BLA before the sponsor submits the complete BLA.

A drug may receive rolling review if it has Fast Track, Breakthrough Therapy, or Regenerative Medicine Advanced Therapy (RMAT) designation and if certain criteria are met; however, FDA must still agree to rolling review. Sponsors obtain preliminary Agency agreement on the proposal at the pre-BLA meeting or earlier (e.g., end-of-phase 2 meeting). A request to submit portions of an application ordinarily should be included in the information package for the pre-BLA meeting. Sponsors should also submit an amendment to their IND describing the proposed submission schedule, including dates each complete module would be submitted. After reviewing the amendment, FDA will indicate its decision on rolling review.

If FDA agrees with a rolling review, FDA will generally accept only complete modules for Modules 3, 4, and 5. FDA may also generally accept select sections of Modules 1 and 2 given their content and relationship to the other modules. For example, a sponsor might initially submit the complete Module 5 along with the related portions of Modules 1 and 2, then submit the complete Module 4 along with the related portions of Modules 1 and 2, and finally submit the complete Module 3 along with the remaining portions of Modules 1 and 2. If FDA agrees to a rolling review, no more than 12 months should elapse from the first submission of BLA content to the final submission to complete the BLA.

FDA's review clock starts once the final module is received and the applicant informs the Agency that a complete BLA or NDA was submitted.[63]

IV. PRODUCT DEVELOPMENT CONSIDERATIONS

Product development issues are addressed in the sections below. More detailed information on CMC for CGT products can be found in the CMC GT INDs Guidance [Ref. 7] and the CMC CT INDs Guidance [Ref. 8].

A. Donor Eligibility

Q12. What are some differences between autologous and allogeneic donor eligibility considerations?

A donor eligibility determination under 21 CFR § 1271.50 and donor screening or testing under 21 CFR §§ 1271.75, 1271.80, and 1271.85 are not required for cells and tissues used in the manufacture of autologous products.[64] However, the manufacturer must include the applicable required labeling on the product.[65] For example, for products intended for autologous use, the manufacturer must prominently label the product with the statement "FOR AUTOLOGOUS USE ONLY."[66] As another example, unless all otherwise applicable donor screening and testing under 21 CFR §§ 1271.75, 1271.80, and 1271.85 are performed, the manufacturer must prominently label the product with the statement, "NOT EVALUATED FOR INFECTIOUS SUBSTANCES".[67, 68] Additionally, FDA recommends that the manufacturer include a minimum of two unique identifiers (e.g., donor identification number (DIN), product tracking number, etc.) for autologous therapies to minimize potential for mix-ups.

For allogeneic donor material, manufacturers are required to determine whether a donor is eligible based upon the results of donor screening and testing in accordance with 21 CFR §§ 1271.75, 1271.80, and 1271.85.[69] A responsible person must determine and document the eligibility of a cell or tissue donor.[70]

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[63] Section 506(d)(2) of the FD&C Act provides that any time period for review of human drug applications shall not apply until the date on which the application is complete. See also Expedited Programs Drug and Biologics Guidance.
[64] 21 CFR 1271.90(a).
[65] 21 CFR 1271.90(c).
[66] 21 CFR 1271.90(c)(1).
[67] 21 CFR 1271.90(c)(2).
[68] For more information on prominence in labelling, see Product Name Placement, Size, and Prominence in Promotional Labeling and Advertisements; Guidance for Industry, December 2017, *available at* https://www.fda.gov/media/87202/download.
[69] 21 CFR 1271.50(a).
[70] 21 CFR 1271.50(a).

Note that screening and testing are two different components. Screening entails reviewing relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases, and communicable disease risks associated with xenotransplantation.[71] Relevant medical records refers to a collection of documents that includes: (1) a current donor medical history interview; (2) a current report of the physical assessment of a cadaveric donor or the physical examination of a living donor; and (3) other available records listed in 21 CFR 1271.3(s).[72] Testing is performed on a specimen from the donor, typically blood. Testing must be performed using FDA-licensed, approved, or cleared test kits according to the manufacturer's instructions for use[73] and must be performed in a Clinical Laboratory Improvement Amendments-certified laboratory or equivalent as determined by the Centers for Medicare and Medicaid Services.[74] The donor specimen must be collected for testing at the time of recovery of cells or tissue from the donor or up to 7 days before or after, except for donors of peripheral blood stem/progenitor cells or bone marrow, in which case the specimen for testing may be collected up to 30 days before recovery.[75]

For more details, refer to FDA's guidance "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Guidance for Industry," August 2007 [Ref. 18].

B. Product Characterization

Q13. What is the difference between product characterization testing and release testing?

Characterization testing provides information about the product, whereas release testing demonstrates that the product is of acceptable quality (safety, identity, purity, and potency). Release tests are part of the product specification, which establishes the set of criteria that a drug product must meet to be considered acceptable for its intended use.[76] A specification should include a list of all release tests, references to analytical procedures, and appropriate acceptance criteria (AC), which are numerical limits, ranges, or other criteria for the tests described [Refs. 7, 19]. Prior to initiating a pivotal study, intended to provide primary evidence of effectiveness of the drug, release tests must be qualified, tests must have predefined AC, and tests must comply with current good manufacturing practice (CGMP).[77] Release tests must be validated prior to BLA

[71] 21 CFR 1271.75(a).
[72] 21 CFR 1271.3(s).
[73] 21 CFR 1271.80(c).
[74] 21 CFR 1271.55(b)(1)(i) and (ii), 21 CFR 1271.80(c)
[75] 21 CFR 1271.80(b).
[76] 21 CFR 211.165
[77] 21 CFR §§ 210.2, 211.165.

submission.[78] In contrast, characterization tests do not need to be qualified, have AC, or comply with the CGMP requirements for testing and release for distribution.

Release test results should be reported on the product certificate of analysis (COA), whereas characterization test results are not reported on a COA. Both release tests and key characterization assay results should be recorded and submitted to an IND application or BLA at relevant places in Module 3 of the CTD at the appropriate phase of development.

The Agency recommends characterization testing of both the DS and the DP. Information gained from characterization testing is valuable for multiple purposes, including identifying CQAs,[79] guiding analytical assay development, and evaluating product comparability following manufacturing changes.

The appropriate characterization tests depend on the unique features of the product type. For example, characterization testing of a cell-based product may include extended assessment of cell surface phenotypic markers, such as those associated with immune-cell activation, differentiation, and exhaustion. For adeno-associated viral vectors, examples of characterization testing may include orthogonal measures of activity, vector genome size analysis, and detection of capsid amino acid modifications by mass spectrometry. For tissue-engineered medical products, examples may include biomechanical testing to assess the ability of a vascular graft to tolerate repeat access without leaking, permeability testing to assess the characteristics of a skin graft, or cellular distribution throughout a cell scaffold construct.

Some tests are necessary to confirm safety of the product prior to release but are not performed on the final product; such samples should be acquired at the necessary and appropriate manufacturing steps. For example, tests for mycoplasma and adventitious agents should be performed on cell culture harvest material prior to further processing. Tests for sterility, endotoxin, and identity should be performed on formulated product in the final labeled container to ensure that microbial contamination and product mix-ups (such as those that may occur during final DP manufacturing steps) do not occur.

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[78] 21 CFR 211.165(e).

[79] For purposes of this guidance, a critical quality attribute is defined as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. See guidance for industry Q8(R2) Pharmaceutical Development (November 2009) available at https://www.fda.gov/media/71535/download.

C. Critical Quality Attributes

Q14. What information should be submitted regarding critical quality attributes?

In the IND, sponsors should describe the quality attributes relevant to the performance of the product, including attributes of the DS, DP, intermediates, and excipients. Sponsors should consider including information related to but not limited to assessments of attributes important to product quality, CQA determination, and justification of specifications based on available data. These quality attributes include physicochemical or biological properties of the product, such as strength used to establish dosing units, genotypic or phenotypic variation, biological activity or potency, and/or immunological activity. CQAs are a subset of quality attributes. It can be crucial to establish CQAs for a product as early as possible, particularly when sponsors plan to make manufacturing changes during product development, because well-established CQAs are generally necessary for assessing analytical comparability between different versions of a product [Ref. 22].

Given the complex nature of CGT products, assuring a product's potency can be one of the more challenging aspects of development. To help manufacturers meet potency requirements for INDs and BLAs, FDA has provided recommendations to manufacturers in its draft guidance, "Potency Assurance for Cellular and Gene Therapy Products: Draft Guidance for Industry," December 2023 [Ref. 20].[80]

FDA acknowledges that understanding and defining product characteristics that are relevant to the clinical performance of the investigational product may be challenging during early stages of product development, when product quality may not be sufficiently understood. Therefore, FDA recommends that sponsors evaluate a number of product characteristics during early clinical development to help identify and understand CQAs.

For more details, refer to FDA's guidance "Q8(R2) Pharmaceutical Development: Guidance for Industry," November 2009 [Ref. 21] and draft guidance "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products: Draft Guidance for Industry," July 2023 (hereinafter referred to as "Manufacturing Changes CGT Draft Guidance") [Ref. 22].[81]

In traditional product development, CQAs of the product are evaluated during each phase of clinical development, and characterization data from many DP lots may be correlated to clinical outcomes. For rare diseases, some aspects of the development programs, such as limited population size and fewer lots

[80] When final, this guidance will represent FDA's current thinking on this topic.
[81] When final, this guidance will represent FDA's current thinking on this topic.

manufactured, may make it challenging to follow traditional product development strategies. For specific guidance on product development approaches for rare diseases, refer to FDA's guidance entitled "Human Gene Therapy for Rare Diseases: Guidance for Industry," January 2020 (hereinafter referred to as "GT for Rare Diseases Guidance") [Ref. 23].

D. Analytical Methods

Q15. How should analytical methods be shown to be fit for purpose for first-in-human trials?

For FIH studies, the IND should contain a description of each non-compendial analytical method used to assess quality of the product (DP, DS, and components), with an evaluation of assay performance characteristics (i.e., accuracy, precision, sensitivity, and specificity) to justify that the method is fit for purpose (i.e., at a stage of development that is phase-appropriate). More information can be found in FDA's guidance "Analytical Procedures and Methods Validation for Drugs and Biologics," July 2015 (hereinafter referred to as "Analytical Procedures and Methods Guidance") [Ref. 24].

Tests performed to assure product safety, including microbial testing, should demonstrate adequate performance including but not limited to suitability under actual conditions of use and an absence of interference from the product, even for the initial IND submission. Notably, to assure safety of gene therapy (GT) products, the sponsor should qualify the assay(s) used to determine dose (e.g., vector genome titer by quantitative polymerase chain reaction (qPCR), transducing units, plaque forming units, transduced cells) prior to initiating clinical studies. In a sponsor's IND submission, a detailed description should be provided of the qualification protocol (e.g., samples; standards; positive/negative controls; reference lots; and controls evaluated, such as operators, reagents, equipment, dates) and data supporting the accuracy, precision, sensitivity, and specificity of the analytical method.

Many tests for DS/DP release are compendial, and their assay performance characteristics have already been established. However, for methods to be considered compendial, they should be found in the United States Pharmacopeia/National Formulary (USP/NF) compendia. If the sponsor plans to reference other compendia to support fitness of a method, the sponsor should include detailed information about how the methods are performed and whether they have the same performance characteristics as the corresponding USP methods.

For more information on establishing AC during product development, please see the CMC GT INDs Guidance [Ref. 7]. While interim AC are acceptable for

Phase 2 and 3 studies, proposed commercial AC should be in place at the time of BLA submission.[82]

E. Process Characterization/Validation

Q16. At what scale should process characterization and validation be executed?

The validation of a commercial manufacturing process should be supported by data from commercial-scale batches. Although use of a scaled down model is not appropriate for process performance qualification (PPQ), scaled-down models can be used at the process design and characterization stages to evaluate process variability, determine appropriate process parameters, and supportive studies such as viral or impurity clearance.[83] Sponsors should demonstrate the validity of the scaled-down process, and the scaled-down version should represent the intended commercial manufacturing process as closely as possible.

Q17. How many process performance qualification lots are recommended for process validation?

There is no fixed number of lots recommended for PPQ. In general, a greater understanding and knowledge of the product and manufacturing process can reduce the number of PPQ lots that should be sufficient to qualify the performance of the manufacturing process. The number of PPQ lots should be informed by a risk assessment and should be sufficient to demonstrate that consecutive runs of the manufacturing process perform as expected and consistently yield a product that meets AC.

For more details, refer to FDA's guidance entitled "Process Validation: General Principles and Practices: Guidance for Industry," January 2011 (hereinafter referred to as "Process Validation Guidance") [Ref. 25] and "Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application," May 2026 [Ref. 39].

F. Manufacturing Changes

Q18. How should manufacturers evaluate comparability of pre- and post-change products?

When evaluating comparability of pre- and post-change products, consider the recommendations in FDA's Manufacturing Changes CGT Draft Guidance [Ref.

[82] See 21 CFR 312.23(a)(7)(i).
[83] Q11 Development and Manufacture of Drug Substances; Guidance for Industry, November 2012, *available at* https://www.fda.gov/media/80909/download

22]. The Agency recommends that sponsors submit a meeting request to their IND to discuss significant manufacturing changes and effect on comparability, particularly when such manufacturing changes would be implemented during later stages of product development.

G. Stability

Q19. What stability information is needed to support first-in-human studies?

Demonstrating product stability is needed at all stages of product development.[84] Sponsors should be able to show that the product is within acceptable quality limits for the duration of its planned usage within a clinical study[85]; however, an incremental approach may be appropriate for setting AC to support stability. For example, data to support stability of the product for Phase 1 studies can be based on data from nonclinical lots, engineering lots, or highly similar product lots that have been stored in the same manner as the clinical material (e.g., the same formulation, concentration, storage temperature, and container), when sufficiently justified. For topics like shipping stability, in-use stability, device compatibility, and additional stability considerations, please see CMC GT INDs Guidance [Ref. 7].

H. Preparing for BLA

Q20. What CMC issues should sponsors consider as they prepare to submit a BLA?

Specific CMC concerns are guided by the stage of product development. Nonclinical and CMC safety testing data must be provided prior to initiation of Phase 1 studies, along with basic product and process characterization data.[86] Product development activities may be implemented incrementally but should progress along with clinical development. For analytical methods, the Agency recommends that sponsors evaluate assay performance throughout product development. When preparing the BLA submission, the manufacturing process and all analytical methods performed to support product quality must be validated[87] and comply with the regulations in 21 CFR 610.

Manufacturing for investigational and approved drugs (including biological products) must comply with CGMP, as required by section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B) and

[84] For purposes of this guidance, "stability" in this context is described in 21 CFR 312.23. See also 21 CFR 211.166.
[85] 21 CFR 312.23(a)(7)(iv)(b)
[86] 21 CFR 312.23(a)(7)-(8).
[87] See 21 CFR 211.165.

21 U.S.C. 351(j)) at all stages of clinical investigation. For example, DP manufacturing must comply with FDA's CGMP regulations for finished pharmaceuticals in 21 CFR part 211, except that most Phase 1 investigational drugs are exempt from the requirement to comply with part 211. See 21 CFR 210.2(c) and FDA's guidance "CGMP for Phase 1 Investigational Drugs: Guidance for Industry," July 2008 [Ref. 26].

Additionally, CMC development (including process and analytical method controls and compliance with CGMP, as outlined in 21 CFR 210 and 211) should evolve concurrently with clinical development. A BLA must contain, among other information, data which demonstrate that the product meets requirements of safety, purity and potency, a full description of manufacturing methods and data establishing stability of the product through the data period.[88] Process characterization and validation studies that must be conducted to meet CGMP are outlined in 21 CFR 211 Subpart F — Production and Process Controls.

For more details, see the CMC GT INDs Guidance [Ref. 7], the Process Validation Guidance [Ref. 25], and the Analytical Procedures and Methods Guidance [Ref. 24].

V. CONDUCTING NONCLINICAL STUDIES

I. Selection of Models

Q21. What are FDA's recommendations regarding adequate animal species selection for certain nonclinical studies of cell and gene therapy products?

When selecting an animal species for nonclinical PT studies, key considerations include whether the investigational CGT product is pharmacologically active in the species, the technical feasibility of using the intended clinical delivery device or procedure for product administration, comparability of the physiology and anatomy between animals and humans for the ROA and target anatomic sites that the product is intended to reach, and the sensitivity of the selected species to potential toxicities for the product.

Specific considerations for cell therapy (CT) products include the ability of the species/strain to support survival and engraftment of the CT product or availability of an appropriate analogous[89] animal product. Additional considerations for GT products include the permissiveness or susceptibility of the species to the vector, vector transduction profile, and the pharmacological

[88] 21 CFR 601.2(a).

[89] For purposes of this guidance, analogous animal product refers to products modified to be compatible with the animal species used for testing that are analogs of the ultimate clinical product in phenotype and biological activity.

response to the vector and the expressed transgene. FDA supports the use of New Approach Methodologies (NAMs) and the principles of the 3Rs (i.e., reduce, refine, and replace animal use) to encourage the judicious use of animals in nonclinical development programs.[90] FDA encourages sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible.

Q22. Does FDA have specific recommendations regarding selection of an animal model for pharmacology studies for assessing the activity of CGT products?

Sponsors should consider the biological relevance of a particular animal or disease model to the target patient population. This may depend on the characteristics of the product, the proposed clinical indication, and the feasibility of using the intended clinical delivery device or procedure when selecting animal models for pharmacology studies. The sponsor should provide scientific justification in pre-IND and IND submissions for the animal model/species selection. A comprehensive discussion, with supporting data, regarding the biological relevancy of each animal model should be provided. This should include, but is not limited to, the following:

(1) Progression of the disease phenotype or injury observed in each animal model
(2) The lifespan of each model
(3) The similarities and differences between the animal model(s) and the proposed patient population (e.g., pathophysiology, biochemistry, functional changes, etc.)
(4) The timing of product administration relative to disease onset and progression as it pertains to the proposed patient population, and
(5) A description of the relevant anatomy and physiology related to the delivery method and target anatomic site(s) in animals versus humans

The selection of animal model(s) of disease should be science-based and allow both sponsors and the FDA to evaluate the safety and bioactivity of the intended clinical product.

Q23. What approach should be taken if there is no available animal model of disease in which the investigational product can be evaluated?

When animal models of the target disease are not available or if the investigational CGT product is incompatible with an animal model, the sponsor should provide supporting data from other sources. Some examples include in

[90] For additional information, see https://www.fda.gov/media/191986/download?attachment and https://www.fda.gov/media/186092/download?attachment.

vitro studies, in silico studies, in vivo studies using an analogous animal product, and relevant nonclinical or clinical data from studies evaluating a related product (products of the same or similar class) or indication.

The sponsor should integrate these data to establish adequate scientific justification to support the proposed clinical trial. If there are no available animal models of the target disease to evaluate activity and safety of the CGT product, the pivotal safety studies are typically conducted in pharmacologically relevant healthy animals to identify potential toxicities related to the CGT product or administration procedure(s).

Q24. Can alternative test methods or new approach methodologies be used in place of animal studies even if animal models exist?

The nonclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section III.B of this guidance). FDA supports the use of NAMs, where feasible, and is open to alternative methods that are backed by science and produce scientifically valid data and will consider whether such an alternative could be used in place of an animal test method within a particular context of use.

J. Product Selection for Nonclinical Studies

Q25. What are important aspects to be considered when evaluating the similarity of human and analogous animal CGT products?

Evaluation of the intended clinical product in animals may not always be feasible. This could be due to potential xenogeneic responses after administration of a human-specific CGT product in animal models or differences in the homology of a transgene product or target between humans and the animal species. Therefore, depending on the type of product, the use of an analogous animal product may be a suitable alternative in animal studies. The analogous animal product should be representative of the intended clinical human product to the extent possible.

A sufficient comparison between the analogous animal product and the intended clinical product should be provided in pre-IND and IND submissions. Depending on the type of CT product, this comparison should include, but is not limited to, the following characteristics: product identity, cell type(s), cell phenotype, function, manufacturing (i.e., procedures, formulation, stability, potency), and other CQAs. For GT products, additional considerations can include vector/transgene sequence, target specificity, and/or transgene expression levels, physical titer, and empty capsid content. For LNP based GT products, additional considerations can include lipid identity and quality, final lipid formulation, cargo

(e.g. mRNA), and manufacturing process. Whether data generated from the in vitro and/or in vivo nonclinical evaluation of an analogous animal product would be appropriate to serve as a comparison is considered on a case-by-case basis.

K. Tumorigenicity

Q26. What is the FDA's recommendation regarding tumorigenicity studies before the first use of CGT products in human subjects?

Evaluation of tumorigenic potential prior to administration of an investigational CGT product in a FIH clinical trial depends on the type of investigational CGT product. For example, the differentiation status of a CT product, the extent of ex vivo cell manipulation, the potential for integration of genetic material into the host genome, the expressed transgene in a GT product, and the in vivo distribution and persistence profile should be considered when determining the need for assessing tumorigenic potential of the CGT product. Tumorigenicity studies are generally recommended for pluripotent stem cell-derived products, which have the potential for aberrant cell proliferation, differentiation, and teratoma formation. The sponsor can conduct tumorigenicity testing in either a dedicated study or as a component of a nonclinical safety/toxicology study. The animal species/strain for in vivo assessment of tumorigenicity should be permissive to the engraftment and long-term survival of the investigational product following administration via the planned clinical ROA.

The number of animals included in an in vivo tumorigenicity study should be sufficient to collect all protocol-specified parameters and detect low-frequency events. Thus, it is important to ensure that a robust number of animals are followed to scheduled sacrifice to allow for meaningful data interpretation. Study duration and selection of the appropriate sacrifice time points for tumorigenicity studies should be based on the in vivo distribution and persistence profile of the investigational CGT product. The sponsor should determine the cellular origin of any detected tumors (i.e., whether they are derived from host or donor cells). It should be noted that an analogous animal product would typically not be appropriate for tumorigenicity testing. If the sponsor considers a **Error! B ookmark not defined.**tumorigenicity study unnecessary, they should provide a scientific justification with supporting data in their submission to OTP for review.

L. Error! Bookmark not defined.Proof-of-Concept Studies

Q27. Why are proof-of-concept data important for CGT products? Can FDA provide details on how much and what type of proof-of-concept data are appropriate prior to conducting a clinical trial?

POC studies are important to evaluate bioactivity, determine the feasibility of the ROA, and provide a rationale for use of an investigational CGT product in the target clinical population. POC studies often characterize the putative mechanism

of action of the investigational CGT product and aid in determining a potentially active dose level range and optimized dosing regimen for the initial clinical trial.

Once POC data have been obtained, it can be helpful for sponsors to discuss the adequacy of these data and the details of the protocol(s) for planned pivotal toxicology studies at a pre-IND meeting. If the POC data submitted are inadequate to support the planned clinical studies, sponsors may be asked to conduct additional POC studies. Additionally, data from POC studies can be used to support a prospect of direct benefit prior to initiating a clinical study in children that presents more than minimal risk.[91] The sponsor should provide pharmacology summaries and final study reports for each POC study in the IND submission. The adequacy of the nonclinical data to support administration of the investigational CGT product in the proposed clinical trial is determined based on the review of the POC and safety data in the IND.

M. Toxicity

Q28. Can sponsors submit INDs without conducting nonclinical toxicology studies for certain products?

An IND must contain adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.[92] The design of nonclinical toxicology/safety studies should be based on the product type, ROA, and intended clinical indication. Toxicology/safety studies are important to characterize potential risks for the administration of investigational CGT products in a proposed clinical trial. For general guidance on safety and toxicology studies in CGTs, refer to Preclinical Assessment CGT Guidance [Ref. 10]. If a sponsor believes adequate information about toxicological risk of the drug can be provided without further toxicology testing for a specific product, they should provide a discussion of the available data (nonclinical or clinical) to support the safety profile of the investigational product and their scientific rationale for why they believe further toxicological assessment is unnecessary in their IND submission.

Q29. For a single-dose administration investigational product, what are the considerations for the duration of the pivotal toxicology study?

The duration for a pivotal toxicology/safety study evaluating a single-dose administration will vary based on the product characteristics and ROA for the intended clinical population. The study duration may be informed by data obtained from pilot safety and biodistribution (BD) studies. The pivotal

[91] See 21 CFR Part 50 Subpart D, 21 CFR 50.52.
[92] 21 CFR 312.23(a)(8).

toxicology/safety study should be of sufficient duration to evaluate potential acute and long-term toxicities, as well as the potential for resolution or stabilization of any findings. Multiple sacrifice time points following administration of an investigational product should be included to comprehensively characterize potential adverse findings. The sponsor should provide their rationale, with supporting data to justify the dose levels, sacrifice timepoints, panel of tissues/biofluids collected for clinical chemistry and pathology assessments, and duration of their safety/toxicology studies.

N. Design of Cell Distribution/Biodistribution Studies

Q30. Does FDA recommend certain testing methods for cell distribution or vector biodistribution studies?

For CT products, various methods have been used to assess in vivo cell distribution, such as imaging modalities for detection of radioisotope-labeled cells, genetically modified cells (e.g., expressing green fluorescent protein), nanoparticle-labeled cells (e.g., iron-dextran nanoparticles), qPCR or droplet digital PCR (ddPCR) analysis and immunohistochemistry to identify cells of human origin or cells of a karyotype different than the host (e.g., sex). A potential advantage of in vivo imaging techniques is that in many instances, the same animal can be evaluated over time, thus decreasing variability and reducing the number of animals used. Data should be provided to support the viability and function of the CT product if the cells are modified to enable use of such imaging techniques. Other detection methods may be considered if scientifically supported.

For GT products, use of a quantitative and sensitive assay such as qPCR or ddPCR for vectors or LC-MS/MS for LNP-based products is recommended to analyze BD and persistence in various tissues/biofluids. For samples that are determined to be positive for vector or LNP presence upon analysis, transgene mRNA, cargo RNA and/or protein expression levels should also be measured using an appropriate method. Determining levels of protein expression resulting from transduction can inform on the safety and potential bioactivity of the product. For details, refer to FDA's guidances entitled "S12 Nonclinical Biodistribution Considerations for Gene Therapy Products: Guidance for Industry," May 2023 [Ref. 27] and "Long-Term Follow-Up After Administration of Human Gene Therapy Products: Guidance for Industry," January 2020 (hereinafter referred to as "LTFU After GT Products Guidance") [Ref. 28].

O. Dose Levels

Q31. What are the recommended methods for dose level extrapolation from animals to humans?

The proposed starting clinical dose level and dose escalation planned for an investigational CGT product should be supported by data from nonclinical POC and safety/toxicology studies. The methods for dose level extrapolation from animals to humans should be based on, for example, body weight, volume of target tissue/organ, organ mass, or surface area depending on the ROA and product type. The proposed starting clinical dose level of an investigational CGT is typically determined based on the bioactivity of the product from nonclinical POC studies performed in an animal model of disease and should also be supported by nonclinical safety studies. The dose level extrapolation and safety margin should be determined for each animal species administered the intended clinical product (or analogous product) in the POC and toxicology studies. When technical limitations do not allow for the determination of a starting clinical dose level from in vivo nonclinical studies, or there are appropriate alternatives to animal studies, data from other sources (e.g., in vitro, NAMs) may be considered with sufficient scientific support.

VI. CONDUCTING HUMAN TRIALS

A. Trial Design

Q32. What is important for sponsors to consider when designing clinical trials for CGTs?

Licensure of biological products, including CGTs, requires a showing that the products are "safe, pure, and potent."[93] Potency has long been interpreted to include effectiveness.[94] FDA has generally considered substantial evidence of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act.[95] Substantial evidence may be satisfied by two adequate and well-controlled clinical investigations to establish effectiveness, but in some cases, FDA may consider data from one adequate and well-controlled

[93] See section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262).
[94] 21 CFR 600.3(s).
[95] In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126) (see former 21 CFR 601.25(d)(2) (2015) (revoked as no longer necessary, 81 FR 7445 (Feb. 12, 2016))). We note that, in section 123(f)) of the Food and Drug Modernization Act of 1997 (FDAMA), Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FD&C Act.

clinical investigation and confirmatory evidence to constitute substantial evidence.[96] For additional guidance, refer to FDA's draft guidance entitled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry[97]," June 2026 [Ref. 35].

A purpose of conducting clinical trials with an investigational product is to distinguish the effect of the product on the target condition from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. When properly conducted, a clinical trial that includes appropriate blinding and random assignment of subjects to either a treatment or a concurrent control group, to optimally promote the similarity of compared groups, will generally allow us to determine if the treatment effect is attributed to the investigational product.

Some of the features of an adequate and well-controlled clinical study include a valid comparison with a control to provide a quantitative assessment of drug effect, a suitable method of assignment to treatment and control groups (e.g., randomization), and adequate measures to minimize bias (e.g., blinding of study subjects and/or evaluators).[98]

There are generally five types of controls: (1) the placebo/sham concurrent control; (2) the active concurrent control, or control therapy that involves an accepted alternative treatment; (3) the dose-ranging concurrent control; (4) the no-treatment concurrent control; and (5) the external or historical control.[99] When feasible and/or ethical, sponsors should first consider study designs using one of the first three types of controls, each of which permits randomization and blinding, making the study results largely free of bias and highly interpretable. Sponsors should next consider the no-treatment control because although the study subjects will know they are not receiving the treatment, they will be otherwise selected and assessed according to the same protocol as those receiving the investigational CGT product. In some cases, such as with rare diseases that have a natural history that does not improve with other interventions, or spontaneously, a well-conducted natural history study may serve as an acceptable external or historical control. Blinding and randomization are feasible when a placebo control, active concurrent control, or dose-ranging concurrent control is used. Sponsors developing an investigational product for a rare disease should consider designing their FIH study to be an adequate and well-controlled clinical study so that the results of such a study may contribute to meeting the substantial evidence standard for effectiveness to support a marketing application. For further information on development of CGT products for rare diseases, refer to the GT for Rare Diseases Guidance [Ref. 23].

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[96] See section 505(d) of the FD&C Act.
[97] When final, this guidance will represent FDA's current thinking on this topic.
[98] See 21 CFR 314.126(b).
[99] See 21 CFR 314.126(b)(2).

For more details, refer to the following draft guidances: "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry," February 2023 [Ref. 29] and "Rare Diseases: Natural History Studies for Drug Development: Draft Guidance for Industry," March 2019 [Ref. 30].[100] Additionally, see FDA's guidance "Rare Diseases: Considerations for the Development of Drugs and Biological Products: Guidance for Industry," December 2023 [Ref. 31] and "Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products: Guidance for Industry," June 2015 (hereinafter referred to as "CGT Early-Phase Trials Guidance") [Ref. 32].

Q33. How many trials are required to demonstrate substantial evidence of effectiveness of a CGT product, with the ultimate goal being FDA licensure?

As noted above, substantial evidence of effectiveness may be satisfied by two adequate and well-controlled clinical investigations but in some cases, FDA may conclude that one adequate and well-controlled clinical study plus confirmatory evidence is sufficient to establish effectiveness.[101] Several factors may be relevant to whether reliance on a single adequate and well-controlled clinical study plus confirmatory evidence is appropriate. These factors may include the persuasiveness of the single trial; the robustness of the confirmatory evidence; the seriousness of the disease; the size of the patient population; and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical study. Additionally, poor execution can cause a trial of any design to be inadequate or not well-controlled, and unable to support a finding of substantial evidence of effectiveness.

For more details, refer to FDA's guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry," May 1998 [Ref. 33] and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry," December 2018 [Ref. 34] (hereinafter referred to as "Cancer Drugs Endpoints Guidance"). Further information can be found in draft guidances "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry," June 2026 (hereinafter referred to as "Substantial Evidence of Effectiveness Draft Guidance") [Ref. 35] and "Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence: Draft Guidance for Industry," September 2023 [Ref. 36].[102]

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[100] When final, these guidances will represent FDA's current thinking on these topics.
[101] See section 505(d).
[102] When final, these guidances will represent FDA's current thinking on these topics.

B. Selecting Endpoints

Q34. What should sponsors consider when using a surrogate endpoint as a primary outcome measure for a later phase clinical trial intended to support approval of a CGT product?

For approval of a CGT, whether through traditional or accelerated approval, the product must be "safe, pure, and potent,"[103] and there must be substantial evidence of effectiveness. As compared to accelerated approval, for traditional approval, the Agency accepts clinical endpoints that directly reflect a meaningful clinical benefit (i.e., how study participants feel or function, or how long they survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit). For accelerated approval, FDA accepts evidence of a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit or on an intermediate clinical endpoint (a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict a clinical benefit).[104] For products approved under accelerated approval, FDA requires post-approval trials to verify the predicted clinical benefit. The importance of the clinical outcome to patients and the feasibility of showing a treatment effect in a trial of reasonable duration are primary considerations for our evaluation of clinical outcomes.

Clinical Versus Surrogate Endpoints

A clinical benefit denotes a positive therapeutic effect that is clinically meaningful in the context of a particular disease. A clinical endpoint directly measures a therapeutic effect of a medical product and assesses how a patient feels, functions or how long they survive. A surrogate endpoint is a marker, such as a laboratory measure, physical sign, radiographic image or other measure that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives.[105] Surrogate endpoints are not direct measures of clinical benefit; however, treatment effects on a surrogate endpoint may predict the clinical benefit of a treatment. Depending on the strength of the evidence supporting the ability of a measure to predict clinical benefit, a marker may be a surrogate endpoint that is known to predict clinical benefit (i.e., a "validated" surrogate endpoint) or could be a surrogate endpoint that is reasonably likely to predict a drug's intended clinical benefit.

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[103] See section 351(a) of the PHS Act.

[104] See section 506(c)(1)(A) of the FD&C Act; see also the Expedited Program for Serious Conditions – Accelerated Approval of Drugs and Biologics Draft Guidance [Ref. 40]. When final, this guidance will represent FDA's current thinking on this topic.

[105] See, e.g. FDA-NIH Biomarker Working Group, BEST (Biomarkers, EndpointS, and other Tools) Resource, Available at: https://www.ncbi.nlm.nih.gov/books/NBK326791/ (Co-published by FDA and the National Institutes of Health).

Biomarker Surrogate Endpoints

Biomarkers are laboratory or imaging test results, or other clinical measures that are indirect measures of physiological function, or physical signs that can tell us something about the state of severity of a disease process and potentially about the activity of an investigational product on the disease process. Biomarkers can also be very useful for identifying toxicity, exploring pharmacodynamic effects, and identifying the right dose.

The utility of a biomarker and the decision regarding how best to use them in clinical studies depends on a number of factors including how well the biomarker tracks the disease process; how likely it is that a pharmaceutical effect on the biomarker would predict a clinically meaningful improvement in the way a patient feels, functions, or survives; and the assay or imaging technique used to measure the biomarker. Scientific data are needed to support the utility of a biomarker.

Some factors considered when assessing whether a biomarker may have utility as a surrogate endpoint are:

(1) To what extent the pathophysiology of the disease is well understood and whether data suggest that the candidate surrogate is on the causal pathway of progression to the clinical outcome(s) of interest
(2) The strength and consistency of the epidemiologic data supporting the relationship between the biomarker and the clinical outcome(s) of interest
(3) Whether treatment effects on the biomarker have been shown to predict treatment effects on the clinical outcome(s) of interest, ideally with different types of interventions

C. Safety Data

Q35. What should sponsors consider for short- and long-term safety monitoring in trials of investigational CGT products?

Short-Term Follow-up

Many CGT products are administered once. Close monitoring of subjects immediately following product administration is critical to capture early safety signals. This means that during and immediately following product administration, there should be intensive safety monitoring with frequent monitoring of vital signs, physical examinations, laboratory studies, radiologic evaluations, and other relevant studies as warranted. During the subsequent weeks and months, subjects should be monitored frequently for assessment of emerging safety signals via clinical evaluation and ancillary testing.

FIH studies of CGT products should generally employ a safety strategy of staggered enrollment and treatment to limit the number of subjects exposed to unknown but potentially significant risks. Staggered enrollment and treatment incorporate a waiting period into the protocol for safety observation between subsequent subjects and between dose cohorts to identify potential safety issues before dosing the next subject. The staggering interval, either within a cohort or between cohorts, is intended to be long enough to monitor for acute and subacute adverse events prior to treating additional subjects at the same dose or prior to increasing the dose in subsequent subjects. The choice of staggering interval should consider the time course of acute and subacute adverse events that were observed in animal studies and in any previous human experience with related products.

Clinical studies of CGT products should have stopping rules which, if met, cause temporary suspension of enrollment and dosing until the situation can be assessed. Well-designed stopping rules allow sponsors to assess and address risks identified as the trial proceeds and to assure that risks to subjects remain reasonable.[106] The protocol should include study stopping rules that specify the number of adverse events, as well as the nature and/or the severity of those events, which would trigger the temporary suspension of drug administration in the study, pending a safety investigation. In addition, stopping rules should be independent of attribution as the safety profile is unknown.

Long-Term Follow-Up

The appropriate duration of follow-up for CGT products depends on the results of nonclinical studies, experience with related products, knowledge of the disease process, and other scientific information.

FDA advises sponsors to observe subjects for delayed adverse events for as long as 15 years following exposure to the investigational product, depending on the type of product, in long-term follow-up trials. One of the main principles is that GT products may be integrated into the genome or cause genome editing and subjects receiving these therapies need to be monitored for the longer period because of the potential higher risk of cancer or other off-target effects.

For more details, refer to the LTFU After GT Products Guidance [Ref. 28].

[106] See, e.g. 21 CFR 312.56(d) (requiring a sponsor to discontinue an investigation if a sponsor determines that its investigational drug presents an unreasonable and significant risk to subjects).

Q36. When investigating CGT therapies in Phase 1 trials, should only safety be tested, or should efficacy endpoints also be incorporated?

FDA advises sponsors to carefully design their early-phase studies in the context of the overall development program's objectives. While Phase 1 studies are primarily geared toward evaluating safety, tolerability, and dose exploration, it is important to explore POC, preliminary efficacy, and pharmacodynamic measures to help inform the design of the later studies. It is important to follow all Phase 1 study subjects in long-term follow-up studies where clinical outcomes measures should also be assessed. Clinical outcomes measured in these early treated subjects may provide confirmatory evidence of effectiveness.

In particular, for rare diseases, a well-designed Phase 1 study designed to assess both safety and efficacy utilizing clinically meaningful endpoints may potentially serve as a pivotal study to support approval. For details, refer to the CGT Early-Phase Trials Guidance [Ref. 32].

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