How are Complex Drug Products Defined and Classified?

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Per the GDUFA II commitment letter, complex drug products generally include products with 1) complex active pharmaceutical ingredients (APIs); 2) complex formulations; 3) complex routes of delivery; 4) complex dosage forms; 5) complex drug-device combination, or 6) other products where there is complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement. This study aimed to establish specific criteria on how to determine complex API, complex routes of delivery, complex dosage forms and formulations, complex drug and device combinations to support complex drug product classification. We considered that complex APIs commonly include products that are heterogeneous mixtures of components (often from natural sources, e.g., conjugated estrogen), that have a distribution of molecular weight or structures (e.g., colesevelam HCl), or that are chemically-synthesized polypeptides (with a majority of chains shorter than 100 amino acids, e.g., glatiramer acetate), peptides (an alpha amino acid polymer with a specific, defined sequence typically between 8 and 40 amino acids, e.g., calcitonin), and oligonucleotides (e.g., nusinersen). We differentiated the route of delivery (i.e., the targeted site of action) from the route of administration (i.e., the location at which the drug product is applied). A complex route of delivery refers to non-systemic, localized site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action). We considered complex dosage forms/formulations to include any non-oral formulation or dosage form, typically with two or more discrete states of matter in the formulation, for which the arrangement of matter, properties, and/or drug release rate are dependent on the manufacturing process (e.g., long-injectable microspheres, liposomes). Some case examples will be presented to illustrate the process and considerations for determining product complexity. Complex product classification is essential for strategic work planning and decision making in CDER, is an integral part of fulfilling the Agency's GUDFA II commitments, and directly supports the implementation of the Drug Competition Action Plan. The complex product classification criteria help clarify the Office of Generic Drugs (OGD)'s consideration regarding complexity designation for the purposes of generic drug development and ensure consistency and efficiency in regulatory decision making.