POLICY AND PROCEDURES

OFFICE OF GENERIC DRUGS

Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes

Table of Contents

PURPOSE

This Manual of Policies and Procedures (MAPP) details how the Office of Generic Drugs (OGD) will classify which approved new drug products[1] and drug-device combination products[2] assigned to the Center for Drug Evaluation and Research (CDER) are complex products for generic drug development purposes.

[1] A drug product is a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. See 21 CFR 314.3(b).
[2] Where this MAPP uses the term "drug product," it may also refer to the drug constituent part of a combination product.

Prospective applicants who plan to submit an abbreviated new drug application (ANDA) referencing a complex product may be eligible for an enhanced pathway for discussions with FDA.[3]

BACKGROUND

I. Complex Product Overview

According to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 letter (GDUFA II Commitment Letter),[4] a complex product generally includes one or more of the following five features:

1. A complex active ingredient
2. A complex route of delivery[5]
3. A complex dosage form or formulation
4. A complex drug-device combination product
5. "[C]omplexity or uncertainty concerning the approval pathway or [a] possible alternative approach [that] would benefit from early scientific engagement"[6]

II. Complex Active Pharmaceutical Ingredient (API)

A. What Is an API?

An active pharmaceutical ingredient (API), or active ingredient, is any component in a drug product that is intended either (1) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or (2) to affect the structure or any function of the body.[7]

B. What Is a Complex API?

[3] See the guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*. (November 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] The GDUFA II Commitment Letter is available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.
[5] FDA does not solely rely on the route of delivery to determine drug product complexity; FDA also considers the dosage form in conjunction with route of delivery to determine the complexity of the drug product.
[6] GDUFA II Commitment Letter at 25.
[7] See 21 CFR 314.3(b).

A complex API is often a mixture of different components and can contain a distribution of molecular weight. Any product whose labeling indicates that it is a mixture of active components or whose chemical structure formula includes repeating structure units or a range of molecular weights is considered complex. A naturally derived product containing a mixture of components is also often classified as a complex API.

OGD considers any drug product containing a complex API, regardless of administration routes and dosage forms, a complex drug product.

C. What Are Some Examples of Complex API Products?

Complex APIs commonly include:

- APIs that are mixtures of different components (from both semi-synthetic and natural sources) with different chemical formulas, such as:
  - Conjugated estrogens, heparin, and low-molecular-weight heparin (e.g., dalteparin sodium and enoxaparin sodium)
  - Botanic drug products (e.g., crofelemer)
  - Complex oils and oil-derived products (e.g., omega-3 acid ethyl esters and ethiodized oil)
- APIs that have a distribution of molecular weight or structures, such as:
  - Synthetic polymers (e.g., colesevelam hydrochloride, patiromer sorbitex calcium, icodextrin, pentosan polysulfate sodium, sevelamer carbonate, and inulin)
  - Metal complex drugs (e.g., ferumoxytol)

  Peptides with no greater than 40 amino acids (AAs) having complex higher-order structure and/or potential immunogenicity concerns are also considered as complex APIs (e.g., liraglutide, calcitonin).[8]
- Oligonucleotides (e.g., eteplirsen, nusinersen)

[8] FDA considers any alpha amino acid polymer with a specific, defined sequence that has 40 or fewer amino acids to be a *peptide* regulated under the Federal Food, Drug, and Cosmetic Act (FD&C Act), not under the Public Health Service Act. See the draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 3). When final, this guidance will represent FDA's current thinking on this topic. Unless a peptide otherwise meets the statutory definition of a *biological product* (e.g., a peptide vaccine), it will be regulated under the FD&C Act.

III. Complex Route of Delivery

A. What Is a Route of Delivery?

A drug product's route of delivery may be different than its route of administration. FDA generally classifies routes of administration by the location at which the drug product is applied.[9] The route of delivery, however, is the route by which the active ingredient is delivered to the target site of action. A route of delivery may be systemic or local. For example, transdermal products are applied to the skin (route of administration is transdermal), but the route of delivery is systemic. Conversely, ophthalmic products are applied to the eye (route of administration is ophthalmic) and the route of delivery is local.

B. What Is a Complex Route of Delivery?

A local route of delivery is considered complex while the systemic route of delivery is not considered complex.

To ascertain if the route of delivery is local or systemic, applicants should determine whether the intended pharmacological/clinical action can be equally achieved if the drug is applied to different sites of the body. If the intended pharmacological/clinical action can be equally achieved when the drug is applied to a different site of the body, the targeted site of action is systemic; if the intended action cannot be equally achieved when the drug is applied to a different site of the body, the targeted site of action is local. For example, the labeling for lidocaine patches instructs patients to cover the most painful area with the patch. If the patient applies the lidocaine patch to a different site, the pain relief may not be as efficient as if applied to the most painful area; therefore, FDA considers lidocaine patches to be locally acting and to have a complex route of delivery.

However, FDA does not solely rely on the route of delivery to determine drug product complexity; FDA also considers the dosage form to determine the complexity of the drug product. FDA does not generally consider solution products with a complex route of delivery to be complex products (see more details in section III.C) if there is no additional complexity involved in the product (e.g., complex API or complex drug-device combination).

C. What Are Some Examples of Complex Route of Delivery Products?

Based on the targeted site of action, FDA has determined whether nonsolution drug products with various administration routes listed in the Attachment have a complex route of delivery.

[9] FDA publishes definitions for standard routes of administration—including buccal, nasal, ophthalmic, oral, otic, oral inhalation, topical, transdermal, vaginal, and others—on FDA's Route of Administration web page, available at https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/datastandardsmanualmonographs/ucm071667.htm.

FDA does not generally classify solution products that are not specifically identified for use with a particular delivery device (e.g., solutions for aerosolization or nebulization with a general-use nebulizer device), even via a complex route of delivery, as complex drug products because their bioequivalence can be considered self-evident under 21 CFR 320.22. However, if a solution product is for use in combination with a complex device (e.g., metered-dose pumps and inhalers), the product will be considered a complex product due to the complexity of the device (see section V).

IV. Complex Dosage Form or Formulation

A. What Is a Dosage Form or Formulation?

Dosage form is the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as (1) the physical appearance of the drug product, (2) the physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, and (4) the design features that affect frequency of dosing.[10]

Pharmaceutical formulation refers to the process in which different chemical substances, including the API, excipients, and processing aids, are combined to produce a drug product. Formulation is also used to describe the composition of a drug product.

Dosage form is generally a broader term than formulation. Two drug products may have the same dosage form but different complexity in formulation/drug delivery system. We combine the two categories, complex formulation and complex dosage forms, for analysis to reduce redundancy.

B. What Is a Complex Dosage Form or Formulation?

Complex dosage forms and formulations include all non-solution products for routes other than oral administration. These formulations often have two or more discrete states of matter. The order and properties of formulations, as well as delivery rates, are dependent on the manufacturing process.

Drug products containing complex dosage forms and/or formulations—including parenteral liposomes, long-acting polymeric microspheres, semisolids, and others—are considered complex drug products.

C. What Are Some Examples of Complex Dosage Form or Formulation Products?

1. Drug Products Containing Nanomaterials

[10] 21 CFR 314.3(b).

Drug products containing nanomaterials broadly refer to a material that has been deliberately manipulated to be in the nanoscale range (1 to 100 nm) or to exhibit properties or phenomena, including physical, chemical, or biological effects that are attributable to its dimensions, up to 1000 nm.[11,12] The majority of drug products containing nanomaterials are for parenteral use where the active ingredient is either encapsulated in a carrier or is associated in a complex form. After parenteral administration, the active ingredient may appear in different forms at different sites in the body.

Parenteral drug products containing nanomaterials are considered complex drug products and include the following:

- Liposome formulations in the submicron range (e.g., doxorubicin, daunorubicin, amphotericin B, verteporfin, vincristine sulfate, irinotecan hydrochloride)
- Iron complex formulations (e.g., ferric oxyhydroxide)
- Nano-suspension (e.g., paclitaxel)
- Self-assembling nanotubes (e.g., lanreotide acetate)
- Nano-emulsions (e.g., cyclosporine, difluprednate)
- Lipid complex drugs (e.g., amphotericin B lipid complex)
- Lipid nanoparticles (e.g., patisiran)

Oral drug products employing nanotechnology are not considered complex drug products because conventional pharmacokinetic studies in human subjects are considered sufficient for ANDAs using nanotechnology formulations or other solubilization approaches.

2. Long-acting Injectable Drug Products

Long-acting injectable drug products are formulated to achieve extended drug release action from days to years when administered via intramuscular (IM), subcutaneous (SC), intra-articular (IA), and other routes. These products can help improve patient compliance in patients who adhere poorly to more frequently injected medications. Examples of FDA-approved long-acting parenteral drug products include:

- Oil-based lipophilic solutions (e.g., haloperidol decanoate oil solution)
- Suspensions (e.g., aripiprazole long-acting injectable (LAI) suspension, paliperidone palmitate LAI suspension, olanzapine LAI suspension)
- Multivesicular liposomes (e.g., bupivacaine liposomes)
- In-situ gels (buprenorphine extended-release injection)

[11] Guidance for industry *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology* (June 2014).

[12] Draft guidance for industry *Drug Products, Including Biological Products, that Contain Nanomaterials* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

- Biodegradable microspheres (e.g., risperidone, octreotide, naltrexone)

Long-acting parenteral drug products are complex-formulation products except for oil-based solutions, since oil-based solutions involve relatively simple solution formulation and manufacturing process, presenting less development challenges.

3. Semisolid Dosage Forms[13]

Semisolid dosage forms such as creams, lotions, gels, ointments, suppositories, vaginal inserts, foams, and others can be comprised of different types of structured arrangements of matter and may include different phase states. APIs may be dissolved in one or more phases of the dosage form and/or suspended as crystals. The drug substance may also exist in different polymorphic forms, which may influence the dissolution of the drug product. These semisolid dosage forms are considered complex.

V. Complex Drug-Device Combination Products

A. What is a Drug-Device Combination Product?

As per 21 CFR 3.2(e),[14] a *combination product* includes the following:

1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (a *single entity* combination product);
2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (a *co-packaged* combination product);
3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of

[13] See guidance for industry *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* "In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase."

[14] See also *Combination Product Definition Combination Product Types*, available at: https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types.

administration, or significant change in dose (a *cross-labeled* combination product); or

4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (also a *cross-labeled* combination product).

A drug-device combination product is a combination product comprising a drug constituent part and a device constituent part. This MAPP addresses combination products in which the drug constituent part and device constituent part are co-packaged, are a single entity, or cross-labeled and have been assigned to CDER as the lead Center.

B. What is a Complex Drug-Device Combination Product?

A complex *drug-device combination product* is a combination product for which the drug constituent part is contained within or co-packaged with a product-specific device constituent part (either as a single entity or co-packaged) or is cross-labeled for use with a specific device in which the device design may impact drug delivery to the site of action and/or absorption (e.g., device design meters the dose,) and/or the user interface may have specific use considerations (e.g., when the product label indicates that users should be trained by a healthcare provider, when the device tracks the dose with an electronic system).

Not all drug-device combination products are complex. When a drug-device combination product has a device design that may not impact drug delivery to the site of action and/or absorption, it is considered a noncomplex drug-device combination product. Some examples of device constituent parts of non-complex drug-device combination products are:

- Dosing cups for oral liquid formulations
- Simple pre-filled syringe and needle for injectable solutions where the device portion of the product does not play a key role in the dose delivery (e.g., the delivery is controlled by the user who administers the injection)
- Dosing cards for topical ointments

C. What are Some Examples of Complex Drug-Device Combination Products?

- Pre-filled syringes having a higher level of complexity (e.g., dual chamber syringe, multi-dose pen injector)
- Pre-filled auto-injector products for injectable formulations
- Orally inhaled and nasal drug products (such as metered-dose inhalers, dry powder inhalers, and metered nasal spray products)
- Inhalation products which require use with a specific delivery system

- Iontophoretic transdermal products
- Transdermal and topical delivery systems (TDS: historically called "patches")
- Metered-dose pumps for topical and transdermal formulations
- Implants with non-biodegradable device parts
- Intrauterine systems
- Electronic device systems (tracking dosage) including both software and hardware
- Vaginal systems

VI. Complexity or Uncertainty That Would Benefit from Early Scientific Engagement

A. What Are Products Involving Complexity or Uncertainty That Would Benefit from Early Scientific Engagement?

This category includes any product where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.

Currently, abuse-deterrent formulations (ADF) belong to this category. ADFs are solid oral opioid drug products with labeling that describes properties to meaningfully deter drug abuse (i.e., intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect). The key challenge in generic abuse-deterrent product development is the need to develop rigorous, meaningful, and reliable measures to demonstrate that a generic solid oral opioid drug product is no less abuse deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse. FDA's guidance *General Principles for Evaluating the Abuse-deterrence of Generic Solid Oral Opioid Drug Products*[15] provides a general framework and approach for designing in vitro, and where necessary, in vivo studies to compare abuse-deterrent properties of generic ADF opioid products with their respective brand-name counterparts. The guidance describes the Agency's current thinking on the general principles for evaluating abuse-deterrence of generic solid oral opioid drug products that are no less abuse-deterrent than the RLD's abuse-deterrence. Extensive physicochemical tests are recommended for ADFs to determine that a proposed generic product exhibits "non-inferior abuse-deterrence" to that of the RLD abuse-deterrent product it references. Early scientific engagement with the Agency will benefit the development of generic abuse-deterrent formulations. Therefore, abuse-deterrent products are considered complex drug products.

[15] Guidance for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (November 2017).

VII. Non-Complex Drug Product Overview

If a drug product does not have any of the five features mentioned above, OGD will classify that product as a non-complex drug product for generic drug development purposes. Generally, non-complex drug products include but are not limited to the following:

- Tablets, capsules, solutions, and suspensions for oral administration that are intended for systemic action
- Most solid oral modified-release dosage forms
- Solutions for topical or parenteral administration

POLICY

FDA considers a complex product to generally include one or more of the following five features: [16]

1. A complex active pharmaceutical ingredient
2. A complex route of delivery[17]
3. A complex dosage form or formulation
4. A complex drug-device combination product
5. "[C]omplexity or uncertainty concerning the approval pathway or [a] possible alternative approach [that] would benefit from early scientific engagement"[18]

- Although the criteria for classifying complex products may evolve over time based on feedback from FDA's CDER and from industry, OGD will use the criteria and examples detailed in this MAPP to determine if a product is complex.

[16] The GDUFA II Commitment Letter is available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf.

[17] FDA does not solely rely on the route of delivery to determine drug product complexity; FDA also considers the dosage form in conjunction with route of delivery to determine the complexity of the drug product.

[18] GDUFA II Commitment Letter at 25.

- Please note that OGD will generally over-classify, rather than under-classify, complex products to ensure that generic applicants are sufficiently supported in their efforts to develop generic products.

RESPONSIBILITIES

OGD, Office of Research and Standards (ORS)

- Designates the Complex Drug Working Group[19] chairperson.

Complex Drug Working Group Chairperson

- Chairs the Complex Drug Working Group meetings.
- Assigns a subject matter expert, or project manager, within the working group to be the primary reviewer for drug product complexity designation.
- Resolves questions regarding complex drug determinations.
- Conducts a secondary review of a complex/non-complex recommendation and makes a final determination.
- If necessary, consults with other offices within OGD and OPQ on the complex/non-complex determination.
- Sends the complex/non-complex determination to the ORS data analytics expert for archiving.

OGD, Office of Research and Standards (ORS) Analytics Expert

- Compiles a list of newly approved new drug applications (NDAs) every month and sends the list to the Complex Drug Working Group.
- Ensures the final complex/non-complex review and determination is archived.

Office of Pharmaceutical Quality (OPQ)

- Designates staff members to attend Complex Drug Working Group meetings, participates in decision-making, and shares work products with appropriate contacts in OPQ.

[19] The Complex Drug Working Group includes members from ORS's Immediate Office (IO); ORS's Division of Therapeutic Performance (DTP) I and DTP II; ORS's Division of Quantitative Methods and Modeling (DQMM); the Office of Pharmaceutical Quality's (OPQ) Office of Testing and Research; and OPQ's Office of Lifecycle Drug Products.

  - Currently OPQ's Office of Testing and Research and Office of Lifecycle Drug Products have representatives who participate in Complex Drug Working Group meetings.

OGD Subject Matter Expert

- Conducts the primary review and recommends whether a drug product should be classified as complex.

Complex Drug Working Group Project Manager

- Collects any inquiries regarding complex drug determinations, coordinates working group meetings, and issues working group meeting minutes.

- May also be designated to conduct the primary review and recommend whether a drug product should be classified as complex.

PROCEDURES

1. The ORS data analytics expert compiles a list of newly approved NDAs every month and sends the list to the Complex Drug Working Group.

2. The Complex Drug Working Group chairperson will assign each approved drug product referred by the ORS data analytics expert to a subject matter expert or project manager within the working group for primary review.

3. The subject matter expert or project manager will perform a primary review of the assigned approved drug product to ascertain if it meets complexity designation criteria detailed in the Policy section of this MAPP.

4. The Complex Drug Working Group chairperson serves as the secondary reviewer and evaluates the primary reviewer's recommendations regarding classification.

    - If the Complex Drug Working Group chairperson agrees with the recommendations, they will share the final determination with ORS data analytics expert to finalize the review and upload it to the archival system.

    - If the Complex Drug Working Group chairperson does not agree with the recommendations of the primary reviewer regarding classification, the matter is discussed further among the Complex Drug Working Group until consensus is reached. The chairperson will then send a final determination to the ORS data analytics expert to finalize the review and upload it to the archival system.

- The complexity designations of monthly approved NDAs and any corrections made to the complex product database are presented at the monthly complex drug product working group meeting.

5. If, during the primary or secondary review, the Complex Drug Working Group decides that it would be beneficial to involve other offices within FDA, the Working Group may initiate consultation with other offices within FDA to assist with their complex/non-complex determination. The Working Group compiles the consulted office comments and considers those comments when deciding whether the drug can be classified as complex.

REFERENCES

1. 21 CFR 3.2(e)
2. 21 CFR 3.2(m)
3. 21 CFR 314.3(b)
4. 21 CFR 320.22
5. GDUFA II Commitment Letter
6. Guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (November 2020)
7. Draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* (Revision 3)
8. Guidance for industry *Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology* (June 2014)
9. Draft guidance for industry *Drug Products, Including Biological Products, that Contain Nanomaterials* (December 2017)
10. Guidance for industry *SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* (May 1997)
11. Guidance for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (November 2017)

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
04/13/2022	N/A	Initial

ATTACHMENT – Complex Routes of Delivery Based on Administration Routes Table

Administration Routes	Routes of Delivery	Complex Route of Delivery?
Conjunctival, dental, intracavernous, intracavitary, intracerebral, intra-articular, intracorneal, intracoronal, intradiscal, intraductal, intraovarian, intrapulmonary, intrapleural, intraprostatic, intraspinal, intrasynovial, intrathecal, intrameningeal, intralymphatic, intralesional, intrauterine, ophthalmic, oral inhalation, otic, periodontal, transplacental, and transtracheal	Local	Yes
Buccal, nasal, oral, rectal, topical, and vaginal	Either systemic or local	Yes, if the route of delivery is local
Transdermal, intravenous, intramuscular, subcutaneous, and sublingual	Systemic	No