Role of Controlled Correspondences in Supporting Safety Assessments in Generic Drug Development

Christopher Morgan, PhD

Pharmacologist
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE)
Office of Generic Drugs (OGD)
CDER | US FDA

Navigating Controlled Correspondences to Support Generic Drug Development
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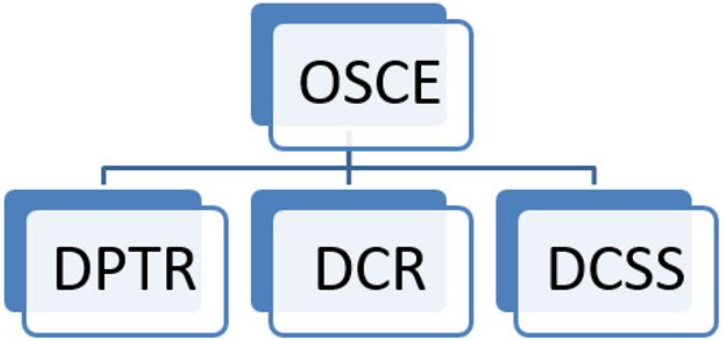
Overview

- Introduction to the Office of Safety and Clinical Evaluation (OSCE)
  - Who we are and what we do
- Role of OSCE in addressing controlled correspondences (CCs) to support generic drug development
  - Common CC requests addressed by OSCE

Who we are

OSCE is comprised of multidisciplinary staff who are organized in three Divisions that play different roles in support of the Generic Drug Program.



OSCE: Office of Safety and Clinical Evaluation
DPTR: Division of Pharmacology Toxicology Review
DCR: Division of Clinical Review
DCSS: Division of Clinical Safety and Surveillance

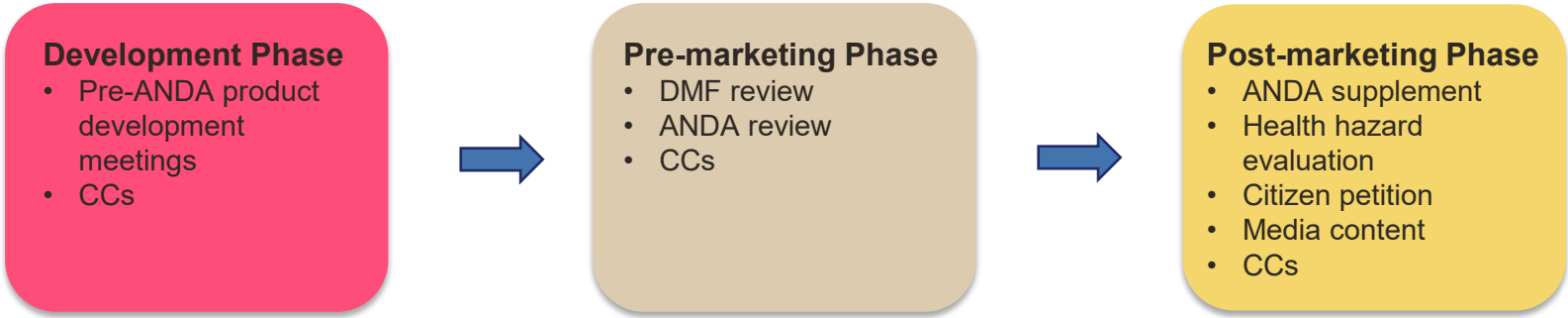
OSCE's Mission

Ensure the American public has **safe** and **therapeutically equivalent** generics:

- Evaluating **clinical and non-clinical** information in support of safety and therapeutic equivalence
- Ensuring compliance with any **safety requirements** such as Risk Evaluation & Mitigation Strategies (REMS)
- Conducting ongoing **safety surveillance** after approval

Role of OSCE in Generics

OSCE is involved throughout the lifecycle of generic drug products.



OSCE and CC requests:

- CC requests to OSCE are classified as Level 2 (i.e.,120 days for response).
- A response will provide guidance. It will not be a safety assessment
- Opportunity to gain alignment with the Agency's current thinking on a specific topic
- Receive guidance on resolving a deficiency or improving submission quality

Common CC topics addressed by OSCE

- Context of use (i.e., dose, route of administration, duration of use, and patient population)
  - Often in support of another discipline's CC response
- Approaches to justify the safety of excipients
- Approaches to qualify impurities (i.e., process/degradation impurities, extractables/leachables, and nitrosamines)
- Covered Product Authorizations

Context of use

Clinical context of use is critical to ensure the safety assessment is appropriate for the drug product.

- What is the maximum daily dose (MDD) and resulting maximum daily exposure (MDE) to an excipient or impurity?
- How does the route(s) of administration impact acceptability of proposed safety endpoints?
- What is the duration of use over a patient's lifetime?
- What developmental windows or population-specific safety concerns should be considered?

Maximum Daily Dose (MDD) & Maximum Daily Exposure (MDE)

- MDD is the highest dose of drug substance reasonably administered in a day based on the Dosage and Administration (D&A) of the Reference Listed Drug (RLD) Labeling.
- Safety of product formulations is assessed based on the exposure to excipients and impurities at MDD (i.e., MDE).
- Applicants can submit a CC for drug products with complex D&A or route of administration.
  - Dosing based on body weight or body surface area
  - Dose to effect (e.g., anesthetics)
  - Complex routes of administration (e.g., topical)
- Example: Provide feedback on an applicant's proposed MDD for a drug product with labeling that recommends it be applied as a thin film to affected areas

Excipients

Safety justification is needed when proposed excipient MDE from a generic exceeds approved level in other products with similar context of use.

CC requests handled by OSCE include:

- Is an inactive ingredient database (IID) entry appropriate to justify proposed MDE in a drug product (i.e., similar context of use)?
- Can safety data for one excipient grade justify the safety of another (i.e., bridging argument)?
- Is a proposed approach to justify the safety of an excipient reasonable?
  - Endogenous (e.g., dietary) exposure, published safety data, etc.

Impurities

Drug substance/product impurities need to be qualified for safety when proposed MDE exceeds applicable thresholds (i.e., allowable limits established in guidances).

CC requests handled by OSCE include:

- What are the applicable safety thresholds for a drug product (e.g., thresholds for mutagenic impurities based on duration of use)?
- Does a drug product fall outside the scope of a guidance (e.g., advanced cancer indications)?
- Is a proposed approach to qualify an impurity exceeding applicable thresholds reasonable?
  - Comparative impurity analysis, metabolite justification, mutagenicity assessment and/or general toxicity (systemic, local safety)

Extractables & leachables (E&L)

E&Ls are compounds that may migrate from manufacturing equipment or container closure systems under exaggerated conditions (extractables) or over shelf-life (leachables).

CC requests handled by OSCE include:

- What is the appropriate safety concern threshold (SCT), which informs the analytical evaluation threshold (AET)?
  - Justify safety of compounds above SCT (based on route of administration and treatment duration)
  - Identify compounds above AET (based on SCT and MDD)
- Is a proposed approach to justify the safety of the worst-case exposure to E&Ls?
  - Mutagenicity assessment and/or general toxicity (systemic, local safety)

Nitrosamines

N-Nitroso impurities can be small molecules or nitrosamine drug-substance related impurities (NDSRI)s. FDA published several guidances on control of nitrosamine impurities in drugs and approaches to determine acceptable intake (AI) limits.

CC requests handled by OSCE include:

- Is a carcinogenic potency categorization approach (CPCA) based AI limit acceptable (i.e., accurate potency category)?
- Is the proposed approach to justify a higher than FDA-recommended AI limit reasonable?
  - Surrogate-based AI, enhanced Ames test, in vitro metabolism, in vivo mutagenicity, study protocol review, etc.

Note: FDA recommended AI limits may differ from those of other regulatory agencies. Applicants should apply FDA-recommended AI limits.

Summary

- OSCE works to ensure generic drugs are safe and therapeutically equivalent.
- OSCE offers multidisciplinary expertise on clinical, Pharm/Tox and post-marketing safety surveillance related topics throughout the generic drug development lifecycle.
- CCs needing OSCE input are classified as Level 2.
- CC responses provide feedback on context of use, proposed approaches to justify the safety of excipients and impurities, and Covered Product Authorizations.
- CCs provide opportunities to align with the Agency's current thinking, improve submission quality, and obtain feedback on approaches to resolve deficiencies.
- CC response is not a safety review. Acceptability of formulation or justification is determined during technical assessment of the ANDA.

Resources

- Guidance for industry *Controlled Correspondence Related to Generic Drug Development* (March 2024)
- Guidance for industry *Good ANDA Submission Practices* (January 2022)
- Guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (March 2005)
- Draft guidance for industry *Using the Inactive Ingredient Database* (July 2019)
- Inactive Ingredients in Approved Drug Products Search: Frequently Asked Questions
- Guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (July 2023)
- Guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008)
- Guidance for industry *Q3B(R) Impurities in New Drug Products (Revision 3)* (August 2006)
- Guidance for industry *Control of Nitrosamine Impurities in Human Drugs* (September 2024)
- Guidance for industry *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities* (July 2023)
- CDER Nitrosamine Impurity Acceptable Limits
- Draft guidance for industry *How To Obtain a Covered Product Authorization* (September 2022)
- FDALabel: Full-Text Search of Drug Labeling
- Drugs@FDA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