Guidance for Industry and FDA Staff:

Interpretation of the Term "Chemical Action" in the Definition of Device under Section 201(h) of the Federal Food, Drug, and Cosmetic Act

DRAFT GUIDANCE

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Food and Drug Administration
Office of Combination Products (OCP) in the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)

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Guidance for Industry and FDA Staff:[1]

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. PURPOSE

This guidance provides information about how FDA interprets the term "chemical action" in the device definition at section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. § 321(h). The Agency is issuing a companion draft guidance *Classification of Products as Drugs and Devices and Associated Product Classification Issues*, ("*Draft Classification Guidance*") (available on OCP's website at http://www.fda.gov/CombinationProducts/default.htm), that addresses how FDA interprets other language in the device definition.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Combination Products in the Office of the Commissioner (OCP), the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH).

II. BACKGROUND

Section 201(h) of the FD&C Act (21 USC 321(h)) provides that the term "device" means:

> … an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--
> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> (3) intended to affect the structure or any function of the body of man or other animals, and
> *which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals* and which is not dependent upon being metabolized for the achievement of its primary intended purposes. (emphasis added).

Under this definition, a product (or a constituent part of a combination product)[2] is not a device if it "achieve[s] its primary intended purposes through chemical action within or on the body of man or other animals." FDA frequently receives questions from product developers concerning the Agency's interpretation of the term "chemical action" in this definition. This guidance describes the agency's interpretation of the term "chemical action." However, the term "chemical action" must be read in the context of the statutory definition of "device" as a whole. As described in the *Draft Classification Guidance*, the determination of whether a product meets the device definition does not depend solely on whether the product exhibits "chemical action." For example, a product that exhibits chemical action within or on the body of man may meet the device definition if the product "does not achieve its primary intended purposes through" that chemical action.

[2] The term "combination product" is defined at 21 CFR 3.2(e). For further information regarding the definition of combination product and the regulation of combination products, please visit the webpage for the Office of Combination Products at www.fda.gov/CombinationProducts/default.htm.

III. WHAT DOES "CHEMICAL ACTION" MEAN ?

Under the Agency's interpretation, a product exhibits "chemical action" for purposes of the device definition at section 201(h) of the FD&C Act if:

Through either chemical reaction or intermolecular forces or both,[3] the product:

- Mediates a bodily response at the cellular or molecular level, or
- Combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals.[4]

For example, when a product binds to a receptor through intermolecular forces, and thereby initiates or inhibits a signaling cascade in a certain type of cell within the body, that product exhibits "chemical action" because it mediates a bodily response at the cellular or molecular level through intermolecular forces. Similarly, a product that binds to a chemical agent through a chemical reaction, inhibiting the agent's effect on the body, exhibits "chemical action" because the product combines with an entity (the chemical agent) through chemical reaction so as to alter that entity's interaction with the body.

For purposes of these factors, the term "chemical reaction" means the formation or breaking of covalent or ionic bonds, and "intermolecular forces"[5] are electrostatic interactions or forces resulting from the interaction of localized, short-range electrical fields among atoms and/or molecules. Intermolecular forces include ion-dipole interactions, permanent dipole-based interactions, and induced dipole-induced dipole forces.

Under this approach, a product that exhibits covalent bonding, ionic bonding, or intermolecular forces does not exhibit "chemical action" under section 201(h) unless the product, through the covalent bonding, ionic bonding, or intermolecular interaction, mediates a bodily response at the cellular or molecular level or combines with or modifies an entity to alter the entity's interaction with the body. For example, dental devices that are used to fill hollowed out spaces in the teeth as a treatment of dental caries may bind to the tooth via covalent bonding, or rely, in part, on intermolecular forces to change from liquid or paste to solid form. However, the product does not mediate a bodily response at the cellular or molecular level or combine with or modify an entity so as to alter that entity's interaction with the body, through these chemical

[3] FDA acknowledges that terminology may vary in the scientific community and literature and that some of the phenomena identified here (e.g., electrostatic interactions, hydrogen bonding) may also be referred to by different terms than those used in this guidance. The types of chemical phenomena discussed in this section are part of the general scientific lexicon and are characterized and/or described in the scientific literature. For further explanation of these phenomena see, e.g., Foye's Principles of Medicinal Chemistry: Receptors and Drug Action, 6th Ed. (2008) or Levine's Pharmacology, Drug Actions and Reactions, 7th Ed. (2005).

[4] For purposes of this approach, the term "entity" includes materials such as chemicals and living things such as microbes.

[5] These types of interactions can also be termed electrostatic forces, electrostatic interactions, electrostatic bonding, or electric field interactions.

interactions.[6] Accordingly, the Agency would not consider such dental devices to exhibit "chemical action" under section 201(h).

IV. EXAMPLES OF "CHEMICAL ACTION"

Following are examples of products that exhibit "chemical action" under the approach set forth in section III.[7]

A. Chemical reaction through which the product mediates a bodily response at the cellular or molecular level:

- *Formation of covalent bonds between atomic or molecular moieties*. The drug acetylsalicylic acid (aspirin) undergoes a chemical reaction in which aspirin donates an acetyl group to a serine residue in the active site of a cyclooxygenase enzyme (COX-1 or COX-2) through covalent bonding that then mediates a bodily response at a cellular level. Specifically, the covalent bonding of the acetyl group to the COX-1 or COX-2 inactivates the enzyme and, thereby, suppresses the body's inflammatory response.

  Catalytic action. In catalyzing a reaction, a catalyst participates in a transient interaction (i.e., it is not consumed or does not permanently change as a result of the reaction), either through intermolecular forces (as discussed below) or through reversible covalent bonding with the reaction substrate. The drug magnesium sulfate, which is used as replacement therapy for magnesium deficiency, is an example of a catalyst. It acts as an electrolyte and reaction cofactor in conjunction with or as part of enzymes, and through intermolecular forces and/or covalent bonding, the product mediates a bodily response at the cellular or molecular level by catalyzing a number of enzymatic reactions of the body without its own chemical or atomic structure being changed in the process.

B. Intermolecular forces through which the product mediates a bodily response at the cellular or molecular level:

- *Selective binding of a chemical agent to a molecular target/receptor*. This type of action occurs at least in part through intermolecular forces. Intermolecular forces mediate a bodily response by contributing to the stereochemistry of a binding interaction. These forces assist a chemical entity to conform to the shape of the receptor molecule's structure, allowing the chemical entity to bind with the

[6] Similarly, the adhesive action of other products, such as liquid sutures, would not constitute "chemical action" because the product does not mediate a bodily response or combine with or modify an entity so as to alter that entity's interaction with the body, through the adhesive action.

[7] Please note that, although the examples in this section describe for each product the way in which the product, through chemical reactions and/or intermolecular forces, mediates a bodily response at the cellular or molecular level or combines with or modifies an entity so as to alter that entity's interaction with the body, this is not meant to imply that these are necessarily the only chemical actions of the product.

receptor. An example of such an interaction would be a small molecule binding to a membrane receptor to either activate or block a molecular signaling cascade and thereby alter a physiological response. Products that act through this mechanism include well known classes of drugs such as beta-blockers (which reduce the strength of cardiac contractions and heart rate), dopamine receptor antagonists (which treat movement disorders), and opioids (which treat pain).

- *Influencing molecular diffusion in liquids*. Generally, molecular diffusion is characterized as the movement of solute molecules in a solvent from an area of net higher concentration to an area of lower concentration. This process can be influenced by intermolecular forces between the solute and solvent. For example, Epsom salts, a solute, mediate a bodily response through intermolecular forces by influencing the diffusion of water from the extracellular space into the intestinal lumen to facilitate bowel movements.

C. Chemical reaction through which the product combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals:

- *Neutralization and detoxification.* Products can rely on chemical reactions to neutralize or detoxify chemical agents that might otherwise injure the body. For instance, the drug hydroxocobalamin has been used as a treatment for cyanide poisoning. Hydroxocabalamin undergoes a chemical reaction that binds the cyanide to its cobalt moiety to form a non-toxic compound, cyanocobalamin, facilitating removal of the cyanide and preventing its toxic effects.

D. Intermolecular forces through which the product combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals:

- *Precipitation and/or crystallization of a solute from a solution and the dissolution of a solute by a solvent*. These behaviors rely on multiple electrostatic interactions between the individual molecules participating in the precipitation or dissolution actions. For example, the clearance of the nasal passage by a saline nasal spray may result, in part, from the spray's dissolving of encrusted foreign material in the nasal passage thereby altering the interaction of that foreign material with the body.

- *Surfactant action.* Surfactants are known to facilitate the dissolving of non-water soluble substances partly through hydrophobic interactions.[8] Surfactants generally have an amphiphilic structure possessing hydrophobic and hydrophilic

[8] Hydrophobic interactions are caused by the tendency of non-polar molecules, or portions of molecules, to be excluded from polar environments (usually water). Likewise, hydrophilic interactions are caused by the tendency of polar molecules to associate with other polar molecules. These interactions are dictated by intermolecular forces.

functional groups. These compounds act as a chemical bridge facilitating the mixing and solubilization of hydrophobic materials in aqueous solutions through the interactions of their functional groups with substances of similar chemical structure and characteristics (i.e. polar and non-polar). Surfactants also act on the solution itself to lower its surface tension, because the polar portions of the surfactant molecule interact via intermolecular forces with the surrounding water, thereby lowering the surface tension of the overall solution by the disruption of individual electrostatic bonds between water molecules.

The antibiotic drug polymyxin b sulfate is an example of a surfactant that acts partially through hydrophobic and hydrophilic interactions. This antibiotic is a cationic protein surfactant that has fatty acid functional groups. This means that the protein consists of hydrophilic group with a net positive charge that is fused to a hydrophobic functional group. Polymyxin b sulfate acts by binding to components of the bacterial membrane through intermolecular forces and by association/fusion of the fatty acid portion of the molecule with the lipid bilayer via hydrophobic interactions. This binding and associative interaction with the foreign bacterium leads to the disruption of the integrity of the bacterial membrane and the subsequent death of the organism, altering the bacterium's interaction with the body.

V. FURTHER INFORMATION

For further information on what might constitute a "chemical action" for purposes of section 201(h) of the FD&C Act, please contact the Office of Combination Products at 301-796-8930 or by e-mail at combination@fda.gov.