Respondents may transmit FAP or CAP regulatory submissions in electronic format or paper format to the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition (CFSAN) using Form FDA 3503. Form FDA 3503 helps the respondent organize their submission to focus on the information needed for FDA's safety review. Form FDA 3503 can also be used to organize information within a master file submitted in support of petitions according to the items listed on the form. Master files can be used as repositories for information that can be referenced in multiple submissions to the Agency, thus minimizing paperwork burden for food and color additive approvals.

We improved the information collection by using the CFSAN Online Submission Module (COSM). COSM provides a real-time user interface process that assists respondents in preparing and making submissions to CFSAN. COSM is a web-based tool that supports electronic submissions, thereby eliminating the need for printing and mailing of paper submissions. COSM is available 24 hours a day and 7 days a week. Further information about COSM, including user instruction, is available on the internet at: *https://www.fda.gov/food/registration-food-facilities-and-other-submissions/cfsan-online-submission-module-cosm.*

Description of respondents: Respondents are businesses engaged in the manufacture or sale of food, food ingredients, color additives, or substances used in materials that come into contact with food.

In the **Federal Register** of February 1, 2023 (88 FR 6757), FDA published a 60-day notice requesting public comment on the proposed collection of information. Although one comment was received, it was not responsive to the four collection of information topics solicited.

We estimate the burden of this collection of information as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

Activity/21 CFR section; or FDA form No.	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours	Total operating and maintenance costs
Submission of Petitions: Color Additive Including Labeling—70.25 and 71.1	2	1	2	1,337	2,674	$5,600
Submission of Petitions: Food Additive Including Labeling—171.1	3	1	3	7,093	21,279	0
Form FDA 3503 [2]	5	1	5	1	5	0
Total	.....	.....	.....	.....	23,958	5,600

[1] There are no capital costs associated with this collection of information.
[2] Form FDA 3503 is used for both CAPs and FAPs.

We have adjusted our burden estimate, which has resulted in a decrease to the currently approved burden by 1 hour. Our estimate of burden attributable to FAPs or CAPs is based on our experience with the information collection, which has not changed since our last review, and reflects the average number of petitions we have received annually over a period of 10 years. The attendant burden we estimate also reflects an industry average, although burden associated with individual petitions may vary depending on the complexity of the petition, and the amount and type of data needed for scientific analysis.

CAPs are subject to fees. The listing fee for a CAP ranges from $1,600 to $3,000, depending on the intended use of the color additive and the scope of the requested amendment. A complete schedule of fees is set forth in 21 CFR 70.19. An average of one Category A and one Category B CAP is expected per year. The maximum CAP fee for a Category A petition is $2,600, and the maximum CAP fee for a Category B petition is $3,000. Because an average of two CAPs are expected per calendar year, the estimated total annual cost burden to petitioners for this startup cost would be less than or equal to $5,600 ((1 × $2,600) + (1 × $3,000) listing fees). There are no capital costs associated with CAPs.

The labeling requirements for food and color additives were designed to specify the minimum information needed for labeling in order that food and color manufacturers may comply with all applicable provisions of the FD&C Act and other specific labeling Acts administered by FDA. Label information does not require any additional information gathering beyond what is already required to assure conformance with all specifications and limitations in any given food or color additive regulation. Label information does not have any specific recordkeeping requirements unique to preparing the label. Therefore, because labeling requirements under § 70.25 for a particular color additive involve information required as part of the CAP safety review process, the estimate for number of respondents is the same for §§ 70.25 and 71.1, and the burden hours for labeling are included in the estimate for § 71.1. Also, because labeling requirements under parts 172, 173, 179, and 180 for particular food additives involve information required as part of the FAP safety review process under § 171.1, the burden hours for labeling are included in the estimate for § 171.1.

Dated: September 18, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–20451 Filed 9–20–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2023–N–3742]

Scientific Challenges and Opportunities To Advance the Development of Individualized Cellular and Gene Therapies; Request for Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for information and comments.

SUMMARY: The Food and Drug Administration (FDA or Agency), Center for Biologics Evaluation and Research (CBER) is requesting information from stakeholders regarding critical scientific

challenges and opportunities to advance the development of individualized cellular and gene therapies (CGTs). FDA intends to gather information and comments submitted in response to this request for information (RFI) to inform potential planning of future town halls, workshops, or discussion papers which could ultimately facilitate the development of additional regulatory science tools, standards, or guidance.

DATES: Either electronic or written comments on the notice must be submitted by November 20, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 20, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2023–N–3742 for ''Scientific Challenges and Opportunities To Advance the Development of Individualized Cellular and Gene Therapies.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Karen Fikes, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911.

SUPPLEMENTARY INFORMATION:

I. Background

Personalized medicine has often been described as the use of individual characteristics, such as genetic markers or other measurable traits, to guide disease prevention or treatment among existing products (Ref. 1). An improved understanding of the molecular basis of disease along with the availability of sensitive diagnostic tools has led to the increasing opportunity to create individualized products based upon such genetic markers or measurable traits. These individualized therapies can now be developed for a single patient (or a very small number of patients) based on designing or engineering a product that specifically targets the mechanism underlying a patient's (or small number of patients') illness (Ref. 2). The opportunities and challenges associated with individualized therapies span the entire development pathway; from robust and consistent manufacturing with assurance of product quality, to nonclinical models and tools to characterize safety and activity, to the generation, collection, and assessment of clinical evidence from an individual patient (or a very small number of patients) (Refs. 3 and 4). For the purposes of this RFI, these types of products will be referred to as individualized CGTs. Examples of these emerging areas of research include:

- Products designed for the same indication with the same mode of action. For instance, a personalized vaccine for pancreatic cancer that consists of autologous dendritic cells pulsed with patient-specific neoantigen peptides (Ref. 5).
- Products designed for different indications with different modes of action. For instance, two gene therapy vector products for separate rare genetic neurological diseases, where both products utilize the same vector backbone but contain different transgene inserts.

This RFI is specifically seeking input on the scientific challenges and opportunities for individualized CGTs. The outcomes of this RFI are meant to complement other ongoing and planned CBER town halls, workshops, and discussion papers designed to educate and seek feedback on a broad range of considerations for the development of

CGTs (Ref. 6). The purpose of this RFI is limited to planning purposes only and should not be construed as a policy, a solicitation for applications, or an obligation on the part of the government to provide support for any ideas identified in response to it.

II. Request for Information and Comments

FDA is requesting information regarding major scientific challenges and opportunities to advance the development of individualized CGTs, with a specific focus on the areas outlined below, including manufacturing (*e.g.,* product quality), nonclinical development (*e.g.,* toxicology, proof of concept, biodistribution), clinical development (*e.g.,* assessing safety and efficacy), and additional questions to consider (*e.g.,* additional scientific needs, best practices, opportunities for collaborations).

A. Manufacturing

All CGTs, including individualized CGTs, need to be manufactured with sufficient quality, purity, and potency to ensure that each batch of the product has adequate safety and full potential to achieve the intended therapeutic outcome. In the case of CGTs for rare diseases, where a single batch of product may be sufficient to treat a small number of patients diagnosed with the rare disease, it can be challenging to develop a consistent manufacturing process and robust control strategy for future batches of the product for additional patients diagnosed with the same rare disease.

Additionally, the manufacturing of some individualized CGTs may need to be tailored to each patient, leading to high variability among each batch of the individualized product. For example, autologous CAR–T cell products are derived from a patient's own cells, and variability in this starting material leads to variability in the drug product. It can be challenging to understand and control the impact of this variability on the safety and efficacy of the product. As additional examples, a tumor neoantigen vaccine may be based on the genetic sequence of the individual patient's tumor, and some genome editing products may be customized to treat the individual patient's genetic mutation. The tailored manufacturing processes needed for these types of products can be difficult to standardize and can also result in significant variability among batches.

- Given the challenges to develop consistent manufacturing strategies for CGTs designed for a very small number of patients or an individual patient, how can manufacturers leverage their prior experience manufacturing one CGT to support subsequent development and approval of another related, but distinct CGT (potential areas for leveraging may include manufacturing process validation, control strategy, assay validation, and drug product stability studies)?
- When the batch size of a CGT is very small, what are some challenges and solutions regarding the volume of product (or number of vials) needed for batch release testing, stability testing, retention of reserve samples, and comparability studies?
- What are some challenges and solutions for individualized CGTs that need to be tested and released rapidly, either because the product has a very short shelf life or because the patient's clinical status may be rapidly declining and treatment is urgently needed?
- For many individualized CGT products, each batch is tailored to an individual patient (*e.g.,* autologous CAR–T cells, tumor neoantigen vaccines, certain genome editing products). For such products, what are some challenges and solutions for assuring that each batch has adequate potency to achieve the intended therapeutic effect?
- What are some challenges and solutions for individualized genome editing products that aim to treat monogenic diseases for which the target gene has different mutations in different patients?

B. Nonclinical Development

There are several challenges in translating nonclinical data to humans for individualized CGTs. Because the final investigational product is unique to an individual or a small number of subjects, it often is not possible to evaluate the final clinical product in nonclinical studies. Additionally, many individualized CGTs target antigens that are human-specific and thus lack relevant animal models to inform safety and activity. An example includes T-Cell receptor-engineered T cells that target a patient-specific neoantigen, or a shared target in the context of an HLA allele specific to a small group of human subjects. There are also opportunities and challenges to utilizing prior knowledge from nonclinical studies of other approved or investigational individualized CGTs that may be leveraged for a related product under development for different populations or indications. An example includes two or more gene therapy vector products for different rare genetic diseases that utilize the same vector backbone while containing different transgene inserts.

With continued scientific advances in the CGT field, it is also important to consider the use of computational approaches to support nonclinical evaluation of individualized CGTs. Computational approaches may present an opportunity to quickly and efficiently screen product safety or activity, but may pose additional challenges in their consistent use and validation.

- What nonclinical studies could be leveraged in support of a related product using similar technologies? What nonclinical studies are important to conduct with each final clinical product?
- What nonclinical development approaches could be considered when there are no relevant animal models or animal models are unable to replicate each individual disease/condition?
- For patient-specific products where evaluating each individual product is infeasible or impractical, what is the role for nonclinical studies conducted with representative product(s)?
- What are the opportunities and challenges with using computational approaches to support nonclinical development?

C. Clinical Development

Assessing efficacy can be a particular challenge in clinical studies of individualized CGTs, particularly for rare diseases with heterogeneous presentations. Randomized controlled designs are desired for interpretability of results, but may be unfeasible or unethical for various reasons in rare disease clinical trials. However, natural history data may be limited and/or lack suitability to support outcome assessments. Additional specific challenges in individuals or small groups include development and interpretation of novel endpoints, limitations in statistical analyses to understand treatment effects, and determining appropriate study design and duration to assess clinically meaningful benefit. An example may be a newly identified specific genetic mutation associated with a unique phenotypic presentation of disease, where only a few individuals with the specific mutation have been identified, and the natural history of disease is poorly understood. Adaptive, Bayesian, and other trial designs may provide different opportunities or challenges, and the approach will likely need to be considered on a case-by-case basis.

Understanding clinical safety of individualized CGTs may also be difficult and may depend on relevant

available data for similar products or other treatments for the disorder or similar disorders.

- What are challenges and strategies/opportunities with interpreting efficacy data from individual patients (including expanded access) and small groups of patients? What opportunities are there in leveraging prior and/or collective experiences?
- What strategies can be utilized to accumulate and interpret safety data in personalized/individualized CGTs?
- For genetic disorders with clear genotype-phenotype associations for disease manifestations or severity, what opportunities are there for tailoring treatments and study design to specific genotypes/phenotypes?

D. Additional Questions To Consider

- What additional major scientific challenges to advance the development of individualized CGTs should be considered?
- What existing best practices or scientific approaches should be leveraged to address any of these challenges? Are there specific opportunities for collaborations to advance the development of individualized CGTs?
- Are there specific areas where flexibility in regulatory approaches would improve the feasibility of developing and commercializing individualized CGTs?

III. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. President's Council of Advisors on Science and Technology, ''Priorities for Personalized Medicine,'' September 2008.
2. FDA, ''Focus Area: Individualized Therapeutics and Precision Medicine,'' 2022. Available at *https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-individualized-therapeutics-and-precision-medicine.*
3. Marks, P. and C. Witten, ''Toward a New Framework for the Development of Individualized Therapies,'' *Gene Therapy,* 28:615–617, 2021.
4. FDA, ''Facilitating End-to-End Development of Individualized Therapeutics'' (Public Workshop) (March 3, 2020). Available at *https://fda.yorkcast.com/webcast/Catalog/Mobile/FolderPresentation/6d6af3ca61754c3c869f7f556bbede9e21/4174764f-a52d-4503-893d-0b8bc35e1da7/b9c6ac08f3d040eba768ef43befb498f1d/.*
5. Fritah, H., R. Rovelli, C.L. Chiang, and C.L. Kandalaft, ''The Current Clinical Landscape of Personalized Cancer Vaccines,'' *Cancer Treatment Reviews,* 106:102383, 2022.
6. FDA, ''OTP Events, Meetings, and Workshop,'' (2023). Available at *https://www.fda.gov/news-events/otp-events-meetings-and-workshops.*

Dated: September 18, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023–20452 Filed 9–20–23; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2023–D–3550]

Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies; Guidance for Industry, Investigators, and Institutional Review Boards; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled ''Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies.'' This guidance recommends approaches that sponsors of clinical trials of medical products can consider when there is a major disruption to clinical trial conduct and operations due to disasters or public health emergencies, which can include but are not limited to hurricanes, earthquakes, military conflicts, infectious disease outbreaks, or bioterrorist attacks. The appendix to this guidance further explains those approaches by providing answers to questions that the Agency has received about conducting clinical trials during major disruptions.

DATES: The announcement of the guidance is published in the **Federal Register** on September 21, 2023.

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2023–D–3550 for ''Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper