

Some of CDER's Top Issues, Priorities, and Goals



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Areas We Will Cover Today



- Availability of medicines
- Safety:
 - Substance use and misuse
 - Supply chain integrity
- Process enhancement and modernization



Availability of Medicines: What CDER Can Do

Drug Shortages



- FDA's Definition
- Prevention: Early Notification is Key
 - Number of prevented shortages, CDER, 2021: **303**
 - Number of new shortages, CDER, 2021: **38**

What we CAN require:

- Notification by manufacturers (FDASIA) of:
 - Supply disruptions
 - Delays
 - Discontinuations
 - Notification of certain manufacturing changes

What we CANNOT require:

- A company to report an increase in demand that might lead to shortage
- A company to make a drug
- A company to make more of a drug
- A distributor to report on how much of a drug is distributed and which purchasers will be given priority

FDA's Approach to Preventing & Mitigating Shortages



- Prioritize medically necessary products
- Maintain availability while minimizing risk to patients
- Work with firms to address problems by:
 - Prompting firms to look at supply and demand
 - Expediting review of company's proposed plan to mitigate/resolve the shortage
 - Regulatory discretion, e.g. on stability data for new manufacturing line
 - Temporarily exercising regulatory flexibility and discretion regarding importation from other countries -- rare; contingencies apply
- In the event a shortage cannot be prevented, FDA and the manufacturer can work together to encourage smart distribution, aka *allocation*

Regulatory Science – BSUFA III



- Pilot a BsUFA regulatory science program broadly applicable to biosimilar & interchangeable biological product development. Project goals should not be specific to a product or product class.
- Two demonstration projects:
 - Advancing the Development of Interchangeable Products
 - Improving the Efficiency of Biosimilar Product Development
- Stakeholder Engagement
 - Includes public mtg on/before 10/2025 to review progress, solicit input on future priorities
 - Before meeting, FDA will issue interim report on project progress
 - Publish final summary report on project outcomes in FY2027
- Deliverable: Publish comprehensive strategy within 12 mos of completing projects
- For additional information, [Biosimilars | Science and Research | FDA](#)

Generic Drug User Fee Amendment (GDUFA III)



Research and Priority Initiatives for 2023

- Develop methods for generics to address impurities, e.g., nitrosamines
- Improve efficiency of BE approaches for oral and parenteral generics
- Facilitate utility of model-integrated evidence to support demonstrations of BE
- Enhance Approval of Complex Generics
 - Enhance efficiency of BE approaches for complex active ingredients, routes of delivery, dosage forms and formulations, drug-device combination products
 - Focus pre-submission meetings on key issues; option for enhanced mid-cycle mtg to resolve issues; new post-CRL mtg to facilitate subsequent cycle approval

GDUFA III (cont'd)



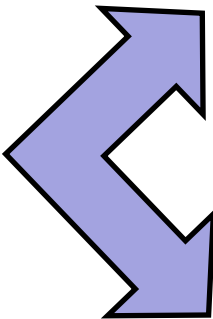
ANDA Communications and Review Enhancements

- Imminent approval, goal date extensions → reduction in number of review cycles
- Revisions to Pre-submission Facility Correspondence pathway requirements
- Expansion of options for advice after a CRL
- New goals around responses to suitability petitions to facilitate development of new ANDAs for different route of administration, strength, dosage form, or one different active ingredient
- Opportunities for telecons, correspondence, scientific mtgs when there are changes in product-specific guidances impacting ongoing BE studies

U.S. Drug and Biological Approval Pathways



**Approval
of Drugs &
Biologics**



AWC Trials

Substantial Evidence

Clinical endpoint or
validated surrogate

Reasonably likely surrogate/
Intermediate clinical endpoint

Traditional approval

Accelerated approval*

AWC – Adequate and Well Controlled Trials
21 CFR 312.126

* 21 CFR Part 314, Subpart H (for drugs)
21 CFR Part 601, Subpart E (for biologics)
Food and Drug Administration Safety and
Innovation Act 506(c)

Accelerated Approval Tradeoff: Speed to Meet Unmet Need vs. Certainty About Clinical Benefit



- Serious and life-threatening diseases without adequate therapies
- Challenges:
 - Ability to identify a **surrogate or intermediate clinical endpoint** that predicts a clinically meaningful outcome
 - Requires sufficient understanding of pathogenesis
 - Limitations of animal models
- Potential advantages:
 - Streamlined development
 - Greater access as/if benefit is confirmed
- Confirmatory trials:
 - Postmarketing trials required to verify and describe drug's clinical benefit
 - Address remaining uncertainty of surrogate endpoint's relation to clinical benefit

Consolidated Appropriations Act, 2023

Section 3210 Modernizing AA



“(D) STUDIES BEGUN BEFORE APPROVAL—The Secretary may require, as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product.”

- Confirmatory: specify conditions for post-approval studies; sponsor reporting on progress of such studies
- Accelerated Approval Council: Engages with product review team on policy development, training, e.g., best practices for communication between sponsors & FDA; product-specific development, review, withdrawal under AA
- Expedited withdrawal: codifies the expedited withdrawal procedures if sponsors fail to conduct required post approval study with due diligence

FDORA: Accelerated Approval Withdrawal



- The Food and Drug Omnibus Reform Act of 2022 (FDORA)'s revisions to the accelerated approval pathway include new streamlined withdrawal procedures
- Prior to the changes, the sponsor could elect to require FDA to hold an informal hearing that included an advisory committee (AC) prior to withdrawal
- As revised by FDORA, section 506(c)(3)(B) of the FD&C Act now provides the opportunity for a written appeal to the Commissioner (or Commissioner's designee) on the proposed withdrawal
 - Sponsor is entitled to a meeting with the appellate decision-maker, but not a hearing.
 - Sponsor can request an AC, but is not entitled to one if an AC has previously advised FDA on the issues related to the proposed withdrawal
 - FDA must provide for public comment on the proposed withdrawal, publish a summary of such comments, and provide FDA's response to such comments

Prescription to Nonprescription Switch Updates



- FDA approved non-prescription Narcan, rapidly reverses effects of opioid overdose
 - Working to ensure all forms of naloxone remain available during and after the switch
 - Marketing status: Approved generic 4 mg naloxone nasal spray products with Narcan as RLD → “misbranded” if labeled as prescription-only
 - Any branded 4 mg naloxone nasal spray product that does not have a clinically meaningful difference from nonprescription Narcan → misbranded
- Timing TBD for approval of other nonprescription naloxone products, including switch of other prescription naloxone products to nonprescription
- FDA issued (4/28) final guidance for industry, Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products to assist sponsors in clinical development of NRT drug products to help cigarette smokers stop smoking
- Proposed Rule: Nonprescription Drug Product with An Additional Condition for Nonprescription Use (ACNU) Published in FR, 6/28/22 (87 FR 38313)

OTC Monograph Updates



- FRN (March 2023), Over-The-Counter Monograph Drug User Fee Rates for Fiscal Year 2023 includes fee calculations and applicability of OMUFA fees
- Draft guidance for industry, Over-the-Counter Monograph Order Requests (OMORs): Format and Content (April 2023)
- Posted five [final administrative orders](#) (April 2023). Section 505G of the Federal Food, Drug, and Cosmetic (FD&C Act), as added by the CARES Act, deemed final monographs and tentative final monographs to be final orders. FDA is issuing a notice to withdraw regulations establishing final monographs in title 21 of the CFR



Safety:

Substance Use and Misuse

Supply Chain Integrity

FDA Overdose Prevention Framework



- 1 Support **primary prevention** by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing
- 2 Encourage **harm reduction** through innovation and education
- 3 Advance development of evidence-based **substance use disorder treatments**
- 4 Protect the public from **unapproved, diverted or counterfeit** drugs presenting overdose risks

CDER's "Opioid Policy Refresh" in Action



September 23, 2022

FDA Issues New Guidance to Help Facilitate Availability of Naloxone to Prevent Opioid Overdoses and Reduce Death

April 3, 2023

FDA Moves Forward with Mail-back Envelopes for Opioid Analgesics Dispensed in Outpatient Settings

Agency Continues to Take Steps to Reduce New Cases of Opioid Use Disorder

June 26-27, 2023

Defining and Evaluating In-Home Drug Disposal Systems for Opioid Analgesics

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FDA Approves First Over-the-Counter Naloxone Nasal Spray

Agency Continues to Take Critical Steps to Reduce Drug Overdose Deaths Being Driven Primarily by Illicit Opioids

FDA announces new safety label changes for opioid pain medicines

March 29, 2023

April 13, 2023

Appropriate Opioid Prescribing -- Safety Labeling Change



- Part of FDA's comprehensive work to support safer opioid analgesic use and shared decision making between HCPs and patients regarding balanced pain management
- FDA is requiring several updates to the prescribing information for immediate-release (IR) and extended-release/long-acting (ER/LA) opioid analgesics
- **Key updates:**
 - Include statement that many acute pain conditions, including surgical procedures, treated in the outpatient setting require no more than a few days of an opioid pain medicine
 - Clarify that ER/LA opioid pain medicines should be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate
 - Include new warning about opioid-induced hyperalgesia and allodynia

Saving Lives by Making Naloxone More Accessible



- Approval of nonprescription naloxone (Narcan 4 mg Nasal Spray)
 - Prescription products will still be available
 - Any generic products affected by the switch of the Narcan nasal spray must switch their products to nonprescription status
 - FDA will continue to work with stakeholders during this period of transition to ensure continued access to naloxone
 - The DSCSA guidance, issued September 2022, will still be in effect to help harm reduction programs continue to purchase naloxone
- FDA will continue to gather information from stakeholders, such as at recently held public workshop, as part of our proactive approach to manage overdoses
 - Speakers and panelists from harm reduction groups did not ask for higher dose naloxone; they called for lower dose or more titratable formulations

Safer Disposal of Unused Opioids: REMS Modification for Mail-Back Envelopes



- FDA is requiring a modification to the Opioid Analgesic REMS
- Manufacturers must make prepaid mail-back envelopes available to outpatient pharmacies and other dispensers
- Part of FDA's comprehensive approach to address the overdose crisis by providing patients an option to safely and securely dispose of unused opioid medicines
 - FDA is also exploring in-home disposal options
 - FDA will participate in NASEM workshop (June 2023) for stakeholders to examine in-home drug disposal systems
 - FDA opened a docket to collect public comments to help determine whether in-home disposal products can mitigate risk of nonmedical use or overdose through a REMS

Xylazine Activities



November 8, 2022

FDA alerts health care professionals of risks to patients exposed to xylazine in illicit drugs

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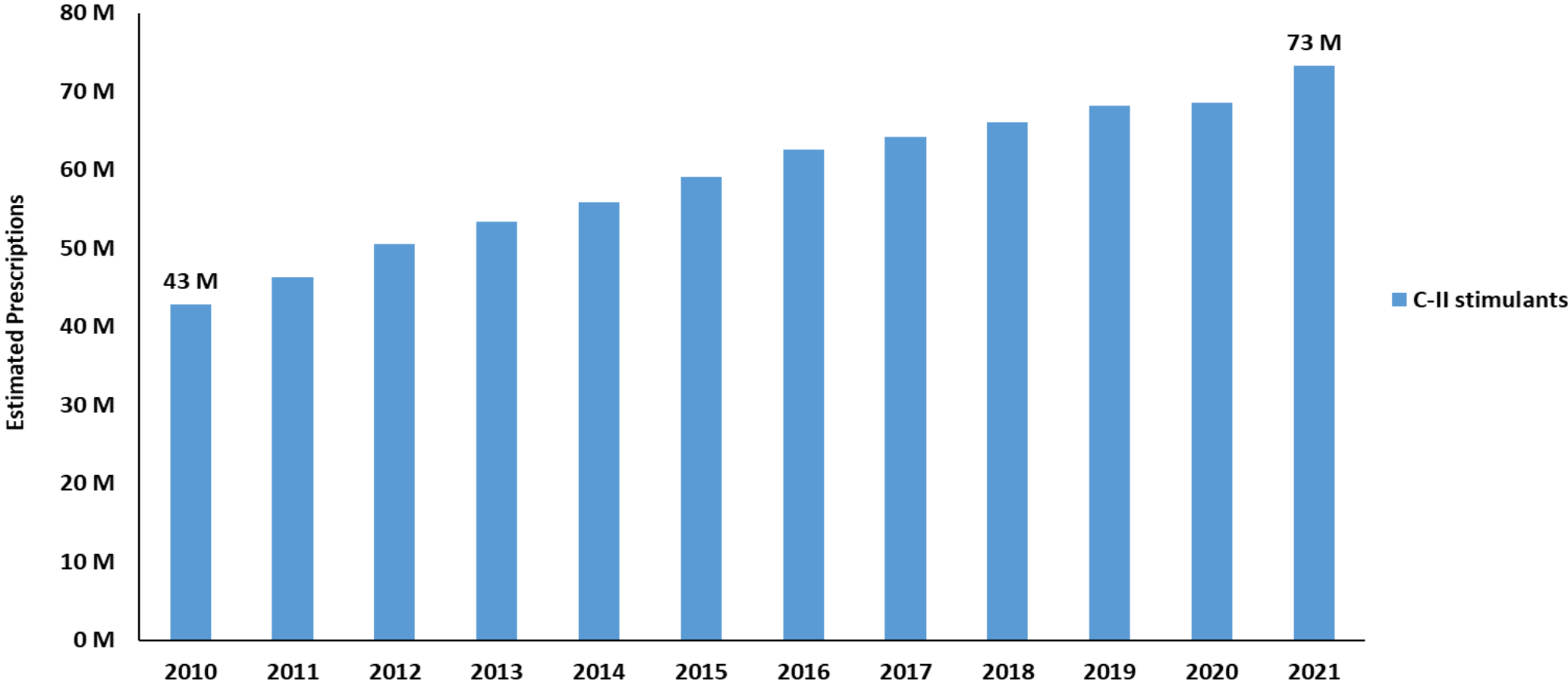
FDA Takes Action to Restrict Unlawful Import of Xylazine

Agency Aims to Maintain Availability for Legitimate Use in Animals while Preventing Importation for Illicit Purposes

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February 28, 2023

Increased Prescription C-II Stimulant Use Years 2010-2021



Estimated prescriptions for scheduled (C-II) stimulants dispensed from U.S. outpatient pharmacies, annually 2010-2021.

Source: Symphony Health Metys™. Study period 2010-2021, data extracted March 2022. Outpatient pharmacies include retail and mail-order pharmacies. Data include all dosage formulations. CII stimulants include amphetamine, dextromethylphenidate, dextroamphetamine, dextroamphetamine/amphetamine, lisdexamfetamine, methamphetamine, methylphenidate, and serdexmethylphenidate/dextromethylphenidate.

C-II = schedule II, M = millions

FDA Updating Warnings to Improve Safe Use of Prescription Stimulants for Treating ADHD & Other Conditions



- Key updates: boxed warning & prescribing info for CII stimulants (amphetamines & methylphenidate)
 - Describes risks of misuse, abuse, addiction, overdose consistently across CII stimulants, including that use of CII stimulants can lead to misuse or abuse even when prescribed to treat a specific condition
 - Includes language that patients should never share prescription stimulants or use differently than directed by health care professionals
 - For details, see the [Drug Safety Communication](#)

Drug Supply Chain Security Act (DSCSA)



- Enacted November 27, 2013
- Outlines steps to achieve interoperable, electronic tracing of product at the package level to identify and trace certain prescription drugs as they are distributed in the U.S.
- Establishes national licensure standards for wholesale drug distributors and third-party logistics providers (3PLs)
- Improves detection and removal of potentially dangerous drugs from the drug supply chain
- Enhances ability to help protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful

DSCSA Implementation



- Stakeholder Readiness and Challenges for November 2023
 - Industry has shown progress -> there is still work to do before the 11/27/2023 deadline (e.g., including industry testing)
 - While most data exchange will be standardized, flexible methods may be needed for small entities (e.g., web portals or email)
 - Continue outreach to trading partners and other stakeholders, as lack of understanding of complexities and needs may still exist, particularly with small entities or State regulators
 - Variety of Implementation Challenges

DSCSA Implementation (cont'd)



- What's Next → 2023 and Beyond
 - Guidances for Industry
 - Small Dispenser Assessment
 - Stakeholder Engagement (e.g., public private partnership, public meeting)
 - Finalize Wholesale Distributor/Third-party Logistics Provider (3PL) proposed regulations
 - Compliance and enforcement

Nitrosamine Impurities Overview



Nitrosamine Issues	Regulatory Activity	Risk Assessments	Mitigation
<p>N-nitrosodimethylamine (NDMA)</p> <ul style="list-style-type: none">FDA became aware of the presence of NDMA in valsartan, an angiotensin II receptor blocker (ARB) in 2018FDA learned that common synthetic pathways could introduce NDMA and other types of nitrosamine impurities <p>Nitrosamine Drug Substance-Related Impurities (NDSRIs)</p> <ul style="list-style-type: none">FDA alerted the public in November 2021 regarding the presence of NDSRIsNDSRIs share structural similarity to the active pharmaceutical ingredient (API) and present unique challenges	<p>FDA issued guidance in September 2020, “Control of Nitrosamine Impurities in Human Drugs”</p> <ul style="list-style-type: none">Provides recommendations on detecting and preventing unacceptable levels of nitrosaminesIdentifies acceptable intake (AI) limits for six nitrosamine impurities <p>FDA updated guidance in February 2021</p> <ul style="list-style-type: none">Extended timeframe for completion of risk assessments <p>FDA issued a statement on NDSRIs in November 2021</p> <ul style="list-style-type: none">Provides possible mitigation strategies and additional information on how NDSRIs are formedEncourages manufacturers to consider mitigation strategies	<p>Ames Testing</p> <ul style="list-style-type: none">Ames tests are typically used to assess mutagenicity. However, Ames tests have been shown to be inadequate in characterizing mutagenic potential in nitrosaminesFDA’s National Center for Toxicological Research (NCTR) has been testing different conditions to develop an enhanced Ames test <p>Computational Toxicology</p> <ul style="list-style-type: none">(Q)SAR can be used to predict the outcome of an Ames test and can be used to classify an impurityCan be done more rapidly than in vitro or in vivo testing and can be an efficient means to assess nitrosamine toxicity in the absence of experimental data	<p>FDA identified on its webpage two examples of mitigation strategies to reduce levels of NDSRIs in drug products</p> <ul style="list-style-type: none">Addition of an antioxidant to inhibit formation of nitrosaminesFormulation in a neutral or basic environment

Nitrosamines: Federal Register Notice and Collaborative Efforts



- Federal Register Notice related to nitrosamine impurities published May 4, 2023
 - FDA is requesting comments from the public regarding the identification, assessment, and control of NDSRIs including scientific and regulatory considerations and areas that may benefit from collaborative efforts
- Collaborative efforts
 - FDA has collaborated with international regulators since 2018 and other groups such as the Health and Environmental Sciences Institute (HESI) to address various issues related to nitrosamine impurities
 - FDA is interested in the feasibility of collaborative efforts within industry to avoid potentially duplicative in vitro or in vivo testing of NDSRIs



Process Enhancement and Modernization

Prescription Drug User Fee Act (PDUFA VII) Fiscal Years 2023-2027



- Provides FDA with resources needed to maintain predictable, efficient review process for human drug and biologic products. Ensures stable, consistent funding that will allow FDA to fulfill its mission to protect and promote public health by helping to bring to market critical new medicines for patients.
- FDA developed proposed enhancements for PDUFA VII in consultation with drug industry representatives, patient/consumer advocates, health care professionals, and other public stakeholders.

Two new formal meeting types:
Type D and INTERACT

Expanded definition of face-to-face formal meetings with industry: includes in-person and virtual on IT platforms with audio and visual communication

PILOT PROGRAMS

Split Real-Time Application Review (STAR) for priority efficacy supplements for unmet medical need

Rare Disease Endpoint Advancement (RDEA) to address developing appropriate efficacy endpoint(s) for CTs evaluating effectiveness of rare disease therapies

Advancing Real-World Evidence (RWE) to identify approaches for generating RWE that meet regulatory requirements in support of labeling for effectiveness or for meeting post-approval study requirements; annual reporting

PDUFA VII (cont'd)



Enhanced overall CMC-related communications during drug development and application review

Includes pilot: 2 additional CMC meetings for development of products for unmet medical needs, accelerated clinical timelines

Training for FDA staff on updated processes for communication with sponsors

FDA to host public workshop on using innovative manufacturing technologies to facilitate their adoption

PMRs

New process, timelines, performance goals to ensure timely availability for public of safety and efficacy information

New process for sponsors to request review of existing PMRs

Will update corresponding MAPPs, SOPs, guidances

FDA reporting quarterly on hiring goals

Decentralized Clinical Trials for Drugs, Biological Products, and Devices



- Bringing the trial to the patient
 - Video and telemedicine visits
 - Digital health technologies
 - Direct distribution of products
 - Electronic informed consent
 - Home visits
 - Use of local health care providers and facilities
- Guidance issued May 2

<https://www.fda.gov/media/167696/download>

Decentralized Clinical Trials for Drugs, Biological Products, and Devices

Guidance for Industry, Investigators, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ryan Robinson, 240-402-9756; (CBER) Office of Communication, Outreach, and Development, 800-835-4709 or 240-402-8010; (CDRH) Office of Clinical Evidence and Analysis, cdhclinicalevidence@fda.hhs.gov; or (OCE) Paul Kluetz, 301-796-9657.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

May 2023
Clinical/Medical

Guidance to Support Use of DCTs



- The DCT guidance includes recommendations on:
 - Design considerations
 - Conduct of remote CT visits and CT-related activities
 - Use of digital technologies to remotely acquire data
 - Roles and responsibilities of sponsor and investigators
 - Obtaining informed consent; IRB oversight of informed consent process
 - Appropriateness of investigational products for use in a DCT
 - Product packaging and shipping
 - Safety monitoring of participants

Advisory Committee Modernization



- CDER is modernizing its Advisory Committee processes to ensure we continue to have access to world-class experts to advise us on scientific, policy and technical matters. To this end, we will:
 - Refine the selection of AC members, so that their expertise applies precisely to the matters under consideration
 - Optimize our internal business processes for planning and managing AC meetings
 - Develop communication strategies to ensure that our stakeholders understand the role of the AC versus the role of the Agency. Committees provide advice; FDA has decision-making authority

Looking Forward



- There is much more, for example:
 - RWD/RWE: do we need an “Operation Warp Speed”?
 - Quantitative medicine: expand use of modeling in drug development through a multidisciplinary approach
 - Clinical trial innovation: need end-to-end, multimodal framework
 - Drug supply chain disruption: what should CDER do and not do, and how can we bring others to the table?
 - Workforce: retention, hiring, hybrid work environment, all in a fiercely competitive labor environment