Project Management of Premarket and Postmarket Generic Drug Safety

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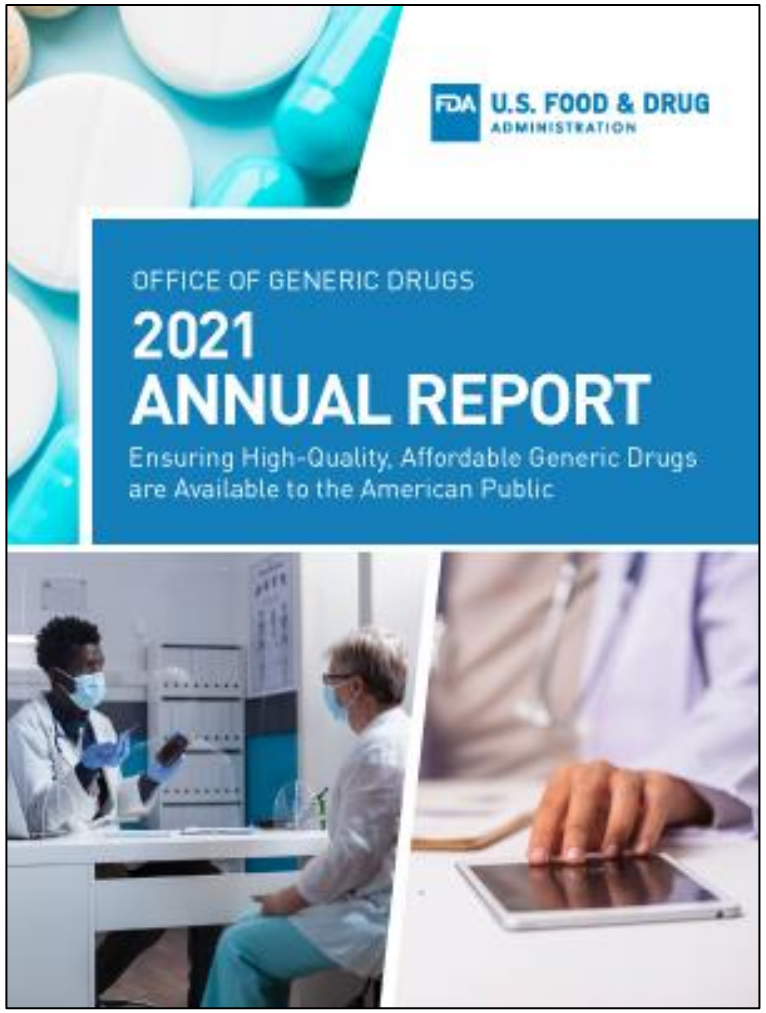
Overview

- Describe collaborative approaches and the regulatory project manager's role in managing generic drug safety issues across OGD and CDER
- Describe the regulatory project manager's perspective regarding clinical reviews of serious adverse events from premarket bioequivalence/bioavailability (BA/BE) studies
- Introduce the Newly Identified Safety Signal (NISS) MAPP and DCSS RHPM's role in this postmarket safety process

OGD's Collaborative Role in CDER's Postmarket Safety Efforts

- Multidisciplinary collaboration across CDER offices
  - Office of Surveillance and Epidemiology (OSE)
  - Office of Pharmaceutical Quality (OPQ)
  - Office of Compliance (OC)
  - Office of New Drugs (OND)
  - Drug Safety Operations
- Collaboration activities
  - Elevates generic drug safety issues to Drug Risk Management Board (DRMB)
  - OGD Clinical Safety and Surveillance Committee
  - Drug safety review modernization efforts

Generic Drug Safety Collaboration in OGD

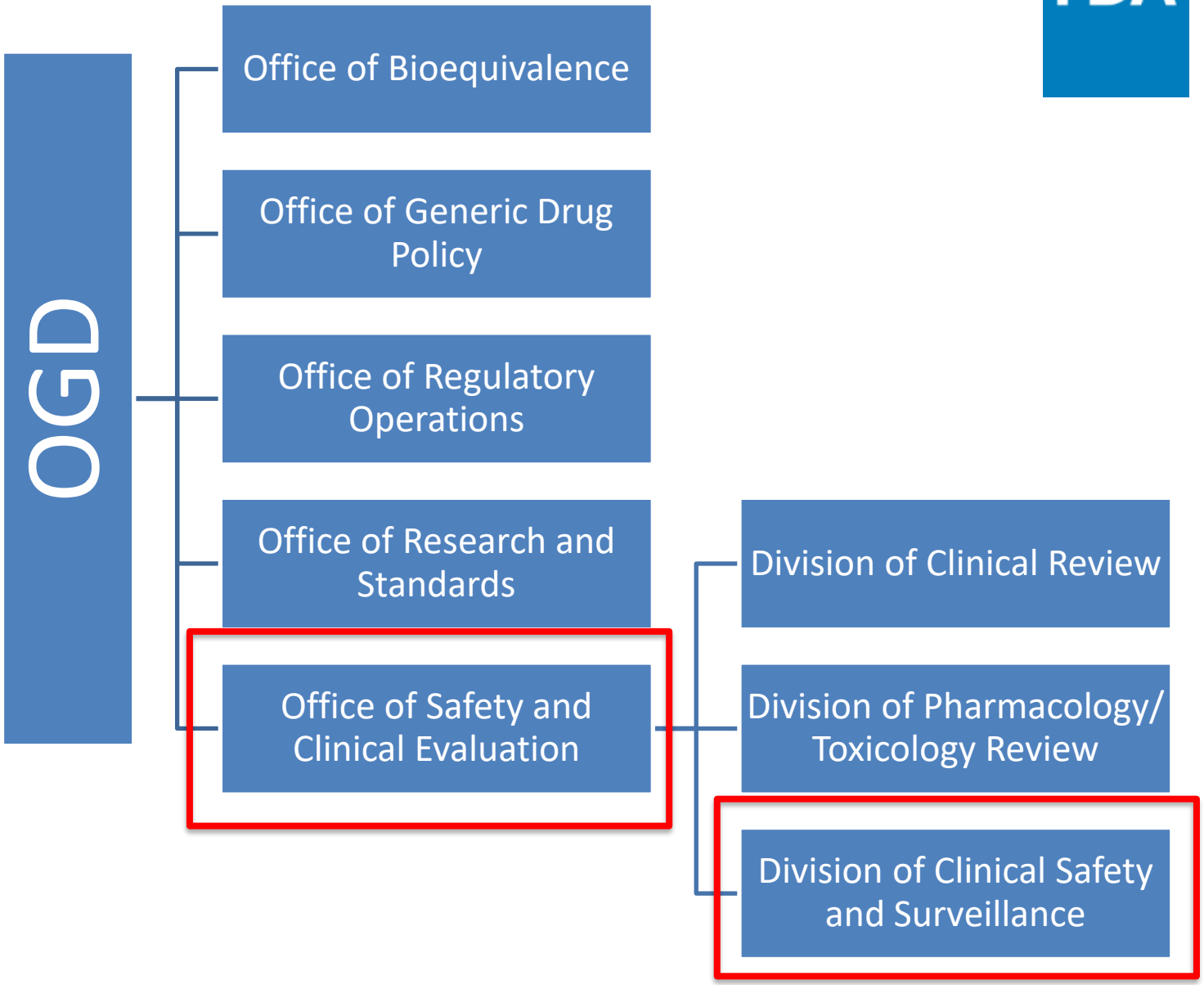


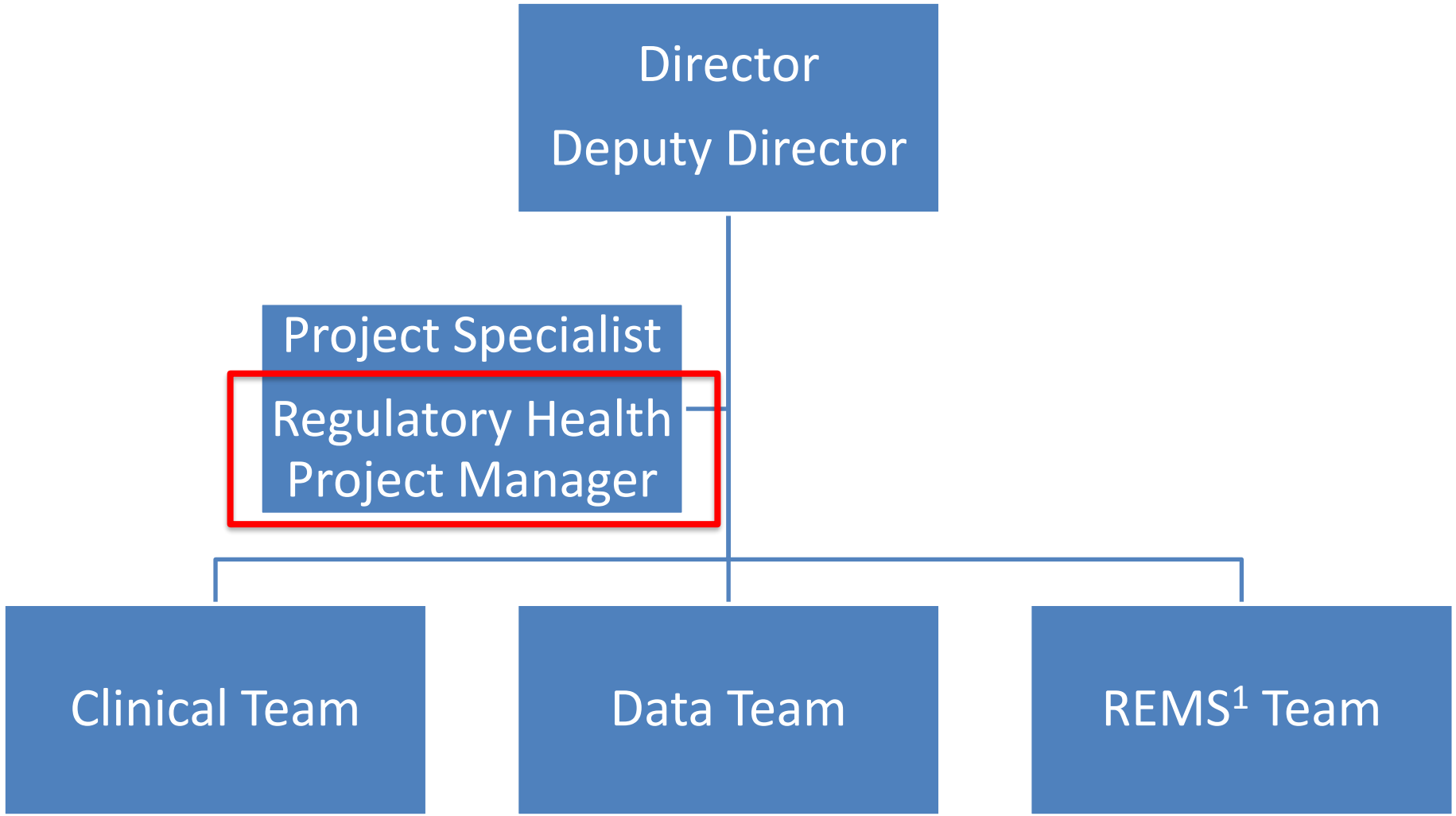
- Division of Clinical Safety and Surveillance (DCSS) in the Office of Safety and Clinical Evaluation (OSCE)
- Collaborators
  - Within OSCE
    - Division of Clinical Review
    - Division of Pharmacology/Toxicology Review
  - Office of Regulatory Operations (ORO)
    - Division of Filing Review (DFR)
    - Division of Labeling Review (DLR)
  - Office of Bioequivalence
  - Office of Research and Standards
  - Office of Generic Drug Policy

Division of Clinical Safety and Surveillance (DCSS)

- Serves as the clinical safety and surveillance point of contact for OGD, CDER, and the generic drug program's premarket and postmarket safety activities.

"Consistently and Efficiently Evaluating Generic Drugs and Monitoring Generic Drug Safety" – OGD Annual Report 2021





DCSS Organization

Multidisciplinary staff of physicians, pharmacists, epidemiologists, nurses, and other scientists performing broad generic drug safety and surveillance activities

[1] Risk Evaluation and Mitigation Strategies (REMS)

Regulatory Health Project Manager (RHPM) in DCSS

- Coordinates and manages the review process for premarket and postmarket activities for OGD/DCSS
- Facilitates discussions among various review disciplines on generic drug safety issues
- Prepares consults to other disciplines and communications to industry
- Serves as liaison between DCSS review team and collaborators within FDA and with industry and other stakeholders

Potential Safety Issues Can Arise for Generic Drugs

- Generic drug safety issues may potentially occur before submission and/or after approval of abbreviated new drug applications (ANDAs)
  - Premarket – before ANDA approval
  - Postmarket – after ANDA approval
- DCSS reviews reports of potential safety issues that may arise for generic drugs throughout this time

Premarket Generic Drug Safety

- DCSS plays a role in evaluating generic drug ***clinical safety*** during BA/BE studies that support generic drug development
  - This includes safety submissions submitted to FDA of (serious) adverse events or adverse events occurring during conduct of BA/BE studies
- Premarket Generic Drug Safety Submissions
  - Bio-INDs (per 21 CFR 320.31)
    - Investigational New Drug Applications (INDs) submitted for BA/BE studies
  - Premarket SAEs (per 21 CFR 320.31(d)(3))
    - Expedited Serious Adverse Event (SAE) reports from IND-Exempt BA/BE studies

Bio-INDs: Premarket Generic Drug Safety Submission Review

- Regulatory submission requirements
- Multidisciplinary 30-day review to determine that studies are safe to proceed
  - Review clocks starts when the Bio-IND application is received in the document room
  - ORO/DFR serves as Bio-IND coordinator for multidisciplinary review
  - DCSS RPM coordinates with ORO/DFR on clinical safety review management and relevant communications to sponsors
- Any safety issues that arise from conducting Bio-IND studies

Premarket SAEs - Generic Drug Safety Submission Review

- Regulatory requirements mandate the timely submission of reports of SAEs occurring during generic drug BA/BE studies
  - Bio-INDs: For serious, ***unexpected*** suspected adverse events (most likely related to drug) [21 CFR 312.23(a)]
  - IND-exempt BA/BE studies: For all serious adverse events[2]
- Premarket SAE Clinical Safety review in DCSS
  - Sent directly to DCSS via the Premarket SAE mailbox (OGD-PremarketSafetyReports@fda.gov)
  - DCSS RPM ensures timely completion of clinical safety assessment and communicates with sponsor-investigators

[2] https://www.fda.gov/media/152530/download, page 9, footnote 20

Challenge Question #1

Which review discipline does the DCSS RPM coordinate review activities for Bio-INDs?

A. Bioequivalence

B. Clinical Safety

C. Filing

D. Product Quality

Postmarket Generic Drug Safety

- OGD continues to monitor and evaluate generic drug safety after ANDA approval throughout the time a generic drug product is available for sale in the United States
  - Proactive postmarket surveillance and pharmacovigilance activities
- Postmarket submissions on emerging generic drug safety-related issues
  - Health Hazard Evaluations (HHEs)
  - Newly Identified Safety Signals (NISS)

HHEs – Generic Drug Safety Postmarket Submission Review

- CDER's Office of Compliance leads in requesting HHEs to appropriate clinical experts
- Clinical safety review supports decisions on product recall classification risk and action
  - HHEs requests clinical assessment on the impact of product defect on clinical safety
- DCSS provides clinical assessment in response to HHEs on behalf of OGD
- The DCSS RHPM:
  - Ensures timely review assignment and completion
  - Coordinates collaboration efforts through consults to other disciplines (OGD/OSCE/DPTR and OPQ's Office of Quality Surveillance)

OGD's Role in CDER's NISS Process

- DCSS is the identified ***Signatory Authority*** for OGD on NISSs when the potential safety issue relates to an ANDA
- Considerations for DCSS serving as the ***Safety Lead***
  - Specific Generic Product Quality/Manufacturing Issues
  - ANDAs of Drug-Device Combination Product, including device component
- DCSS RHPM serves as the ***Project Manager*** when OGD is the Safety Lead or Signatory Authority
  - NISS Action Phase with OGD/DCSS signatory authority

Challenge Question #2

When would DCSS be the Signatory Authority to a NISS according to the NISS MAPP?

A. Safety issues for a class of drug products

B. Safety issues for an active ingredient

C. When a safety issue relates to a biosimilar

D. When a safety issue relates to a specific generic drug

Resources

- MAPP 5210.5: Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs
- Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and BA/BE studies
- Investigator Responsibilities – Safety Reporting for Investigational Drugs and Devices
- MAPP 4121.3: Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS)
- OGD 2021 Annual Report (FDA Voices article)
- CDER Drug Safety Priorities 2021

Summary

The DCSS RHPM:

- Supports collaboration efforts DCSS engages across OGD and CDER on generic drug safety related issues
- Provides regulatory project management support for timely completion of regulatory submission reviews
- Serves as the primary contact for the division to collaborators within CDER/OGD and with industry

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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