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Rethinking FDA Regulation of Complex Products

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On the outside, modern pharmaceuticals may look much the same as they have for decades—colorful two-tone capsules, nondescript tablets, and mysterious names—but inside each dose is an increasingly complex arrangement of components. Today, many drugs derive their therapeutic properties not only from the presence of a single pharmacologically-active compound, but from the interplay and assembly of multiple active components.[1] In some cases, the resulting product is so complex that current science is not capable of explaining all aspects that impart therapeutic effects.[2] Even when these products consist solely of non-biological molecules, they can nonetheless bear a closer resemblance to biological and mechanical products than to conventional small molecule pharmaceuticals.[3] Other complex modern products include

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1. *See* JILL B. CONNER ET AL., *Copaxone® in the Era of Biosimilars and Nanosimilars*, *in* HANDBOOK OF CLINICAL NANOMEDICINE: NANOPARTICLES, IMAGING, THERAPY, AND CLINICAL APPLICATIONS 790 (2016); Markham C. Luke, Director, Division of Therapeutic Performance, U.S. Food & Drug Admin., Address at Generic + Biosimilar Medicines Conference (Nov. 6, 2019), https://accessiblemeds.org/sites/default/files/2019-11/Complex-Product-Workshop-GRxBiosims.pdf; CROMMELIN ET AL., NON-BIOLOGICAL COMPLEX DRUGS THE SCIENCE AND THE REGULATORY LANDSCAPE 1–8 (2015); Xiaohui Jiang, Deputy Director, Division of Therapeutic Performance, Address at Demonstrating Equivalence of Generic Complex Drug Substances and Formulations (Oct. 6, 2017), https://www.fda.gov/media/108937/download; OFFICE OF GENERIC DRUGS, 2019 ANNUAL REPORT (2020), https://www.fda.gov/media/135329/download; U.S. FOOD & DRUG AMIN., GENERIC DRUG USER FEE AMENDMENTS (GDUFA) SCIENCE AND RESEARCH PRIORITY INITIATIVES FOR FISCAL YEAR 2020 (2019), https://www.fda.gov/media/132370/download; *see also* Vinod Shah, *Non-Biological Complex Drugs*, *Non-Biological Complex Drugs (NBCD) Working Group*, Address at Complex Medicines: Science, Regulation, and Accelerating Development (May 13, 2019), https://www.fda.gov/media/125176/download.

2. *See* Shah, *supra* note 1; Teva Neuroscience, Inc. Citizen Petition, No. FDA-2015-P-1050-0001 (U.S. Food & Drug Admin. Apr. 1, 2015). *See also* CROMMELIN ET AL., *supra* note 1 at 1–8.

3. *See* Shah, *supra* note 1.

combinations of drugs and devices, in which the functioning of the drug is linked to the output of a diagnostic test, mechanical delivery system, computer, or other device.[4] Medicine that is personalized to each patient or adapts to patient outcomes is on the horizon.[5] Other products incorporate nanotechnology-based materials, or operate via unfamiliar mechanisms, such that merely determining the appropriate regulatory framework is challenging.[6] Each of the above could be considered a "Complex Product."[7] In this Note, the term Complex Products will be used primarily to refer to non-biologic drugs, devices, and combination products that involve nanotechnology-based features[8] or operate at the boundary between drug and device.[9]

Complex Products do not fall neatly into the Food and Drug Administration ("FDA")'s existing regulatory schemes for drugs, devices, biologics, or combinations thereof. The distinction is not merely semantic: each product classification offers differing regulatory hurdles and differing mechanisms for permitting follow-on competition.[10] For example, approval of generic non-

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4. U.S. FOOD & DRUG AMIN., USER INTERFACE CONSIDERATIONS FOR DRUG-DEVICE COMBINATION PRODUCTS SUBMITTED IN AN ANDA, http://pqri.org/wp-content/uploads/2017/02/6-PQRI-Chan.pdf (last visited Apr. 16, 2020).

5. *See id.*; Press Release, U.S. Food & Drug Amin., *FDA Approves Pill with Sensor that Digitally Tracks if Patients Have Ingested their Medication*, U.S. FOOD & DRUG ADMIN. (Nov. 13, 2017), https://www.fda.gov/news-events/press-announcements/fda-approves-pill-sensor-digitally-tracks-if-patients-have-ingested-their-medication (describing Abilify MyCite as a schizophrenia drug that contains a sensor in each pill that records that the medication was taken and reports to a wearable patch, embedded in the pill, that records that the medication was taken).

6. *See* C. Lee Ventola, *Progress in Nanomedicine: Approved and Investigational Nanodrugs*, 42 PHARMACY & THERAPEUTICS 723, 742–55 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5720487/.

7. *See* U.S. FOOD & DRUG ADMIN., GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018–2022 (2016), https://www.fda.gov/media/101052/download (defining "Complex Product").

8. *Id.*

9. *See* discussion *infra* Section I(C)(ii).

10. In this note, the term "follow-on" refers to products or manufacturers seeking to replicate the success of a prior-approved product of another. This term is used rather than "generic," which refers specifically to 510(k)-type drugs but without intending to specifically refer to generics. Examples of follow-on products are generics, biosimilars, and 510k devices. Follow-on companies, e.g., generic manufacturers, represent subsequent market entrants that serve as competition to bring prices down. The initial innovator is commonly referred to as brand side, pioneer, or innovator.

biologic complex drugs (NBCDs) proceeds via an abbreviated new drug application (ANDA) pathway. This pathway typically requires an identical active ingredient and equivalent bioavailability and bioequivalence, yet NBCDs often cannot be fully characterized in terms of active ingredient and bioavailability.[11] Devices containing nanomaterials can be approved for market and serve as predicates upon which further approvals can be based, but minor variations in nanomaterials can result in significant changes in biological risk. Complex drug-device combinations can tie the functioning of a drug to the operation of a device, which can confound models for predicting bioequivalence.[12]

The U.S. Government Accountability Office (GAO) has urged regulatory development in the area of Complex Products,[13] but the FDA has indicated that regulatory progress is presently limited by current science.[14] Congress has

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11. *See e.g.*, Teva Neuroscience, Inc. Citizen Petition, No. FDA-2015-P-1050-0001 (Apr. 1, 2015), FDA-2014-P-0933-0001 (July 2, 2014); *see also* Teva Pharmaceuticals USA v. Sandoz, Inc., 573 U.S. 318 (2015); *see also FDA Approves a Generic for Teva's Copaxone, Bringing Longstanding Regulatory Battles Near an End*, PHARMACEUTICAL COMMERCE (Apr. 16, 2015), http://www.pharmaceuticalcommerce.com/latest-news/fda-approves-a-generic-for-tevas-copaxone-bringing-longstanding-regulatory-battles-near-an-end/.

12. *See, e.g.*, IKARIA, INC. (Kleinfeld, Kaplan, and Becker, LLP) - Citizen Petition, https://www.regulations.gov/contentStreamer?documentId=FDA-2013-P-0070-0001&attachmentNumber=1&contentType=pdf. (objecting to 510k clearance for a follow-on nitric oxide delivery system; citizen petitions are often submitted to the FDA when an interested party is concerned that a follow-on product will be approved despite differences in equivalency).

13. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-18-80, GENERIC DRUGS: FDA SHOULD MAKE PUBLIC ITS PLANS TO ISSUE AND REVISED GUIDANCE ON NONBIOLOGICAL COMPLEX DRUGS (2017), https://www.gao.gov/assets/690/689047.pdf; U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-17-452, GENERIC DRUG USER FEES: APPLICATION REVIEW TIMES DECLINED, BUT FDA SHOULD DEVELOP A PLAN FOR ADMINISTERING ITS UNOBLIGATED USER FEES (2017), https://www.gao.gov/assets/690/684950.pdf (noting that generic competition around complex drugs poses unique scientific and regulatory challenges and should be a primary focus area for regulatory development).

14. *See Upcoming Product-Specific Guidances for Complex Generic Drug Product Development*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development (last updated Nov. 21, 2019) (listing complex products for which the FDA plans to provide additional product specific guidances). Such guidances are in line with the FDA's GDUFA II commitment letter and Congress's mandate under FDAMA. *See e.g.*, U.S. FOOD & DRUG ADMIN., *supra* note 7; *see also* FDA Reauthorization Act of 2017,

repeatedly pushed for the FDA to better facilitate approval of follow-on competition for Complex Products.[15] In response, the FDA has focused on new efforts to bring complex generic products to market. By 2020, Complex Products accounted for eleven percent of prior-year generic approvals and more than fifty percent of all prior-year product specific guidances (PSGs).[16]

This Note will discuss challenges surrounding Complex Products, particularly where such products do not find a suitable place in existing regulatory pathways. In part one, this Note will provide an overview of Complex Products, discuss the existing regulatory pathways for drugs, biologics, and devices, and explain how the FDA determines which regulatory framework applies to a given product. In part two, this Note will examine problems with the FDA's current approach to handling Complex Products within its regulatory framework. In part three, this Note suggests rethinking the chemistry-based requirements written into the Food, Drug & Cosmetic Act ("FD&C Act") and adjusting the delineations between product classifications. Lastly, this Note proposes that Congress provide an incentive to innovators to disclose data, tolerances, and know-how that will lower overall costs for development in the industry and improve scientific understanding of Complex Products and nanotechnology in medicine.

Pub. L. No. 115-52, 131 Stat. 1005 (2017) (providing provisions to facilitate generic drug approval, including generic complex products).

15. *See* January 17, 2020 Letter to FDA Commissioner Stephen Hahn, Committee on Energy and Commerce, House of Representatives; *see also* GENERIC DRUG USER FEE AMENDMENTS OF 2017, TITLE III, FDA REAUTHORIZATION ACT OF 2017 PUB. L. 115-52, §§ 301-307, 131 STAT. 1005, 1020-28 (2017) (providing provisions to facilitate generic drug approval, including of Complex Products); GENERIC COMPLEX DRUGS SAFETY AND EFFECTIVENESS FOR PATIENTS ACT OF 2015, H.R. 1576, 114TH CONG. (2015) (discussing a failed bill proposing to require a study by the Government Accountability Office (GAO) to assess the Food and Drug Administration's current regulatory pathway for reviewing generic versions of nonbiologic complex drug products).

16. OFFICE OF GENERIC DRUGS, 2019 ANNUAL REPORT (2020), https://www.fda.gov/media/135329/download.

I. BACKGROUND

A. COMPLEX PRODUCTS AND NANOTECHNOLOGY-BASED PRODUCTS

FDA efforts are increasingly focused on Complex Products, which can be more difficult to develop due to technological and regulatory uncertainty.[17] In 2019, the FDA approved more than a hundred generic forms of Complex Products (eleven percent of total generic approvals in 2019) and more than half of the FDA's product specific guidances (PSGs) were for Complex Products.[18] Starting in 2020, the FDA began providing a forward-looking list of the product specific guidances it plans to release for generic Complex Products. This focus is largely a response to congressional pressure to increase competition and reduce prices of Complex Products.[19] However, as discussed below, the FDA is still exploring a precise definition for Complex Products.

The FDA first defined Complex Products in response to congressional concern that the existing ANDA-type generic pathway was not suitable for complex modern pharmaceuticals. The FDA initially defined Complex Products as follows:

> 1. Products with complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); complex formulations (e.g., liposomes, colloids); complex routes of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and optic dosage forms that are formulated as suspensions, emulsions or gels) or complex dosage forms (e.g., transdermals, metered dose inhalers, extended release injectables);
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> 2. Complex drug-device combination products (e.g., auto injectors, metered dose inhalers); and
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> 3. Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement.[20]

Subsequent characterizations of Complex Products by the Division of Therapeutic Performance and Office of Pharmaceutical Quality have provided the following taxonomy:

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17. *Id.*

18. *Id.*

19. *See* GENERIC DRUG USER FEE AMENDMENTS OF 2017, TITLE III, FDA REAUTHORIZATION ACT OF 2017 PUB. L. 115-52, §§ 301-307, 131 STAT. 1005, 1020-28 (2017) (providing provisions to facilitate generic drug approval, including the approval of Complex Products).

20. *See* U.S. FOOD & DRUG ADMIN., *supra* note 7 (providing a definition for Complex Product).

complex active ingredients (e.g., mixtures of APIs, polymeric compounds, synthetic peptides, and naturally sourced ingredients), complex formulations (e.g., liposomes, suspensions, gels, emulsions and other colloids), complex routes of delivery (e.g., complex ophthalmic products, locally-acting drugs including dermatologic products, and inhaled products), complex dosage forms (e.g., long acting injectables, implantables, transdermals, aerosols), complex drug-device combinations (e.g., dry powder inhalers, metered dose inhalers, nasal sprays, autoinjectors), and other Complex Products (e.g., abuse deterrent opioid formulations).[21]

The 2019 Annual Report from the Office of Generic Drugs and the Generic Drug User Fee Amendments (GDUFA) Regulatory Science Priority Initiatives for Fiscal Year 2020 further organizes such Complex Products into three groups: "Complex active ingredients, formulations, and dosage forms"; "Complex routes of delivery"; and "Complex drug-device combinations."[22]

In each case, the FDA has found it easiest to define Complex Products by way of examples. Table 1, below, provides examples of Complex Products referring to the above three groups. The products in group "A" present challenges related to characterization and distribution of molecular and nanoscale features.[23] Group "B" products involve challenges related to pharmacokinetics (describing absorption and distribution through the body) and bioequivalence (showing no difference in therapeutic effect compared to a reference).[24] Group "C" products are combination products, but for which the interplay of drug and device is sufficiently complex that drug effects are not readily modeled or predicted based on the functioning of the device, e.g., due to ergonomics, usability, and human-factor

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21. *See* Jiang, *supra* note 1; *See also* Katherine Tyner, Associate Director for Science, Office of Pharmaceutical Quality, An Overview of Complex Drug Substances and Complex Formulations—A Quality Perspective, https://pqri.org/wp-content/uploads/2019/04/2-TynerPQRI.pdf (last accessed Apr. 18, 2020).

22. *See* OFFICE OF GENERIC DRUGS, 2019 ANNUAL REPORT (2020), https://www.fda.gov/media/135329/download; GENERIC DRUG USER FEE AMENDMENTS (GDUFA) SCIENCE AND RESEARCH PRIORITY INITIATIVES FOR FISCAL YEAR 2020 (2020), https://www.fda.gov/media/132370/download.

23. *See* OFFICE OF GENERIC DRUGS, 2019 ANNUAL REPORT, *supra* note 22.

24. *Id.*

effects.[25] In some contexts, Complex Products have been described as nanomedicine.[26] Indeed, the challenges in classifying Complex Products reflect more general challenges in describing the application of nanotechnology to non-biologic drugs and devices.[27]

Table 1. Examples of Complex Products.

Brand Product	**Generic Name**	**Description**	**Indication**	**Author's Suggested Complex Product Group**
Renvela®[28]	Sevelamer carbonate	Mixture of linear, branched and crosslinked polymer structures	Phosphorus control in patients with chronic kidney disease on dialysis	A
Doxil®[29]	Liposomal doxorubicin	Chemotherapy drug encapsulated in a nano-scale lipid bilayer vesicle	Ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma	A and B

25. *Id.*

26. Daan J. A. Crommelin & Jon S. B. de Vlieger, *Non-Biological Complex Drugs*, in AAPS ADVANCES IN THE PHARMACEUTICAL SCIENCES SERIES 20, 1–2 (2015).

27. *Id*.

28. *See Renvela Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022127s011lbl.pdf (last accessed Apr. 18, 2020).

29. *See Doxil Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf (last accessed Apr. 18, 2020).

Tobradex ®[30]	Tobramycin and dexamethasone ophthalmic suspension	A suspension of topical antibiotic and corticosteroid	Superficial bacterial ocular infection	A and B
Copaxone ®[31]	Glatiramer acetate injection	Polymeric mixture of peptide fragments in a pre-filled autoinjector	Multiple sclerosis	A and C
Risperdal ® Consta®[32]	Risperidone long acting injection	Risperidone impregnated in microscale poly lactic-co-glycolic acid microspheres	Schizophrenia	A and C
Voltaren ® Gel[33]	Diclofenac sodium topical gel	Nonsteroidal anti-inflammatory drug in topical formulation	Osteoarthritis pain at joints amenable to topical treatment	B

30. *See Tobradex Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050818lbl.pdf (last accessed Apr. 18, 2020).

31. *See Copaxone Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020622s102lbl.pdf (last accessed Apr. 18, 2020).

32. *See Risperdal Consta Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021346_s31_s35_s38_s39lbl.pdf (last accessed Apr. 18, 2020).

33. *See Voltaren Gel Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022122s006lbl.pdf (last accessed Apr. 18, 2020); *see also Certara's Simcyp PBPK M&S Technology Achieves First FDA Virtual Bioequivalence Approval for 'Complex' Generic Drug*, CERTARA (June 12, 2019), https://www.certara.com/pressreleases/certaras-simcyp-pbpk-modeling-and-simulation-technology-achieves-first-fda-virtual-bioequivalence-approval-for-complex-generic-drug/?.

Epi-Pen®[34]	Epinephrine injection	Epinephrine formulation in pre-filled autoinjector	Emergency treatment of anaphylactic reactions	C
ProAir® HFA[35]	Albuterol sulfate inhalation aerosol	Albuterol sulfate in a metered dose inhaler	Bronchospasm	B and C
Advair Diskus®[36]	Fluticasone and salmeterol oral inhaler	Mixture of a corticosteroid and beta2-adrenergic bronchodilator in a metered dose inhaler	Asthma, COPD	A, B, and C
NuvaRing ®[37]	Etonogestrel and ethinyl estradiol vaginal ring	Polymeric vaginal ring infused with hormones	Contraceptive	A, B, and C

This Note suggests a more specific working definition for Complex Products, loosely based around the characteristics of Groups A, B, and C.[38]

Lawmakers have focused on non-biological complex drug products because the generic-type pathway for follow-on drugs requires certain technical showings that are challenging for

34. *See EPIPEN® Label*, U.S. FOOD & DRUG ADMIN., U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019430s053lbl.pdf (last accessed Apr. 18, 2020).

35. *See ProAir HFA Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021457s036lbl.pdf (last accessed Apr. 18, 2020).

36. *See Advair Diskus Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021077s029lbl.pdf (last accessed Apr. 18, 2020).

37. *See NuvaRing Label*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021187s012lbl.pdf (last accessed Apr. 18, 2020).

38. *See infra* Section II.

Complex Products.[39] In contrast, Complex Products that are regulated as devices and biologics allow follow-on competition to proceed via the more-flexible PMA or biosimilar pathways.[40] Although Complex Products are not synonymous with non-biological products, this Note focuses on the drug-device distinction and unique challenges posed by non-biological Complex Products.[41]

i. Non-Biological Complex Drugs (NBCDs)

Non-Biological Complex Drugs (NBCDs) likely represent the most important subset of Complex Products, due to the unique regulatory challenges surrounding approval of complex generic equivalents.[42] An industry-supported working group has described NBCDs as drugs in which the active substance is not a single, discrete molecular structure, but instead derives its activity from a particular mixture or nanoscale arrangement of components.[43] In some cases, it may not be feasible to fully characterize or describe the active substance by present analytical methods and subtle variations can impart dramatic changes in functioning.[44] Arguably, the defining aspect of NBCDs is that they "cannot be fully isolated, quantitated, characterized or described by physicochemical analytical means."[45] Moreover, the biological and therapeutic activity of NBCDs is often highly dependent on its manufacturing

39. *See* U.S. FOOD & DRUG ADMIN., *supra* note 7 (providing a rationale for its pre-ANDA program and enhanced pathway for Complex Products and providing a definition for combination products focused around drug and device features).

40. *See infra* Sections I(E)(ii) and I(E)(iii).

41. *See infra* Sections I(C) and II.

42. *See Equivalence of Complex Drug Products*, GENERICS AND BIOSIMILARS INITIATIVE (Apr. 14, 2017), http://www.gabionline.net/Non-Biological-Complex-Drugs/Reports/Equivalence-of-complex-drug-products (summarizing that showing therapeutic equivalence of generic complex drugs has unique challenges).

43. *See* Shah, *supra* note 1 (stating NBCDs are an "active substance that is not homo-molecular but contains different (closely related, often nano-particulate) structures").

44. *See* Víctor R. Campos-García et al., *Process Signatures in Glatiramer Acetate Synthesis: Structural and Functional Relationships*, 7 SCIENTIFIC REP. 12525, at 1–7 (Sept. 21, 2017), https://www.nature.com/articles/s41598-017-12416-1 (showing that subtle changes in epitope abundance in glatiramer acetate results in substantial changes in therapeutic function); *see also* Shah, *supra* note 41.

45. Campos-García et al., *supra* note 44 at 1.

process.[46] NBCDs have been described as non-biologic products that have complexity approaching that of biological products.[47]

NBCDs are a structurally and functionally diverse family of medical products, including: (1) polymeric micelles; (2) liposomes; (3) glatiramoids; (4) iron carbohydrate complexes; (5) drug nanocrystals; (6) low molecular weight heparins; and (7) albumin-bound drugs.[48] For example, glatiramoids, such as Copaxone® and Glatopa®, comprise a mixture of polymer building blocks that self-assemble in the human body to form biologically active structures.[49] Liposome-based drugs, such as Doxil®, involve tiny vesicles that encapsulate a potent therapeutic and carry it to a desired part of the human body.[50] As another example, Abraxane® involves nanocrystals of paclitaxel bound to albumin, a water-soluble globular protein obtained from human blood, which serves as a delivery vehicle for the chemotherapy agent.[51] The FDA has created a working group dedicated to investigating regulatory challenges associated with NBCDs.

ii. Complex Drug-Device Combinations

The FDA does not necessarily deem combination products to be Complex Products, but certain "complex" drug-device combinations such as metered dose inhalers and injectors can

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46. *See* Amneal Pharm. LLC v. FDA, 285 F. Supp. 3d 328, 337 (D.D.C. 2018) (stating that the FDA requires disclosure of "commercial-scale data" for "certain complex drug products and/or a complex manufacturing process").

47. *See* Shah, *supra* note 1.

48. *See* Jon S. B. de Vlieger et al., *Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: "Drug Products, Including Biological Products, That Contain Nanomaterials"*, 21 AAPS J. 55, 56 (2019), https://link.springer.com/content/pdf/10.1208/s12248-019-0329-7.pdf (providing an overview of the complex drug landscape).

49. *See* J. Y. Song et al., *Glatiramer Acetate Persists at the Injection Site and Draining Lymph Nodes via Electrostatically-Induced Aggregation*, 293 J. CONTROLLED RELEASE 36, 36–47 (2019).

50. *See, e.g.*, *Doxil*, U.S. FOOD & DRUG ADMIN. 21 (2007), https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf ("DOXIL is doxorubicin HCl encapsulated in long-circulating . . . liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs.").

51. *See, e.g.*, *Abraxane*, U.S. FOOD & DRUG ADMIN. 1 (2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf ("ABRAXANE® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound)").

fall within the category.[52] Two examples, discussed above, are the Epi-Pen® epinephrine autoinjector and Advair® metered dose inhaler.

Combination products seek to address classification challenges by using a primary mode of action (PMOA) inquiry to determine whether a given product will progress through the drug, device, or biologic framework. Yet, such an inquiry does not remedy the challenges associated with Complex Products, namely, where present scientific tools and understanding fail to furnish the information required to transit through the regulatory framework. Like the drug-device distinction, PMOA is determined predominantly by the presence of chemical action and thus chemical action serves as a regulatory gatekeeper even if the complex product is a combination product. For example, in the case of an inhaler containing a drug, the drug aspect would be deemed by the FDA Office of Combination Products to embody the PMOA while the device aspect would be deemed to serve a secondary function. However, if a hypothetical competitor wishes to make a generic inhaler, it is uncertain how similar the drug and device aspects must be to the referenced product. Most notably, even an apparently identical copy of a drug and device may nevertheless result in different bioavailability and therapeutic function. One reason for this difference is that complex drug-device combinations are susceptible to user interface and human factor effects. That is, the look, feel, and ergonomics of a device can affect how a person administers or accepts the drug, thus ultimately affecting therapeutic effect. The device may also affect the structural characteristics of a drug both before and after administration. These device-based effects can interplay with drug-based effects in unpredictable ways, resulting in complexity that makes regulatory approval uncertain and stymies follow-on competition.

iii. Medical Nanotechnology and Nanodevices

Complex Products also include medical products that involve nanotechnology, "nanodevices" (drug-like, molecular-scale products that do not involve chemical action to achieve

52. *See* U.S. FOOD & DRUG ADMIN., GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018-2022, at 25 (2016), https://www.fda.gov/media/101052/download (providing a definition for Complex Products that includes "metered dose inhalers" and "extended release injectables").

their therapeutic result, e.g., gold nanoparticles), and other products for which existing classification or approval pathways pose a challenge.[53] Whether the FDA will deem a given nanotechnology-based product to be a drug or a device is, again, determined by whether the intended effect involves "chemical action."[54] While products involving nanotechnology are not automatically assigned any special classification, the presence of nanotechnology can introduce sufficient complexity to render the FDA's approval pathway uncertain. Nanotechnology-based products might thus meet the FDA's definition of Complex Products.[55]

The FDA has taken into account the advent of nanotechnology-based medicine in its regulatory framework.[56] Wisely, the FDA has determined that it will not issue general regulatory requirements or limitations on the use of

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53. *Id*.

54. *See* Jordan Paradise, *Reassessing Safety for Nanotechnology Combination Products: What Do Biosimilars Add to Regulatory Challenges for the FDA?*, 56 ST. LOUIS U. L.J. 465, 495 (2012) (citing 21 U.S.C. § 321(h) (2006)) ("[T]he FDCA requires . . . that a device 'does not achieve its primary intended purposes through chemical action . . . . '").

55. *See FDA's Approach to Regulation of Nanotechnology Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/science-research/nanotechnology-programs-fda/fdas-approach-regulation-nanotechnology-products (last updated Mar. 23, 2018) ("[The] FDA has long encountered the combination of promise, risk, and uncertainty that accompanies emerging technologies. Nanotechnology is not unique in this regard."); *see also* MARK DUVALL, FDA REGULATION OF NANOTECHNOLOGY 101 (2012) ("In light of the potential uncertainty surrounding the debate, it may be helpful for FDA to issue guidance on the subject [of nanotechnology-based devices]."). *See generally* Paradise, *supra* note 50.

56. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DRUG PRODUCTS, INCLUDING BIOLOGICAL PRODUCTS, THAT CONTAIN NANOMATERIALS (2017), https://www.fda.gov/media/109910/download (proposing, in a Draft Guidance document for comment purposes, a "risk-based" approach to products containing nano-technology). The document notes, among other things, that inclusion of nanotechnology "may result in product attributes that differ from those of products that do not contain such materials," *id.* at 1, "nanomaterial carriers may exhibit inherent biological activity that is not related to the loaded active ingredient (e.g., immunogenicity) and could also affect the safety and effectiveness of the drug," *id*. at 17, and "[a]ny critical structural change [by generics] in the multiple components of nanomaterial-based products can influence the bioequivalence, pharmacology, and toxicology profiles, . . . [therefore] conventional [bioequivalence] studies alone may or may not be sufficient . . . ," *id*. at 21.

nanotechnology in medicine.[57] Still, nanoscale features can introduce new biological effects that are not otherwise present in the product and can serve to modulate existing biological effects.[58] The FDA has further recognized that conventional analytical approaches to evaluating therapeutic products may not be sufficient when changes are made to nanotechnological features are altered or introduced.[59] Such concerns parallel those of Complex Products generally. The medical products that the FDA regulates contain a variety of nanomaterials: for example, liposomes, micelles, specified nano-scale particle distributions, nanobubbles, nanocrystals, polymer-based therapeutics, and complex-based therapeutics—many of the same features which impart complexity to the products previously listed in Table 1. [60] Indeed, while nanomaterials are already commonly used in drugs,[61] they can also be used in drug-device combination products[62] and non-drug products as well.[63]

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57. The FDA has instead opted for a scientifically-guided risk-based approach. *See generally id.*

58. *See id.* at 5 ("[T]he interaction of nanomaterials with multiple plasma proteins . . . may endow nanomaterials with new biological properties.").

59. *Id*. *See also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ASSESSING THE EFFECTS OF SIGNIFICANT MANUFACTURING PROCESS CHANGES, INCLUDING EMERGING TECHNOLOGIES, ON THE SAFETY AND REGULATORY STATUS OF FOOD INGREDIENTS AND FOOD CONTACT SUBSTANCES, INCLUDING FOOD INGREDIENTS THAT ARE COLOR ADDITIVES (2014), https://www.fda.gov/media/115075/download.

60. FDA provides guidance documents for products using nanomaterials in combination with drugs. *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: LIPOSOME DRUG PRODUCTS (2018), https://www.fda.gov/media/70837/download (providing guidelines for liposome-containing drug product applications and recognizing the challenges for both ANDA and NDA applicants, particularly with respect to determining bioavailability); *See generally* Mary C. Till et al., *Nanotech Meets the FDA: A Success Story About the First Nanoparticulate Drugs Approved by the FDA*, 2 NANOTECHNOLOGY L. & BUS. 163 (2005) (describing the first wave of nano-sized drugs that the FDA evaluated).

61. Jordan Paradise has provided a useful review and list of FDA-approved drugs that involve nanoscale features. *See* Paradise, *supra* note 54 at 518–19 (providing a list of both FDA approved drugs and devices that involve nanotechnology).

62. *See* U.S. FOOD & DRUG ADMIN., *supra* note 60 at 10 (providing guidelines for liposome-containing drug product applications and recognizing the challenges for both ANDA and NDA applicants, particularly with respect to determining bioavailability).

63. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY, at 6 (2014),

To determine if a product involves nanotechnology, the FDA considers whether the "product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm)" and if the "product is engineered to exhibit properties. . . attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)."[64] Here, the FDA's focus on "engineered" nanoscale features is an attempt to distinguish from conventionally-occurring and incidental nanoscale features from those that are intentionally imparted.[65]

B. OVERVIEW OF FDA REGULATION OF MEDICAL PRODUCTS

The FD&C Act imposes regulatory requirements on products intended for medical use.[66] The FD&C Act requires that the safety and efficacy of all new drugs be evaluated and approved by the FDA prior to being introduced into interstate commerce.[67] Since its promulgation in 1938, Congress has expanded the FDA's regulatory authority to include additional classifications of medical products, notably medical devices[68] and drug-like biologics.[69]

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https://www.fda.gov/media/88423/download (providing two factors to consider in determining if the product involves nanotechnology which may suggest a need for additional risk assessment and stating "[n]anotechnology is an emerging technology that can be used in a broad array of FDA-regulated products, including . . . foods[,] . . . and cosmetics . . . .").

64. *Id.* at 6.

65. *Id. See* U.S. FOOD & DRUG ADMIN., NANOTECHNOLOGY: A REPORT OF THE U.S. FOOD AND DRUG ADMINISTRATION NANOTECHNOLOGY TASK FORCE 11 (2007), https://www.fda.gov/media/74257/download ("In addition to other resources, the Task Force also considered the US Government-wide evaluation of Environmental, Health, and Safety Research Needs for Engineered Nanoscale Materials in developing this discussion and these recommendations.").

66. *See e.g.*, 21 U.S.C. §§ 331(a) (2011), 331(ll) (2011), 355(a) (2011), 360(k) (2012) (prohibiting introduction into interstate commerce of misbranded or unapproved drugs, devices, and biologics).

67. *See* 21 U.S.C. § 355(a) (2011) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an [NDA or ANDA] application. . . ."); *Cf.* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR FDA STAFF AND INDUSTRY, MARKETED UNAPPROVED DRUGS – COMPLIANCE POLICY GUIDE, SEC. 440.100 MARKETED NEW DRUGS WITHOUT APPROVED NDAS OR ANDAS (2011), https://www.fda.gov/media/71004/download.

68. Medical Device Amendments of 1976, 21 U.S.C. § 301 (1976) (expressly delegating to FDA the authority to regulate medical devices).

69. The FDA's authority to regulate biological products derives from both the Public Health Service Act ("PHS Act") and the FD&C Act, which were

The FDA applies distinct regulatory schemes to medical products depending on whether it classifies the product as a drug,[70] a device,[71] a biologic,[72] or a combination thereof.[73] Jurisdiction over each product is separately designated to different centers within the FDA.[74] Generally, drugs are designated to the Center for Drug Evaluation and Research (CDER),[75] devices to the Center for Devices and Radiologic Health (CDRH),[76] and biologics to the Center for Biologics Evaluation and Research (CBER).[77] Devices are further categorized as Class I, Class II, or Class III, based on the extent that safety and efficacy can be inferred due to the nature of the device.[78] Combination products and other products that do not fall neatly into existing product classifications are evaluated by the Office of Combination Products (OCP) and designated to one

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subsequently amended and largely harmonized with drug regulations by the Food and Drug Administration Modernization Act of 1997 ("FDAMA"). *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, 111 Stat. 2296 (1997). Oversight over biologics, generally, extends back to the Biologics Control Act, which became effective in 1903. *See also* Pure Food and Drug Act of 1906, Pub. L. No. 59–384, 34 Stat. 768 (1906).

70. 21 U.S.C. § 201(g)(1) (2011) (defining a "drug").

71. 21 U.S.C. § 201(h) (2011) (defining a "device").

72. 42 U.S.C. § 262(i) (2011) (defining a "biologic").

73. 21 C.F.R. § 3.2(e) (2010) (defining a "combination product").

74. *See RFD Jurisdictional Decisions*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/jurisdictional-information/rfd-jurisdictional-decisions (last updated Feb. 16, 2018).

75. *See Capsular Decisions—Products Assigned to CDER*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/rfd-jurisdictional-decisions/capsular-decisions-products-assigned-cder (last updated Feb. 16, 2018).

76. *See* Capsular Decisions, *supra* note 71.

77. *See id.*, many notable exceptions to jurisdiction apply and centers cooperate and share their expertise where appropriate. *See e.g.*, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research (last updated Feb. 16, 2018) (transferring jurisdiction of therapeutic monoclonal antibodies, immunomodulators, and growth factors from CBER to CDER); *see also Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/jurisdictional-information/intercenter-agreement-between-center-biologics-evaluation-and-research-and-center-devices-and (last updated Feb. 16, 2018) (transferring jurisdiction of in vitro blood diagnostics to CBER from CDRH).

78. 21 U.S.C. § 360c (2012).

of the centers, i.e., CDER, CDRH, or CBER, which have primary jurisdiction for premarket review and regulatory life of the product.[79]

C. CLASSIFICATION OF MEDICAL PRODUCTS

i. Is it a Drug, Device, or Biologic?

Product classification determines the structure of the FDA's premarket review and regulatory pathways for follow-on competition. The scope and burden of premarket review varies enormously between product classifications: drug pre-clinical investigations, clinical trials, and regulatory approval take an average of twelve years and over $350 million[80] while the most burdensome form of device clinical investigation and approval averages 4.5 years and $75 million.[81] Further, for medical products that make it to market, the strength and duration of regulatory exclusivity differs based on the product's classification.[82]

The FD&C Act defines drugs to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" as well as articles listed in certain pharmacopeial compendia and components of any of the same.[83]

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79. *See Jurisdictional Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/classification-and-jurisdictional-information (last updated Apr. 9, 2020).

80. Matthew Herper, *The Cost of Creating a New Drug Now $5 Billion, Pushing Big Pharma to Change*, FORBES PHARMA & HEALTHCARE (Aug. 11, 2013), https://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/#7753cc096bfc.

81. Brian Buntz, *FDA Planning Faster PMA Pathway for Some Products*, MEDICAL DEVICE AND DIAGNOSTIC INDUSTRY (Jan. 31, 2014), https://www.mddionline.com/fda-planning-faster-pma-pathway-some-products.

82. *See e.g.*, 21 C.F.R. §§ 314.108 (2012), 316.31 (2011), & 316.34 (2004); *see also* FD&C Act, 21 U.S.C 9 §§ 505A, 505E, & 505(j)(5)(B)(iv) (2012) (providing various regulatory extensions). *Compare* 21 U.S.C. § 355(b) (2011), *and* 21 U.S.C. § 360(k) (2012), *with* 42 USC § 262(l) (2011) (providing the ANDA process for a generic drug, 510(k) process for a substantially equivalent device, and process for a biosimilar).

83. 21 U.S.C. § 321(g)(1) (2011) (defining a "drug").

Within the FD&C Act, devices are defined as a subset of article, specifically "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article."[84] The statutory definition of a device is further categorized according to intended use, similar to that for a drug, but with an important limitation. Mirroring the language used to define drugs, the FD&C Act defines devices as "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 "intended to affect the structure or any function of the body of man or other animals . . . ."[85] However, in the FD&C Act, Congress expressly required that a device "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 . . . ."[86]

In the FD & C Act, a product is classified as a biologic if it is:

> [A] virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[87]

That is, biologics are defined by origin, while drugs and devices are defined by intended use.

Although the FDA relies on these statutory definitions to determine how to classify a given product, the agency has historically interpreted these definitions broadly so as to preserve its authority to regulate.[88] For example, the FDA

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84. 21 U.S.C. § 321(h) (2011) (defining a "device").

85. *Id.*

86. *Id.*

87. 42 U.S.C. § 262(i) (2011) (defining a "biologic").

88. *See* United States v. Bacto-Unidisk, 394 U.S. 784, 800 (1969) (deferring to the FDA's authority to interpret an antibiotic diagnostic apparatus as a drug rather than a device). Even after subsequent amendments provided express distinctions between drugs and devices, the FDA retained its willingness to use discretion to classify a product according to the interest of the public health. *See* U.S. FOOD & DRUG ADMIN., CLASSIFICATION OF PRODUCTS AS DRUGS AND DEVICES AND ADDITIONAL PRODUCT CLASSIFICATION ISSUES (2017), https://www.fda.gov/media/80384/download. However, at least one district court has suggested that the FDA's position is not tenable. *See* Bracco Diagnostics Inc v. Shalala, 963 F. Supp. 20, 28, 31 (D.D.C. 1997).

presently considers that, conceptually, *all medical products* meet the definition of a drug.[89] Indeed, the definition of a device can be interpreted as defining a subset of the drug definition; specifically, a subset having the limitation that they do not achieve their primary intended purposes via chemical action, or metabolism, within or on the body.[90] The genera of products listed in the biologics definition can be likewise interpreted as another subset of drugs.[91] Products that meet the definition of both a drug and a biologic are classified as a biologic, while products that meet the definition of both a drug and a device are classified as a device.[92] Whether a product is a device rather than a drug or biologic will hinge on whether the product achieves its primary intended purposes through "chemical action" within or on the body.[93] Because neither drugs nor biologics include food, the provision that devices exclude products that achieve their purpose through metabolism has not been a meaningful distinction.[94]

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89. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88.

90. Congress chose to expressly remove a provision of the FD&C Act that excluded devices from being drugs. *See* Safe Medical Devices Act of 1990, Pub. L. No. 102-629, § 14, 104 Stat. 4511, 4524–25. Still, while still standing safely outside the rabbit hole of FD&C definitions, it is worth acknowledging that interpreting all medical products to be drugs invites some absurd consequences. At the very least, it seems reasonable to expect that products meeting the definition as device should be permitted passage through the regulatory domain while classified as devices. *See*, Genus Med. Tech. v. United States Food & Drug Admin., Civil Action No. 19-544 (JEB), 2019 U.S. Dist. LEXIS 210397 * 2019 WL 6683777.

91. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88; *see also* Biologics Price Competition and Innovation Act of 2009, S. 1695, 100th Cong. § 7002(e) (2007). *See also* U.S. FOOD & DRUG ADMIN., INTERPRETATION OF THE "DEEMED TO BE A LICENSE" PROVISION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (2018), https://www.fda.gov/media/119272/download.

92. *See* U.S. FOOD & DRUG ADMIN., *supra* note 91.

93. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88 (defining chemical action).

94. *See id.* (explaining the FDA's current thinking on chemical action).

Table 2. Example Classification of Medical Products

Medical Product	**Classification**
An artificial hip implant	Device
Beta blockers, which interact with beta receptors and block access to the receptor	Drug
A recombinant human granulocyte colony stimulating factor	Biologic
An autoinjector configured to provide metered doses of a synthetic myelin protein	Combination
A complex mixture of polymers that assemble into a variety of structural forms that serve to attenuate an immune response in the human body	Examples of Complex Products. Classification is based on whether the primary intended purpose is through "chemical action" within or on the body.
A liposome containing a collection of non-biological molecular components, including a sensor, a cytotoxin, and a molecular switch configured to jettison the cytotoxin upon stimulus of the sensor	
A synthetic tissue embedded with biologically active components	

Applicants often seek to have their products classified as a device rather than a drug or biologic due to the less burdensome premarket review process afforded to devices.[95] Unexpected classification of a device as a drug can preclude further development of that product.[96] The Office of Combination

95. *Id*. *See also* Letter from Jill Hartzel Warner, Assoc. Comm'r for Special Medical Programs, Food and Drug Admin., to Jeffrey N. Gibbs and Anne K. Walsh, Attorneys for Prevor (Jan. 13, 2015) (on file with Food and Drug Administration); Letter from Suzanne O'Shea, Product Jurisdiction Officer, Food and Drug Admin., to LuAnn Erlich, Senior Dir. of Pharm. and Comput. Services, Apotex Corp. (Sept. 8, 2003) (on file with Food and Drug Administration).

96. *See* Bracco Diagnostics Inc v. Shalala, 963 F. Supp. 20, 28–32 (explaining that small device companies might not be able to afford to bring a drug to market). Sometimes extensive the consequences of classification justify repeated and presumably expensive litigation. *Cf.* Prevor v. FDA, 895 F. Supp.

Products (OCP) handles the FDA's classification and jurisdiction assignments.[97] Those pursuing regulatory review can submit informal inquiries or formal Requests for Designation (RFDs) to classify the product and identify the center having jurisdiction.

ii. Chemical Action

The FDA recently issued guidance[98] regarding how it applies "chemical action" to distinguish drugs and biologics from devices.[99] Specifically, the FDA has defined chemical action as follows: "a product exhibits 'chemical action' if it interacts at the molecular level with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) so as to alter that entity's interaction with the body."[100]

Perhaps recognizing the futility of defining "chemical action" as interactions "at the molecular level," the FDA has further provided that:

For purposes of this interpretation, an interaction at the molecular level occurs through either chemical reaction (i.e., formation or breaking of covalent or ionic bonds), intermolecular forces (e.g., electrostatic interactions), or both. The mere exchange of non-chemical energy (e.g., electromagnetic or thermal energy between a product and the body would not constitute "chemical action."[101]

2d 90 (D.D.C. 2012); Prevor v. U.S. Food & Drug Admin., 67 F. Supp. 3d 125 (D.D.C. 2014).

97. *See Combination Products, Jurisdictional Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/classification-and-jurisdictional-information (last accessed Apr. 9, 2020).

98. The FDA publishes its current thinking on various topics by way of guidance documents. While guidance documents do not have the force of law and are not binding, they have proven to be an effective means of regulating industry and developing policy. *See Guidances*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/fda-basics-industry/guidances (last updated May 24, 2018) (summarizing the FDA's use of guidance documents).

99. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88 (defining chemical action and explaining the FDAs current thinking on the same).

100. *Id.* at 7. For a more reasoned take on chemical action, see, e.g., W.J. Koolage & R. Hall, *Chemical Action: What Is It, and Why Does It Really Matter?*, 13 J. NANOPARTICLE RES. 1401, 1401–17 (2011); *see also FDA Finalizes Product Classification Guidance*, HYMAN, PHELPS & MCNAMARA PC: FDA L. BLOG (Oct. 3, 2017), http://www.fdalawblog.net/2017/10/fda-finalizes-product-classification-guidance/; *Drug or Device?— FDA Provides More Clarity—or Does It?*, CAMARGO PHARMA: CAMARGO BLOG.

101. U.S. FOOD & DRUG ADMIN., *supra* note 88, n. 12.

This is, again, somewhat circular: "chemical action" is defined as interactions on the "molecular" level, which are interactions that include "chemical" reactions. However, recent guidance provides at least one bright line rule: chemical action is not mere transfer of electromagnetic or thermal energy.[102] Pacemakers, electrocauteries, cryotherapy, and neurostimulation devices are thus firmly on the device side. The FDA has provided several examples to illustrate products that do, and do not, achieve their primary purpose through chemical action.

Table 3. Examples of Medical Products that Illustrate Chemical Action.[103]

Medical Product	**Does this product achieve its primary intended purpose through "chemical action"?**
Inert synthetic polymers used to reduce post-operative tissue adhesions	No
Acrylate polymer bone filler	No
Topical surgical adhesive	No
Gold nanoparticles that absorb electromagnetic radiation and radiate thermal energy damaging nearby tissue and killing cancer cells	No
Liquid nitrogen gas used to treat warts	No
Hydroxocobalamin, which binds to cyanide to act as an antidote	Yes
Polymyxin B sulfate, a cationic surfactant that is attracted to and electrostatically adheres to the bacterial membrane, lysing and killing the bacteria	Yes

102. *Id.*
103. *Id.*

Magnesium sulfate for treating magnesium deficiency	Yes
Beta blockers, which interact with beta receptors and block access to the receptor	Yes

Lastly, the FDA has clarified that the concept of chemical action relates to the "primary intended purposes" of the device "as a whole" and thus does not hinge on whether the product involves any chemical action at all.[104] Further, as noted above, the FDA considers devices to be a subset of drugs, rather than being a mutually exclusive category. Thus, while a device can be said to work by means other than chemical action or metabolic action, the definition for drugs is not restricted with respect to mode of action.[105]

D. CLASSIFICATION OF COMBINATION PRODUCTS

i. Combination Products

When a product comprises two or more separately classified components, i.e., a mixed pairing of drug, device, or biologic components, the FDA classifies the product as a combination product.[106] Combination products thus correspond to drug/device, biologic/device, drug/biologic, or drug/device/biologic component mixtures. The Federal Code defines combination products as a product comprising two or more regulated components:

> (1) . . . that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
>
> (2) . . . packaged together in a single package or . . . ;
>
> (3) . . . packaged separately . . . intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use . . . ; or

104. *Id.*

105. The FDA's approach may be challenged by a recent district court decision in Genus Medical Technologies, which may force the FDA to reconsider whether at least a contrast agent can be regulated as a drug if it lacks chemical action, particularly in light of other contrast agents being regulated as devices. *See* Genus Medical Tech. v U.S. Food and Drug Admin., Civil Action No. 19-544 (JEB), 2019 U.S. Dist. LEXIS 210397 * | 2019 WL 6683777. Note, also, that drugs exclude food. *See* 21 U.S.C. § 321(g)(a) (2011).

106. 21 C.F.R. § 3.2(e) (2005) (defining combination products).

> (4) . . . packaged separately . . . for use only with another individually specified . . . drug, device, or biological product where both are required to achieve the intended use.[107]

Combination products are important in the context of Complex Products since the FDA expressly enumerated complex drug-device combinations as an example of Complex Products.

ii. Primary Mode of Action

To determine how any given combination product should be regulated, the FDA first determines the PMOA of the product.[108] Specifically, the FDA will identify the single mode of action that it expects makes the greatest contribution to the overall intended therapeutic effect of the product.[109] The FDA looks to determine the "means" by which the product achieves its intended therapeutic effect. Typically, combination products exhibit multiple modes of action.[110] Unintuitively, this means that PMOA is based on the action *intended*, not necessarily the action that occurs.

Once the PMOA has been identified, the product is classified based on whether the PMOA corresponds to "[t]he actions provided by a biological product, a device, and a drug."[111] A combination product is classified as a biologic if its PMOA "acts by means of" a product defined as a biologic.[112] The combination product is a device if its PMOA acts by means of a device, but not if it acts by means of a biological product, or through chemical action within or on the body, or if it is dependent upon being metabolized. Lastly, drug classification is a catch all: the combination product is a drug if it has a PMOA that does not meet either of their two definitions.[113] When looking at device-

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107. *Id.*
108. 21 U.S.C. § 353(g)(d) (2016).
109. 21 U.S.C. § 353(g)(c) (2016).
110. 21 C.F.R. § 3.2(k) (2005).
111. 21 C.F.R. § 3.2(k) (2005).
112. 21 C.F.R. § 3.2(k) (2005). S*ee also* 21 U.S.C. § 351(i) (2017) (listing products that are deemed biologics).
113. Of course, drugs, devices, and biologics do not necessarily function according to generalized modes of action. Ideally, the FDA prefers to think of itself as taking a science-based, product-specific approach to regulation, but Congress has expressly set forth a distinction between drugs, devices, and biologics. PMOA is simply an unavoidably blunt tool for separating products into the product categories devised by Congress without any particular scientific basis.

drug combination products, classification ultimately depends, again, on the FDA's interpretation of chemical action.

It is worth noting that such classification is merely for determining primary jurisdiction over the product. Even if the FDA assigns a drug-device combination product to CDRH, constituent parts of the product will still be regulated as needed to assure safety and efficacy.[114] That is, due to the broad regulatory power vested in the FDA, it can later regulate such products as it deems necessary and, in any event, the FDA will maintain quality control requirements of the non-primary components.[115] Nonetheless, the PMOA determination and the resulting combination product classification has significant consequences due to the differing regulatory burdens between drugs, devices, and biologics.[116] Indeed, the differing PMOA-based determination of product classification has led to some unintuitive and seemingly unfair outcomes.[117] Recognizing that this is an area of uncertainty for applicants, the Office of Combination Products encourages applicants to submit an informal inquiry or a Request for Determination (RfD) prior to seeking premarket review of products for which classification is uncertain.[118] Applicants can further appeal such determinations by way of a Request for Reconsideration.[119]

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114. *See* U.S. Food & Drug Admin., GUIDANCE FOR INDUSTRY AND FDA STAFF: CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS (2015), https://www.fda.gov/media/90425/download ("The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined.").

115. *Id*.

116. *See* Genus Med. Tech. v. United States Food & Drug Admin., No. 19-544 (JEB), 2019 U.S. Dist. LEXIS 210397 * 2019 WL 6683777 (indicating that if a particular contrast agent were classified as a device it could obtain approval for about $60,000, whereas obtaining drug approval would be "over half a million dollars in addition to a continuing annual cost north of $186,000.").

117. Response to Request for Designation from U.S. Food & Drug Admin., to AWBAT Plus Wound Dressing (Dec. 3, 2009).

118. *See Jurisdictional Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/combination-products/classification-and-jurisdictional-information (last updated Apr. 9, 2020).

119. *Id.*

E. BARRIERS TO MARKET ENTRY

i. Drugs

To market a new drug in the U.S., an innovator must submit a new drug application (NDA) to the FDA demonstrating that the drug is safe and effective for its intended use, and seek to obtain the FDA's express approval.[120] For new drugs, applicants can proceed through the premarket review process via either a 505(b)(1) NDA or a 505(b)(2) NDA (a type of "paper" NDA).[121] In either case, the NDA is intended to be a complete, candid, and authoritative report of an applicant's relevant knowledge arising from scientific and clinical investigations of the drug.[122]

A 505(b)(1) NDA requires that applicants conduct and report the results of their own well-controlled clinical studies evaluating safety and efficacy.[123] These clinical studies typically take the form of Phase 0, Phase 1, Phase 2, and Phase 3 trials.[124] The NDA must also include a complete description of the drug, all components, its method of manufacture, its manufacturing facility and controls, specimens of the drug, and proposed labeling.[125] Drugs are deemed to be a new molecular entity (NME) if the structure of one of the active ingredients (i.e., "active moiety") does not correspond to a previously approved structure, or esters, salts, clathrate, and other noncovalent derivatives thereof.[126] Whether a drug is an NME is factor that

120. *See* 21 U.S.C. § 355(a) (2011).

121. *See* 21 U.S.C. § 355(b) (2011).

122. *See* 21 U.S.C. § 355(b)(1)(A) (2011). For example, the clinical studies should have objective end points that are clinically relevant to the intended use, should conform with good clinical practice, and should be conducted and reported in a manner such that they are scientifically credible.

123. *See* 21 U.S.C. § 355(i)(2)(A) (2011).

124. *Id.*

125. *See* 21 U.S.C. § 355(b)(1)(B-F) (2011).

126. The FDA uses the NME designation for internal administration and regulatory research purposes. Still, the classification is important because it may guide internal policy and decision making. *See* U.S. FOOD & DRUG ADMIN., OFFICE OF PHARMACEUTICAL QUALITY, POLICY AND PROCEDURES: NDA CLASSIFICATION CODES (2015), https://www.fda.gov/media/94381/download (summarizing the various ways CDER classifies NDA products). *See also* 21 C.F.R. § 314.3 (2016) ("*Active moiety* is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance."). The FDA uses NCE, which relates to a five-year market exclusivity incentive for

the FDA weighs when considering investigation new drug (IND) applications,[127] risk evaluation and mitigation strategies (REMS) submissions, [128] and its evaluation of NDAs.[129]

In contrast with the 505(b)(1) process, a 505(b)(2) NDA can reference a prior finding by the FDA of the same drug's safety and efficacy, published clinical data, or prior clinical investigations conducted for someone other than applicant but for which the applicant does not have right of reference.[130] In a 505(b)(2) NDA, the applicant need only provide additional clinical or scientific information in connection with the difference between the new drug product and the prior approved drug.[131] A 505(b)(2) NDA is commonly used to pursue a new use, indication, formulation, dosage, route of administration, prodrug, or to label a previously approved drug.[132] However, a 505(b)(2) NDA should not be used as a substitute entry point for generic products that are below the bioequivalence requirements of the 505(j) abbreviated new drug application (ANDA) pathway.[133]

In considering whether to approve a new drug, the FDA conducts a risk-benefit analysis that considers the applicant's

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bringing such products to market. *See* 21 C.F.R. § 314.108 (2012) ("*New chemical entity* means a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act."). *See also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: NEW CHEMICAL ENTITY EXCLUSIVITY DETERMINATIONS FOR CERTAIN FIXED-COMBINATION DRUG PRODUCTS (2014), https://www.fda.gov/media/87932/download (indicating that the NCE incentive is determined based off of each drug substance, so mixtures of old and new APIs can qualify for the NCE incentive).

127. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND REVIEW STAFF: BEST PRACTICES FOR COMMUNICATION BETWEEN IND SPONSORS AND FDA DURING DRUG DEVELOPMENT (2017), https://www.fda.gov/media/94850/download (urging pre-IND meetings for sponsors of NME INDs).

128. *See* 21 U.S.C. § 355-1 (2011).

129. *See* U.S. FOOD & DRUG ADMIN., HUMAN GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 (2012), https://www.fda.gov/media/82022/download (setting forth a program for improving transparency and communication surrounding NME NDAs).

130. U.S. FOOD & DRUG ADMIN., GUIDANCE OF INDUSTRY: APPLICATIONS COVERED BY 505(b)(2) (1999), https://www.fda.gov/media/72419/download.

131. *Id.*

132. *Id.*

133. In other words, if the product to be approved is identical or generic to a prior approved product, then it must be equal or better to be suitable for the 505(b)(2) pathway. *Id.*

clinical data, currently-available alternative treatments, and whether the risks can be addressed by risk management and mitigation strategies (REMS).[134] Refusal is typically on the basis that the NDA fails to sufficiently establish that the drug is safe and effective under the conditions set forth in the proposed labeling.[135] However, applications can also be refused on various other grounds, including failure to list patents for submission to the Orange Book, inadequate manufacturing controls, or the FDA's determination that a proposed label is false or misleading.[136] The NDA review and approval process is highly technical and product-specific.[137] To assist applicants and in the interest of transparency, the FDA provides product-specific and general guidances.[138] The CDER further provides a directory listing many of its internal policies and procedures with respect to NDA approval.[139]

Generic drug makers can seek approval of follow-on products by way of an ANDA, i.e., a 505(j), or by way of the 505(b)(2) approval process discussed above.[140] The ANDA process requires the applicant to show that the follow-on product is bioequivalent, and has the same active ingredient, route of administration, dosage form, and strength as a previously-approved reference product.[141] 21 C.F.R. § 314.3 defines bioequivalence, active ingredient, dosage form, and strength.

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134. *See Drugs: Development and Approval Process*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/development-approval-process-drugs (last updated Oct. 28, 2019) (explaining the FDA's risk-benefit approach to drug approval).

135. *See* 21 U.S.C. §§ 355(c)-(d) (2011) (setting forth approval, refusal, and rationales for the same).

136. *See* 21 U.S.C. § 355(d) (2011).

137. *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PRUSSIAN BLUE DRUG PRODUCTS—SUBMITTING A NEW DRUG APPLICATION (2003), https://www.fda.gov/media/71071/download (providing guidance for a particular class of products); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY STUDIES SUBMITTED IN NDAS OR INDS—GENERAL CONSIDERATIONS (2019), https://www.fda.gov/media/121311/download (providing general guidance for how to best meet bioavailability requirement for NDA applications set forth in 21 C.F.R. § 320).

138. *Id.*

139. *CDER Manual of Policies & Procedures (MAPP)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp (last updated Apr. 17, 2020) (providing a searchable directory of its published policies and procedures).

140. *See* 21 U.S.C. § 355(b)(1) (2011); *see also* 21 U.S.C. § 355(j) (2011).

141. *See* 21 U.S.C. § 355(j) (2011).

The sameness of the active ingredient, i.e., drug substance, is established by showing that the follow-on active has the same chemical structure as the reference product.[142] Bioequivalence is typically shown by demonstrating an absence of significant difference in bioavailability, which is the rate and extent to which the active ingredient is absorbed into the bloodstream and made available to the target treatment site.[143] Alternative approaches to showing bioequivalence exist but applicants often do not have certainty regarding what approaches the FDA will deem suitable,[144] particularly for products that have not yet seen generic entry.

As required by the Hatch-Waxman Act, the FDA publishes a list of all approved NDA drugs in a compendium called the Orange Book, together with a list of patents supplied by each drug's sponsor.[145] Before any generic drug can be approved by the FDA, whether under 505(j) or 505(b)(2), a generic drug maker must first certify that marketing its generic drug would not infringe any valid, listed patents.[146] In this manner, the regulatory approval process for generic drugs involves use of the U.S. patent system, a separately regulatory regime, to act as a secondary gatekeeper for generic approval.

ii. Devices

a. Class I, Class II, and Class III

The FD&C Act provides for a risk-based approach to device regulation.[147] Once a product is recognized as a device, CDRH further classifies the device as Class I, Class II, or Class III,

142. *See* 21 U.S.C. § 320 (2012).

143. *See* 21 U.S.C. § 314.3 (2012); *see also* 21 U.S.C. § 320 (2012).

144. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOEQUIVALENCE RECOMMENDATIONS FOR SPECIFIC PRODUCTS (2012), https://www.fda.gov/media/71401/download (explaining FDA's process for conveying its bioequivalence expectations, which can be product specific and deviate from general guidance).

145. *See* 21 U.S.C. § 355(b)(1) (2011); *see also* 21 C.F.R. § 314 (2012).

146. *See* 21 U.S.C. § 355(b)(2)(A) (2011); *see also* 21 U.S.C. § 355(j)(2)(vii) (2011).

147. *See* 21 U.S.C. § 360c(a) (2011); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: FDA AND INDUSTRY PROCEDURES FOR § 513(G) REQUESTS FOR INFORMATION UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2012), https://www.fda.gov/media/78456/download (summarizing the FDA's device classification scheme).

corresponding to what controls are warranted to assure safety and efficacy.[148] Class I devices are regulated by general controls applicable to all devices.[149] Class II devices are those that can be sufficiently regulated by way of incorporating additional special controls, but for which general controls are not themselves sufficient to assure safety and efficacy.[150] Class III devices are typically devices that support or sustain human life and require premarket approval due to greater risk of harm.[151] The FDA provides a searchable online database listing the device classifications and the Federal Code is regularly updated with classification details.[152] A Section 513(g) request can be submitted to the FDA to inquire what class a device falls within; whether a PMA, 510(k), or neither, would be required before bringing the product to market; and if any special requirements or guidances apply to such product types.[153] A device is automatically assigned to Class III unless it is a type of device already categorized by the FDA as Class I or Class II and the

148. *See* U.S. FOOD & DRUG ADMIN., *supra* note 147.

149. The FDA describes general controls as statutory requirements authorized by FD&C Act. For example, general controls include the adulteration and misbranding provisions, the premarket review processes, the requirements to register drug and device producers, statutorily banned devices, recall provisions, adverse event reporting, product tracking systems, inspections, GMP requirements, public notices, and other notices. *See Regulatory Controls*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (last updated Mar. 27, 2018) (defining general controls and listing examples).

150. Special controls are described as regulatory requirements not applicable to all devices and typically product specific, e.g., performance standards, postmarket surveillance, patient registries, black box warnings and other special labeling requirements, premarket data requirements, and compliance with guidelines. *See Regulatory Controls*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (last updated Mar. 27, 2018) (defining special controls and listing examples).

151. *Id.*

152. *See Product Code Classification Database*, U.S. FOOD & DRUG ADMIN. (2019), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm; *see also* 21 C.F.R. §§ 862–892 (2012) (listing virtually all medical device types along with their classifications, product codes, and FDA premarket review organizations).

153. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: FDA AND INDUSTRY PROCEDURES FOR SECTION 513(G) REQUESTS FOR INFORMATION UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (2012), https://www.fda.gov/media/78456/download (summarizing the FDA's current thinking on the 513(g) process).

device is substantially equivalent to another device already on the market as determined by a 510(k) submission.[154] In response to, or as an alternative to, the default classification of new devices into Class III, a device manufacturer can submit a De Novo Classification Request.[155] In response, the FDA conducts a risk-based evaluation of the device and assigns it to Class I or Class II if general and special controls are sufficient to provide reasonable assurance of safety and efficacy.[156]

b. Exempt Devices, 510(k), and Premarket Approval

Almost all Class I devices and some Class II devices are exempted from the requirement to obtain premarket approval or provide the FDA with premarket notification.[157] Some Class I devices are further exempted from satisfying GMP general requirements, provided records and complaint files are kept, and the device is not labeled as sterile when it is sold.[158] The FDA provides an online database of all exempt devices.[159]

The FDA requires premarket notification by way of a 510(k) submission at least 90 days before a device is marketed in the U.S. for the first time, or before a device already marketed is modified in a manner which may significantly affect safety or effectiveness.[160] In some cases, changes to a product's packaging or label can require submission of a 510(k).[161] This notification requirement applies to every Class I, Class II, and Class III medical device unless it is exempt or engaged in the separate

154. 21 U.S.C. § 513(f) (2019).

155. *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III DESIGNATION) (2017), https://www.fda.gov/media/72674/download (summarizing the De Novo Classification pathway).

156. *Id.*

157. *See Medical Device Exemptions 510(k) and GMP Requirements*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm (last accessed Dec. 2, 2019) (listing medical devices exempt from premarket notification and premarket approval requirements).

158. *Id.*

159. *Id.*

160. *See Premarket Notification 510(k)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k (last updated Mar. 13, 2020).

161. *Id.*

premarket approval (PMA) process.[162] Devices subject to the 510(k) premarket requirement are not cleared for market until the FDA provides a written order declaring that the device is "substantially equivalent" to a predicate device and that it may be marketed in the U.S.[163]

A device is deemed "substantially equivalent" to a predicate device if the following criteria are satisfied: Firstly, it must have the same intended use. Secondly, it must either have the same technological characteristics, or, if it has different technology characteristics that do not raise questions of safety and effectiveness, the 510(k) submission must contain information demonstrating that the new device is at least as safe and effective as the predicate device.[164] Technological characteristics are deemed to be different if there is a significant change in the materials, design, or energy source.[165] In considering whether there is substantial equivalence to a predicate device, the FDA also looks at differences in manufacturing process, labeling, and chemical composition.[166] The use of nanotechnology in devices is likely to make determinations of substantial equivalence and technological sameness challenging.

The FDA has recently provided several alternative pathways for manufacturers to show that their devices are substantially equivalent.[167] The Special 510(k) Program provides a simplified pathway for manufacturers to update and

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162. *Id*.

163. *Id*. 510(k) must also satisfy general controls and any prescribed special controls. *See Regulatory Controls*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (last updated Mar. 27, 2018).

164. *See* 21 U.S.C. § 360c(i) (2011); *see also* U.S. FOOD & DRUG ADMIN., *supra* note 146; *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: THE 510(K) PROGRAM: EVALUATING SUBSTANTIAL EQUIVALENCE IN PREMARKET NOTIFICATIONS (2014), https://www.fda.gov/media/82395/download (summarizing the 510(k) decision making process, how the FDA interprets substantial equivalence, and how it defines technological characteristics).

165. 21 U.S.C. § 360c(i)(1)(B) (2011).

166. U.S. FOOD & DRUG ADMIN., *supra* note 146.

167. *See* Tom Cowan, *FDA Issues Guidance on "Abbreviated" and "Special" 510(k) Pathways*, KNOBBE MEDICAL, http://knobbemedical.com/medicaldeviceblog/article/fda-issues-guidance-on-abbreviated-and-special-510k-pathways/ (last visited Apr. 17, 2020).

modify their own, previously cleared products.[168] In a Special 510(k) submission, a manufacturer can establish substantial equivalence by way of its own design controls and conformance with quality system regulations.[169] The Abbreviated 510(k) Program facilitates approval of devices that have been the subject of the FDA's previously-issued product-specific guidances, special control standards, or voluntary consensus standards.[170] In an abbreviated 501(k) application, a manufacturer can establish substantial equivalence by following such guidances or standards and assuring its conformance.[171]

Premarket Approval (PMA) is the most rigorous form of premarket review that the FDA conducts for medical devices.[172] The PMA process is roughly analogous to an NDA or Biologics License Application (BLA), except that the standard for approval of a PMA is a "reasonable assurance" of safety and efficacy.[173] A PMA application involves submission of data from laboratory and clinical studies, device and manufacturing details including trade secret information, quality system controls, comparison to commercially-available alternatives, and scientifically-based

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168. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: THE SPECIAL 510(K) PROGRAM (2019), https://www.fda.gov/media/116418/download (describing the new Special 510(k) program and how to determine whether a product modification is suitable for review under this program).

169. *Id.*

170. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: THE ABBREVIATED 510(K) PROGRAM (2019), https://www.fda.gov/media/72646/download (summarizing the new Abbreviated 510(k) program and how to determine whether a product modification is suitable for review it). *See also* U.S. FOOD & DRUG ADMIN., APPROPRIATE USE OF VOLUNTARY CONSENSUS STANDARDS IN PREMARKET SUBMISSIONS FOR MEDICAL DEVICES (2018), https://www.fda.gov/media/71983/download (explaining that voluntary consensus standards are effective regulatory tools recognized in the FD&C Act per 21 U.S.C. § 360d(1)(A)).

171. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: THE ABBREVIATED 510(K) PROGRAM (2019), https://www.fda.gov/media/72646/download (describing the new Abbreviated 510(k) program and how to determine whether a product modification is suitable for review).

172. *See Premarket Approval*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma (last updated May 16, 2019); *see also* 21 C.F.R. § 814 (1996) (outlining the PMA process).

173. *Compare* 21 U.S.C. § 393(b) (2011) *with* 21 U.S.C. § 355(j) (2011). *See also* The Biologics Price Competition and Innovation Act of 2009, S. 1695, 100th Cong. § 7002(e) (2007).

conclusions linking the device's medical claims to the results of studies.[174] The studies should be based on accepted scientific and clinical practices and, when applicable, FDA guidances.[175] In evaluating safety and efficacy, the FDA considers the intended patient population, the conditions for use of the device, the risk-benefit of the device, and the device's reliability.[176]

Follow-on devices gain access to the market the same way as new devices. For Class I and II, no premarket review is required if the device is an exempted device; otherwise, the manufacturer will likely proceed through a 510(k) process. If the innovator device requires PMA, then follow-on devices will also require a PMA unless the FDA down-classified the device class in the interim.[177] Moreover, the prior PMA approval would have provided the innovator with six years of data exclusivity.[178] PMA devices do not have an abbreviated approval path that is analogous to the generic ANDA pathway.[179] The 510(k) path is the closest approximation of a follow-on pathway in the device framework, which although not used to reference clinical data, is similarly used to obtain approval by pointing to an already-approved product.

iii. Biologics

Biologics are regulated under the Public Health and Safety Act (PHSA) which requires approval of a BLA prior to marketing any biologic.[180] Approval is based on the applicant establishing that the product is safe, pure, and potent.[181] The BLA process is

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174. *See PMA Application Contents*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-approval-pma/pma-application-contents (last updated May 16, 2019) (outlining required and suggested elements of a PMA application).

175. *See PMA Clinical Studies*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies (last updated Feb. 21, 2019) (summarizing best practices for clinical investigations and factors that the FDA considers for safety and effectiveness).

176. *See* 21 U.S.C. § 860.7 (2012).

177. *See* Erika Leitzan, *Data Exclusivity for Medical Devices*, OBJECTIVE INTENT (Oct. 10, 2017), https://objectiveintent.blog/2017/10/10/data-exclusivity-for-medical-devices/.

178. *Id*.

179. *Id*.

180. 42 U.S.C. § 262 (1993).

181. *See Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-

largely analogous to an NDA and, in fact, the PHSA expressly adopts for biologics all the general FD&C provisions except for the replacement of the NDA process with a BLA.[182] A BLA differs from an NDA in that BLA holders can have more stringent manufacturing validation requirements, must retain certain product samples after expiration of each lot of product, and have particular post-market responsibilities including submission of reports regarding batch information and adverse events.[183]

Due to the complexity of biologics as well as their economic and therapeutic importance, Congress has provided unique regulatory provisions for follow-on biologics products.[184] The Biologics Price Competition and Innovation Act (BPCIA) provided for an abbreviated BLA pathway, analogous to an ANDA, except that instead of requiring follow-on products to have identical structure and activity. The BPCIA permits approval of "biosimilar" products that are merely expected to produce the same clinical result.[185] The FDA defines a product as a biosimilar when there are "no clinically meaningful

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process-cber (last updated Feb. 2, 2018) (defining biological products and summarizing certain ways that approval of biological products differs from the drug approval process).

182. 42 U.S.C. §262(j) (1993).

183. *See* Keith Webber, *FDA's Interpretation of the "Deemed to Be a License" Provision of the Biologics Price Competition and Innovations Act*, FDA WATCH, https://www.lachmanconsultants.com/wp-content/uploads/2019/03/deemed-to-be-a-license-20-22-FDA-0319.pdf (summarizing the differences between an NDA and BLA).

184. *See* The Biologics Price Competition and Innovation Act of 2009, S. 1695, 100th Cong. § 7002(e) (2007) (creating an accelerated approval system for biological products that are biosimilar to, or interchangeable with, an FDA licensed reference biological product).

185. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (2019), https://www.fda.gov/media/124907/download (reporting on recent developments in the biosimilar approval process); *see also* U.S. FOOD & DRUG ADMIN., GUIDANCE CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT (2016), https://www.fda.gov/media/88622/download; U.S. FOOD & DRUG ADMIN., GUIDANCE QUESTIONS AND ANSWERS ON BIOSIMILAR DEVELOPMENT AND THE BPCI ACT GUIDANCE FOR INDUSTRY (2018), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/questions-and-answers-biosimilar-development-and-bpci-act-guidance-industry; U.S. FOOD & DRUG ADMIN., INTERPRETING SAMENESS OF MONOCLONAL ANTIBODY PRODUCTS UNDER THE ORPHAN DRUG REGULATIONS (2014), https://www.fda.gov/media/77256/download.

differences" between the reference product in terms of safety, purity, and potency.[186] However, a biosimilar is not so similar that, for any given patient, one can assume the same clinical result when switching from the reference product.[187] The omission of any requirement for structural sameness or bioequivalence is a key distinction between generic drugs and biosimilars.[188] In some cases, biosimilars can be shown to be interchangeable, on the basis of additional clinical testing and analysis of switching risks.[189] An "interchangeable" biosimilar may be substituted for the reference product at the pharmacy-level without requiring physician intervention.[190] Biosimilars are a particularly active area of regulatory development as the FDA and Congress are still exploring how 'similar' biosimilars should be.[191]

Additionally, unlike the generic approval process for drugs, the approval process for biologics does not tether the FDA to the patent system. Instead, BLA approval of follow-on products follows a process that is separate from an innovator's patent enforcement efforts.[192]

F. CONSEQUENCES OF PRODUCT CLASSIFICATION

Product classification is a critical determining factor of the time and cost of obtaining regulatory approval. Development and approval of drugs and biologics involves enormous costs, estimated to be as high as $100 million to $2 billion.[193] Yet, a device can be developed and approved with as little as $1 million

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186. *Biosimilar and Interchangeable Products,* U.S. FOOD & DRUG ADMIN. (Oct. 2017), https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar.

187. This limits the ability of a pharmacy to substitute certain biosimilars for pioneer biologic without the agreement of the prescriber. *Id.*

188. *Id.*

189. *Id.*

190. *Id.*

191. *Id.*

192. *Cf.* 42 USC § 262(l) (1993) (allowing the so-called "patent dance" process in which biosimilar entrants can negotiate an initial, early wave of patent litigation during the BLA process, although the FDA's approval does not hinge on any particular litigation outcome).

193. Thomas Sullivan, *A Tough Road: Cost to Develop One New Drug Is $2.6 Billion; Approval Rate for Drugs Entering Clinical Development Is Less Than 12%*, POL'Y & MED., https://www.policymed.com/2014/12/a-tough-road-cost-to-develop-one-new-drug-is-26-billion-approval-rate-for-drugs-entering-clinical-de.html (last updated Mar. 21, 2019).

to $10 million if its developer can follow a 510(k) path.[194] Even in the case of a device PMA, estimated to have an average cost between $10 million and $100 million, costs are still typically far below the average cost of development and approval of NDA and BLA products.[195] Moreover, bringing a new drug or biologic to market takes far longer, about twelve years on average, which would typically include about two years of pre-clinical testing, about eight years of clinical trials, and about two years of NDA/BLA approval.[196] In contrast, bringing a new device to market averages between three and seven years.[197] The new device timeline would typically include two to three years of pre-clinical bench and animal testing (which can sometimes be sufficient to show that a 510k device is substantially equivalent) and can also involve one to two years of clinical trials, which may involve a thousand or more patients.[198]

This eight-year difference in timeline is enormously meaningful. Each additional year of clinical investigation and regulatory review not only delays a future income stream, but also eats away at the remaining term of the product's patents.[199]

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194. *See Medical Device User Fees*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions/medical-device-user-fees (last updated Jan. 14, 2020) (discussing the different fee and payment structures of submitting a drug to the FDA); *See also* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: BUNDLING MULTIPLE DEVICES OR MULTIPLE INDICATIONS IN A SINGLE SUBMISSION (2007), https://www.fda.gov/media/73500/download (discussing a method of cutting down costs by bundling multiple products into one application).

195. *See* U.S. FOOD & DRUG ADMIN. *supra* note 194 (discussing the different fee and payment structures of submitting different types of drugs to the FDA for approval).

196. Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 70, 70–79 (2016); *see also* Matthew Herper, *The Cost of Creating a New Drug Now $5 Billion, Pushing Big Pharma to Change*, FORBES (Aug. 11, 2013), https://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/#7753cc096bfc.

197. Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 2: An Overview of Approval Processes: FDA Approval of Medical Devices*, 1 JACC: BASIC TO TRANSLATIONAL SCIENCE 277, 277–87 (2016).

198. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: FORMAT FOR TRADITIONAL AND ABBREVIATED 510(K)S (2019), https://www.fda.gov/media/130647/download (discussing the timeline for submission and approval of 510(k) devices).

199. *Lifetime Trends in Biopharmaceutical Innovation*, QUINTILESIMS (Jan. 2017), https://www.statnews.com/wp-

The shorter the remaining patent term, the higher the company will need to set its prices in order to counterbalance its development and opportunity costs. If the remaining patent timeline is too short, then development and commercialization of the product may not be justified.

Each of the different regulatory pathways reward applicants with differing periods of data and market exclusivity.[200] For example, drug products representing a new chemical entity (NCE) having a new active moiety[201] and approved under an NDA pathway will typically be provided with five years of data exclusivity per the Hatch-Waxman Act,[202] which also effectively provides more than seven years of market exclusivity by way of a thirty-month stay pending generic entry.[203] Other clinical investigations, for example, studying a substantial change to a previously approved drug, can provide three years of market exclusivity.[204] Devices can be provided with six years of data exclusivity after approval of a PMA.[205] Approval of biologic under the BLA pathway provides four years of data exclusivity and twelve years of market exclusivity.[206] Various additional incentives further apply to each, such as the six-month extension of exclusivity provided for pediatric testing and the seven-year market exclusivity provided by the Orphan

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content/uploads/2017/01/Lifetime_Trends_in_Biopharmaceutical_Innovation.pdf.

200. *See* Bo Peng & Marta C. Tomas, *A Cheat Sheet to Navigate the Complex Maze of Exclusivities in the United States*, 3 PHARMACEUTICAL PAT. ANALYST 339 (Oct. 7, 2014), https://www.future-science.com/doi/10.4155/ppa.14.30.

201. Here, the term "active moiety" simply refers to a new drug substance, not just a new pharmacophore portion of drug. The term "new active moiety" serves to distinguish from previously FDA-approved drug substances, and esters, salts, and clathrates thereof. *See* Scott Whittaker & Anthony Walker, *Pharmaceutical Patent Term Extension: An Overview*, ALACRITA, https://www.alacrita.com/whitepapers/pharmaceutical-patent-term-extension-an-overview (last accessed Apr. 16, 2020).

202. 34 U.S.C. § 156(g)(6)(C) (2018).

203. *Id*.

204. *Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, U.S. FOOD & DRUG ADMIN. (2016), https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity.

205. *See* Erika Lietzan, *Data Exclusivity for Medical Devices*, OBJECTIVE INTENT (Oct. 10, 2017) https://objectiveintent.blog/2017/10/10/data-exclusivity-for-medical-devices/ (summarizing the different data exclusivity provisions regarding different medical devices).

206. *Id*.

Drug Exclusivity incentive for treatment of a rare disease affecting fewer than 200,000 people in the United States.[207] Drug and biologic products can also take advantage of the Qualified Infectious Disease Product exclusivity which provides five years of supplemental market exclusivity.[208] Patent term extensions of up to five years are granted to one of a sponsor's U.S. patents covering the product for which premarket testing approval was required.[209]

As discussed in Section E, classification also controls how follow-on competition is regulated. A table is provided below that summarizes the differences between the drug, device, and biological regulatory schemes.

Table 4. Summary of Differences Between Regulatory Pathways

	Drug	**Device**	**Biologic**
Premarket Review	NDA	PMA, 510(k), or none depending on risk	BLA
Average Time for Preclinical, Clinical, and Approval	12 years	3–7 years	12 years
Average Cost for Approval	$100M–$2B	$1M–$100M	$100M-$2B
Data Exclusivity	5 years (Paragraph IV can be submitted at 4 years)	6 years	4 years

207. *FDA Exclusivity and Generic Drugs: What Does It Mean?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity (last updated Feb. 5, 2020).

208. US. FOOD & DRUG ADMIN., DRAFT GUIDANCE, QUALIFIED INFECTIOUS DISEASE PRODUCT DESIGNATION QUESTIONS AND ANSWERS GUIDANCE FOR INDUSTRY (2018), https://www.fda.gov/media/111091/download.

209. U.S. FOOD & DRUG ADMIN., PATENTS AND EXCLUSIVITY (2015), https://www.fda.gov/media/92548/download.

Market Exclusivity	7.5 years (5 years plus 30-month stay)		12 years
Patent Term Extension	≤ 5 years	≤ 5 years	≤ 5 years
Follow on pathway	505(j)	510(k) Pathway	Biosimilar Pathway
Standard of Equivalence for Follow-On Products.	Same route of administration, dosage form, and strength, and bioequivalence [210]	Substantial equivalence	Can be expected to produce the same clinical result in any given patient[211]

II. ANALYSIS

A. COMPLEX PRODUCTS HAVE COMPLEX PROBLEMS

i. The Problem of Rising Healthcare Costs

Congress is increasingly concerned with the rising costs of healthcare and is searching to find new ways to lower prescription drug costs.[212] Medical innovation is an expensive and uncertain process. The cost of this uncertainty is reflected in the enormous amount of resources required to develop new medical products. After accounting for the cost of clinical failures, the total cost of developing a new drug is now estimated

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210. *See* 21 U.S.C. §355(j)(8)(B) (2010) (defining bioequivalence when the rate and extent of absorption of the reference drug do not show a significant difference).

211. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (2019), https://www.fda.gov/media/124907/download (summarizing recent developments in the biosimilar approval process).

212. *See* Shelley Starkey, *Congress Seeks to Address Rising Health Care Costs*, NAT'L COUNCIL FOR BEHAV. HEALTH (May 30, 2019), https://www.thenationalcouncil.org/capitol-connector/2019/05/congress-seeks-to-address-rising-health-care-costs/; *see also FDA Drug Competition Action Plan*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan (last updated Apr. 8, 2020).

to be as high as $2.6 billion, but of which sixty percent is incurred during clinical validation and FDA approval.[213] Drug candidates can expect a failure rate of more than ninety percent and costs of approximately $1.5 billion during clinical testing and regulatory approval—that is, most costs are incurred under the purview of seeking regulatory approval and within frameworks set forth by the FDA.[214] The cost and risk of development necessarily leads to high drug costs, as innovators seek to justify their development expenses while earning a return on capital commensurate with their risks of failure. The factors that determine pricing of medical products are enormously complex, including the cost of existing standard of care, perceived value, payor dynamics, patient population, length of treatment, geography, and even soft factors like payor outcry or political concerns.[215] What is clear, at least, is that competition can significantly reduce average prices.[216] Entry of a single competitive generic product can lower prices by thirty to forty percent, while the presence of six or more competitive products can lower prices by up to ninety-five percent.[217] Complex Products, however, can involve both high development costs and unique barriers to competitor entry—this is a recipe for runaway drug costs.

Recent reports from the U.S. GAO identify Complex Products as an important area for further regulatory development.[218] The GDUFA, reauthorized in 2017 (GDUFA II)

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213. *Prescription Medicines: Costs in Context*, PHARM. RES. & MFRS. AM., http://phrma-docs.phrma.org/sites/default/files/pdf/prescription-medicines-costs-in-context-extended.pdf (last updated Aug. 2016).

214. C. Heem et al., *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 BIOSTATISTICS 273, 273–86 (Apr. 2019), https://academic.oup.com/biostatistics/article/20/2/273/4817524.

215. *See, e.g.*, STAFF OF COMMITTEE OF FINANCE, 114TH CONG., THE PRICE OF SOVALDI AND ITS IMPACT ON THE U.S. HEALTHCARE SYSTEM 1, 1–28 (Comm. Print 2014), https://www.govinfo.gov/content/pkg/CPRT-114SPRT97329/html/CPRT-114SPRT97329-Part1.htm (discussing the pricing method used to price the drug Sovaldi incorporating these factors).

216. WAYNE WINEGARDEN, PACIFIC RESEARCH INSTITUTE, THE ECONOMICS OF PHARMACEUTICAL PRICING 5, 5–27 (2014), https://www.pacificresearch.org/wp-content/uploads/2017/06/PhamaPricingF.pdf.

217. *Generic Competition and Drug Prices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices (last updated Dec. 13, 2019).

218. *See generally* U.S. GOV'T ACCOUNTABILITY OFF., GAO-18-80, GENERIC DRUGS: FDA SHOULD MAKE PUBLIC ITS PLANS TO ISSUE AND REVISE GUIDANCE

under the FDA Reauthorization Act of 2017 (FDARA), requires the FDA to develop a program to facilitate approval of Complex Product, especially generics.[219] The FDA issued formal letters committing to these goals and summarizing specific steps it would take.[220] These letters, representing a decade of associated regulatory objectives, expressly identify Complex Products as an area requiring further science-based regulatory development.[221] Prior to departing from the FDA in 2019, former FDA Commissioner Scott Gottlieb suggested that legislators further consider changing Hatch-Waxman to accommodate complex drugs.[222] On January 17, 2020, the House Committee on Energy

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ON NONBIOLOGICAL COMPLEX DRUGS 12 (2017), https://www.gao.gov/assets/690/689047.pdf; *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-17-452, GENERIC DRUG USER FEES: APPLICATION REVIEW TIMES DECLINED, BUT FDA SHOULD DEVELOP A PLAN FOR ADMINISTERING ITS UNOBLIGED USER FEES 6–14 (2017), https://www.gao.gov/assets/690/684950.pdf (identifying generic competition around complex drugs to have unique scientific and regulatory challenges and should be a primary focus area for regulatory development).

219. *See e.g.,* FDA Reauthorization Act of 2017, Pub L. No. 115-52, 131 Stat. 1005 (2017) (providing provisions to facilitate generic drug approval, including of complex products); *see generally* GENERIC COMPLEX DRUGS SAFETY AND EFFECTIVENESS FOR PATIENTS ACT OF 2015, H.R. 1576, 114TH CONG. (2015) (a failed bill proposing to require a study by the Government Accountability Office (GAO) to assess the Food and Drug Administration's current regulatory pathway for reviewing generic versions of nonbiologic complex drug products).

220. Here, the FDA's performance goals relate primarily to providing product specific guidances. GDUFA II sets an ambitious timeline for the FDA to issue product-specific guidance for new generics for ninety percent of drugs having NDAs approved after October 1st, 2017, though this timeline does not apply to Complex Products, which have scientific and regulatory research challenges. *See* U.S. FOOD & DRUG ADMIN., GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018-2022 (2016), https://www.fda.gov/media/101052/download (exempting Complex Products from its product-specific timeline).

221. *See* U.S. FOOD & DRUG ADMIN., HUMAN GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 (2012), https://www.fda.gov/media/82022/download (summarizing various FDA goals related to Complex Products, including continued development of science-based recommendations for Complex Products, and the FDA's intention to issue guidances to clarify its recommendations); *See also* U.S. FOOD & DRUG ADMIN., GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018-2022 (2016), https://www.fda.gov/media/101052/download (providing a pre-ANDA pathway to facilitate development and approval of generic Complex Products).

222. Beth Wang, *Gottlieb: Changes to Hatch-Waxman May Boost Complex Generic Market*, INSIDEHEALTHPOLICY (Apr. 4, 2019, 12:09PM), https://insidehealthpolicy.com/daily-news/gottlieb-changes-hatch-waxman-may-boost-complex-generic-market (stating that the FDA chief "told lawmakers

and Commerce sent a letter to the FDA voicing its concerns regarding lagging approvals of Complex Products and demanding documents reflecting the FDA's efforts to date.[223]

Currently, Complex Products are regulated according to the FDA's conventional regulatory scheme based on whether the product is classified as a drug, device, biologic, or combination product. To the extent Complex Products raise new challenges, the FDA has preferred to approach each product on a case-by-case basis as scientifically-grounded guidance cannot be easily generalized across Complex Products.[224] The FDA's current efforts to facilitate approval of Complex Products are centered around increasing transparency, for example, by way of guidance[225] on frequent trouble areas, reasoning that doing so will lead to better prepared applicants and fewer unexpected regulatory outcomes.[226] The FDA is expected to issue new guidance on Complex Products soon.[227] To encourage competition, the FDA has started publishing a list of all off-

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they could contemplate changes to Hatch-Waxman that would allow the agency to look at small complements of clinical data when approving generics of complex drugs").

223. Letter from Frank Pallone, Chairman Comm. Energy and Commerce, et al., to Stephen Hahn, Comm'r of U.S. Food & Drug Admin. (Jan. 17, 2020) (on file with House Energy Committee).

224. Jon S. B. de Vlieger et al., *Report of the AAPS Guidance Forum on the FDA Draft Guidance for Industry: "Drug Products, Including Biological Products, that Contain Nanomaterials"*, 21 AM. ASS'N OF PHARM. SCIENTISTS 55, 55 (Apr. 17, 2019), https://doi.org/10.1208/s12248-019-0329-7 (summarizing a meeting discussing appropriate regulatory pathways for drug products containing nanomaterials).

225. *See Guidances*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/fda-basics-industry/guidances (last updated May 24, 2018) (describing the FDA's use of guidance documents).

226. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88 (defining chemical action and explaining the FDA's current thinking on the same).

227. *See Upcoming Product-Specific Guidances for Complex Generic Drug Product Development*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development (last updated Mar. 2, 2020) (listing complex products for which FDA plans to provide additional product specific guidances). Such guidances are in line with FDA's GDUFA II commitment letter and Congress's mandate under FDAMA. *See, e.g.*, U.S. FOOD & DRUG ADMIN., GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018-2022 (2016), https://www.fda.gov/media/101052/download; *see also* FDA REAUTHORIZATION ACT OF 2017, PUB. L. NO. 115-52, §§501-905, 131 STAT. 1005, 1036– 90 (2017) (providing provisions to facilitate generic drug approval, including generic complex products).

patent approved drugs that have no generic competition.[228] The FDA has also committed to issuing more product-specific guidance, targeting ninety percent of all new chemical entity drugs, but does not expect to meet that mark for Complex Products.[229] Product specific guidance for Complex Products requires the development of scientific recommendations.[230] The FDA has also set up a Pre-ANDA Program and a mid-review meeting program to assist applicants developing Complex Products.[231] The goal of the program is to speed up the approval process for generic Complex Products, but also to inform innovators regarding the FDA's intended approach for bioequivalence alternatives and other product-specific challenges.

Each of these programs aim to decrease regulatory uncertainty and facilitate competition primarily by increasing FDA communication. However, the challenges surrounding Complex Products are statutory and technical in nature, not a result of lacking FDA transparency. The statutory problem is that the FD&C Act relies on inherently flawed *chemistry-based* distinctions to delineate its regulatory framework. The

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228. *List of Off-Patent, Off-Exclusivity Drugs Without an Approved Generic*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/list-patent-exclusivity-drugs-without-approved-generic (last updated Dec. 13, 2019). *See also Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. (last updated Apr. 2020) (listing all approved drug products, including corresponding patents that must be overcome prior to marketing a generic).

229. *See* U.S. FOOD & DRUG ADMIN., HUMAN GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013-2017 (2012), https://www.fda.gov/media/82022/download (summarizing various FDA goals related to Complex Products, including continued development of science-based recommendations for Complex Products, and FDA's intention to issue guidances to clarify its recommendations); *see also* U.S. FOOD & DRUG ADMIN., GENERIC DRUG PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018-2022 (2016), https://www.fda.gov/media/101052/download (providing a pre-ANDA pathway to facilitate development and approval of generic Complex Products).

230. *Id.*

231. *See* U.S. FOOD & DRUG ADMIN., FORMAL MEETINGS BETWEEN FDA AND ANDA APPLICANTS OF COMPLEX PRODUCTS UNDER GDUFA: GUIDANCE FOR INDUSTRY (2017), https://www.fda.gov/media/107626/download (explaining that mid-review-cycle meetings are used "to discuss issues identified during review with the applicant"); *see also* U.S. FOOD & DRUG ADMIN., GDUFA II COMMITMENT LETTER (2016), https://www.fda.gov/media/101052/download (providing a pre-ANDA pathway to facilitate development and approval of generic Complex Products).

technological problem is that development of follow-on competition for Complex Products requires substantial, but redundant, technological efforts on the part of each applicant.

ii. The Problem with Chemical Action

Congress requires the FDA to distinguish devices from drugs and biologics based on whether the intended therapeutic function involves chemical action on the human or animal body, or if the function is dependent on metabolism. However, the precise meaning of chemical action is a frequent area of confusion that leads to significant uncertainty, particularly in the case of drug-device combinations and products having both device-like and drug-like characteristics.[232] The FDA's reliance on this distinction has led to unintuitive product classifications.[233] For drug-device combination products, nanodevices, or other devices involving nanotechnology, the uncertainty of classification poses a significant regulatory risk. Experts have wrestled with how to rationalize the chemical action requirement in a manner that provides a predictable result. One analysis suggests interpreting chemical action occurs when there is (1) a chemical transformation occurring at the site of treatment and involving the article, (2) the transformation is causally linked to the therapeutic effect, and (3) the transformation is consistent with concepts currently considered as chemistry.[234] While this is a useful framework,

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232. *See FDA Finalizes Product Classification Guidance*, FDA L. BLOG (Oct. 3, 2017), http://www.fdalawblog.net/2017/10/fda-finalizes-product-classification-guidance/ (explaining how earlier draft guidance topics on the subject of chemical action were criticized by numerous objections); *see also Drug or Device?—FDA Provides More Clarity—Or Does It?*, CAMARGO BLOG (Oct. 11, 2017), https://camargopharma.com/resources/blog/drug-device-fda-clarity (explaining that the FDA issued a guidance document in response to the difficulty in understanding whether "a combination product would be reviewed as a device or a drug"); *see generally* Koolage & Hall, *supra* note 97 (discussing what is meant by "chemical action" and its significance).

233. *See* Letter from Dep't of Health and Human Services to Dr. Ronald A. Sherman (Oct. 7, 2002) (online at https://www.fda.gov/media/74541/download) (explaining that "medical maggots do not meet the definition of a medical device in that that they appear to achieve their primary intended purpose through chemical action" and are instead "a biological product, as defined by the Public Health Service Act").

234. *See* Koolage & Hall, *supra* note 97, at 1414.

there remains a question about what types of transformations should be deemed to be consistent with chemistry.[235]

Recent FDA guidance regarding chemical action attempts to further define chemical action by introducing the concept of interaction "at the molecular level" and mediating "a bodily response" or altering a foreign entity's interaction with the body.[236] The guidance also clarifies that chemical action excludes interactions mediated solely by thermal and electromagnetic radiation.[237] This updated definition provides surprisingly little clarity when considering Complex Products and other device-like products having functional nanotechnology-based features.[238] Indeed, the definition permits such a broad definition of chemical action that it encompasses virtually any interaction beyond purely electromagnetic and kinetic energy transfers.

As the "central" science, chemistry describes the mechanisms by which virtually all substances interact. When examined on the molecular or "nano" scale, virtually all medical products interact with their surroundings by way of chemical interactions. For example, even a scalpel can be described as involving chemical action: the tool disrupts Van der Waals[239]

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235. It may be easier to carve things away from chemistry if looking "downward" toward the field of physics rather than "upward" toward molecular ensembles and macroscopic phenomena. For example, one could carve out physical phenomena such as universal force interactions, subatomic changes, quantum-based changes, and changes in internal molecular states like vibrational, translational, and thermal energy states. This appears to be what the FDA has determined in its recent guidance and is similar to the "chemicality" principal suggested by Koolage and Hall. *See id.* at 1410–11. However, both of these approaches do not address how to delineate between nonspecific chemical interactions, chemically-specific resulting from macroscopic devices, device-like interactions on the nanoscale, and other nanotechnology-type interactions that rely on aspects like structural design, particle size, pore size, and machine-like mechanics.

236. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88 at 7 ("[A] product exhibits 'chemical action' if it interacts at the molecular level with bodily components (e.g., cells or tissues) to mediate (including promoting or inhibiting) a bodily response, or with foreign entities (e.g., organisms or chemicals) so as to alter that entity's interaction with the body.").

237. *Id*. at n.12.

238. *See generally* Raj Bawa et al., *Nanopharmaceuticals: Patenting Issues and FDA Regulatory Challenges*, 5 A.B.A. SCITECH LAW, no. 2, 2008, at 2–3 (describing the FDA's regulatory framework for nanopharmaceuticals)..

239. Van der Waals forces are electrical interactions that provide the adhesive force that holds complex mixtures (like the human body) together. All molecules have a given distribution of positive and negative charge across the

interactions and non-covalent bonding[240] while stretching and separating tangled biopolymers to divide tissue.[241] Consider a very tiny scalpel: Is there a point at which the scalpel is so small that it becomes a drug? Should it matter whether someone is controlling the scalpel or whether the scalpel is adapted for a specific type of tissue or biopolymer? Existing explanations of chemical action have trouble distinguishing between drugs and devices when both products can be said to interact with the body via the same type of chemical interactions.[242]

These are the types of interactions one would expect in Complex Products like low-weight heparins and carbohydrate complexes. For example, pentosan polysulfate sodium is a low-weight "heparin-like macromolecular carbohydrate derivative" indicated for relief of interstitial cystitis.[243] It is classified by the FDA as a drug.[244] While its structure and mechanism are not fully known, the drug is thought to collect on the bladder wall and adhere to mucosa, thus serving as a protective coating.[245] Here, the therapeutic effect of the drug is unlikely to involve any chemical changes of the article itself. Instead, the drug likely interacts with the body by way of non-specific electrostatic and non-covalent intermolecular interactions. These are the same chemical interactions that govern most macroscopic interactions, such as the adhesiveness of a bandage, the lubricating and cushioning effect of an ointment, the ability of soap to dislodge filth, and the cohesive integrity of artificial

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electron cloud that constitutes the molecule's structure, but the presence of other molecules nearby shifts this charge distribution. Naturally, some parts of one molecule will tend toward positive, while parts of another will tend toward negative. Van der Waals forces can be thought of as the result of these attractive interactions.

240. Non-covalent bonding includes hydrogen bonding, which mediates many solvent-based effects and protein folding.

241. *See generally* J.G. Williams et al., *Fundamentals of Cutting*, 6 INTERFACE FOCUS 1 (2016) (discussing the mechanics of cutting), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4843621/pdf/rsfs20150108.pdf.

242. For example, interacting with the body via non-bonding Van der Waals interactions and generalized non-covalent intermolecular binding.

243. *Elmiron*, U.S. FOOD AND DRUG AMIN., https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020193s009lbl.pdf (last accessed Apr. 17, 2020).

244. *See* U.S. FOOD & DRUG ADMIN., LIST OF OFF-PATENT, OFF-EXCLUSIVITY DRUGS WITHOUT AN APPROVED GENERIC (2019), https://www.fda.gov/media/133524/download (listing pentosan polysulfate sodium as a drug).

245. *See* Elmiron, *supra* note 238.

skin.[246] The fields of statistical mechanics and material science provide models relating how macroscopic activity relates to chemical activity.[247] A detailed enough inquiry of any given therapeutic effect should virtually always uncover some type of chemical action.[248]

Lastly, even if a consistent rationale can be provided to delineate between drugs and devices based on chemical action, there is a problem that such a rationale may not ultimately line up with Congress's primary purpose for such a distinction. Any valid interpretation of Congress's purpose should reflect a non-arbitrary policy goal.

iii. The Problem with the Sameness Requirement for Drugs.

Classification as a drug, rather than as a device or biologic, results in enormous consequences for later follow-on development of competitor products. For drugs, the path for follow-on approval, an ANDA, is achieved by developing a generic having the same active ingredient, route of administration, dosage form, and strength as a previously approved reference product, and showing bioequivalence of the same. That is, the pathway for follow-on drugs requires sameness, and thus is far narrower than the pathway for biosimilars and 510(k) devices.[249] This sameness requirement arose during an era when most drugs were based on small molecules that could be evaluated based on bioavailability and

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246. *See* Benjamin E. Russ, *What Exactly Is the Physical or Chemical Process that Makes Adhesive Tape Sticky?*, SCI. AM. (July 14, 1997), https://www.scientificamerican.com/article/what-exactly-is-the-physi/ (explaining "[w]hen two materials are brought into contact with each other, the surface molecules interact, giving rise to attractive forces that may be physical, chemical, or electrostatic").

247. *See* HARVEY GOULD & JAN TOBOCHNIK, STATISTICAL AND THERMAL PHYSICS WITH COMPUTER APPLICATIONS 2 (2010) (characterizing statistical mechanics as "a bridge between the microscopic and macroscopic worlds").

248. On the other hand, one rigorous philosophical inquiry has suggested that the presence of chemical action is not enough if it is sufficiently linked causally, too remote from the site of treatment, or not grounded in the article itself. *See* Koolage & Hall, *supra* note 97 (exploring challenges related to defining chemical action, including the questions of where in the causal chain the chemical action occurs, and how removed the chemical can be from the site of therapeutic action).

249. *See* U.S. FOOD & DRUG ADMIN, ABBREVIATED APPROVAL PATHWAYS FOR DRUG PRODUCT: 505(B)(2) OR ANDA? (2019), https://www.fda.gov/media/130898/download (explaining how "active ingredient sameness" is evaluated).

which had a readily characterizable and reproducible active ingredient. Today, many drugs involve complex structures, for which demonstrating sameness may not be feasible.[250] Bioequivalence is also problematic for complex products, which may involve unconventional methods of conveying the drug to the site of action, for instance, drugs involving nanotechnology-based carriers or device-controlled delivery.[251] Lack of an alternative drug pathway based on "similarity" rather than "sameness" gives competitors fewer options for developing a competing complex drug product.

Complex drug products thus present three barriers likely to increase prices and reduce competition: (1) high costs to develop and approve pioneer product; (2) technological challenges to producing follow-on competition; and (3) regulatory restrictions to follow-on competition. Table 5 illustrates the consequences that converge when Complex Products are classified as drugs.

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250. For example, NBCDs might not contain a single, discrete active ingredient, or it may not be feasible to show bioequivalence. *See Food Drug Cosmetic Law Reports Letter No.* 2570, Food Drug Cosm. L. Rep. 839392 (C.C.H.), 2018 WL 839392, at 8–9.

251. *See* JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, FOOD AND DRUG ADMINISTRATION §13:131 (4th ed. 2019) (describing the "challenges of reviewing generic versions of nonbiological complex drugs"); *see also In re* Restasis (Cyclosporine Ophthalmic Emulsion) Antitrust Litig., 352 F. Supp. 3d 207 (E.D.N.Y. 2019) (deciding a motion to compel discovery on documents related to a suit brought by buyers of a dry-eye medication); Exhibit 13, *In re* Restasis, 352 F. Supp. 3d 207 (E.D.N.Y. 2019) (No. 1:18-md-02819-NG-LB) (describing how non-biological complex drugs, such as RESTASIS, require thorough analysis to evaluate bioequivalence).

Table 5. Consequences of Classification on Example Medical Products

Medical Product	**Classification**	**Cost to Get Approval**	**Does Current Technology Permit Follow-On Competition Based on Readily-Validated, Measurable Physical Properties?**	**Does the Current Legal Regime Permit Follow-On Competition Based on Similar Properties?**
An artificial hip implant.	Device	Low	Yes	Yes
Small Molecule Drug	Drug	High	Yes	No
A recombinant human granulocyte colony stimulating factor.	Biologic	High	No	Yes
A complex mixture of non-biological materials that self-assemble into a variety of structural forms having features on the nanoscale. . .	Example of a complex product. The burden of approval and barriers to competition depend on classification.			
. . . primarily for serving a mechanical purpose in the human body.	Device	Low	No	Yes

. . . primarily for measuring or identifying a condition of the human body.	Drug	High	No. Complex products classified as drugs suffer from both technological and legal barriers to follow on competition.
. . . primarily for acting as a depot for extended release of drugs.	Drug	High	
. . . primarily for inducing immune activity.	Drug	High	

iv. Technological Challenges of Complex Products.

Technological challenges, not regulatory issues, likely represent the greatest barrier to Complex Product competition. For Complex Products, it can be incredibly challenging to scientifically prove "sameness" or other types of equivalence, when structure and function are not yet fully understood. Typically, those who try to bring follow-on Complex Products to market must do substantial additional research and development, particularly with respect to structure-function validation, and sometimes involving additional clinical trials.[252] Even though an innovator may have obtained approval for a complex new product, it is another thing entirely for a competitor to learn how the product's structure, manufacture, and function interrelate, and then produce it and obtain FDA approval. Follow-on competitors must conduct further research prior to seeking approval to address these concerns.[253] This

252. *See* C. Lee Ventola, *Biosimilars: Part: Proposed Regulatory Criteria for FDA Approval*, 38 PHARMACY & THERAPEUTICS 270, 270 (2013) (explaining that "[t]he structure–function relationships of biologics are very sensitive").

253. For example, Complex Products may involve nuances to structural aspects or sensitive manufacturing relationships that influence therapeutic properties. An attempted copy of a Complex Product may appear to have all the same recognizable and obvious features, but overlooked or indecipherable nuances may be essential to achieving the desired therapeutic effect. *See* Luke,

research burden represents a significant "technological" barrier to follow-on competition.

Secondly, there is a problem that such research efforts are redundant. Prior to obtaining approval of a Complex Product, the innovator likely dedicated significant resources into researching the structural, functional, and manufacturing tolerances of its product. This research may relate to deciphering which minute manufacturing aspects are acceptable and which are not, or it may relate to a way of characterizing structure that can be used to discern equivalent versus non-equivalent versions of the product. The results of this research are economically valuable but often not suitable for patent protection.[254] Accordingly, such information is typically kept as a trade secret.[255] Clinical data generated by the innovator and shared with the FDA will ultimately be made available after approval of its product, but usable only after any period of data exclusivity

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supra note 1 (describing the regulatory process for pre-ANDA Complex Generic Products); *see also* Jiang, *supra* note 1 (describing the considerations involved in analyzing complex generic drugs); *see also* U.S. FOOD & DRUG ADMIN. OFFICE OF GENERIC DRUGS, 2019 ANNUAL REPORT: ENSURING ACCESS TO SAFE, AFFORDABLE, AND EFFECTIVE GENERIC DRUGS (2019), https://www.fda.gov/media/135329/download (providing an overview of the generic drug state of affairs); *see also* FED. DRUG ADMIN., GENERIC DRUG USER FEE AMENDMENTS (GDUFA) SCIENCE AND RESEARCH PRIORITY INITIATIVES FOR FISCAL YEAR 2020 (2020), https://www.fda.gov/media/132370/download (listing FDA's priority initiative regarding the acceleration of access to generic drug products); *see also* Vinod Shah, *Non-Biological Complex Drugs: Challenges for Approval Standards and Opportunities!*, NON-BIOLOGICAL COMPLEX DRUGS (NBCD) WORKING GROUP (Apr. 22, 2019), https://www.fda.gov/media/125176/download (discussing challenges for approval standards of NBCDs).

254. *See infra* Section II(B)(ii). For example, it may be vulnerable to attack on obviousness or anticipation grounds over the innovator's own pre-clinical disclosures. Such information is often developed late in the development process while conducting detailed investigations of scale-up manufacturing and validation. Sometimes even if a patent were obtained based on the new information, it may be vulnerable to work around or difficult to enforce. In other cases, the information relates to similar products, but not the approved product, so any resulting patent would not sufficiently protect the innovator's own product.

255. *See* Kristan Lansbery, Protecting Trade Secrets in the Medical Approval Process, https://www.fdli.org/2018/04/update-protecting-trade-secrets-medical-product-approval-process/ (last accessed August 15, 2020) (discussing the value of maintaining trade secrets of medical products during FDA approval).

expires.[256] In contrast, the information kept as a trade secret might never be shared.

When competitors subsequently pursue follow-on products, they must independently and redundantly develop an understanding of the structural, functional, and manufacturing tolerances of the product in order to reproduce a product with the requisite sameness or therapeutic equivalence. These development efforts must be underway well before any earlier research will be publicly disclosed, in order to obtain generic approval at the earliest opportunity. Moreover, each competitor will likely keep their own results secret from each other, thus resulting in further redundant efforts.

B. PROPOSED SOLUTION—RETHINKING CHEMICAL-BASED STATUTORY LANGUAGE AND TECHNOLOGICAL BARRIERS TO COMPETITION

Rethinking the chemistry-based requirements of 21 U.S. Code § 321(h)(3) and 21 U.S.C. §355(j) will better align regulatory burdens and incentives, reduce regulatory uncertainty, and provide more appropriate pathways for Complex Product competition. One possible resolution is incentivizing disclosure of pro-competitive information in exchange for a period of exclusivity.

First, a clearer definition of Complex Products is needed. This Note suggests the following definition, which is couched in terms of the technological uncertainty related to establishing equivalence:

A Complex Product is a drug, device, biologic, or combination product for which the critical qualities necessary for determining equivalency of relevant follow-on products are not predictably ascertainable using publicly known technology.

For example, Complex Products can include products that exhibit: *structural complexity* in which the structural aspects that influence safety or efficacy cannot be predictably ascertained, characterized, or controlled using publicly known technology; *functional complexity* in which the functional properties, including physiologic properties, that influence safety or efficacy cannot be predictably ascertained, modeled, or controlled using publicly known technology; and *operational*

256. Such data exclusivity periods are statutorily prescribed and provide an essential window for innovator profitability that delays generic entry.

complexity in which the use or operation of the product influences safety or efficacy in a manner which cannot be predictably ascertained, modeled, or controlled using publicly known technology.

i. Redefining Chemical Action As Biochemical Action

The chemical action clause should be interpreted to provide a non-arbitrary result, even in borderline cases. A proper definition of "chemical action" should result in a delineation between drugs and devices that reflects a meaningful legislative goal, not simply an attempt to square Congress's word choice with current scientific understanding. In 1970, President Richard Nixon established the Cooper Committee to report on the need for medical device legislation, noting that devices present different issues than drugs.[257] When Congress passed the Medical Device Amendments of 1976, it specifically introduced a new risk-based approach to the FDA's premarket review.[258] Devices were considered to pose different risks based on recognizing how much control an operator had over the therapeutic effect and any risk of harm.[259] Indeed, the device regulatory scheme is organized around general and special controls providing a reasonable assurance of safety and efficacy. In contrast, new drugs were considered to always require rigorous premarket approval and clinical evaluation. When Congress passed the Medical Device Amendments of 1976, it introduced its risk-based approach to devices only, establishing that devices would be treated differently than drugs and that chemical action would distinguish devices from drugs.[260] The

257. *See A History of Medical Device Regulation & Oversight in the United States*, U.S. FOOD & DRUG ADMIN. (June 24, 2019), https://www.fda.gov/medical-devices/overview-device-regulation/history-medical-device-regulation-oversight-united-states (noting that the committee "[r]ecommended that any new legislation be specifically targeted to the devices because devices present different issues than drugs").

258. *See id.* (noting that the act "[c]reated a three-class, risk-based classification system for all medical devices").

259. *See Regulatory Controls*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (last updated Mar. 27, 2018) ("Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness.").

260. *See id.* (describing intent of amendments as to "provide reasonable assurance of the safety and effectiveness"); *See also* 21 U.S.C. §201(h) (defining a "device").

FDA has since interpreted "chemical action" based on a purely scientific, but overly literal, definition.[261] This leads to results that can be arbitrary, based on scientifically dated semantics, rather than based on risk to patients.

A different statutory interpretation of chemical action would permit the FDA more flexibility to avoid arbitrary classification of drugs and devices. First, "chemical action within or on the body of man or . . . dependent upon being metabolized . . . "[262] should be interpreted as referring to the chemical processes that provide for the complex functioning of the body, i.e., biochemistry. Second, the statutory requirement that a device does not "achieve its intended purposes through chemical action,"[263] reflects that chemical action is an intrinsic quality of the article itself, and that there is a distinction between therapeutic results that arise as a result of this intrinsic quality, rather than by other means. Moreover, it should be clear that Congress intended the chemical action distinction to be consequence driven.

The following two-step inquiry, based on the above-suggested interpretation of chemical action, should be used to determine if a product can be a device:

1) Is the primary intended purpose achieved due to (a) extrinsic control over the article by a human or (b) intrinsic features of the article? If (a), the product can be a device. If (b), continue to step 2.

2) If step 1 is (b), are the intrinsic features of the article expected to modulate or participate in any specific biochemical or metabolic functioning of the human or animal? If not, then the product can be a device.

One benefit of this interpretation is that it ties classification to expected risk of biological consequences that cannot be predictably controlled. This two-step inquiry narrows the concept of "chemical action" to focus specifically on the type of chemical action occurring in humans and animals, and thus avoids an interpretation that could apply to virtually all medical products. The intrinsic versus extrinsic distinction serves to identify the therapeutic function that derives from the product

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261. *See* U.S. FOOD & DRUG ADMIN., *supra* note 88 at 7 (2017) (expounding on the definition of "chemical action").

262. 21 U.S.C. §201(h) (2011) (defining a "device").

263. *Id.*

itself, e.g., a chemical structure, rather than deriving the therapeutic function from the skill of a user.[264] Another benefit is that this interpretation satisfactorily provides a means to classify Complex Products and other borderline cases in a manner that is non-arbitrary and based on expected consequences in patients.

ii. Applying a Standard Beyond Sameness

The sameness requirement for drug follow-on products is overly limiting: some products that are classified as drugs have greater tolerance to structural variation than did traditional small-molecule drugs.[265] There should be alternative approval paths for follow-on drugs when the FDA expects that such products would likely be safe and effective despite being merely "similar" or "substantially equivalent" to the reference product.

The follow-on drug pathway should be updated to incorporate the "similar" pathway from biologics and the 510(k) pathway from devices. This change could be implemented by qualifying each new approved product according to its tolerance to structural variation and risk. For example, an approved drug that has different therapeutic properties when the structure is altered should be limited to a sameness-type (ANDA) path. For approved drugs that demonstrate that minor variations can result in the same therapeutic effects, a similar-type (biosimilars) path would be suitable. For approved drugs where significant variations could be possible without effecting therapeutic effects, for instance, surfactant-based products or

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264. An alternative analysis focused on locality, singularity, and causality, which are loosely analogous to the therapeutic effect deriving from intrinsic properties of the article. *See* Koolage & Hall, *supra* note 94.

265. When the Hatch-Waxman Act was enacted, drugs were primarily based on small molecule compounds. Such compounds typically had very narrow tolerance for structural variation—even replacing a single atom or functional group risked unexpected properties. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, at 190 (1999) ("One major assumption underlying the Hatch-Waxman Act was that duplicates of pioneer drugs would be the same as the innovator's drug.") *See also Is Biosimilar Insulin Available?*, BIOSIMILARS RESOURCE CTR., https://www.biosimilarsresourcecenter.org/faq/biosimilar-insulin-available/ (explaining that, for historical reasons, insulin is regulated as a drug and so biosimilar competition is not legally permitted, while at the same time generic competition is not technologically feasible since insulin is not a small molecule drug for which exact structural duplicates can be made by a follow-on competitor).

pH neutralization products, then a 510(k)-type pathway would be suitable for follow-on competition.

Table 6. Summary of Different Rationales for Permitting Follow-On Product Entry.

Sameness-type	**Similar-type**	**510(k)-type**
Minor variations in chemical structure of an active ingredient are not permitted because minor variations would be expected to provide different therapeutic effects.	Minor variations in chemical structure may be permitted where the product is expected to produce the same clinical result.	Significant variations in chemical structures may be permitted where such variations would not be expected to reduce the safety or functioning of the device.

The benefits of this approach are that it would permit additional paths for follow-on competition of drugs and conform the regulatory framework for follow-on products across classes. This also permits the FDA additional flexibility to determine the appropriate, science-based restrictions on follow-on products.

iii. Incentivize Early Disclosure of Pro-Competitive Information

Significant research is required to determine how to separately produce Complex Products that are therapeutically equivalent to a reference product. When a competitor pursues approval of a generic or similar, there is a question regarding precisely how identical or similar the Complex Product must be in order to be therapeutically equivalent.[266] Each competitor must independently and redundantly solve this problem to the FDA's satisfaction before it will receive approval.[267] However, similar problem-solving efforts occur during an innovator's pioneer development efforts. For example, the innovator may

266. *See* Jiang, *supra* note 1, at 25 (posing the question "[h]ow similar is equivalent?").

267. *See* Shah, *supra* note 1, at 4 (explaining that non-biological complex drugs "cannot be fully characterized by physicochemical analytical means" and stating that "[a] well-controlled robust manufacturing process is fundamental to ensure quality, safety and efficacy").

discover during product optimization that certain variations in structure (such as variation in particle sizes, crystal shapes, glycosylation patterns, or polymer-chain distribution) might cause the product to fail while other changes result in an equivalently functioning product. During manufacturing scale-up, the innovator may discover nuanced manufacturing details (such as the importance of a steel tanks, a delay between process steps, or the order excipients are added), which might influence therapeutic functioning but for which no structural difference can be determined. During clinical trials, the innovator might discover that the way the product is used is influenced by seemingly trivial features (such as the color or shape of an inhaler influencing how deeply a patient breaths). These types of findings can identify critical quality attributes that are relevant to obtaining a conforming pioneer product, or they can be relevant to understanding which minor variations will be therapeutically equivalent. Fortunately, such discoveries naturally arise as a normal part of preparing a pioneer new drug for FDA approval, e.g., when studying characterization, batch conformation, method validation, and product specifications. Yet, the innovator has every reason to keep such insights as confidential trade secrets and no incentive to disclose them to the public—especially if a patent is unavailable because the innovator's prior disclosed product inherently embodied the same parameters. As a result, competitors must redundantly labor to uncover know-how that was likely previously ascertained by the innovator.[268] This represents a redundant, cumulative waste of resources that contributes to the high cost of health care.[269]

Redundant and costly development efforts can be eliminated by incentivizing early disclosure of critical quality attributes for

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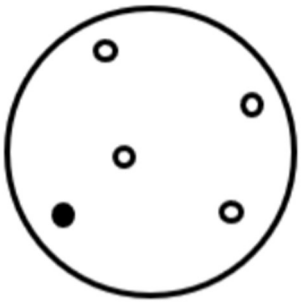
268. *See* U.S. FOOD & DRUG ADMIN., *supra* note 60 at 5 ("Liposome drug products are sensitive to changes in the manufacturing conditions . . . . Appropriate process controls should be established during product development. Prior knowledge can be leveraged and risk assessment techniques can be used to identify manufacturing process parameters that potentially affect finished product quality.").

269. *See* Scott Gottlieb, M.D., *Reducing the Hurdles for Complex Generic Drug Development*, U.S. FOOD & DRUG ADMIN. (Oct. 2, 2017), https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/reducing-hurdles-complex-generic-drug-development ("While the FDA doesn't control drug pricing, our policies do affect competition in the market. This is the nexus of our current efforts on drug pricing.").

therapeutic equivalence. The patent system is the primary governmental tool for incentivizing disclosure of new and useful technological progress.[270] Yet, present patent doctrine will not reward a party that discloses additional information about key qualities of a previously used or disclosed product, even if those qualities were never appreciated or are critically important for the development of a competitive equivalent product. Several aspects of patent doctrine prevent innovators from patenting subsequent discoveries about features of earlier inventions, and yet the doctrine also lends little support to competitors seeking to make therapeutic equivalents of an innovator's product. These aspects of the doctrine include: (1) a prior disclosure of a species anticipates a subsequent broader, encompassing genus; (2) an invention is anticipated if a prior disclosure invention inherently had the same features, even if not appreciated; (3) there is no requirement that a patent disclosure should enable quick, low-cost copying; and (4) there is no requirement that a patent disclosure identifies features critical for meeting FDA's bioequivalence requirements.

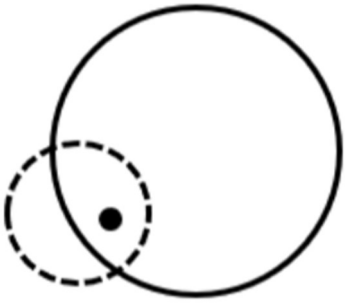


Scheme 1

A patent, with its many embodiments, can be represented as illustrated in Scheme 1. The outer perimeter represents the scope of the broadest disclosure. The block dot represents a lead product, submitted to the FDA pending approval. Other

270. Rebecca S. Eisenberg, *The Shifting Functional Balance of Patents and Drug Regulation*, 19 HEALTH AFF. 119, 123 (2001) ("It is awkward to meet such [pharmaceutical] industry-specific needs for exclusivity through provisions of a unitary patent system designed to provide innovation incentives for all industries.").

products also fall within the scope of the patent's claims. These other products, represented by white dots, might have equivalent, or different, functioning compared to the clinical candidate. The written description and enablement requirements under 35 U.S.C. §112 require that patents clearly define the claim scope and describe how to "enable" others to make and use the claimed invention, even if doing so would be time-consuming, expensive, and involve reasonable experimentation.[271] There is no requirement that enablement describe how to make an exact copy of the product that FDA ultimately approves, or even how to make a therapeutically equivalent product. Moreover, nothing in the patent doctrine requires an innovator to identify which of its embodiments are equivalent to the others, or how exactly a competitor should optimize manufacturing to achieve matching therapeutic equivalence.



Scheme 2

Scheme 2 illustrates how the scope of a patent disclosure differs from the scope of possible therapeutic equivalents of a lead product. Here, the scope of therapeutic equivalents would be defined by FDA's requirements for follow-on products, e.g., under 505(j), 510(k), or BPCI Act. The solid circle represents patent scope, while the dashed circle represents product space containing suitable variant products that are equivalent to the lead product. For Complex Products, determining the metes and

271. *See* 35 U.S.C §112 (2012); *see also* U.S. PAT. & TRADEMARK OFF., MANUAL OF PATENT EXAMINING PROCEDURE §2164 (2018), https://www.uspto.gov/web/offices/pac/mpep/s2164.html [hereinafter MPEP]; *see also In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

bounds of what exactly is therapeutically equivalent, can be far more challenging than for conventional products. Developing any follow-on product involves the challenges and costs of identifying what attributes of the pioneer product affect equivalence, and how to measure, make, and control those attributes. For Complex Products, this technology and know-how is either not within the reach of current science, or is not publicly known.

After filing a patent and beginning clinical trials, an innovator typically develops technology that identifies critical quality attributes that can distinguish between equivalent a non-equivalent variations of their product, i.e., that can define the scope of FDA approvable therapeutic equivalents. For example, the innovator would have investigated a wide variety of structural and functional variants prior to selecting the final lead product for clinical testing. Moreover, manufacturing modifications likely lead to development of critical validation and characterization methods that are useful for predicting which batches and similar variants will have therapeutic properties.

However, the innovator cannot necessarily obtain a patent claiming a product defined by these critical quality attributes. Such claims would be inherently anticipated—and thus unpatentable—over an earlier, pre-clinical disclosure of the lead product assuming the product had previously exhibited those same attributes. Although the innovator is typically first to bear the costs of identifying critical quality attributes associated with therapeutic equivalence, the innovator has no incentive to disclosure these critical attributes without the ability to obtain a patent. These costs are then redundantly borne out by each competitor who, in turn, have no incentive to disclose their insights. Redundant development efforts would be eliminated if the innovator had an incentive to disclose how much variation in structure, formulation, and manufacture is permissible, as well as the corresponding validation and characterization methods that identify equivalent variants.

A statutory mechanism should be created that rewards innovators with an extended period of exclusivity on their new Complex Product in exchange for disclosing information that enables others to predictably manufacture, identify, and obtain approval for an ANDA-type or similar-type therapeutic

equivalent.[272] The period of extended exclusivity would be conditioned on the sufficiency of the disclosure. A sufficiently strong incentive may encourage the innovator to go beyond what is needed for approval of its lead product, and to further seek formal confirmation from the FDA that certain similars would indeed be approvable. The integrity of the system could be assured by permitting competitors to litigate over the sufficiency of the disclosure.

This disclosure could take the form of a patent application submitted to the USPTO, or it could take the form of a public disclosure submitted to the FDA. In the form of a patent, the patent would recite claims to "an FDA-validated therapeutic equivalent" of the innovator's lead product and providing critical quality attributes that are sufficient for obtaining an approvable equivalent.[273] The FDA could facilitate such disclosures by cooperating with the innovator to establish critical quality attributes, and even indicate to innovators when suitable variations of their lead product would be approvable as well. Although permitting such patents could significantly extend patent exclusivity on branded compositions, the accompanying disclosure would contain enough data and know-how that any number of competitors could readily produce an approvable follow-on at minimal cost. If the disclosure is not adequate, the patent will be quickly disposed of. In the form of a disclosure to the FDA, the FDA could review it for sufficiency and then make it public in exchange for providing the innovator with a period of regulatory exclusivity or patent term extension.[274]

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272. This statutory mechanism could take the form of a patent, a patent term extension, or regulatory exclusivity.

273. If the incentive takes this form, there may need to be a rule to exempt this claim format from inherency-type anticipation over prior disclosures of products having the same structure, but not used as a therapeutic equivalent and lacking an equivalency label. *See* 35 U.S.C §102 (2000); *see also* MPEP §§ 2112 & 2131, https://www.uspto.gov/web/offices/pac/mpep/s2112.html. Enablement should require a showing of the FDA's indication of approvability, in contrast with the conventional standard of *In re* Brana since, here, the proposed claims expressly invoke FDA action. *Cf. In re* Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995) ("FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws."). Additionally, the patent should include an accompanying disclosure sufficient for those of ordinary skill in the art to manufacture and obtain FDA approval of the claimed products.

274. *See* 35 U.S.C. §156 (2012) (outlining requirements for an extension of patent term).

The benefit of this proposed system is that redundant development efforts would be eliminated, and valuable information is made public. Dissemination of this information will benefit the pharmaceutical industry as a whole and advance technological understanding of challenging areas like Complex Products and medical nanotechnology. Although the cost of brand drugs may enjoy a longer period of monopoly pricing, the system would reduce overall costs to drug development, and ultimately enable a greater number of competitors to enter the market at once.

CONCLUSION

Complex Products involve regulatory and technological barriers to competitor entry. Specifically, the "chemical action" distinction of 21 U.S. Code § 321(h)(3) introduces uncertainty into the regulatory process and can lead to arbitrary distinction between FDA regulatory schemes. The "sameness" requirement of 21 U.S.C. §355(j) limits follow-on drug competition to generic-type products that are bioequivalent and have the same active ingredient, route of administration, dosage form, and strength as a previously-approved reference product. This limitation is especially restrictive for Complex Products, for which showing bioequivalence of the "same" active ingredient may not be feasible. Lastly, because Complex Products involves technology that is not yet fully understood, competitors have the burden of identifying how structural aspects, manufacture, and therapeutic properties interrelate. This technology and know-how is redundantly developed by the initial innovator and subsequent competitors, each of which presently have every incentive to keep the information confidential from the others. This Note suggests rethinking the chemistry-based requirements written into the FD&C Act and further proposes a new incentive to innovators to disclose data, tolerances, and know-how that will lower overall costs for development in the industry and improve scientific understanding of Complex Products.