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# Artificial Intelligence in Pharmaceuticals, Biologics, and Medical Devices: Present and Future Regulatory Models

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# ARTIFICIAL INTELLIGENCE IN PHARMACEUTICALS, BIOLOGICS, AND MEDICAL DEVICES: PRESENT AND FUTURE REGULATORY MODELS

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## INTRODUCTION

Artificial intelligence (AI) and AI-assisted technologies are set to transform the pharmaceutical, biologic, and medical device industries. AI is accelerating a convergence in the pharmaceutical and medical device industries and, in the health-care industry more broadly, is similar to the convergence of the media, entertainment, and communications industries.[1] For media and communications, AI-fueled convergence might mean new video entertainment generated on the fly or sophisticated, analytical, autonomous versions of the AI-generated auto-replies that have started to show up in our email and text apps over the past year, reducing the drudgery of clearing an inbox.[2] For health care, big datasets and complex algorithms will integrate the development and delivery of small- and large-molecule drugs, genetic therapies, and medical devices tailored to specific user profiles and even to individual consumers, with dynamic, real-time updates and adjustments.[3] The lines between software code, device, and drug will blur, and new regulatory models will be required. As a recent "Global Life

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1. For a discussion of convergence, see Henry Jenkins, *Convergence?: I Diverge.*, MIT TECH. REV. (June 1, 2001), https://www.technologyreview.com/s/401042/convergence-i-diverge/ [https://perma.cc/UU37-D5RQ].

2. *See, e.g.*, Christy Roland, *The Convergence of Convergence: Examples of Digital, Media, Video, Technology and Industry Converging in the 21st Century*, AT&T SHAPE (Nov. 20, 2018), https://shape.att.com/blog/examples-of-convergence [https://perma.cc/5HB4-SN56].

3. *See, e.g.*, Nic Fleming, *Computer-Calculated Compounds*, 557 NATURE S55, S55–S57 (2018); Denise Myshko & Robin Robinson, *Artificial Intelligence: Molecule to Market*, PHARMAVOICE (Jan. 2019), https://www.pharmavoice.com/article/2019-01-pharma-ai/ [https://perma.cc/TE29-26M3].

Sciences Outlook" report by the consultancy Deloitte states, "[t]he physical, digital, and biological worlds converge in Industry 4.0."[4]

The U.S. Food and Drug Administration (FDA) has begun to address some of the opportunities and challenges that AI presents for drug, biologic, and medical device regulation. This is particularly true for medical devices and for certain kinds of virtual patient models. In the short term, the FDA should pay more attention to protocols for AI-assisted drug and biologic trials and to privacy and cybersecurity in medical devices. In the longer term, AI could dramatically lower development costs and transform the blockbuster patent-driven model of drug development. At the same time, AI could shift control of drug, biologic, and device markets from the biopharmaceutical industry to Silicon Valley. Before this shift happens, U.S. and international policymaking bodies should consider how regulatory and intellectual property policy regarding AI and drugs, biologics, and devices could lead to a more equitable and sustainable future for global health.

Part I of this Essay surveys the current legal and economic framework for drugs, biologics, and medical devices in the United States, and discusses some ways in which AI might disrupt that framework. Part II examines currently emerging policies at the FDA for in silico trials—trials conducted by computer models, often involving AI technologies—and AI-enabled medical devices. Part II also discusses how AI might stretch those policies over the next ten to twenty years and takes a speculative look at AI-enabled drugs and devices in the year 2050. Part III concludes.

## I. THE CURRENT LEGAL AND ECONOMIC FRAMEWORK FOR PHARMACEUTICAL PRODUCTS AND MEDICAL DEVICES IN THE UNITED STATES

Pharmaceutical drugs, medical devices, and biologic products are essential to both public health and big business.[5] There are different regulatory pathways for drugs, biologics, and devices in the United States. The Federal Food, Drug, and Cosmetic Act[6] ("FD & C Act") governs the sale of prescription drugs through the FDA.[7] Under the FD & C Act, the FDA is also responsible for regulating biologics and medical devices.[8] The economics of drugs, biologics, and devices differ in important ways. The economics of drug and device markets also differ significantly, in no small part because of these regulatory differences.

4. DELOITTE, 2019 GLOBAL LIFE SCIENCES OUTLOOK 23 (2019), https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-ls-outlook-2019.pdf [https://perma.cc/CR38-EE5P].

5. The Pharmaceutical Research Manufacturer's Association claims that biopharmaceutical companies invest $90 billion in research and development and support 4.7 million jobs in the United States. *2018 Profile: Biopharmaceutical Research Industry*, PHRMA 1, http://phrma-docs.phrma.org/industryprofile/2018/pdfs/2018_IndustryProfile_Brochure.pdf [https://perma.cc/J988-958F] (last visited Oct. 6, 2019).

6. Ch. 675, 52 Stat. 1040 (1938) (codified as amended in scattered sections of 21 U.S.C.).

7. 21 U.S.C. §§ 351–60 (2012).

8. *Id.*

### *A. Pharmaceutical Drug Regulation*

Before the FDA authorizes a new drug for sale, the manufacturer must demonstrate that the drug is safe and effective for its proposed uses and that its benefits outweigh its risks.[9] The manufacturer must also show that the product will be accompanied by appropriate labeling, including any required warnings, and that the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.[10] This information must be presented to the FDA's Center for Drug Evaluation and Research in a "New Drug Application" (NDA).[11]

#### 1. Discovery, Development, and Preclinical Research

The drug development process begins with a "discovery and development" phase, which involves basic research into public health issues, disease processes, new technologies, and new molecular compounds.[12] Promising drug candidates identified during the discovery and development phase move into a "preclinical research" phase.[13] In this phase, the drug candidate is tested "in vitro," in a test tube, and "in vivo," on living organisms other than humans.[14] The primary purpose of this phase is to obtain information about dosage and toxicity levels to determine whether the drug should be tested on humans.[15]

#### 2. Clinical Research

If the preclinical research phase suggests that a drug might be a good candidate for human trials, the next step is the clinical research phase. Before beginning clinical research, the drug developer or sponsor must submit an "Investigational New Drug Application" to the FDA.[16] This application must include animal study and toxicity data, manufacturing information, clinical protocols for proposed studies, data from any prior human research, and information about the investigator.[17]

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9. *Id.* § 355.
10. *Id.*
11. *See generally Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/office-medical-products-and-tobacco/center-drug-evaluation-and-research [https://perma.cc/96UZ-CMDU] (last updated Sept. 19, 2018).
12. *See Step 1: Discovery and Development*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-1-discovery-and-development [https://perma.cc/8NKN-9R7T] (last updated Jan. 4, 2018).
13. *See Step 2: Preclinical Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research [https://perma.cc/Y92S-6C2R] (last updated Jan. 4, 2018).
14. *Id.*
15. *Id.*
16. *Step 3: Clinical Research*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-3-clinical-research [https://perma.cc/3CJC-4LRQ] (last updated Jan. 4, 2018).
17. *Id.*

The clinical research phase includes three subphases of clinical trials plus a possible fourth postapproval phase. A drug candidate may fail at any of the first three phases. Phase 1 tests for safety and dosage, involves 20 to 100 healthy volunteers or people with the target disease or condition, and lasts for several months.[18] Approximately 70 percent of drug candidates pass this phase.[19] Phase 2 tests for efficacy and side effects, involves up to several hundred people with the disease or condition, and lasts up to two years.[20] Only 33 percent of drug candidates pass this phase.[21] Phase 3 tests for efficacy and adverse reactions, involves 300 to 3000 people who have the disease or condition, and lasts one to four years.[22]

If the drug developer believes the evidence from the clinical research phase shows the drug is safe and effective for its intended use, the developer can submit an NDA to the FDA.[23] The FDA review team must determine whether to approve the NDA within six to ten months of the filing.[24] If the FDA review team finds issues that must be addressed before approval, it may require further information or additional studies.[25] Approximately 80 percent of NDAs ultimately are approved by the FDA.[26] After marketing approval, the drug may proceed to Phase 4 clinical trials.[27] Phase 4 involves several thousand people who have the disease or condition and postmarket tests for safety and efficacy.[28] Altogether, it can cost up to $2.8 billion to bring a drug all the way through to FDA review.[29]

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18. *Id.*
19. *Id.*
20. *Id.*
21. *Id.*
22. *Id.*
23. *Step 4: FDA Drug Review*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review [https://perma.cc/6E8W-RPKY] (last updated Jan. 4, 2018).
24. *Id.*
25. *See id.*
26. *See* Rebecca Trager, *FDA New Drug Approvals More Than Doubled in 2017*, CHEMISTRY WORLD (Jan. 26, 2018), https://www.chemistryworld.com/news/fda-new-drug-approvals-more-than-doubled-in-2017/3008575.article [https://perma.cc/RWV4-EWJS].
27. In some cases, the FDA requires Phase 4 trials, but in other cases Phase 4 trials are voluntary. *See, e.g.*, Viraj Suvarna, *Phase IV of Drug Development*, 1 PERSP. CLINICAL RES. 57, 58 (2010).
28. *See id.* at 57.
29. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 27 (2016). Some other studies argue that this estimate is too high. *See, e.g.*, Nancy L. Yu et al., *R&D Costs for Pharmaceutical Companies Do Not Explain Elevated US Drug Prices*, HEALTH AFF. (Mar. 7, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170307.059036/full/ [https://perma.cc/8DEU-YR2L]. *But see* Henry Grabowski & Richard Manning, *Drug Prices and Medical Innovation: A Response to Yu, Helms, and Bach*, HEALTH AFF. (June 2, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170602.060369/full/ [https://perma.cc/X35K-QK93]; Donald W. Light, *Debunking the Pharmaceutical Research 'Free Rider' Myth: A Response to Yu, Helms, and Bach*, HEALTH AFF. (June 2, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170602.060376/full/ [https://perma.cc/D9DD-RVZF]; Nancy L. Yu & Peter Bach, *US Drug Prices and R&D, Take 2: A Reply to Grabowski and Manning, and to Light*, HEALTH AFF. (July 27, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170727.061220/full/ [https://perma.cc/ZDH7-XWMP].

The FDA has approved an average of forty-three new drugs per year since 2015.[30] The total of fifty-nine drugs approved by the FDA in 2018 was an all-time high.[31] Approval numbers have rebounded after a decade-long lull between 2001 and 2010, for a variety of macroeconomic and business reasons.[32]

### *B. Biologics and Gene Therapies*

The description above relates to traditional small-molecule pharmaceutical drugs, which still make up about 90 percent of all drugs on the market.[33] Such drugs are relatively simple chemical entities synthesized by chemical reactions.[34] They are usually processed into easily ingestible capsules or tablets and are absorbed directly into the bloodstream after ingestion.[35] In recent years, researchers increasingly have focused on large-molecule biologic products and on genomics.[36]

Large-molecule or "biologic" drugs are made of proteins, usually copied or modified from existing human proteins.[37] They are typically synthesized using genetically modified organisms such as bacteria or yeasts, or by cultivating human cell lines.[38] Proteins bind to cell receptors, which means they can be engineered to bind selectively to diseased cells, such as cancer cells.[39] They are taken by injection or infusion because they would be digested if taken orally, and the method of delivery often involves the use of antibodies or virus carriers.[40] Biologic drugs in the United States are subject to the same approval process as small-molecule drugs, but their complexity makes them even harder to develop and test for human use, which is one reason why they comprise such a small percentage of overall new drug approvals.[41]

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30. *See Novel Drug Approvals for 2019*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019 [https://perma.cc/WU83-DQVS] (last updated July 22, 2019).

31. *See* John LaMattina, *Can the Record Breaking Number of FDA New Drug Approvals Continue?*, FORBES (Jan. 9, 2019, 7:59 AM), https://www.forbes.com/sites/johnlamattina/2019/01/09/can-the-record-breaking-number-of-fda-new-drug-approvals-continue/ [https://perma.cc/SP48-JATY].

32. *Id.*

33. *See Small and Large Molecules*, BAYER PHARMACEUTICALS, http://pharma.bayer.com/en/innovation-partnering/technologies-and-trends/small-and-large-molecules/ [https://perma.cc/T6R7-3Q7B] (last visited Oct. 6, 2019).

34. *Id.*

35. *Id.*

36. *See id.*

37. *Id.*

38. *Id.*

39. *Id.*

40. *Id.*

41. *See How Do Drugs and Biologics Differ?*, BIOTECHNOLOGY INNOVATION ORG., https://www.bio.org/articles/how-do-drugs-and-biologics-differ [https://perma.cc/L7XF-V8TN] (last visited Oct. 6, 2019); *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-

Like small-molecule drugs, applied research in biologics is mostly conducted by private pharmaceutical and biotechnology firms that hope to achieve large returns secured by patents, but universities are also engaged in significant applied research.[42] The patent landscape for biologics is in flux and is perhaps more uncertain than for small-molecule drugs, although this uncertainty may suggest substantial opportunity for investment.[43]

Genetic therapies could involve repairing a mutated gene, "knocking out" a damaged gene, or "introducing a new gene into the body."[44] New gene-editing technologies such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are making gene editing cheaper, faster, and more precise.[45] Such technologies also are raising the possibility of germ-line genetic editing, that is, genetic editing of egg and sperm cells, to eliminate diseases in the future human population or select for certain traits or "improvements."[46]

Biologic drugs entail similar regulatory hurdles to small-molecule drugs: their effects must be modeled in the lab, in animals, and in humans before FDA approval.[47] However, there are important differences in the approval pathway for "biosimilar" products, those that might qualify for an abbreviated approval process because they are similar to an existing approved product.[48]

Genetic therapies are a subset of biologics. Such therapies could involve repairing a mutated gene, knocking out a damaged gene, or introducing a new

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research-cber/what-are-biologics-questions-and-answers [https://perma.cc/WBR7-E9KL] (last updated Feb. 6, 2018).

42. *See generally* Kevan M. A. Gartland & Jill S. Gartland, *Opportunities in Biotechnology*, 282 J. BIOTECHNOLOGY 38 (2018).

43. *See* CHRISTOPHER MCKENNA & STEVE ARLINGTON, CLARIVATE ANALYTICS, THE LIFE SCIENCES INNOVATION REPORT: A DATA-DRIVEN VIEW OF EMERGING R&D TRENDS 8–11 (2018), https://clarivate.com/wp-content/uploads/dlm_uploads/2018e/10/Life-Sciences-Innovation-2018.pdf [https://perma.cc/D9M2-4CLA]; Nicholas Jones & Alexander Bruce Dean, Editorial, *Current Patenting Trends for Biologics Versus Small Molecules*, 1 PHARMACEUTICAL PATENT ANALYST 225, 227 (2012); Adam Houldsworth, *University Domination of the Biologics Patent Landscape Points Way to Heightened Deal-Making in the Coming Years*, IAM (Jan. 17, 2019), https://www.iam-media.com/market-developments/university-domination-biologics-patent-landscape-points-way-heightened-deal [https://perma.cc/KVT6-AWYD].

44. *What Is Gene Therapy?*, GENETICS HOME REFERENCE (Sept. 10, 2019), https://ghr.nlm.nih.gov/primer/therapy/genetherapy [https://perma.cc/5NXX-CEXS].

45. *See What Are Genome Editing and CRISPR-Cas9?*, GENETICS HOME REFERENCE (Aug. 6, 2019), https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting [https://perma.cc/EG8V-8VWH].

46. *See What Are the Ethical Issues Surrounding Gene Therapy?*, GENETICS HOME REFERENCE (Aug. 6, 2019), https://ghr.nlm.nih.gov/primer/therapy/ethics [https://perma.cc/7U8E-VEAS].

47. *See Frequently Asked Questions About Therapeutic Biologic Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products [https://perma.cc/X9JE-AJJ3] (last updated July 7, 2015).

48. *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, 490–94 (2012).

gene into the body.[49] Some somatic cell gene therapies have been approved by the FDA.[50] The United States presently does not permit federal spending on human germ-line editing research.

Constructing trials for biologics and genetic therapies is even more complex than for small-molecule drugs. Because of their chemical complexity and the complexity of the enzymatic systems in which they function, the effects of introducing large-molecule biologics into the body are far less controllable and predictable than for small-molecule drugs.[51] Genetic therapies can be even less predictable, particularly if they affect the germ line.[52] Changes to the germ line could cause a cascade of genetic changes generations into the distant future.[53]

### *C. Medical Device Regulation*

The FDA's Center for Devices and Radiologic Health regulates medical devices and radiation-emitting products.[54] Medical devices are classified according to three classes corresponding to their level of risk.[55] The degree of regulation increases in each class.[56]

Class I devices are those that are considered reasonably safe and effective with only "general" controls or that are "not life-supporting or life-sustaining or for a use which is of substantial importance in preventing impairment of human health, and which does not present a potential unreasonable risk of illness of injury."[57] "General controls" include basic regulatory requirements relating to adulteration, misbranding, registration, banned devices, notification and other remedies, records and reports, and other general provisions of the FD & C Act.[58]

Class II devices are those that require "special controls," such as "the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents . . . , recommendations, and other appropriate actions as the Commissioner deems

49. *What Is Gene Therapy?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy [https://perma.cc/H8UG-VQLW] (last updated July 25, 2018).

50. *See generally* Ali Golchin & Tahereh Zarnoosheh Farahany, *Biological Products: Cellular Therapy and FDA Approved Products*, 15 STEM CELL REVIEWS & REP. 166 (2019); *Approved Cellular and Gene Therapy Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products [https://perma.cc/8A4D-HL37] (last updated Mar. 29, 2019).

51. *See How Do Drugs and Biologics Differ?*, *supra* note 41.

52. *See What Are the Ethical Issues Surrounding Gene Therapy?*, *supra* note 46.

53. *Id.*

54. *See Overview of Device Regulation*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/overview-device-regulation [https://perma.cc/PH9S-A6WD] (last updated Aug. 31, 2018).

55. *Id.*

56. *Id.*

57. 21 C.F.R. § 860.3(c)(1) (2019).

58. *Id.*

necessary" to provide reasonable assurance that the device is safe and effective.[59]

A device falls in Class III if it is "life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury" or is not substantially equivalent to a Class II device for which special controls are sufficient.[60] Class III devices require "premarket approval" (PMA) or "premarket notification" (PMN).[61] PMAs for Class III devices traditionally require clinical trials, but the 21st Century Cures Act[62] (the "Cures Act") permits the use of observational studies or clinical experience in some cases in lieu of clinical trials.[63]

A PMN, also called a 510(k) application, may be available if the applicant can demonstrate the device is substantially equivalent to an approved predicate Class I or Class II device and can be marketed with special controls.[64] Under section 510(k) of the FD & C Act and related regulations, device manufacturers must notify the FDA of their intent to market a medical device at least ninety days before marketing.[65] During this period, the FDA will determine whether the device is new or is substantially equivalent to an existing device.[66]

In 2017, the FDA published guidance for "De Novo Classification Requests" to classify new kinds of devices in Class I or II that would otherwise automatically fall into Class III.[67] The De Novo process is available for devices determined to be "not substantially equivalent" to existing devices because of "(1) the lack of an identifiable predicate device, (2) a new intended use, or (3) different technological characteristics that raise different questions of safety and effectiveness."[68] The applicant must demonstrate that the device appears, "based on what is known about the device, to meet the statutory standards for classification into class I or class

59. *Id.* § 860.3(c)(2).

60. *Id.* § 860.3(c)(3).

61. *Id.*

62. *See* Pub. L. No. 114-255, 130 Stat. 1033 (2016) (codified as amended in scattered sections of the U.S.C.).

63. *See id.* § 1002, 130 Stat. at 1042; Gail A. Van Norman, *Drugs, Devices and the FDA: Part 2*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 277, 279 (2016).

64. *Premarket Notification 510(k)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k [https://perma.cc/A8NS-RHUZ] (last updated Sept. 27, 2018). A very limited number of Class III devices also potentially can be approved under an abbreviated humanitarian device exemption. *See Humanitarian Device Exemption*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/premarket-submissions/humanitarian-device-exemption [https://perma.cc/T2NS-33SN] (last updated Mar. 27, 2018).

65. 21 C.F.R. § 807.81 (2019).

66. *Id.*; *510(k) Clearances*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/510k-clearances [https://perma.cc/332F-J53V] (last updated Sept. 4, 2018).

67. *See generally* FDA, DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III DESIGNATION): GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2017), https://www.fda.gov/media/72674/download [https://perma.cc/R6CQ-UVTN].

68. *Id.* at 4–6.

II."[69] The applicant must also "sufficiently understand and be able to explain . . . the probable risks to health and probable benefits of the device, explain the measures needed to effectively mitigate all probable risks, and explain how device safety and effectiveness can be assured through the application of general controls or general and special controls."[70]

A device may be reclassified from Class III to Class II, either by sponsor petition or FDA initiative, if available scientific evidence shows that general and special controls provide a reasonable assurance of the device's safety and efficacy.[71] This can be important for a number of reasons, including that the reclassified device can serve as a basis for a PMN. A manufacturer might obtain approval for a novel Class III device, have the device reclassified, and then obtain PMNs for incremental modifications, which establish a market position, usually supported by patents, around a core concept.[72]

### *D. Economic Effects of the Current Model*

Because of the expense, complexity, and time horizon of the clinical research phase, many approved drugs are either sponsored by large multinational pharmaceutical companies or acquired by such companies after initial development by smaller companies. The top twenty companies for total new drug and new therapeutic biologic product approvals from 2015 to 2018, for example, were as follows:

69. *Id.* at 6.

70. *Id.*

71. *See Reclassification*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/cdrh-transparency/reclassification [https://perma.cc/VW4J-6HTK] (last updated Feb. 14, 2019).

72. *See* Van Norman, *supra* note 63, at 278.

*Table 1*[73]

| Company | Number of Approvals | Publicly Traded | Market Capitalization in 2019 ($bn) |
|---|---|---|---|
| Pfizer Inc. | 9 | NYSE | 194.743 |
| Eli Lilly & Co. | 7 | NYSE | 103.985 |
| AstraZeneca PLC | 5 | NYSE | 112.238 |
| Alexion Pharmaceuticals, Inc. | 4 | Nasdaq | 21.481 |
| Amgen Inc. | 4 | Nasdaq | 116.58 |
| Array BioPharma | 4 | No[74] | — |
| Genentech | 4 | No | — |
| Gilead Sciences, Inc. | 4 | Nasdaq | 79.445 |
| Janssen Pharmaceuticals | 4 | No | — |
| AAA USA Inc. | 3 | No | — |
| AbbVie Inc. | 3 | NYSE | 107.336 |
| Allergan PLC | 3 | NYSE | 54.514 |
| Astellas Pharma Inc. | 3 | Tokyo Stock Exchange | 26.942 |
| GlaxoSmithKline PLC | 3 | NYSE | 104.912 |
| Novartis AG | 3 | NYSE | 196.594 |
| Shire Dev LLC | 3 | No[75] | — |
| Sun Pharmaceutical Industries Ltd. | 3 | National Stock Exchange (India) | 907.748 |
| Teva Pharmaceutical Industries Ltd. | 3 | NYSE | 7.491 |
| Vertex Pharmaceuticals Inc. | 3 | Nasdaq | 43.24 |

73. This chart was compiled using information from the FDA's website and Yahoo! Finance. *See New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm [https://perma.cc/2MNZ-423Q] (last updated Feb. 2, 2018); YAHOO! FIN., https://finance.yahoo.com [https://perma.cc/V653-QPP4] (last visited Oct. 6, 2019). The financial information is current as of October 6, 2019.

74. Array BioPharma was acquired by Pfizer in 2019. Jared S. Hopkins & Kimberly Chin, *Pfizer to Buy Cancer Drug Maker Array BioPharma for $10.64 Billion*, WALL ST. J. (June 17, 2019, 3:43 PM), https://www.wsj.com/articles/pfizer-to-acquire-array-biopharma-for-11-4-billion-enterprise-value-11560769500 [https://perma.cc/3JTJ-8QFA].

75. Shire Dev LLC was acquired by Takeda in 2019. Preetika Rana, *Takeda Wins Shareholder Approval for Its Shire Megadeal*, WALL ST. J. (Dec. 5, 2018, 11:54 AM), https://www.wsj.com/articles/takeda-wins-shareholder-approval-for-its-62-billion-shire-bid-1543982265?mod=mktw [https://perma.cc/8M2G-DGGG].

The role of major pharmaceutical companies in the clinical research phase leading up to FDA approval means that most applied drug research in the United States is funded by private capital and directed by the market. This is in stark contrast to basic research, which is funded largely by governmental spending of tax dollars and directed by public officials through the National Institutes of Health (NIH).[76]

The role of private capital in applied drug research determines the fundamental importance of patents in the drug development process.[77] Drug companies apply for patents on the chemical composition of promising new compounds early in the development cycle. Patents can also be obtained on new uses and combinations of existing compounds. A patent confers an exclusive right to make, use, sell, or offer for sale the patented invention, which expires twenty years after the date the patent application is filed, with some possible extensions for some drug products.[78]

Because of the long regulatory approval lead time, by the time an approved new drug reaches the market, only four to six years of patent life usually remain.[79] Drug companies and their investors and lenders therefore rely on a model in which a relatively small number of research targets eventually produce a large market return over a short time window. This dynamic means that consumers must pay prices for new drugs that are many multiples over a competitive market price.[80] Traditional small-molecule pharmaceuticals are relatively cheap and easy to manufacture, even with regulatory requirements for good manufacturing practices.[81] The market price of a new small-molecule drug might reflect a multiplier of hundreds or even thousands over the marginal cost of production per dose.[82] At least this was the industry's business model until the new drug pipeline began to dry up.[83]

The need to obtain such a high price premium means that drug development is geared toward segments of the market with low price

76. *See Grants & Funding*, NAT'L INSTITUTES HEALTH, https://www.nih.gov/grants-funding [https://perma.cc/8U9K-JNHV] (last visited Oct. 6, 2019).

77. *See* David W. Opderbeck, *Patents, Essential Medicines, and the Innovation Game*, 58 VAND. L. REV. 501, 518–19 (2005).

78. 35 U.S.C. § 154 (2012).

79. *See* Dennis S. Fernandez et al., *The Interface of Patents with the Regulatory Drug Approval Process and How Resulting Interplay Can Affect Market Entry*, ipHANDBOOK BEST PRACTICES 968–70, http://www.iphandbook.org/handbook/chPDFs/ch10/ipHandbook-Ch%2010%2009%20Fernandez-Huie-Hsu%20Patent%20and%20FDA%20Interface%20rev.pdf [https://perma.cc/DV45-FPZ6] (last visited Oct. 6, 2019).

80. *See generally* Patricia Danzon, *Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context*, 24 HEALTH ECON. 294 (2015).

81. *See, e.g.*, Opderbeck, *supra* note 77, at 522–27.

82. *See id.*

83. *See* Editorial, *Lessons from Lipitor and the Broken Blockbuster Drug Model*, 378 LANCET 1976, 1976 (2011). *But see* Richard Harrison, *2018 Could Be a Record Year for Blockbuster Drugs*, PHARMATIMES ONLINE (Apr. 9, 2018), http://www.pharmatimes.com/web_exclusives/2018_could_be_a_record_year_for_blockbuster_drugs_1230918 [https://perma.cc/CGG8-LQ8W].

elasticity of demand.[84] Low price elasticity of demand means that demand responds relatively slowly to changes in price.[85] Demand for health care is relatively inelastic in developed economies where consumers are more affluent or have access to health insurance that covers prescription drugs. The patent-distorted market, therefore, not surprisingly, directs drug discovery away from remedies for conditions that primarily affect the poor or excludes the poor from access to treatments for conditions that afflict the rich and poor alike.[86]

This dynamic raises both distributional and other economic concerns. From the perspective of distributive justice, it seems unfair that rich people receive a much higher share of society's resources for new drug treatments than low income individuals. From an economic perspective, the high cost of drugs and other health care contributes to increased concentrations of wealth by ensuring that those who are already wealthy are also healthier and therefore better able to produce more wealth for themselves, while those who are low income experience health problems as economically catastrophic.

The primary way the United States deals with the high cost of drugs and other health care is through private and public health insurance.[87] A middle- or upper-class American with a job likely can obtain health insurance from a private insurer via an employer-sponsored plan or through a private plan. These payers exert downward pressure on health-care costs by negotiating rates with providers and by managing the care provided, for example, through procedure approvals and drug formularies.[88] Medicaid and Medicare provide public, government-funded health insurance for the poor and elderly, respectively, and also attempt to contain costs through managed care and approved drug formularies. Obamacare was meant to provide access to affordable health insurance for people outside of Medicaid or Medicare who otherwise might be uninsured, although the U.S. Supreme Court and Congress have since limited key elements of the Obamacare scheme.[89]

The extent to which private payers, Medicaid, or Medicare can contain provider costs is often limited, particularly in relation to patented prescription medications that are medically indicated for a patient's treatment. Moreover, although private health insurance is available to many working Americans well beyond the superrich, in *global* terms a middle-class American with a job that provides an employer-sponsored health plan is comparatively

84. *See* Opderbeck, *supra* note 77, at 525–30.
85. *Id.*
86. *See id.*
87. *See* Simon F. Haeder, *Why the U.S. Has Higher Drug Prices Than Other Countries*, CONVERSATION (Feb. 7, 2019, 6:31 AM), http://theconversation.com/why-the-us-has-higher-drug-prices-than-other-countries-111256 [https://perma.cc/7TMR-C3RX]; Ben Hirschler, *How the U.S. Pays 3 Times More for Drugs*, SCI. AM. (Oct. 13, 2015), https://www.scientificamerican.com/article/how-the-u-s-pays-3-times-more-for-drugs/ [https://perma.cc/W3PV-G3MA];
88. *See generally* Danzon, *supra* note 80.
89. *See* Haeder, *supra* note 87.

wealthy.[90] It remains true, then, that private capital, secured by patents owned by private pharmaceutical companies, channels much of the global capacity in applied drug research towards conditions that affect wealthy Americans and thereby further entrenches national and global income disparities.[91]

Many of the same market dynamics apply to biologics, but the picture is less clear because of the complexity of these products, the differences in the regulatory pathway particularly for biosimilars, and corresponding differences in patent protection. Some scholars argue that, even aside from patents, biologics are a form of natural monopoly because of high infrastructure costs, scientific uncertainty, and other barriers to entry.[92] Others dispute the idea that biologics are natural monopolies but agree that the current biosimilar pathway is not working.[93] In any event, although these scholars disagree on some of the causes, they agree that, like drugs, biologic prices are too high.

Finally, since medical devices encompass everything from wooden tongue depressors to artificial hearts, it is much more difficult to generalize about the interplay between regulatory law, intellectual property law, and market forces than it is for prescription drugs. One thing all analysts agree upon is that the "medtech" industry is growing. A recent Deloitte report, for example, states that "[M]edtech is projected to grow at a 5.6 percent [compound annual growth rate] over the forecast period 2017–2024" to $595 billion in global sales.[94] As this rapidly growing industry converges with drugs and biologics through AI-assisted devices, economic concerns about cost and access will persist.

### *E. How AI Will Disrupt the Current Model*

#### 1. Scientific and Regulatory Disruption

As the brief description above suggests, the pharmaceutical, biologic, and medical device industries are ripe for disruption by AI. For drugs and

90. The costs of Medicare and Medicaid, of course, are borne by the American tax base, that is, by relatively well-off middle- and upper-class Americans whose private insurance pays for their own health care—or the costs are added to a massive public debt that will bankrupt these programs if not fixed in coming decades. *See* H.R. DOC. NO. 116-29, at 18 (2019); H.R. DOC. NO. 116-28, at 9–11 (2019).

91. *See generally* Opderbeck, *supra* note 77.

92. *See* Preston Atteberry et al., *Biologics Are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition*, HEALTH AFF. BLOG (Apr. 15, 2019), https://www.healthaffairs.org/do/10.1377/hblog20190405.396631/full/ [https://perma.cc/9VLZ-G3J2]; Mark Trusheim et al., *Biologics Are Natural Monopolies (Part 2): A Proposal for Post-Exclusivity Price Regulation of Biologics*, HEALTH AFF. BLOG (Apr. 15, 2019), https://www.healthaffairs.org/do/10.1377/hblog20190405.839549/full/ [https://perma.cc/5G2T-WS8K].

93. *See* Alex Brill & Benedic Ippolito, *Biologics Are Not Natural Monopolies*, HEALTH AFF. BLOG (July 2, 2019), https://www.healthaffairs.org/do/10.1377/hblog20190701.349559/full/ [https://perma.cc/3ZKJ-EPBC].

94. DELOITTE, *supra* note 4, at 10.

biologics, at the basic research stage, the science involves, at least, all of the possible large and small molecules that might interact with the human body, all of the naturally occurring human genetic variations that may produce health effects, and all of the possible engineered genetic alterations that may produce health effects. That is, the starting dataset is as big as all of human evolutionary history, biochemistry, and genetics. Of course, there is already a wealth of prior art on the findings of about two hundred years of modern basic and applied biochemical science and about fifty years of modern genomics research, but all this cumulative human effort over the past two centuries has only begun to unlock nature's secrets. AI could accelerate the pace of basic biochemical and genetic research exponentially, for example, by in silico modeling of chemical reactions or genetic changes using very large datasets.

At the applied research stage, for traditional and biologic drugs, the current paradigm involves costly, lengthy, and relatively imprecise modeling in test tubes and on animals, followed by even more costly and less precise modeling in human subjects, which also entails ethical questions about human trials.[95] AI could also exponentially reduce the time and cost, increase the precision, and mitigate ethical concerns about human trials at this stage through in silico modeling.

Indeed, techniques such as high-throughput screening are already being used for basic and applied drug research. The FDA is taking a proactive but cautious approach towards the use of in silico trials at least as part of the in vitro component of the standard drug approval framework. The AI technology is not yet as robust in this area as the hype about its potential suggests, but there are good reasons to think the hype is not merely hype.[96] Perhaps in the foreseeable future AI will not relegate every old-school bench scientist to the historical footnotes or replace the need for all animal or human trials; but as the wealth of literature on the subjects suggests, there is no doubt

95. These include the circumstances under which it is acceptable to administer placebos to control groups of human subjects or to conduct research with persons who lack the mental capacity to provide informed consent. Existing guidelines hold that properly constructed and administered double-blind human trials can be ethically appropriate in light of the need to test drugs for efficacy and safety. *See, e.g.*, Cecilia Nardini, *The Ethics of Clinical Trials*, ECANCERMEDICALSCIENCE, Jan. 16, 2014, at 1, 5; *Patient Recruitment: Ethics in Clinical Research*, NAT'L INSTITUTES HEALTH, https://clinicalcenter.nih.gov/recruit/ethics.html [https://perma.cc/8WEH-ATBJ] (last updated June 28, 2019).

96. For a small sampling of the outpouring of writing on this issue, see generally, Hongming Chen et al., *The Rise of Deep Learning in Drug Discovery*, 23 DRUG DISCOVERY TODAY 1241 (2018); Wlodzislow Duch et al., *Artificial Intelligence Approaches for Rational Drug Design and Discovery*, 13 CURRENT PHARMACEUTICAL DESIGN 1497 (2007); Sean Elkins, *The Next Era: Deep Learning in Pharmaceutical Research*, 33 PHARMACEUTICAL RES. 2594 (2016); Erik Gawehn et al., *Deep Learning in Drug Discovery*, 35 MOLECULAR INFORMATICS 3 (2016); Edward J. Griffen et al., *Can We Accelerate Medicinal Chemistry by Augmenting the Chemist with Big Data and Artificial Intelligence?*, 23 DRUG DISCOVERY TODAY 1373 (2018); David Hecht, *Applications of Machine Learning and Computational Intelligence to Drug Discovery and Development*, 72 DRUG DEV. RES. 53 (2011); and Matthew A. Sellwood et al., *Artificial Intelligence in Drug Discovery*, 10 FUTURE MEDICINAL CHEMISTRY 2025 (2018).

that current methods of drug discovery and drug testing are ripe for AI disruption.

Relating to genetic therapies, there are already research projects underway to interpret the entire human genetic sequence and to create large databases of single nucleotide polymorphisms (SNPs) across human populations, with the hope of identifying specific effects or conditions that correlate with certain nucleotide variants.[97] Among the significant challenges for this research include the number of nucleotides in the human genome (approximately 3.2 billion), the number of SNPs in each human individual's genome (approximately 5 million), the number of human population-level SNPs so far identified (approximately 100 million), and epigenetic, environmental, and other factors that might contribute to conditions correlated with genetic variations.[98] This is a classic case for big data analytics. For example, a Google-sponsored team has employed a neural network tool it calls "DeepVariant" to read an individual's genetic data.[99] Some researchers predict that, in the not-distant future, AI-driven pharmacogenetics "will be widely used to predict personalized drug response and optimize medication selection and dosing, using knowledge extracted from large and complex molecular, epidemiological, clinical, and demographic datasets."[100]

Concerning medical devices, software and connectivity has already created the "Internet of Medical Things" (IoMT), a segment of the medical device market valued at over $40 billion and expected to rise to over $155 billion by 2022.[101] These include wearable and implantable devices with sensors that provide information to users and their doctors.[102]

In addition to the IoMT, analysts describe "Software-as-a-Medical-Device" (SaMD) as yet another industry segment.[103] This can include software embedded in medical device hardware or stand-alone software that performs medical functions such as diagnosis.[104] For example, researchers at DeepMind, a health-care AI initiative acquired by Google in 2014, recently

97. *See Databases & Tools*, HUM. GENOME VARIATION SOC'Y, https://www.hgvs.org/content/databases-tools [https://perma.cc/UW2J-ULP7] (last updated July 30, 2019); *dbSNP*, NCBI, https://www.ncbi.nlm.nih.gov/snp/ [https://perma.cc/5SMU-YGV3] (last updated Apr. 8, 2019); *What Are Single Nucleotide Polymorphisms (SNPs)?*, GENETICS HOME REFERENCE (Aug. 6, 2019), https://ghr.nlm.nih.gov/primer/genomicresearch/snp [https://perma.cc/VHU2-JU9X]; *What Is the Encyclopedia of DNA Elements (ENCODE) Project?*, GENETICS HOME REFERENCE (Aug. 6, 2019), https://ghr.nlm.nih.gov/primer/genomicresearch/encode [https://perma.cc/6SPB-TA6D].

98. *See* TERRENCE A. BROWN, GENOMES § 1.2 (2d ed. 2002); *What Are Single Nucleotide Polymorphisms (SNPs)?*, *supra* note 97.

99. *See generally* Alexandr A. Kalinin et al., *Deep Learning in Pharmacogenomics: From Gene Regulation to Patient Stratification*, 19 PHARMACOGENOMICS 629 (2018); Ryan Poplin et al., *A Universal SNP and Small-Indel Variant Caller Using Deep Neural Networks*, 36 NATURE BIOTECHNOLOGY 983 (2018).

100. *See generally* Kalinin et al., *supra* note 99; Poplin et al., *supra* note 99.

101. DELOITTE, *supra* note 4, at 25.

102. *See id.*

103. *See id.* at 26.

104. *See id*.

reported that deep learning–based analysis of optical coherence tomography (OCT) scans to detect retinal disease met or exceeded the performance of human experts on the same dataset.[105]

Significant hurdles remain before AI can replace humans in clinical diagnostic settings. As the DeepMind team noted in its OCT paper, these include the following: (1) "AI (typically trained on hundreds of thousands of examples from one canonical dataset) must generalise to new populations and devices without a substantial loss of performance, and without prohibitive data requirements for retraining"; (2) "AI tools must be applicable to real-world scans, problems and pathways, and designed for clinical evaluation and deployment"; and (3) "AI tools must match or exceed the performance of human experts in such real-world situations."[106] All of these, however, are problems the technology should begin to overcome in the relatively near future.

### 2. Economic Disruption

As the discussion above suggests, there is a great deal of hype and buzz—much of it justified—over the potential for AI to revolutionize health-care technology. AI could also disrupt the current *economic* model for drug and device discovery and development. Most obviously, AI could reduce the enormous sunk costs of finding and testing new drugs, which could upset the blockbuster patent cycle. This could make drugs more affordable, while also challenging pharmaceutical industry's dominant business model—or, it could heighten calls for regulation of the industry that continues to sell drugs at high, patent-supported prices even as development costs fall.

AI could also help identify personalized drug treatments, design custom-tailored implants, or even create highly customizable genetic therapies applicable only to a small population, perhaps even to specific individuals who could afford them.[107] This could spur niche industries in personalized pharmaceuticals, devices, and genetic treatments, creating jobs and economic opportunities for workers and investors in those businesses. It could also increase economic inequality, perhaps dramatically.

Today, wealthy people who can afford quality health care are more economically productive because they are healthier. Those economic

105. Jeffrey De Fauw et al., *Clinically Applicable Deep Learning for Diagnosis and Referral in Retinal Disease*, 24 NATURE MED. 1342, 1343 (2018). On DeepMind generally, see DEEPMIND, https://deepmind.com/ [https://perma.cc/LVX9-VG5D] (last visited Oct. 6, 2019).

106. *See* De Fauw et al., *supra* note 105, at 1342.

107. It is already the case that computer-assisted design (CAD) software and 3-D printers are used to create orthodontic aligners, dental implants, and orthopedic implants. *See, e.g.*, Rick Ferguson, *2018—The Year of 3-D Printing in the Dental Office?*, DENTAL ECON. (Apr. 1, 2018), https://www.dentaleconomics.com/science-tech/article/16385056/2018the-year-of-3d-printing-in-the-dental-office [https://perma.cc/TV9D-NNDG]; P. D. Olson, *100,000 Patients Later, the 3D-Printed Hip Is a Decade Old and Going Strong*, GE REP. (Mar. 5, 2018), https://www.ge.com/reports/100000-patients-later-3d-printed-hip-decade-old-going-strong/ [https://perma.cc/CS6D-P5XX].

benefits are passed on to their children, who also can thereby enjoy higher levels of health and wealth, while low-income people who cannot afford quality health care become trapped in cycles of declining health and wealth.[108] With personalized health care, including drug and genetic treatments (and enhancements), the wealthy could become so physically robust that low-income people cannot possibly compete. It could even happen that in the distant future the wealthy might evolve into a different "transhuman" species while the poor remain ordinary humans.[109] A trope in science fiction involves an elite genetically and/or cybernetically enhanced master class that dominates the unenhanced masses who cannot afford enhancements.[110] This is still science fiction, but it is fiction rooted in the real capabilities of technologies being developed today.

With less human involvement in the drug and device process, treatments may be found that are unpatentable under existing patent law because there is no human "inventor." And since a deep learning AI is only as good as its training data, access to patient information and demographic data will serve a role similar to oil today—a basic resources that fuels other industries.[111] The most valuable intellectual property in the pharmaceutical sector may shift from patents on particular compounds or treatments to copyrights and trade secrets in the AI's code and algorithms and to the datasets the AI consumes. Silicon Valley, the economic Borg, may one day assimilate the multinational pharmaceutical industry.[112]

At the same time, at a global level, AI could provide a more accurate understanding of the treatments that could do the most good for more of the world's population, based on massive epidemiological and genetic datasets. Specifically, AI could paint an even clearer picture of how a blockbuster patent model of applied drug discovery funded by equity markets benefits the minority of people in the rich global North at the expense of the majority of

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108. *See, e.g.*, Dhruv Khullar & Dave A. Chokshi, *Health, Income, & Poverty: Where We Are & What Could Help* 1–2, HEALTH AFF. (Oct. 4, 2018), https://www.healthaffairs.org/do/10.1377/hpb20180817.901935/full/HPB_2017_RWJF_05_W.pdf [https://perma.cc/X2S9-7S8R].

109. *See, e.g.*, HUMANITY+, https://humanityplus.org/ [https://perma.cc/B9M8-5QQR] (last visited Oct. 6, 2019).

110. Pierce Brown's *Red Rising* series provides a good example. *See generally* PIERCE BROWN, DARK AGE (2019); PIERCE BROWN, GOLDEN SON (2015); PIERCE BROWN, IRON GOLD (2018); PIERCE BROWN, MORNING STAR (2016); PIERCE BROWN, RED RISING (2014). Kim Stanley Robinson's *Mars* trilogy provides another perspective, at first more sanguine but also hortatory. *See generally* KIM STANLEY ROBINSON, BLUE MARS (1996); KIM STANLEY ROBINSON, GREEN MARS (1994); KIM STANLEY ROBINSON, RED MARS (1993).

111. *See The World's Most Valuable Resource Is No Longer Oil, but Data*, ECONOMIST (May 6, 2017), https://www.economist.com/leaders/2017/05/06/the-worlds-most-valuable-resource-is-no-longer-oil-but-data [https://perma.cc/8995-2XD4]. *But see* Antonio García Martínez, *No, Data Is Not the New Oil*, WIRED (Feb. 26, 2019, 7:00 AM), https://www.wired.com/story/no-data-is-not-the-new-oil/ [https://perma.cc/64B3-JF6V].

112. For readers who are not sci-fi geeks, the "Borg" was a collective entity in the *Star Trek: The Next Generation* television and film series that sought to assimilate all life into its technologically advanced but soulless hive. *See Borg*, STAR TREK, https://www.startrek.com/database_article/borg [https://perma.cc/2KT7-2L7N] (last visited Oct. 6, 2019).

people in the poor global South.[113] In the future—not the immediate future, but within a present lifetime—AI might be capable of making policy judgments about resource allocation for drug development and discovery that make any moral case for reliance on patent-fueled markets definitively untenable. But the increased use of AI in this area will also raise ethical problems relating to accountability, equity, and privacy that have already become apparent in AI applications today.[114] All of this suggests that we should begin thinking now about how AI-enabled drug discovery and development should be regulated, which is the subject of Part II below.

## II. NEW REGULATORY FRAMEWORKS

This Part begins with a discussion of the FDA's current perspectives on in silico trials for drugs and medical devices. It then turns to possible regulatory frameworks for plausible uses of AI in drug discovery and development in the near- to medium-term, that is, over the next five to twenty years. The middle subsection of this Part considers possible regulatory frameworks over a longer horizon of twenty to thirty years. The final subsection of this Part offers a somewhat more fanciful, but not implausible, peek at AI-enabled drug development and discovery in the year 2050 and into the next century.

### *A. FDA's Current Perspective on In Silico Trials for Drugs*

The FDA recognizes the potential benefits of in silico trials. In the Cures Act, Congress appropriated $500 million over eight years for an FDA "Innovation Account."[115] The Cures Act further directed the secretary of the Department of Health and Human Services to work on a number of specific priorities, including consultations about novel clinical trial designs.[116] In announcing the FDA's work plan under the Act, FDA Commissioner Scott Gottlieb highlighted plans to increase the use of in silico trials and other forms of data monitoring as part of the agency's innovation plan.[117] In a report accompanying the Senate's 2016 FDA appropriations bill, the Senate Committee on Appropriations stated that:

> In Silico trials may potentially protect public health, advance personalized treatment, and be executed quickly and for a fraction of the cost of a full scale live trial. The FDA has advocated the use of such systems as an additional innovative research tool. Therefore, the Committee urges FDA to engage with device and drug sponsors to explore greater use, where

113. *Cf. generally* Opderbeck, *supra* note 77.

114. *Asilomar AI Principles*, FUTURE LIFE INST., https://futureoflife.org/ai-principles/ [https://perma.cc/LNG7-MYQT] (last visited Oct. 6, 2019).

115. 21st Century Cures Act, Pub. L. No. 114-255, § 1002, 130 Stat. 1033, 1042–45 (2016).

116. *Id.* § 3021, 130 Stat. at 1095–96 (codified as amended at 21 U.S.C. § 355 note (Supp. 2017)).

117. Scott Gottlieb, *How FDA Plans to Help Consumers Capitalize on Advances in Science*, U.S. FOOD & DRUG ADMIN. (July 7, 2017), https://www.fda.gov/news-events/fda-voices-perspectives-fda-experts/how-fda-plans-help-consumers-capitalize-advances-science [https://perma.cc/FRJ3-3BGK].

> appropriate, of In Silico trials for advancing new devices and drug therapy applications.[118]

These statements reflect U.S. policy in favor of exploring the use of in silico trials. However, the FDA has not yet issued any guidance, and the technology remains nascent.[119]

### *B. FDA's Current Regulatory Framework for AI and Devices*

The FDA's thinking about in silico trials seems more advanced in the area of medical devices. This is because of several factors. First, the FDA already defines certain kinds of software used in disease detection, diagnosis, or other medical applications as a regulated "medical device"—SaMD.[120] Second, today's medical devices are increasingly IoT devices, and like any software-dependent device, they can be updated remotely. Such updates can be remedial measures for bugs or security flaws, but a device also can be designed to respond dynamically to its environment, sending and receiving performance data and making algorithmically determined adjustments in real time. The FDA must determine when regulatory approval is required for a software or software-based update that materially changes a device's performance. Finally, since many medical devices are mechanical devices (such as, for example, hip replacements), the design and performance of medical devices can be modeled in silico, just as is the case for the myriad of other things designed using computer-aided design (CAD) software. Machine learning combined with CAD software could eventually allow the

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118. S. REP. NO. 114-82, at 86 (2015).

119. Some observers suggest that the FDA has been slow to implement some of these priorities because the funding is relatively small, and the agency is understaffed. *See, e.g.*, Stephen Barlas, *The 21st Century Cures Act: FDA Implementation One Year Later*, 43 PHARMACY & THERAPEUTICS 149, 150 (2018). The FDA has, however, issued guidance on drug development tools (DDTs), which are "methods, materials, or measures that have the potential to facilitate drug development," including, for example, biomarkers, clinical outcome assessments, and animal models. *See Drug Development Tool Qualification Programs*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-qualification-programs [https://perma.cc/R934-THA5] (last updated June 28, 2019); *see also Drug Development Tools: Fit-for-Purpose Initiative*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative [https://perma.cc/T89S-D49L] (last updated June 28, 2016). DDTs could encompass tools used in AI algorithms. The FDA also has issued guidance on physiologically based pharmacokinetic and pharmacodynamic modeling, which are mathematical models that can be "iteratively modified and updated when new knowledge in drug and physiology become available." *Program of Physiologically-Based Pharmacokinetic and Pharmacodynamic Modeling (PBPK Program)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/center-drug-evaluation-and-research/program-physiologically-based-pharmacokinetic-and-pharmacodynamic-modeling-pbpk-program [https://perma.cc/4VLR-7UK3] (last updated Sept. 4, 2018). This kind of modeling also is a good candidate for AI applications.

120. *See* INT'L MED. DEVICE REGULATORS FORUM, SOFTWARE AS A MEDICAL DEVICE (SAMD): KEY DEFINITIONS 4 (2013), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf [https://perma.cc/26PJ-T876].

computer to make fundamental design decisions.[121] The FDA is considering the extent to which in silico modeling can used to help determine how a device should be classified or whether it should be approved.

SaMD is defined as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."[122] In 2017, the FDA issued a guidance document incorporating clinical evaluation criteria for SaMD developed by the International Medical Device Regulators Forum (IMDRF).[123] The guidance is organized around the categories of "valid clinical association," "analytical validation," and "clinical validation," as follows: (1) "Is there a valid clinical association between your SaMD output and your SaMD's targeted clinical condition?"; (2) "Does your SaMD correctly process input data to generate accurate, reliable, and precise output data?"; and (3) "Does use of your SaMD's accurate, reliable, and precise output data achieve your intended purpose in your target population in the context of clinical care?"[124]

The guidance document suggests that the SaMD's performance under each of these categories may be subject to independent clinical evaluation depending on the level of risk presented by the SaMD.[125]

These categories might be relatively easy to apply in relation to traditional software products that process data according to a fixed program against a well-defined data range. For example, diagnostic software could be preprogrammed with known correlations between certain health conditions and a standard blood chemistry profile test, whereby inputting different ranges of numbers produces certain results—such as that a phosphorous level outside a normal range suggests a kidney problem.[126]

The criteria might be more difficult to apply, however, in relation to machine learning AI. The expected degree of accuracy, reliability, and precision will vary as the machine learns, just as it does when a human learns. Further, the expected degree of accuracy, reliability, and precision may vary as the problem presented becomes more complex or novel—again, just as may be the case for a human. Finally, because the AI system changes as it learns, it creates a never-ending series of iterations of itself that would have

121. *See* Rachel Gordon, *Reshaping Computer-Aided Design*, MIT NEWS (July 24, 2017), http://news.mit.edu/2017/reshaping-computer-aided-design-instantcad-0724 [https://perma.cc/7RVT-QPLF]; Anand Rajagopal et al., *The Rise of Machine Learning in Construction*, AUTODESK U., https://www.autodesk.com/autodesk-university/article/Rise-AI-and-Machine-Learning-Construction-2018 [https://perma.cc/H2FL-EX7S] (last visited Oct. 6, 2019).

122. *Software as a Medical Device (SaMD)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/digital-health/software-medical-device-samd [https://perma.cc/28GZ-59KN] (last updated Aug. 31, 2018).

123. *See generally* FDA, SOFTWARE AS A MEDICAL DEVICE (SAMD): CLINICAL EVALUATION; GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2017), https://www.fda.gov/media/100714/download [https://perma.cc/RV85-6A5B] [hereinafter SOFTWARE AS A MEDICAL DEVICE].

124. *Id.* at 7.

125. *Id.*

126. *See Phosphorous*, AACC: LAB TESTS ONLINE, https://labtestsonline.org/tests/phosphorus [https://perma.cc/8SLC-WZE6] (last updated Dec. 21, 2018).

to be tested and retested—yet again, just like a human whose performance must regularly be reevaluated. AI's promise exceeds that of traditional software precisely in its ability to make the kinds of probabilistic, intuitive leaps associated with human intelligence and to adapt dynamically in response to new information as humans do.

The IMDRF criteria recognize these possibilities to some extent by providing for postmarket information gathering but specifically place "machine learning software" into a different category.[127] Building on the IMDRF criteria, the FDA has promulgated guidelines for when to file a new 510(k) PMN for a software change to an existing device and has developed a voluntary software precertification program that provides a streamlined premarket review with ongoing postmarket oversight as the product is refined through use.[128] Under this guidance, the kinds of changes that may require a new 510(k) include: (1) "[a] change that introduces a new risk or modifies an existing risk that could result in significant harm"; (2) "[a] change to risk controls to prevent significant harm; and" (3) "[a] change that significantly affects clinical functionality or performance specifications of the device."[129]

The FDA recognizes that these categories raise questions about AI applications and accordingly has issued a discussion paper and request for feedback on how to assess AI applications.[130] In the discussion paper, the FDA notes that "[t]o date, FDA has cleared or approved several AI/ML-based SaMD" that "[t]ypically . . . have only included algorithms that are 'locked' prior to marketing, where algorithm changes likely require FDA premarket review for changes beyond the original market authorization."[131] According to the discussion paper, "[t]he highly iterative, autonomous, and adaptive nature of [AI/ML] tools requires a new, total product lifecycle (TPLC) regulatory approach that facilitates a rapid cycle of product improvement and allows these devices to continually improve while providing effective safeguards."[132]

In the TPLC approach, the FDA's focus first would be on whether the applicant's "culture of quality and organizational excellence" provides "reasonable assurance of the high quality of [the applicant's] software development, testing, and performance monitoring of [its] products."[133] A

127. SOFTWARE AS A MEDICAL DEVICE, *supra* note 123, at 20.

128. FDA, DECIDING WHEN TO SUBMIT A 510(K) FOR A SOFTWARE CHANGE TO AN EXISTING DEVICE: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 1 (2017), https://www.fda.gov/media/99785/download [https://perma.cc/Z543-TTFX]; FDA, DEVELOPING A SOFTWARE PRECERTIFICATION PROGRAM: A WORKING MODEL 18–20 (2019), https://www.fda.gov/media/119722/download [https://perma.cc/QY32-5Y48] [hereinafter DEVELOPING A SOFTWARE PRECERTIFICATION PROGRAM].

129. FDA, PROPOSED REGULATORY FRAMEWORK FOR MODIFICATIONS TO ARTIFICIAL INTELLIGENCE/MACHINE LEARNING (AI/ML)-BASED SOFTWARE AS A MEDICAL DEVICE (SAMD): DISCUSSION PAPER AND REQUEST FOR FEEDBACK 3 (2019), https://www.fda.gov/media/122535/download [https://perma.cc/YPU3-2XNX].

130. *Id.*

131. *Id.*

132. *Id.*

133. *Id.* at 7.

key question here would be whether the applicant uses "Good Machine Learning Practices (GMLP)," which include practices relating to data selection and management, model training and tuning, model validation, and model monitoring with feedback into further model training and tuning.[134]

The FDA would then examine the AI/ML SaMD as it does other SaMDs, based on the level of risk presented. For an AI/ML SaMD that requires premarket review, in addition to the SaMD clinical evaluation criteria, the applicant could submit a "predetermined change control plan" that would include "SaMD Pre-Specifications (SPS)" and an "Algorithm Change Protocol (ACP)."[135] The SPS would define a "region of potential changes" for the device when it is in use, and the ACP would establish specific controls over data management, retraining objectives and methods, performance evaluation, and update procedures.[136] After initial approval, if changes to the device are within the SPS and ACP parameters, usually the applicant would only need to document the changes rather than to file a 510(k).[137] In some cases, the applicant may seek postmarket modifications to the SPS or ACP without filing a 510(k), while changes materially beyond the SPS or ACP might require a new 510(k).[138] In short, the FDA anticipates a premarket process for defining a range of possible changes in an AI/ML SaMD while in use, along with preapproved protocols for how those changes can occur without requiring a new 510(k).

In addition to SaMD, the FDA also recognizes the potential for computational modeling to transform the device approval process for physical devices. It is now common practice to supplement traditional bench, nonclinical in vivo, and clinical trials with computational models for device approvals.[139] Such computational models can involve, for example, risk assessments and performance and mechanics simulations in a "virtual" patient model.[140] The FDA has issued guidance on how to report computational modeling studies as part of a medical device submission, including detailed guidelines relating to computational fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, and

134. *Id.* at 8–9.
135. *Id.* at 10.
136. *Id.* at 10–11.
137. *Id.* at 13–14.
138. *Id.*
139. *See generally, e.g.*, Tina M. Morrison et al., *The Role of Computational Modeling and Simulation in the Total Product Life Cycle of Peripheral Vascular Devices*, HHS PUB. ACCESS (Feb. 22, 2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5823268/pdf/nihms943392.pdf [https://perma.cc/4ULL-X6XQ].
140. *See, e.g.*, Owen Faris & Jeffrey Shuren, *An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials*, 376 NEW ENG. J. MED. 1350, 1353 (2017) (noting that "[d]evice manufacturers are increasingly developing stochastic engineering models that may have the capability to simulate clinical outcomes for 'virtual patients' by modeling a relationship between bench outcomes and clinical endpoints"). For an example of such a virtual patient model, see *Simulia Living Heart: Advancing Cardiovascular Science with Realistic Simulation*, DASSAULT SYSTÈMES, https://www.3ds.com/products-services/simulia/solutions/life-sciences/living-heart-human-model/ [https://perma.cc/2CFH-ZQS4] (last visited Oct. 6, 2019).

heat transfer.[141] It also has worked with the American Society of Mechanical Engineers to develop a standard for assessing the credibility of such computational models.[142]

Although computational modeling is common for medical devices, however, the technology and its use for regulatory purposes is only beginning to show its potential, particularly as augmented by AI. As Dr. Tina Morrison, deputy director of the Division of Applied Mechanics in the FDA's Office of Science and Engineering Laboratories, noted in a recent paper, under a product lifecycle management approach, the medical device industry could "more fully harness the power of simulation in each phase of the product's lifecycle and utilize AI tools to implement knowledge gained from real-world data to enhance their understanding of performance, support continuous improvement, and inform new designs and therapies."[143] Further, Deputy Director Morrison said, the "FDA also believes that computational modeling is poised to become a critical tool for accelerating regulatory decision-making."[144]

### *C. Proposals for the Near Future (Five to Twenty Years)*

#### 1. Regulatory Approval Pathways

As the discussion above shows, the FDA is ahead of the game in creating guidance relating to AI and medical devices, including SaMD, but seems to be behind concerning drugs, biologics, and genetic therapies—despite expressions of support for in silico trials for drugs. This is largely because the IoMT is already here, while the high-throughput screening methods used by pharmaceutical companies today operate prior to filing for regulatory approvals and the technology for in silico drug trials remains nascent at best.

It seems easy to suggest that the FDA should prepare to move as rapidly concerning in silico drug and biologic trials as it has for AI in devices. The regulatory category of "devices," however, is much broader than drugs or biologics, as the different classes of devices in the regulations suggest. The public health consequences of device malfunctions can be easier to predict and constrain with many kinds of devices than many kinds of drugs. For biologics and genetic therapies, the public health risks can be even broader, particularly if a genetic change becomes inheritable. This suggests that regulatory caution is appropriate until the technology develops. Two areas ripe for further regulatory development are privacy and security.

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141. *See generally* FDA, REPORTING OF COMPUTATIONAL MODELING STUDIES IN MEDICAL DEVICE SUBMISSIONS: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2016), https://www.fda.gov/media/87586/download [https://perma.cc/34Q2-TNX5].

142. *See generally* ASME, ASSESSING CREDIBILITY OF COMPUTATIONAL MODELING AND SIMULATION RESULTS THROUGH VERIFICATION AND VALIDATION: APPLICATION TO MEDICAL DEVICES (2018); FDA, *supra* note 141.

143. Tina M. Morrison et al., *Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories*, FRONTIERS MED., Sept. 2018, at 1, 8.

144. *Id.*

2. Privacy and Security Requirements at the FDA?

The FDA's Software Precertification Program requires the manufacturer to demonstrate "excellence in protecting cybersecurity and proactively addressing cybersecurity issues through active engagement with stakeholders and peers."[145] This program cross-references an IMDRF standard[146] and a 2016 FDA guidance document on cybersecurity to flesh out this requirement.[147]

The IMDRF standard notes that security analysis can include "intrusion detection, penetration testing, vulnerability scanning, and data integrity testing" but also states that "the manufacturer should ensure that security risk controls do not take precedence over safety considerations."[148] It provides no further detail about how these goals should be accomplished.

The FDA "Postmarket Management of Cybersecurity in Medical Devices" guidance provides a framework for distinguishing routine software updates and patches for cybersecurity purposes from device changes that need to be reported to the FDA.[149] This guidance also recommends that manufacturers participate in an "Information Sharing Analysis Organization" and utilize the National Institute of Standards and Technology (NIST) "Framework for Improving Critical Infrastructure Cybersecurity."[150] The NIST framework is widely recognized as a gold standard for cybersecurity compliance.[151] The FDA has also issued guidance on premarket submissions for management of cybersecurity in medical devices, which likewise refer to controls in the NIST framework, as well as an earlier guidance document on cybersecurity for networked devices containing off the shelf software such as database programs.[152]

While the FDA has emphasized cybersecurity in medical devices, it has not issued any guidance on privacy. The FDA's guidance on postmarket management of cybersecurity in medical devices suggests that privacy issues are addressed under the Health Insurance Portability and Accountability Act

145. DEVELOPING A SOFTWARE PRECERTIFICATION PROGRAM, *supra* note 128, at 11.

146. *See id.* at 18.

147. *See id.* at 39. *See generally* FDA, POSTMARKET MANAGEMENT OF CYBERSECURITY IN MEDICAL DEVICES: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2016), https://www.fda.gov/media/95862/download [https://perma.cc/UQ8T-6HTN].

148. INT'L MED. DEVICE REGULATORS FORUM, SOFTWARE AS A MEDICAL DEVICE (SAMD): APPLICATION OF QUALITY MANAGEMENT SYSTEM 14 (2015), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-151002-samd-qms.pdf [https://perma.cc/KV3U-LPC9].

149. FDA, *supra* note 147, at 9–10.

150. *Id.* at 7, 14.

151. *See generally Cybersecurity Framework*, NAT'L INST. STANDARDS & TECH., https://www.nist.gov/cyberframework [https://perma.cc/DD6X-2LPC] (last visited Oct. 6, 2019).

152. FDA, CONTENT OF PREMARKET SUBMISSIONS FOR MANAGEMENT OF CYBERSECURITY IN MEDICAL DEVICES: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2014), https://www.fda.gov/media/86174/download [https://perma.cc/7RNZ-VR7D]; FDA, GUIDANCE FOR INDUSTRY: CYBERSECURITY FOR NETWORKED MEDICAL DEVICES CONTAINING OFF-THE-SHELF (OTS) SOFTWARE (2005), https://www.fda.gov/media/72154/download [https://perma.cc/K2RE-NH4G].

as administered by the Department of Health and Human Services Office for Civil Rights.[153] This represents a regulatory silo problem that should be addressed in relation to security, privacy, and AI in medical devices.[154] Privacy and security are intimately related. Devices that lack adequate privacy safeguards are less secure and more susceptible to exploitation, including exploitation that comprises safety and effectiveness. The FDA's guidances on SaMD and AI therefore should include a recommendation that manufacturers employ "privacy by design" principles.[155]

The connection between privacy, security, and safety and efficacy is particularly dynamic and difficult in relation to AI systems, even more so for systems that exchange information with a government agency.[156] This was illustrated in 2017, for example, by the controversy over whether the DeepMind partnership with the Royal Free London NHS Foundation Trust, which allowed Google to access patient data in a trial of a kidney disease detection app, violated the United Kingdom's 1998 Data Protection Act.[157]

As a 2018 report by the influential AI Now Institute notes, "[t]he implementation of AI systems is expanding rapidly, without adequate governance, oversight, or accountability regimes," and "[w]e need a sector-specific approach that does not prioritize the technology, but focuses on its application within a given domain."[158] As the regulator with most immediate oversight over drugs and medical devices, the FDA should not simply defer privacy regulation to the Department of Health and Human Services or the Federal Trade Commission.

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153. *See* FDA, *supra* note 147, at 10–11.

154. *Cf.* Theodore T. Lee, *Recommendations for Regulating Software-Based Medical Treatments: Learning from Therapies for Psychiatric Conditions*, 73 FOOD & DRUG L.J. 66, 87–91 (2018) (discussing "regulatory fragmentation" relating to mobile medical apps); Nicolas P. Terry, *Regulatory Disruption and Arbitrage in Health-Care Data Protection*, 17 YALE J. HEALTH POL'Y L. & ETHICS 146, 146–48 (2017) (discussing regulatory silos and regulatory arbitrage in relation to health data protection).

155. *See, e.g.*, FTC, PROTECTING CONSUMER PRIVACY IN AN ERA OF RAPID CHANGE: RECOMMENDATIONS FOR BUSINESSES AND POLICYMAKERS 22–34 (2012), https://www.ftc.gov/sites/default/files/documents/reports/federal-trade-commission-report-protecting-consumer-privacy-era-rapid-change-recommendations/120326privacyreport.pdf [https://perma.cc/KF2M-UL8N]; Ann Cavoukian, *Privacy by Design: The 7 Foundational Principles*, IAPP, https://iapp.org/media/pdf/resource_center/Privacy%20by%20Design%20-%207%20Foundational%20Principles.pdf [https://perma.cc/Y29W-5NA2] (last visited Oct. 6, 2019); *Privacy by Design: Setting a New Standard for Privacy Certification*, DELOITTE, https://www2.deloitte.com/content/dam/Deloitte/ca/Documents/risk/ca-en-ers-privacy-by-design-brochure.PDF [https://perma.cc/7HJX-2E6C] (last visited Oct. 6, 2019).

156. *See* Nicolas P. Terry, *Appification, AI, and Healthcare's New Iron Triangle*, 20 J. HEALTH CARE L. & POL'Y 117, 157–59 (2018).

157. *See* Letter from Elizabeth Denham, U.K. Info. Comm'r, to Sir David Sloman, Chief Exec., Royal Free London NHS Found. Tr. (July 3, 2017), https://ico.org.uk/media/action-weve-taken/undertakings/2014353/undertaking-cover-letter-revised-04072017-to-first-person.pdf [https://perma.cc/3GYN-QLJ6]. *But see* LINKLATERS LLP, AUDIT OF THE ACUTE KIDNEY INJURY DETECTION SYSTEM KNOWN AS STREAMS 36–39 (2018), http://s3-eu-west-1.amazonaws.com/files.royalfree.nhs.uk/Reporting/Streams_Report.pdf [https://perma.cc/L3K2-ZM96].

158. MEREDITH WHITTAKER ET AL., AI NOW INST., AI NOW REPORT 2018, at 4 (2018), https://ainowinstitute.org/AI_Now_2018_Report.pdf [https://perma.cc/HQJ6-7KKR].

### 3. Virtual Patient Models

As noted in Part II.B above, one of the most promising developments in predictive analytics for drugs and devices is in the use of "virtual patient" models for in silico trials, and the FDA has already issued guidance on employing such models in device approvals.[159] A "virtual patient" model uses data analytics to simulate an organ or system in the human body, such as the heart.[160] A researcher can analyze, and with some models even visualize in three dimensions, the predicted effects of an action such as the introduction of a drug or medical device to the body.[161] Sophisticated models use forms of AI to predict how the system will change over time.

The FDA guidance recommends that applicants submit information that validates the computer model, such as an in vivo, ex vivo, or in vitro comparator or test data.[162] There is no other guidance on the source, ownership, or use of model data. This is another area in which the FDA should provide further guidance.

Concerning the source of data for virtual patient models, the FDA should distinguish different kinds of models and note issues that can arise from biases in the selection of training data in AI models. A model of an organ such as the heart seems less problematic regarding potential algorithmic bias. Besides exceptional cases in which a patient is kept alive with an artificial heart, every living human has a heart, and the organ has a well-known and relatively limited set of functional parameters.[163] Imagine, instead, a much more sophisticated model of parts of the nervous system used to test the effects of an antidepressant or other psychotropic drug on substance abuse and addiction. Addiction is both a social and a biological problem with many risk factors, so training data that draws from too narrow a demographic could skew the model's predictions of the drug's safety and efficacy.[164]

Concerning ownership and use of model data, the FDA should note a preference for open-source/open-access models.[165] Ideally, the FDA would

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159. *See supra* notes 139–43 and accompanying text.

160. *See, e.g.*, Mark Nicholls, *A 3D Virtual Heart Tool*, 37 EUR. HEART J. 2813, 2813 (2016); *The Living Heart Project: A Translational Research Initiative to Revolutionize Cardiovascular Science Through Realistic Simulation*, DASSAULT SYSTÈMES, https://www.3ds.com/products-services/simulia/solutions/life-sciences/the-living-heart-project/ [https://perma.cc/6W34-4VX8] (last visited Oct. 6, 2019).

161. *See The Living Heart Project*, *supra* note 160.

162. FDA, *supra* note 142, at 6.

163. For an example of a patient kept alive for an extended period on an artificial heart, see Kevin Joy, *Living for Years Without a Heart Is Now Possible*, MICH. HEALTH (Sept. 6, 2016, 7:00 AM), https://healthblog.uofmhealth.org/heart-health/living-for-years-without-a-heart-now-possible [https://perma.cc/GP6U-VZ5N].

164. *See generally, e.g.*, SUBSTANCE ABUSE & MENTAL HEALTH SERVS. ADMIN., TREATMENT FOR STIMULANT USE DISORDERS (1999), https://www.ncbi.nlm.nih.gov/books/NBK64328/ [https://perma.cc/9F8C-EG8U].

165. By "open source," I mean that the source code for the model is available for modification by the user and developer community under a viral license. *See generally* David W. Opderbeck, *The Penguin's Genome, or Coase and Open Source Biotechnology*, 18 HARV. J.L. & TECH. 167 (2004). By "open access," I mean available to the public free of direct charge and with minimal transaction costs, with or without a viral license. *See* David W. Opderbeck,

*require* that virtual patient models be open source and open access, but this could sit beyond the FDA's current regulatory authority and might require changes to intellectual property law. The question is important, however, because control over virtual patient models could significantly impact public health outcomes and health-care costs.

Presently there are no intellectual property–related transaction costs to obtaining human test subjects for clinical trials required for FDA approval of drugs, biologics, or devices, and access to such test subjects is not controlled by any private entity. Instead, access to human test subjects is governed by ethical and legal rules, including rules focused on the informed consent of the subject.[166] This means that human clinical trials ultimately entail at least some level of legal accountability grounded in medical ethics and science. This democratic ideal, of course, is compromised by the expense and complexity of running a well-designed clinical trial, which is why manufacturers often turn to clinical research organizations (CROs) to design and run clinical trials.[167] But neither the pharmaceutical companies nor the CROs own the test subjects they recruit and they cannot restrict other CROs from running clinical trials, whether on the same product or on other products.

Imagine, instead, that a private company owns the intellectual property in a proprietary virtual patient model. This intellectual property could include method patents relating to the modeling as well as a copyright in the model's computer code. The owner of this intellectual property could collect a license fee every time the model is used or could refuse to license the model for certain uses.

In some ways the potential economic and ethical problems raised by this hypothetical resemble issues arising from the "Oncomouse" and other kinds of genetically engineered and traditional research tools.[168] Concerning those technologies, the policy in the United States and in Europe is generally to leave cost and access issues to the market. In fact, the prospect of intellectual property protection over a valuable research tool in an otherwise lightly regulated market provides an incentive for someone to invest in developing

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*The Penguin's Paradox: The Political Economy of International Intellectual Property and the Paradox of Open Intellectual Property Models*, 18 STAN. L. & POL'Y REV. 101, 104 (2007).

166. *See Informed Consent for Clinical Trials*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials [https://perma.cc/8LL9-85KH] (last updated Jan. 4, 2018).

167. *See, e.g.*, Allie Nawrat, *Ranking the Top Ten Clinical Research Organisations in the World*, PHARMACEUTICAL TECH. (Sept. 26, 2018), https://www.pharmaceutical-technology.com/features/top-ten-clinical-research-organisations/ [https://perma.cc/QX67-WE5S].

168. *See generally* Jerry Adler, *The First Patented Animal Is Still Leading the Way on Cancer Research*, SMITHSONIAN MAG. (Dec. 2016), https://www.smithsonianmag.com/smithsonian-institution/first-patented-animal-still-leading-way-cancer-research-180961149/ [https://perma.cc/9Q4W-GNRE]; Michael B. Dilling & Terese L. Rakow, *Licensing Transgenic Mice and Other Research Tools: A Practical Guide*, *in* 4 AUTM TECHNOLOGY TRANSFER PRACTICE MANUAL (3d ed. 2010), https://www.autm.net/AUTMMain/media/ThirdEditionPDFs/V4/TTP_V4_ResearchTools.pdf [https://perma.cc/G3M7-8EZ7].

the tool. The social cost of the intellectual property right is the price paid to incentivize innovation.

*Human* virtual patient models seem different, however, because ownership of these kinds of models suggests ownership of human characteristics that should remain the common property of humanity. The policy issues here resemble those raised by *Association for Molecular Pathology v. Myriad Genetics, Inc.*,[169] where the Supreme Court struck down a patent on naturally occurring genetic markers. The *Myriad* Court, however, held that synthetic DNA could be patentable.[170] Further, *Myriad* had nothing to do with copyright in computer code. Although the copyright "idea/expression" dichotomy is analogous to the "product of nature" doctrine in patent law, code that represents a biological model is easily distinguishable from the idea of the model and usually should be copyrightable.[171] Existing intellectual property law would ordinarily allow patents and copyrights relating to human virtual patient models.[172]

Currently the FDA maintains a repository of data, models, and software developed by government employees and therefore not protected by intellectual property rights.[173] At least in one instance, however, the FDA has encouraged a private company to develop a virtual "living heart" model by entering into a five-year agreement to develop testing parameters for cardiovascular devices using the model.[174] Although this kind of partnership can encourage innovation, it also raises difficult questions about the use of public resources for basic research platforms that will be controlled by private entities.

One possible approach for addressing this kind of issue is the NIH's Public Access Policy, which requires that publications resulting from NIH funding be placed into the PubMed Central database no later than twelve months after the official date of publication in a peer-reviewed journal.[175] The FDA could require that virtual patient models used for in silico trials that support a drug, biologic, or device approval be placed into an open-source repository upon marketing approval of the drug, biologic, or device.

This would not destroy the incentives for private entities to develop such models because there is significant lead time between the use of a novel model and a product approval and because, as with the NIH's Public Access

169. 569 U.S. 576 (2013).
170. *Id.* at 594–95.
171. *See* 17 U.S.C. § 102 (2012).
172. *See id.*
173. *Public Domain Data, Modeling, and Software*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/cdrh-offices/public-domain-data-modeling-and-software [https://perma.cc/5AVF-8V5V] (last updated Nov. 13, 2017).
174. Kellen Owings, *Dassault Systèmes, FDA Collaborate on Living Heart Project*, FDA NEWS (Nov. 14, 2014), https://www.fdanews.com/articles/168507-dassault-systmes-fda-collaborate-on-living-heart-project [https://perma.cc/PL4Z-FHLU].
175. *See NIH Public Access Policy Details*, NIH PUB. ACCESS POL'Y, https://publicaccess.nih.gov/policy.htm [https://perma.cc/QP9P-5CHF] (last updated Mar. 25, 2016); *When and How to Comply*, NIH PUB. ACCESS POL'Y, https://publicaccess.nih.gov/ [https://perma.cc/Q9DA-9EF8] (last updated Mar. 18, 2014).

Policy, a deposit in an open-source/open-access repository does not divest the author of copyright.[176] Open-source/open-access deposits effectively amount to compulsory licenses for the repository to copy and distribute the work and, for users of the repository at least, to make such copies as are required to use the repository.[177] However, mere access to a copyrighted work in an open-source/open-access repository does not authorize the user to make further copies or to further distribute the work. In the case of a software model, a "copy" is made whenever the source code is loaded into memory, so an end user would still need a license to run the code.[178]

At the same time, publication would allow follow-on innovators to examine the source code to design around elements of the program that might be protected by copyright, appropriate elements of the program that are not copyrightable or in the public domain, or negotiate licenses for refinements or add-ons that would constitute derivative works.[179] Publication would also facilitate transparency and accountability. The public, including watchdog groups and academic researchers, should have full access to the source code for any models used as the basis of public health regulatory decisions.

### *D. Proposals for the Longer Term (Twenty to Thirty Years)*

The convergence of drugs, biologics, genetics, AI, and medical devices will likely accelerate rapidly over the next twenty to thirty years. Consider nanoscale devices that can create images and deliver drugs within individual cells.[180] Such devices can be linked with machine learning systems to run diagnostic tests at the cellular and even molecular level.[181] These systems will learn from the wealth of information being generated by "omics" research—the use of high-throughput technologies to identify associations across entire genomes, proteomes, metabolomes, epigenomes, transcriptomes, and microbiomes.[182] Some researchers are even theorizing about a "human brain/cloud interface," which they describe as a "stable, secure, real-time system . . . for interfacing the cloud with the human brain."[183]

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176. *Cf. NIH Public Access Policy Details*, *supra* note 175.

177. *See id.*

178. *See* MAI Sys. Corp. v. Peak Comput., Inc., 991 F.2d 511, 519 (9th Cir. 1993).

179. For a general discussion of software copyright, see 1 MELVILLE B. NIMMER & DAVID NIMMER, NIMMER ON COPYRIGHT § 2A.10 (rev. ed. 2019).

180. *See, e.g.*, Dhruba J. Bharali et al., *Nanoparticles and Cancer Therapy: A Concise Review with Emphasis on Dendrimers*, 4 INT'L J. NANOMEDICINE 1, 2 (2009); Carolyn L. Waite & Charles M. Roth, *Nanoscale Drug Delivery Systems for Enhanced Drug Penetration into Solid Tumors: Current Progress and Opportunities*, 40 CRITICAL REV. BIOMEDICAL ENGINEERING 21, 22 (2012).

181. *See generally* G. M. Sacha & P. Varona, *Artificial Intelligence in Nanotechnology*, NANOTECHNOLOGY, Oct. 2013, at 1; Liam Critchley, *The Convergence of AI and Nanotechnology*, NANO MAG. (Aug. 22, 2018), https://nano-magazine.com/news/2018/8/22/the-convergence-of-ai-and-nanotechnology [https://perma.cc/L9QC-X6CA].

182. *See generally* Yehudit Hasin et al., *Multi-omics Approaches to Disease*, GENOME BIOLOGY, May 5, 2017, at 1.

183. Nuno R. B. Martins et al., *Human Brain/Cloud Interface*, FRONTIERS MED., Mar. 2019, at 1, 1.

### 1. Regulatory Pathways

These hybrid systems will challenge the current regulatory distinctions between drugs, biologics, and devices. For example, the FDA has issued a guidance document on nanotechnology, which notes that "nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit particular examination" but that the FDA "does not categorically judge all products that involve the application of nanotechnology as intrinsically benign or harmful."[184] Another draft guidance document suggests considerations regarding nanomaterials in drug products, including possible unique issues arising from the physical structure and administration of such materials.[185] No current or draft guidance directly discusses the coming convergence of nanotechnology and AI, which might result in a swarm of microscopic, autonomously controlled devices within the body. As these technologies mature and converge, the FDA may need to consider new regulatory categories, or Congress may need to create such categories.

### 2. Privacy

In addition to new regulatory pathways, the acceleration of omics research and the convergence of drugs, devices, and AI will require even more careful thought about privacy, accountability, and access beyond the FDA's remit. The current minimalist, sector-specific approach to federal privacy regulation in the United States is inadequate to the task. We will require a more comprehensive data privacy and security regime such as the European Union's General Data Protection Regulation (GDPR).[186]

Some provisions of the GDPR, however, will be difficult to apply to AI systems, so the United States should not simply adopt a carbon copy of the GDPR. For example, Article 22 of the GDPR states that a person has the right "not to be subject to a decision based solely on automated processing, including profiling, which produces legal effects concerning him or her or similarly significantly affects him or her" without the subject's "explicit consent" or in some other limited circumstances.[187] The European Commission has stressed that this provision applies to AI systems.[188]

184. FDA, CONSIDERING WHETHER AN FDA-REGULATED PRODUCT INVOLVES THE APPLICATION OF NANOTECHNOLOGY: GUIDANCE FOR INDUSTRY 4 (2014), https://www.fda.gov/media/88423/download [https://perma.cc/ZEG5-LJQN].

185. FDA, DRUG PRODUCTS, INCLUDING BIOLOGICAL PRODUCTS, THAT CONTAIN NANOMATERIALS: GUIDANCE FOR INDUSTRY (2017), https://www.fda.gov/media/109910/download [https://perma.cc/PW5Z-C777].

186. *See generally* Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the Protection of Natural Persons with Regard to the Processing of Personal Data and on the Free Movement of Such Data, and Repealing Directive 95/46/EC (General Data Protection Regulation), 2016 O.J. (L 119) 1 (EU) [hereinafter GDPR].

187. *Id.* at 46.

188. *See Artificial Intelligence for Europe*, § 3.3, COM (2018) 237 final (Apr. 25, 2018) (stating that "[t]he Commission will closely follow the Regulation's application in the context of AI and calls on the national data protection authorities and the European Data Protection

Although consent is the most obvious exception to this prohibition, it is difficult to know what "explicit consent" might mean in connection with something like a nanoscale drug delivery system that is actively learning and changing as it fights a disease.[189]

In addition, Articles 13 and 15 of the GDPR both state that an individual is entitled to "meaningful information about the logic involved," as well as "the significance and the envisaged consequences" of the processing of the subject's data, which some commentators suggest gives data subjects a "right of explainability" of how an AI model works.[190] Some kind of right of explainability is important, but its parameters need to be specified, particularly in relation to a system that directly affects the body. Further, it is unclear whether the GDPR's provisions regarding the data subject's right to revoke consent and obtain the return of their data means that an AI system must be retrained without a subject's data if that subject originally consented to the use of his or her data but later revokes consent.[191] Finally, it is unclear whether the right of rectification and the right to be forgotten relate to a subject's data within an AI system.[192] These kinds of provisions would need to be clarified if the United States were to adopt a GDPR-like model.

### 3. Intellectual Property

AI will begin to challenge intellectual property paradigms in pharmaceuticals and medical devices as well as privacy paradigms. As therapies become more personalized based on what a predictive analytics

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Board to do the same"); *see also* Article 29 Data Prot. Working Party, *Guidelines on Automated Individual Decision-Making and Profiling for the Purposes of Regulation 2016/679*, at 20–21, WP251rev.01 (Oct. 3, 2017), https://iapp.org/media/pdf/resource_center/W29-auto-decision_profiling_02-2018.pdf [https://perma.cc/MZS8-H69N].

189. *See* Andrew Burt, *How Will the GDPR Impact Machine Learning?*, O'REILLY (May 16, 2018), https://www.oreilly.com/ideas/how-will-the-gdpr-impact-machine-learning [https://perma.cc/NW9U-PUEG].

190. *See id.*; Andrew Burt, *Is There a 'Right to Explanation' for Machine Learning in the GDPR?*, IAPP (June 1, 2017), https://iapp.org/news/a/is-there-a-right-to-explanation-for-machine-learning-in-the-gdpr/ [https://perma.cc/EQW3-VXTB]. *But see generally* Sandra Wachter et al., *Why a Right to Explanation of Automated Decision-Making Does Not Exist in the General Data Protection Regulation*, 7 INT'L DATA PRIVACY L. 76 (2017).

191. In a recent opinion on clinical trials and the GDPR, the European Data Protection Board stated that:

> Under the GDPR, if consent is used as the lawful basis for processing, there must be a possibility for individuals to withdraw that consent at any time (Article 7(3)), and there is no exception to this requirement for scientific research. As a general rule, if consent is withdrawn, all data processing operations that were based on consent remain lawful in accordance with the GDPR (Article 7(3)); however, the controller shall stop the processing actions concerned and if there is no other lawful basis justifying the retention for further processing, the data should be deleted by the controller (see Article 17(1)(b) and (3) GDPR).

European Data Prot. Bd., *Opinion 3/2019 Concerning the Questions and Answers on the Interplay Between the Clinical Trials Regulation (CTR) and the General Data Protection Regulation (GDPR) (art. 70.1.b)* 6–7 (Jan. 23, 2019), https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_opinionctrq_a_final_en.pdf [https://perma.cc/3BMT-BYEU] (footnote omitted).

192. *See* GDPR, *supra* note 186, at 36–37, 43–44; Burt, *supra* note 189.

system says about an individual patient's genome, for example, compared to known variations, the patent-based blockbuster pharmaceutical model will begin to diminish. The intellectual property in the AI system will start to become as important as the intellectual property in the chemical formula of a drug. The convergence of drugs, biologics, and devices will accelerate this trend. The medical device market is already so diverse and segmented, and the pace of change so rapid, that the blockbuster drug model centered on a single unique patented formula does not apply in the same way as for drugs.[193] The biologics market is growing rapidly, but the complexity of biologic molecules and the law restricting the patentability of naturally occurring genetic sequences could limit the extent to which a drug-like blockbuster cycle develops.[194] Even with drugs, if high-throughput screening and in silico trials significantly reduce the time and expense of finding suitable drug candidates, the blockbuster model should further fracture. These market dynamics in relation to intellectual property mean that pharmaceuticals and medical devices will start to look like Silicon Valley industries as much as traditional life science industries. Indeed, as Google's acquisition of DeepMind shows, Silicon Valley is eager to enter this space.[195]

From an intellectual property policy perspective, this dynamic will raise some difficult challenges. Patents are important in the AI space. As a recent World Intellectual Property Organization report notes, "50 percent of all AI patents have been published in just the last five years—a remarkable illustration of how rapidly innovation is advancing in this field."[196] The importance of drug patents to public health prompted the adjustments found in the Hatch-Waxman Act, including the ability of generic manufacturers to challenge drug patents without incurring the risk of damages.[197] A related, though more complicated, mechanism was adopted as part of the Biologics Price Competition and Innovation Act of 2009.[198] It is unclear whether a similar procedure should exist for AI patents that would apply to drugs, biologics, or devices, but we should begin having the conversation, particularly concerning AI-based SaMD or devices incorporating AI approved by the FDA.

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193. *See* MEDICARE PAYMENT ADVISORY COMM'N, REPORT TO THE CONGRESS: MEDICARE AND THE HEALTH CARE DELIVERY SYSTEM 207–35 (2017), http://www.medpac.gov/docs/default-source/reports/jun17_reporttocongress_sec.pdf [https://perma.cc/Y6DQ-PDYL].

194. *See* Nicola Davies, *The Future of Biologics*, PHARMA LETTER (Apr. 17, 2017), https://www.thepharmaletter.com/article/the-future-of-biologics [https://perma.cc/6CJ9-AYHZ]. *Cf.* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1046–47 (2016).

195. *See* DEEPMIND, *supra* note 105.

196. WORLD INTELLECTUAL PROP. ORG., WIPO TECHNOLOGY TRENDS 2019: ARTIFICIAL INTELLIGENCE 7 (2019), https://www.wipo.int/edocs/pubdocs/en/wipo_pub_1055.pdf [https://perma.cc/PB25-72M9].

197. *See* Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of the U.S.C.). The Hatch-Waxman framework, of course, has not been without controversy. *See generally* David W. Opderbeck, *Rational Antitrust Policy and Reverse Payment Settlements in Hatch-Waxman Patent Litigation*, 98 GEO. L.J. 1303 (2010).

198. 42 U.S.C. § 262 (2012).

Even more troubling, because AI is constructed with software code, copyright law also will apply. Presently there are debates about whether works *created by* an AI without direct human input can qualify for copyright protection, and the answer to that question so far seems to be no, although the law is unsettled.[199] There is no doubt, however, that the human-made code and algorithms that comprise the baseline AI system are copyrightable just like any computer code.[200]

Copyrights last longer and are harder to challenge than patents. Patents generally last twenty years from the date of the patent application and can be challenged if they are not novel or nonobvious over the prior art, as well as on other technical grounds.[201] Copyrights in the United States last for the life of the author plus seventy years or, for works made for hire, for ninety-five years from first publication or 120 years from creation, whichever expires first.[202] Access to AI systems also can be protected by technological measures such as encryption, which invokes the anticircumvention provisions of the Digital Millennium Copyright Act.[203] The notion that a system being developed today could become vital to public health and might be controlled under copyright and paracopyright by a private commercial entity well into the next century is frightening. We need to consider a compulsory licensing mechanism for AI copyrights that become vital to public health.[204]

Finally, AI technology can be protected by trade secret law. A company might choose to patent some parts of its AI technology and to keep other parts secret.[205] While a patent disclosure destroys a trade secret claim for anything disclosed in the patent, copyright does not require public disclosure. Copyright protection subsists without registration, and even if registration is sought, the applicant can deposit software code without disclosing trade secrets.[206] Trade secrecy in the initial AI code compounds the "black box" problem—the fact that, once an AI system begins learning, it can become

199. *See, e.g.*, Andres Guadamuz, *Artificial Intelligence and Copyright*, WIPO MAG. (Oct. 2017), https://www.wipo.int/wipo_magazine/en/2017/05/article_0003.html [https://perma.cc/D74P-T8J4].

200. *See generally* U.S. COPYRIGHT OFFICE, COPYRIGHT REGISTRATION OF COMPUTER PROGRAMS (2017), https://www.copyright.gov/circs/circ61.pdf [https://perma.cc/9MHB-NUB2].

201. 35 U.S.C. § 154(a)(2) (2012).

202. 17 U.S.C. § 302 (2012). These terms are for works created on or after January 1, 1978. *Id.* For works created before that date, the term is different and is based on the details of publication and renewal under the Copyright Act of 1909. *See* 17 U.S.C. §§ 303–05 (2012).

203. 17 U.S.C. § 1201.

204. *Cf.* Agreement on Trade-Related Aspects of Intellectual Property Rights; Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 1869 U.N.T.S. 299.

205. For a discussion of the relationship between patents and trade secrets, see generally David W. Opderbeck, *Social Network Analysis of Trade Secrets and Patents as Social Relations*, 41 AIPLA Q.J. 355 (2013).

206. *See* U.S. COPYRIGHT OFFICE, *supra* note 200, at 3–4.

difficult or even impossible to determine the basis for its decisions.[207] As noted above, current FDA draft guidance states that "good machine learning practices" require the explainability of results, and the European Union's GDPR also appears to contain a "right of explainability."[208] Whether through the FDA or otherwise, we should consider rules that require public disclosure notwithstanding trade secret claims when an AI system is critical to public health.

### *E. AI Enabled Drugs and Devices: 2050*

How will AI impact health care by the year 2050? In their book *The Second Machine Age*, Erik Brynjolfsson and Andrew McAfee argue that computing technologies such as AI will continue to improve logarithmically and that the "second half of the chessboard" will bring both dramatic increases in overall prosperity and dramatic increases in the "spread" between the poor and the well-off.[209] Of course, no one knows if Moore's Law will continue to hold, never mind how war, pandemic, climate change, or other disasters might impact the future, but let us assume for a moment that Brynjolfsson and McAfee are at least partly correct.[210]

One possibility is that AI will become smarter than humans, perhaps even self-aware, and it will be impossible for humans to control the AI "singularity."[211] If that is the case, there is little that can be done to plan for it, and it likely will either comprise an unprecedented boon or an apocalyptic disaster for humanity. Most AI scientists, however, do not believe an AI "singularity" is likely any time in the next century, if ever.[212]

Hype about the "singularity" aside, it *is* possible that by 2050 the available volume of global health data collected through connected devices and other sensors together with more powerful algorithms could provide comprehensive and accurate predictions about what kinds of research programs and technological investments would yield the most benefits with the least costs in terms of global public health.[213] At the same time, advances in AI and other technologies will facilitate not only health remediation and disease prevention but also human enhancement assisted by predictive

207. *See generally* FRANK PASQUALE, THE BLACK BOX SOCIETY: THE SECRET ALGORITHMS THAT CONTROL MONEY AND INFORMATION (2015).

208. *See supra* notes 129, 186 and accompanying text.

209. ERIK BRYNJOLFSSON & ANDREW MCAFEE, THE SECOND MACHINE AGE: WORK, PROGRESS, AND PROSPERITY IN A TIME OF BRILLIANT TECHNOLOGIES 6–12 (2014).

210. Your correspondent will be eighty-two and hopes he will look back fondly on the time when he wrote this Essay.

211. *See* Jolene Creighton, *The 'Father of Artificial Intelligence' Says Singularity Is 30 Years Away*, FUTURISM (Feb. 14, 2018), https://futurism.com/father-artificial-intelligence-singularity-decades-away [https://perma.cc/S4TG-VDN3].

212. *See* Branko Blagojevic, *AI, Optimists vs Pessimists and Why the Singularity Isn't Near*, MEDIUM (Oct. 8, 2018), https://medium.com/ml-everything/ai-optimists-vs-pessimists-and-why-the-singularity-isnt-near-5d3a614dbd45 [https://perma.cc/988Q-KZ24].

213. *See A Digital Revolution in Health Care Is Speeding Up*, ECONOMIST (Mar. 2, 2017), https://www.economist.com/business/2017/03/02/a-digital-revolution-in-health-care-is-speeding-up [https://perma.cc/3ZMB-C7CE].

algorithms about the future risks and benefits of such enhancements.[214] These prospects should challenge our current economic paradigm for drug and device development.

One of the proposed moral justifications advanced for leaving most applied drug and device research to private markets is that consumer demand is a better proxy for public health needs than centralized government planning.[215] There are of course some good and well-known reasons for this belief: resource limitations, agency costs, corruption, and other inefficiencies can impair regulatory resource allocations, while markets are supposed to be self-correcting.[216] Even so, there is no such thing as a truly free, efficient market for health care, including drugs and medical devices.[217] In particular, for drugs, price elasticity of demand rather than global public health needs determines where resources are invested and who has access to treatment.[218] Given the global public health burden of diseases such as malaria and tuberculosis, which mostly affect poor parts of the world, the moral case is tenuous at best.[219] Nevertheless, given the enormous sunk costs of drug development and the limits of existing predictive models, there is some moral justification for a privatized pharmaceutical industry founded on patents.

If AI both brings development costs down and increases the accuracy of public health outcome predictions, however, that justification may evaporate. At the same time, as noted above, intellectual property rights in AI systems could further cement the capacity of a small number of large private technology companies to direct the course of public health policy. If we believe health care really is a human right, we should seize the present opportunity to imagine a world in which AI enables more equitable access to treatments rather than furthering the divide between rich and poor.

Many AI theorists recognize that over the long term, AI will raise these sorts of big questions about global equity. The highly regarded "Asilomar AI Principles," for example, state that "AI technologies should benefit and empower as many people as possible," "[t]he economic prosperity created by AI should be shared broadly, to benefit all of humanity," and "[s]uperintelligence should only be developed in the service of widely shared ethical ideals, and for the benefit of all humanity rather than one state or

214. *See* Jolene Creighton, *World Leaders Have Decided: The Next Step in AI Is Augmenting Humans*, FUTURISM (Feb. 10, 2018), https://futurism.com/ai-augmenting-humans [https://perma.cc/U4XZ-EUAM]; Nicholas Thompson, *Will Artificial Intelligence Enhance or Hack Humanity?*, WIRED (Apr. 28, 2017, 7:00 AM), https://www.wired.com/story/will-artificial-intelligence-enhance-hack-humanity/ [https://perma.cc/E7HA-RLFK].

215. *See generally* James Capretta & Kevin Dayaratna, *Compelling Evidence Makes the Case for a Market-Driven Health Care System*, HERITAGE FOUND. (Dec. 20, 2013), https://www.heritage.org/health-care-reform/report/compelling-evidence-makes-the-case-market-driven-health-care-system [https://perma.cc/8UET-ZJQ5].

216. *See id.*

217. *See generally* Kenneth J. Arrow, *Uncertainty and the Welfare Economics of Medical Care*, 53 AM. ECON. REV. 941 (1963).

218. *See* Opderbeck, *supra* note 77, at 508–09, 525–29.

219. *See id.* at 503.

organization."[220] A recent report, "Ethics Guidelines for Trustworthy AI," prepared by an independent working group of the European Commission similarly suggests that "[t]he development, deployment, and use of AI systems must be fair," including "equal and just distribution of both benefits and costs."[221] These remain high-level exhortations, however, with little concrete reflection on how they might apply to specific sectors such as pharmaceuticals and medical devices.

Indeed, such statements about distributive justice sit in some tension with current governmental policies designed to promote the growth of private AI industries. The European Commission's communication "Artificial Intelligence for Europe," for example, focuses at least as much on developing a private European AI industry as on ethical principles.[222] In the United States, the first line of President Trump's February 11, 2019 executive order entitled "Maintaining American Leadership in Artificial Intelligence" states that "Artificial Intelligence (AI) promises to drive growth of the United States economy, enhance our economic and national security, and improve our quality of life."[223] At the same time, both the European Union and the United States have begun work on programs to open public sector information for use in AI health-care research, framed not only in terms of public health but also in terms of boosting the health-care industry sector.[224]

Although the prospect seems politically impossible in our current environment, this suggests that a conversation about AI in drug and medical device development should happen at the international level. In 1994, the World Trade Organization's Trade Related Aspects of Intellectual Property (TRIPS) treaty encoded minimum standards for national patent laws that strongly favored multinational pharmaceutical companies in the United States and Europe, to the detriment of the global South, and specifically responded to the growing generic industry in India.[225] Only later were compulsory licensing provisions for the benefit of developing countries clarified, and those provisions have largely proved too clumsy and complicated to be useful.[226] While there has been discussion of the risks of "AI arms proliferation" and of an "AI arms treaty," there has been little

220. *Asilomar AI Principles*, *supra* note 114.

221. High-Level Expert Grp. on Artificial Intelligence, *Ethics Guidelines for Trustworthy AI*, at 12 (Apr. 8, 2019) (EU), https://ec.europa.eu/newsroom/dae/document.cfm?doc_id=60419 [https://perma.cc/Q3B7-AE6E].

222. *See generally Artificial Intelligence for Europe*, *supra* note 188.

223. Exec. Order No. 13,859, 84 Fed. Reg. 3967 (Feb. 11, 2019).

224. *See generally Artificial Intelligence in Europe*, *supra* note 188; *Artificial Intelligence for the American People*, WHITE HOUSE (May 10, 2018), https://www.whitehouse.gov/briefings-statements/artificial-intelligence-american-people/ [https://perma.cc/FPQ9-T26V].

225. *See* Amy Kapczynski, *Harmonization and Its Discontents: A Case Study of TRIPS Implementation in India's Pharmaceutical Sector*, 97 CALIF. L. REV. 1571, 1571–72 (2009); Opderbeck, *supra* note 77, at 506–07.

226. *See Compulsory Licensing of Pharmaceuticals and TRIPS*, WORLD TRADE ORG., https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm [https://perma.cc/3TB9-2LFG] (last updated Mar. 2018).

discussion of an AI health or intellectual property treaty.[227] That discussion should begin in earnest. At the very least, such a treaty should provide minimum standards for compulsory licenses on intellectual property in AI for pharmaceutical and medical products and should include clear exceptions to intellectual property and related technological anticircumvention rights in such products for public health research.

## CONCLUSION

AI is already impacting the development and function of drugs, biologics, and medical devices. The trend towards convergence of these products, assisted by AI, will accelerate rapidly in coming years. In the United States, the FDA already has taken important steps toward incorporating in silico trials and evaluating the use of AI in SaMD and other medical devices. The FDA could do more, however, to ensure that AI in pharmaceuticals and medical devices reflect "privacy by design" principles and is accessible through open-source and open-access publishing models. Over the coming decades, AI could significantly disrupt the already fragile blockbuster model of pharmaceutical development and shift the drug, biotech, and medical device industries away from their life sciences roots and toward Silicon Valley. Congress should consider new regulatory models to address the related intellectual property, privacy, and accountability issues these changes will entail. By 2050, even aside from an unlikely AI "singularity," advances in AI could herald a new era in which goals of distributive justice relating to global public health could be more fully realized—if public policy prompts a shift away from entrenched intellectual property models that could increase current disparities in health care between rich and poor. Over the longer term, we need a new international AI treaty regime that accounts for public health values.

227. *See generally* GREG ALLEN & TANIEL CHAN, BELFER CTR. FOR SCI. & INT'L AFFAIRS, ARTIFICIAL INTELLIGENCE AND NATIONAL SECURITY (2017), https://www.belfercenter.org/sites/default/files/files/publication/AI%20NatSec%20-%20final.pdf [https://perma.cc/Z4N7-ELQJ]; *Autonomous Weapons: An Open Letter from AI & Robotics Researchers*, FUTURE LIFE INST. (July 28, 2015), https://futureoflife.org/open-letter-autonomous-weapons/ [https://perma.cc/5ZCC-LBSN]; Neena Bhandari, *UN Treaty Against Killer Robots Urged*, SCIDEV.NET (Aug. 23, 2017), https://www.scidev.net/asia-pacific/technology/news/un-treaty-against-killer-robots-artificial-intelligence-urged.html [https://perma.cc/FB3F-XEN6]; Douglas Frantz, *Op-Ed: We've Unleashed AI. Now We Need a Treaty to Control It*, L.A. TIMES (July 16, 2018, 4:15 AM), https://www.latimes.com/opinion/op-ed/la-oe-frantz-artificial-intelligence-treaty-20180716-story.html [https://perma.cc/TC5Z-GBCC].