Least Burdensome: A Lighter Lift for FDA's "Substantial Evidence" Gold Standard

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ABSTRACT

Medical products continuously evolve in both complexity and sophistication. As the number of products in development—and urgency of patient access—grows, it is stakeholders' collective responsibility to optimize regulatory oversight to enable more robust access to safe and efficacious products; such optimization is integral to the U.S. Food and Drug Administration's (FDA or agency) mission to safeguard public health. As regulatory policy evolves, incorporating the "Least Burdensome" principles as mandated by Congress and developed across the Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) can help achieve this sought-after optimization. Patients waiting for access to new and genericized medical products are not FDA's fault, but neither are they an "Act of God" to be ignored.[1] This Paper examines the Least Burdensome principle as a solution to benefit all stakeholders, while maintaining FDA's gold standard of regulatory rigor Americans trust and depend upon for their individual and collective health.

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[1] *See, e.g.*, Gillian Woollett & Bruce Pyenson, *A "Gold Standard" For Population Health? Revisiting the FDA's Relationship With the Hippocratic Oath*, HEALTH AFF. BLOG (Apr. 13, 2018), https://www.healthaffairs.org/do/10.1377/hblog20180409.11749/full/ ("[C]ritics complain that the Food and Drug Administration's (FDA's) deliberate processes delay approvals at the expense of patients . . . . In the five decades since [efficacy requirements became required in 1964], the FDA has adopted a Precautionary Principle approach in which the fear of doing harm comes first—even before benefit for patients. The resulting mindset considers the death of a patient waiting for a treatment to be an "Act of God," but all risks, however minor, must be scrutinized through repeated Phase III trials. The creation of the FDA "Breakthrough Designation," attempts to address the perception of slow approvals.").

I. INTRODUCTION

From its pre-agency origins in the 19th century as a small group of scientists in the basement of the Department of Agriculture, to its statutory evolution as the FDA in the 20th, the agency has aspired to be a science-based regulatory authority which bases every decision in sound, scientific inquiry for the betterment of public health. This foundation of data-driven decision-making has withstood the test of time since the agency's creation. FDA has accommodated advances in science that have revolutionized our understanding of disease as well as food and drug products themselves. Tragedies in the 20th[2] and 21st[3] centuries have prompted Congress to add to FDA's statutory authority.[4] One of the agency's most impactful policy levers is its ability to ensure efficient, consistent, predictable, and—wherever reasonable—transparent regulatory processes.[5] Throughout its history, FDA has continued to remain flexible and responsive to public health needs while maintaining the gold standard for determining safety and efficacy of products—when used as directed—in the United States.

FDA's responsibility to the public health, along with the flexibility needed to accommodate changing and emergent needs, requires FDA to issue and amend regulations and formulate guidance to ensure efficient and clear systems are in place, which are then implemented in the interest of citizens and patients without compromising the gold standard of review. As FDA grew, multiple "Centers"—including CDRH, CDER, and CBER—formed to address specific product types. Yet, the principles of science-based and decisive, risk-reward-balanced decision-making remain consistent across the agency, as does its overall mission to improve public health.[6]

CDRH explicitly utilizes the Least Burdensome principle to balance facilitating innovative rigor with ensuring proof of safety and efficacy. As with drugs and biologics, CDRH's device premarket review framework is designed to ensure that the benefits to the patient outweigh the risk of harm. This approach fosters efficiency for regulators and industry alike. The Least Burdensome principle is codified primarily in

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[2] *See, e.g.*, *Kefauver-Harris Amendments Revolutionized Drug Development*, NEWSWIRES (June 16, 2020), https://www.einnews.com/pr_news/519582409/kefauver-harris-amendments-revolutionized-drug-development (noting the thalidomide controversy gave rise to the Kefauver-Harris Amendments, adding an efficacy requirement for new medical products).

[3] *See, e.g.*, *Drug Supply Chain Security Act (DSCSA)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/drug-supply-chain-integrity/drug-supply-chain-security-act-dscsa (noting DSCSA is Title II of the Drug Quality and Security Act [DQSA], enacted Nov. 27, 2013 after the New England Compounding Center fungal meningitis outbreak killed over 100 people) (last updated May 7, 2024).

[4] *E.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, EMERGENCY USE AUTHORIZATION FOR VACCINES TO PREVENT COVID-19 1 (Mar. 31, 2022), https://www.regulations.gov/document/FDA-2020-D-1137-0114 ("FDA is issuing this guidance to provide sponsors of requests for Emergency Use Authorization (EUA) for COVID-19 vaccines . . . under section 564 of the FDCA . . . for the duration of the COVID-19 public health emergency.").

[5] FDA maintains a publicly available, searchable repository of Good Review Practice documents and Guidance. *See Good Review Practices*, U.S. FOOD & DRUG ADMIN. (Feb. 20, 2018), https://www.fda.gov/drugs/guidance-compliance-regulatory-information/good-review-practices-grps.

[6] *See, e.g.*, *What We Do*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/what-we-do (last updated Nov. 21, 2023).

Section 513 of the Federal Food, Drug, and Cosmetic Act (FDCA)[7] as amended by the Food and Drug Administration Modernization Act[8] (FDAMA) in 1997, the Food and Drug Administration Safety and Innovation Act[9] (FDASIA) in 2012, and the 21st Century Cures Act[10] (Cures Act) in 2016. FDA's mandate regarding device premarket review is circumscribed by statute, and subject to certain Least Burdensome review requirements. In the pre-market approval (i.e., PMA) context, for example, the FDCA requires (through use of the imperative language "shall") the agency (through the Secretary of Health and Human Services) to "consider" the "least burdensome appropriate means" of "evaluating device effectiveness that would have a reasonable likelihood of resulting in approval" and to "consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness."[11] Similarly, in the pre-market notification (i.e., 510(k)) context, the FDCA requires FDA to "consider the least burdensome means of demonstrating substantial equivalence and [to] request information accordingly."[12] FDA defines the Least Burdensome principle in guidance as "the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time."[13]

This Paper proposes FDA extend its use of Least Burdensome principles to all medicinal products under its existing authorities. This would both maintain intra-agency and inter-Center consistency and better optimize access to more affordable medicines based on appropriate, expeditious, and resource-optimized developmental and evaluative programs. In applying Least Burdensome principles to the drug and biologics Centers CDER and CBER, respectively, FDA would maintain science-based regulatory decision-making, while also emphasizing the need for regulatory efficiency as a matter of intentional agency policy, in the interests of patients' urgent need for timely regulatory decisions and access to affordable medicines. In so doing, FDA would maintain the gold standard of review but more explicitly emphasize timely and

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[7] *See* 21 U.S.C. § 360c(a)(3)(D)(ii) ("Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary *shall consider*, in consultation with the applicant, *the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval*." (emphasis added)); *see also* 21 U.S.C. § 360e(c)(5)(A) ("In requesting additional information with respect to an application under this section, the Secretary *shall consider the least burdensome appropriate means necessary to demonstrate a reasonable assurance of device safety and effectiveness*." (emphasis added)); *see also* 21 U.S.C. § 360e(c)(5)(C) ("For purposes of this paragraph, the Secretary *shall consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness*." (emphasis added)); s*ee also* 21 U.S.C. § 360e-3(g)(1) (specifying that breakthrough device designations and corresponding priority review does not affect "consideration and application of the least burdensome means of evaluating device effectiveness"); *see generally* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY & FOOD & DRUG ADMINISTRATION STAFF, THE LEAST BURDENSOME PROVISIONS: CONCEPT AND PRINCIPLES 4–6 (Feb. 5, 2019), https://www.fda.gov/media/73188/download [hereinafter FDA, THE LEAST BURDENSOME PROVISIONS].

[8] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 205(a) (1997).

[9] Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 602(a) (2012).

[10] 21st Century Cures Act, Pub. L. No. 114-255, §§ 3034, 3051, 3058 (2016).

[11] 21 U.S.C. § 360e(c)(5)(C) .

[12] 21 U.S.C. § 360c(i)(D)(i).

[13] FDA, THE LEAST BURDENSOME PROVISIONS, *supra* note 7, at 4.

right-sized informational exchange with sponsors by requiring—and reviewing—no more data than are necessary to meet the statutory requirements for approval. By examining legal and regulatory policy examples across the FDA-regulated medical products universe, this Paper describes how and why Least Burdensome principles are useful, pragmatic, and consistent with regulatory and public health policy. In explicitly embracing the concept across its medical product review Centers, FDA can enable more efficient and timely patient access to therapies by explicitly minimizing sponsor and agency resource encumbrance, without ultimately compromising the gold standard of substantial evidence of safety and efficacy.

II. MEDICAL DEVICES—*DE JURE* LEAST BURDENSOME

CDRH authorizes most medical devices for human use through the Pre-Market Approval (PMA), De Novo Classification, and 510(k) Premarket Notification (PMN) pathways. CDRH reviews a sponsor's data, including "one or more well-controlled investigations,"[14] by applying the statutorily required "least burdensome appropriate means"[15] principle to adjudge the proposed device's effectiveness, as instituted by FDAMA, and expanded in the FDASIA and Cures Act. This approach requires as much information as necessary—but *no more* information than necessary—to make a well-considered determination on whether to authorize a device for sale in the United States.

CDRH elaborated upon this principle in three guidance documents in the early 2000s, and in a fourth guidance document, "The Least Burdensome Provisions: Concept and Principles," published as Final Guidance in February 2019.[16] CDRH stated therein that it will apply the Least Burdensome principle "consistently and widely"[17] to ensure "earlier and continued access to high quality, safe and effective devices."[18] Furthermore, FDA names seven core guiding principles which encompass the Least Burdensome approach:

> (1) FDA requests the "minimum information necessary" to sufficiently address its inquiries;
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> (2) The sponsor should submit materials to FDA that are least burdensome for it to review;
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> (3) FDA uses the "most efficient means" to resolve its inquiries;
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> (4) The sponsor provides the right information, at the right time, to address the right questions;
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> (5) FDA takes regulatory approaches designed to fit the technology considering innovation cycles, evidence generation needs, and timely patient access;

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[14] *See* 21 U.S.C. § 360c(a)(3)(D)(ii).

[15] 21 U.S.C. §§ 360c, 360e (indeed, the relevant statutes for devices use the term "least burdensome" fourteen times).

[16] *See generally* FDA, THE LEAST BURDENSOME PROVISIONS, *supra* note 7.

[17] *Id.* at 7.

[18] *Id.*

> (6) FDA intends to leverage data from other countries and decisions by ex-U.S. regulatory authorities "to the extent appropriate and feasible"; and
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> (7) FDA intends to apply Least Burdensome principles in international device convergence and harmonization efforts.[19]

FDA presents the Least Burdensome principle as a two-way street: CDRH requests the sponsor provide the "minimum amount of information necessary" to answer its questions; so, too, FDA expects sponsors to "provide information to FDA that is least burdensome for FDA to review."[20] The anticipated rewards are two-fold: industry sponsors present a concise—but thorough—information package supplying all necessary data to CDRH for review and authorization, and CDRH does not get mired in reviewing extraneous data or other submission materials, consuming unnecessary time, labor, and budgetary dollars (including user fees). The data included in the package are thus not meant to be unduly exhaustive or extraneous, as they provide all the information required to reach a reasonable assurance of safety and efficacy in as few pages as are necessary; FDA analysts then process the submission in a timely and efficient manner. That neither side is incented to overbuild is key to its success.

The anticipated result is faster patient access to both innovative technologies that are broad and quickly evolving as well as incremental improvements to well-understood device predicates through the 510(k) pathway. CDRH balances a thorough examination with reviewing only the necessary information to reach well-reasoned conclusions, decreasing lag time for products to enter the market and reach patients and reducing opportunity costs for product sponsors, resulting in a win-win-win for all stakeholders. Thus, approval of a PMA takes a total time to decision (TTD)—inclusive of both FDA and sponsor days—of about nine months, while 510(k) premarket clearance for a substantially equivalent device takes about four months, with CDRH pursuing ever more ambitious review timelines.[21]

III. WHY THIS MATTERS AND THE OPPORTUNITY

FDA, by congressional mandate, has thus developed and executed Least Burdensome principles explicitly for regulating medical devices—and continues to do so. FDA has implicitly done likewise for drugs and biologics in its ongoing efforts to streamline regulatory efficiencies generally and has stated as much;[22] we provide examples below. This Paper recommends that FDA take the next step to continue to be expeditious to support the approval of safe and effective medicinal products as

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[19] *See id.* at 8–9.

[20] *Id.* at 24.

[21] *See, e.g.*, U.S. FOOD & DRUG ADMIN., PERFORMANCE REPORT TO CONGRESS, MEDICAL DEVICE USER FEE AMENDMENTS, FY 2022 19, https://www.fda.gov/media/167825/download?attachment (noting MDUFA IV's Shared Outcome Goals, showing a TTD Performance of 272 days for PMA decision in FY 2018, 123 days for 510(k) decision in FY 2018); *cf.* U.S. FOOD & DRUG ADMIN., Performance Report to Congress, for the Medical Device User Fee Amendments, FY 2016 13, https://www.fda.gov/media/102724/download (MDUFA III Shared Outcome Goal Total Time to Decision (Days), showing a TTD Performance of 350 days for PMA decision in FY 2013, 124 days for 510(k) decision in FY 2013).

[22] *See* FDA, THE LEAST BURDENSOME PROVISIONS, *supra* note 7, at 7 n.19 ("[W]hile the statutory least burdensome expectation does not apply to drugs or biological products, FDA is committed to the principle of avoiding unnecessary regulatory burden for all medical products including combination products.").

efficiently as is reasonable. FDA can do so in a way that allows much-needed products to be available in a timely manner, while not only maintaining FDA's gold standard for safety and efficacy but also recognizing stakeholders' inherent resource limitations, especially patients' most critical resources—time and money:

> (1) Time, because delays in bringing innovative, safe, and effective products to market—owed to unduly burdensome data generation and evaluation—may only come after certain patients have died or their conditions worsened, potentially irreversibly, and
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> (2) Money, because competitive products facing unnecessarily high data burdens will launch later, delaying competition and maintaining the high cost of single-source innovator products.

Excess studies and cumbersome review are ultimately costs that patients will bear. Indeed, the Accelerated Approval Program streamlined efficacy requirements for drugs and biologics "treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments,"[23] particularly those that "filled unmet clinical need,"[24] by allowing approval based on a "surrogate endpoint that is reasonably likely . . . to predict clinical benefit . . . ."[25] This program has resulted in more novel therapies reaching patients, quicker.[26] Additionally, the Right to Try Act[27] of 2017 allows eligible patients "expanded access" to use eligible investigational drugs, which are unapproved medical products in at least Phase II, requiring patients' informed consent and after having unsuccessfully exhausted the existing standard of care.[28] Both recognize that timely access to medical products of likely benefit is a desirable policy outcome, allowing for regulatory flexibility *before* the presentation of substantial evidence for traditional approval.

In the case of Accelerated Approval, FDA conditions continued marketing of a medical product on post-approval studies to verify clinical benefit.[29] In other words, patients can access a medical product earlier than they would under traditional

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[23] 21 C.F.R. § 314.500 (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses).

[24] *Accelerated Approval*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval (last updated Feb. 24, 2023).

[25] 21 C.F.R. § 314.510.

[26] *See, e.g.*, Julia A. Beaver, Lynn J. Howie, Lorraine Pelosof, Tamy Kim, Jinzhong Liu, Kirsten B. Goldberg, Rajeshwari Sridhara, Gideon M. Blumenthal, Ann T. Farrell, Patricia Keegan, Richard Pazdur & Paul G. Kluetz, *A 25-Year Experience of US Food and Drug Administration Accelerated Approval of Malignant Hematology and Oncology Drugs and Biologics: A Review*, 4 JAMA ONCOLOGY 6, 849–56 (2018), https://pubmed.ncbi.nlm.nih.gov/29494733/.

[27] Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, (2018) [hereinafter Right to Try Act].

[28] *Id.* at §§ 2(a) (amending the FDCA § 561B(a)(1) (codified at 21 U.S.C. § 360bbb-0a(a)(1)(A-C), defining "eligible patient," 360bbb-0a(a)(2), defining "eligible investigational drug"); *see also, e.g.*, *Right to Try*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try (last updated Dec. 12, 2024).

[29] *See* 21 U.S.C. § 356(c)(2)(A)(i) ("Approval of a product under this subsection may be subject to 1 or both of the following requirements: (i)That the sponsor conduct an appropriate postapproval study or studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.").

approval pathways based on promising clinical data rooted in a surrogate endpoint, and continued access is contingent upon the sponsor providing FDA with additional, confirmatory data post-launch to meet the requirements of traditional approval. In the case of the Right to Try Act, patients can have expanded access to Investigational New Drugs at least in Phase II[30] only under the most dire prognoses (life-threatening disease or condition, having exhausted approved treatment options)[31] the use of which generally has no bearing (positive or negative) on eventual approval,[32] but "only expands the scope of individual liberty and agency among patients, in limited circumstances . . . ."[33] In each case, the conclusion is the same: FDA, through congressional acts, enables earlier patient access in certain circumstances without ultimately compromising its standards of review.

FDA cannot allow development to become more onerous than necessary simply because analytical technologies allow for more things to be measured more accurately than was historically the case.[34] Casting inappropriate blame—whether it be on sponsors or the agency itself—is itself costly and distracting when the real priority is aligning on what evidence is necessary for a given level of assurance in patient outcomes—and optimal application of current best scientific methods is a shared responsibility of both sponsors and FDA. Applying the Least Burdensome principles more broadly for drug and biologic reviews would have a tremendous positive impact, as would initiatives which likewise harmonize agency-wide policies for regulatory considerations, including their extrapolation worldwide in the form of regulatory reliance.[35] A profound example of such alignment is in how the agency responded to COVID-19.

The global COVID-19 pandemic compelled the agency, through appropriately invoked emergency authorities and Operation Warp Speed, to accelerate vaccine and therapeutic candidates through development in an urgent, often real-time, and rolling basis. The federal Public Health Emergency (PHE) accelerated diagnostic, therapeutic, and vaccine development efforts and allowed FDA to operate under urgent flexibilities without which those products may have taken years or even decades to develop for traditional FDA approval. Instead, Emergency Use Authorizations (EUA) could be granted in a matter of days if "based on the totality of scientific evidence available . . . it is reasonable to believe that . . . (A) the product may be effective in diagnosing, treating, or preventing" COVID-19, and "(B) the known and potential benefits of the product . . . outweigh the known and potential risks of the product . . . ."[36] This is a *de facto* Least Burdensome approach owing to extraordinary and urgent circumstances. As such, an EUA ceases to be in effect when the Secretary

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[30] *See* 21 U.S.C. § 360bbb-0a(a)(2).

[31] *Id.* at (a)(1).

[32] *Id.* at (c)(1); *but see id.* ("unless – (A) the Secretary makes a determination, in accordance with paragraph (2), that use of such clinical outcome is critical to determining the safety of the eligible investigational drug; or (B) the sponsor requests use of such outcomes.").

[33] Right to Try Act, *supra* note 27, at § 3(3).

[34] *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, ANALYTICAL PROCEDURES AND METHODS VALIDATION FOR DRUGS AND BIOLOGICS (2015), https://www.fda.gov/media/87801/download.

[35] Christopher Webster, Kelly George & Gillian Woollett, *Comparability of Biologics: Global Principles, Evidentiary Consistency and Unrealized Reliance*, 35 BIODRUGS 379 (2021), https://link.springer.com/article/10.1007/s40259-021-00488-5.

[36] 21 U.S.C. § 360bbb-3(c)(2) (Authorization for medical products for use in emergencies).

of Health and Human Services (HHS) determines that the circumstances justifying the EUA no longer exist.[37]

That is not to say that *over a longer period of time* the totality of the evidence that was acceptable in the EUA context is durably sufficient, much less a replacement, for a full New Drug Application (NDA) or Biologics License Application (BLA) dossier submission, review, and approval, but it demonstrates that risk and benefit can be rapidly assessed in a way that is less burdensome for both the sponsor and FDA. For those gaining access, however, that time and the data they can contribute to subsequent regulatory decisions remains invaluable to their individual health and the shared public good, respectively. More timely product development can reasonably be interpreted to have saved lives. Indeed, FDA and industry are increasingly understanding and appreciating the value of real-world evidence (RWE) confirming these assumptions.[38] Thus, FDA should continue to apply and build on the lessons from the COVID-19 pandemic outside the PHE context to improve and streamline regulatory processes.[39]

IV. 505(B)(2)S AND 505(J)S—*DE FACTO* LEAST BURDENSOME APPROACHES TO SMALL MOLECULE DRUGS

CDER is responsible for "making sure that safe and effective drugs are available to improve the health of people in the United States."[40] While the premarket review pathways for devices by statute incorporate Least Burdensome principles, NDAs approved under 505(b)(1) of the FDCA require the four "full-s" (full reports, full lists, full statements, full descriptions), samples, specimens, and assessments to assure FDA of the drug candidate's safety and efficacy when used as indicated. An NDA can exceed 100,000 pages,[41] and CDER takes ten to twelve months to conduct a standard, substantive review.[42]

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[37] *See id.* at (g)(2).

[38] *See, e.g.*, Carolyn Magill, *Industry Voices—COVID-19 Vaccine Rollout Shows Real-World Evidence was Ready for the Spotlight*, FIERCE HEALTHCARE (Oct. 5, 2021), https://www.fiercehealthcare.com/tech/industry-voices-covid-19-vaccine-rollout-shows-real-world-evidence-was-ready-for-spotlight.

[39] *See, e.g.*, INT'L COAL. OF MEDS. REGUL. AUTHS., ICMRA STATEMENT ON COVID-19 (Apr. 28, 2020), http://www.icmra.info/drupal/sites/default/files/2020-04/ICMRA%20statement%20on%20COVID-19_final%2027%20April%202020.pdf (From the start of the pandemic, the organization's stated goals included, *inter alia*, "working together to ensure the regulatory processes related to COVID-19 are as *efficient as possible* to support the development and delivery of effective and safe medical products to populations in need worldwide; aligning on regulatory requirements and collaborating on accelerated procedures from the development to the approval, including rolling reviews and approval of trials, drugs, biologics and vaccines . . . ." (emphasis added)).

[40] *See generally Center for Drug Evaluation and Research (CDER)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/office-medical-products-and-tobacco/center-drug-evaluation-and-research-cder (last updated Feb. 29, 2024).

[41] Gail A. Van Norman, *Drugs, Devices, and the FDA: Part 1 – An Overview of Approval Processes for Drugs*, 1 JACC 170–79, 176 (2016).

[42] 21 U.S.C. § 355(c) (New Drugs) ("Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies . . . .").

The abbreviated pathways, the 505(b)(2) NDA and the 505(j) Abbreviated New Drug Application (ANDA), created in 1984 as part of the Hatch–Waxman Act,[43] incorporate prior agency conclusions with the express goal of efficiency and enabling broader patient access. Indeed, the 505(b)(2) pathway requires such NDAs to incorporate the agency's prior approval decision by reference for which the 505(b)(2) sponsor does not have a right of reference,[44] while the 505(j) ANDA pathway requires sufficient information to show, most relevantly, that the:

> (1) Active moiety of the new drug is "the same" as that as the listed drug;[45]
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> (2) Route of administration, dosage form, and strength is either the same or different than that of the reference listed drug;[46] and
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> (3) New drug is bioequivalent and "can be expected to have the same therapeutic effect" as the listed drug.[47]

The generic sponsor need only provide FDA with enough data to satisfy the therapeutic equivalence requirements, in order to demonstrate that their follow-on product candidate is just as safe and effective as the reference product. In effect, this requires the sponsor to submit no more data than are necessary for that limited purpose. The required clinical data for such a submission are limited to confirmatory bioequivalence data—full-scale safety and efficacy randomized controlled trials are not needed; indeed, the statute precludes providing additional clinical data.[48] Because such 505(j) ANDA products are determined by FDA to be therapeutically equivalent to their reference product, they are automatically substitutable (subject to state law) for their reference product. While FDA review of these applications is not subject to *de jure* Least Burdensome principles as with devices, generic drugs (and, to a lesser extent, 505(b)(2) new drugs) are regulated consistently with *de facto* Least Burdensome principles. As then-acting director of CBER Dr. Paul Parkman wrote in an April 10, 1987 letter to industry, "it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug."[49] Notably, in some cases, it may also be unethical.[50]

FDA has gradually lessened the burden in some respects on sponsors of small molecule drug applications. In a recent procedural guidance, FDA permitted sponsors to retain fewer reserve samples for bioequivalence and bioavailability testing purposes

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[43] *See* Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act, 1984), Pub. L. 98-417 (1984), 21 U.S.C. § 355(j).

[44] 21 U.S.C. § 355(b)(2).

[45] *E.g.*, 21 U.S.C. § 355(j)(2)(a)(ii)(I).

[46] 21 U.S.C. § 355(j)(2)(a)(iii).

[47] 42 U.S.C. § 262(j)(a)(a)(iii).

[48] 21 U.S.C. § 355(j)(2)(A).

[49] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, APPLICATIONS COVERED BY SECTION 505(b)(2) 3 (1999), https://www.fda.gov/media/72419/download.

[50] World Med. Ass'n, *WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects*, 310 JAMA 2191, 2192 (1964, revised 2018) ("16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.").

than previously required.[51] In announcing this new guidance, the agency stated that it "has made this determination . . . because, with technological advances, the reduced quantity of reserve samples is now sufficient for FDA testing; this reduced quantity will provide a less burdensome approach for applicants and CROs but remains consistent with the Agency's mission to ensure public health."[52] A small step for the agency, perhaps, but a tangible, lesser burden on sponsors. In this vein, a full FDA audit of existing procedural requirements to identify areas for potential optimization through the lens of Least Burdensome principles would go a long way to streamlining the industry as a whole.

V. BIOLOGICS—NECESSARILY BURDENSOME

The United States has an additional statutory framework for premarket review of biological products, codified in the Public Health Service Act (PHSA).[53] Most biologics have their origin in living cells, and these are inherently complex relative to small molecule drugs. The PHSA requires that before a biological product can be marketed, a sponsor must demonstrate that the product is safe, pure, and potent for its intended use.[54] Sponsors seeking licensure of a new biological product must submit a BLA, and while clinical data are the prevailing standard of evidence for establishing safety, purity, and potency, the PHSA does not expressly require that a BLA contain data from clinical studies, but rather approved "on the basis of a demonstration" that the product is safe, pure, and potent, and is made in a qualified facility.[55] For biologics, the practicalities of their manufacture often depend on the consistency of methods rather than definitive specifications, this being particularly true for naturally sourced products such as blood and blood derivatives, and for some vaccines subject to annual variation such as influenza.[56]

While FDA initially licenses biologics based on, prevailingly, evidence from clinical studies, they are also often subject to post-licensure manufacturing changes (for example if a new facility is needed for scale-up). Additional clinical studies are rarely required to support authorization of such manufacturing changes.[57] The changes are allowed, with regulatory oversight, based on the results of a comparability

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[51] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, COMPLIANCE POLICY FOR THE QUANTITY OF BIOAVAILABILITY AND BIOEQUIVALENCE SAMPLES RETAINED UNDER 21 CFR 320.38(C) (2020), https://digirepo.nlm.nih.gov/master/borndig/9918227359206676/GUI_Final_Quantity_of_Samples_Retained_Under_21_CFR_320.38%28c%29_Published__August_2020%5B1%5D.pdf.

[52] Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c); Guidance for Industry, 85 Fed. Reg. 51036 (Aug. 10, 2020).

[53] The Public Health Service Act, Pub. L. 78-410 (1944), 42 U.S.C. § 201 et seq.

[54] 42 U.S.C. § 262(a)(2)(C) ("(C)The Secretary shall approve a biologics license application—(i) on the basis of a demonstration that—(I) the biological product that is the subject of the application is safe, pure, and potent; and (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and (ii) if the applicant (or other appropriate person) consents to the inspection of the facility that is the subject of the application, in accordance with subsection (c).").

[55] 42 U.S.C. § 262(a)(2)(C).

[56] *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products (last updated May 16, 2024).

[57] *See, e.g.*, Webster, George & Woollett, *supra* note 35.

exercise.[58] This exercise is designed to confirm that pre- and post-change biologics are highly similar in terms of quality before the post-change biologics can be marketed. FDA often permits comparability to be supported by analytical studies alone (limited or comprehensive analysis of critical quality attributes, as appropriate to the magnitude of the manufacturing change),[59] but occasionally are supported by clinical bridging studies.[60] In some instances, dozens of manufacturing changes have been made over the lifetime of a biological product.[61]

FDA has applied regulatory discretion extensively to biologics, and it was only with recombinant technology that the regulatory requirements approached those of drugs, in part concurrent with the reassignment of recombinant biologics to CDER in 2003.

VI. BIOSIMILARS—MOST BURDENSOME

Title VII of the Patient Protection and Affordable Care Act, the Biologics Price Competition and Innovation Act (BPCIA) of 2010,[62] created a new statutory framework for the licensure of biosimilar products. The BPCIA amended Section 351 of the PHSA to include Section 351(k), a separate approval pathway for follow-on biologics that, like 505(j) and 505(b)(2) for drugs, allows a sponsor to rely on prior FDA licensure of a reference product, and hence implicitly rely on the reference product sponsor's data without follow-on sponsor access to the data itself, if certain criteria are met.

Biosimilars can be reviewed and authorized by either CDER or CBER. To date, all authorized biosimilars have referenced recombinant products and been licensed by CDER.[63] "Biosimilars" are defined as biological products which are "highly similar to the reference product notwithstanding minor differences in clinically inactive components; and [that] there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[64] Indeed, the submissions can be massive, up to an order of magnitude larger than NDAs, exceeding 1,000,000 pages in at least one case.[65]

The BPCIA gives FDA the explicit authority to waive any of the principal requirements used to establish biosimilarity—including analytical studies, animal

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[58] U.S. FOOD & DRUG ADMIN. & INT'L COUNCIL FOR HARMONISATION OF TECH. REQUIREMENTS FOR PHARM. FOR HUM. USE, GUIDANCE FOR INDUSTRY, Q5E COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS 4 (2005), https://www.fda.gov/media/71489/download.

[59] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, COMPARABILITY PROTOCOLS FOR POSTAPPROVAL CHANGES TO THE CHEMISTRY, MANUFACTURING, AND CONTROLS INFORMATION IN AN NDA, ANDA, OR BLA (2022), https://www.fda.gov/media/162263/download.

[60] *Id.*

[61] *See* Balázs Vezér, Zsuzsanna Buzás, Miklós Sebeszta & Zsombor Zrubka, *Authorized Manufacturing Changes for Therapeutic Monoclonal Antibodies (mAbs) in European Public Assessment Report (EPAR) Documents*, 32 CURRENT MED. RSCH. & OP. 829 (2016).

[62] Patient Protection and Affordable Care Act, Title VII – Improving Access to Innovative Medical Therapies, Pub. L. 111-148, § 7002 (2010).

[63] *See Biosimilar Product Information*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-product-information (last updated Mar. 11, 2025).

[64] 42 U.S.C. § 262(i)(2).

[65] Personal communication from a successful biosimilar sponsor.

studies, and clinical studies—if they are considered "unnecessary."[66] Arguably, FDA has amended expectations for the purpose of clinical studies, across the board, given its guidance that clinical studies are being done to *confirm* the biosimilarity established analytically, and not to *demonstrate* safety, purity, and potency *a priori* even in the single, most sensitive indication where clinical studies are currently conducted.[67] Further, multiple analyses of the biosimilars authorized to date have established that a pharmacokinetics (PK) match alone can be determinative of a positive approval decision.[68]

Furthermore, biosimilars which meet additional requirements set forth at PHSA Section 351(k)(4) are deemed "interchangeable."[69] An interchangeable biosimilar "may be substituted [subject to state law] for the reference product without the intervention of the health care provider who prescribed the reference product."[70] FDA

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[66] 42 U.S.C. § 262(k)(2)(A)(ii) ("The Secretary may determine, in the Secretary's discretion, that an element described in clause (i)(I) is unnecessary in an application submitted under this subsection.").

[67] *See, e.g.*, *Virtual Workshop, Increasing the Efficiency of Biosimilar Development Programs—Reevaluating the Need for Comparative Clinical Efficacy Studies*, U.S. FOOD & DRUG ADMIN. (2023), https://www.fda.gov/drugs/news-events-human-drugs/increasing-efficiency-biosimilar-development-programs-reevaluating-need-comparative-clinical; *see also*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, DEVELOPMENT OF THERAPEUTIC PROTEIN BIOSIMILARS: COMPARATIVE ANALYTICAL ASSESSMENT AND OTHER QUALITY-RELATED CONSIDERATIONS 7 (2019), https://www.fda.gov/media/125484/download ("Comparative analytical data provide the foundation for the development of a proposed product for submission in an application under section 351(k) of the PHSA and *can influence decisions about the type and amount* of animal and clinical data needed to support a demonstration of 237 biosimilarity." [emphasis added]).

[68] *See* Arnold Vulto, *Delivering on the Promise of Biosimilars*, 33 BIODRUGS 599 (2019), https://pubmed.ncbi.nlm.nih.gov/31606870/; *see also* Christopher Webster, Anny Wong & Gillian Woollett, *An Efficient Development Paradigm for Biosimilars*, 33 BIODRUGS 603 (2019), https://pubmed.ncbi.nlm.nih.gov/31388969/; *see also* Arnold Vulto, *Evolution of the EU Biosimilar Framework: Past and Future*, 33 BIODRUGS 621 (2019), https://pubmed.ncbi.nlm.nih.gov/31541400/; *see also* R. Martijn van der Plas, Marcel H. N. Hoefnagel, Hans L. Hillege & Kit C. B. Roes, *Pragmatic Rules for Comparability of Biological Medicinal Products*, 63 BIOLOGICALS 97 (2020), https://pubmed.ncbi.nlm.nih.gov/31836276/; *see also* Martin Schiestl, Gopinath Ranganna, Keith Watson, Byoungin Jung, Karsten Roth, Björn Capsius, Michael Trieb, Peter Bias & Julie Maréchal-Jamil, *The Path Towards a Tailored Clinical Biosimilar Development*, 34 BIODRUGS 297 (2020), https://pubmed.ncbi.nlm.nih.gov/32266678/; *see also* Hillel P. Cohen, Matthew Turner, Dorothy McCabe & Gillian R. Woollett, *Future Evolution of Biosimilar Development by Application of Current Science and Available Evidence: The Developer's Perspective*, 35 BIODRUGS 583 (2023), https://pubmed.ncbi.nlm.nih.gov/37542600/.

[69] 42 U.S.C. § 262(k).

[70] 42 U.S.C. § 262(i)(3).

has previously concurred[71] with the European Medicines Agency[72] (EMA) that, for the purposes of physician prescribing, all biosimilars are already interchangeable. The agency issued a Final Guidance in 2019,[73] and in a joint statement issued on September 19, 2022, EMA and the Heads of Medicines Agencies confirmed that, as a regulatory matter in Europe, and a scientific matter generally, that biosimilars are interchangeable with the reference biologic.[74] In 2023, FDA itself published its review of switching between biosimilars and their reference product, concluding "no differences in terms of major safety parameters such as deaths, SAEs [serious adverse events], and discontinuations were observed when patients are switched (to or from a biosimilar and its reference biologic) or not switched."[75]

In 2024, the Biden Administration's FY2025 budget, as part of its ongoing effort to reduce the cost of prescription drugs, included a provision to "Permit biosimilar substitution without Food and Drug Administration (FDA) determination of interchangeability."[76] In parallel, the Centers for Medicare and Medicaid Services (CMS) finalized a rule change to enable Part D sponsors to "treat formulary substitutions of all biosimilars for their reference products as 'maintenance changes' that would not require explicit approval from CMS."[77] FDA, too, has begun to signal

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[71] *E.g.*, Dr. Leah Cristl (as then-Director of FDA Therapeutic Biologics and Biosimilars Staff, Office of New Drugs, CDER), Medicines for Europe, 16th Biosimilars Meeting, London, April 27–28, 2018 (but clarified then that interchangeability is a designation solely for the purposes of substitution by [someone] other than the prescriber. For such pharmacist substitution the law was clear that an additional designation from FDA was available). *See* Richard Kirkner, *FDA's Gottlieb Aims to End Biosimilar Groundhog Day*, 28 MANAGED CARE 1, 5–6 (2019); *referenced in* Hillel P. Cohen & Dorothy McCabe, *The Importance of Countering Biosimilar Disparagement and Misinformation*, 34 BIODRUGS 407, 410 (2020), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7391388/ ("It is interesting to note that the FDA and the EMA agree that for the purposes of physician prescribing, all approved biosimilars may be freely substituted by prescribing physicians without the need for additional clinical studies."); *referenced in* Joseph P. Park, Byoungin Jung, Hyung Ki Park, Donghoon Shin, Jin Ah Jung, Jeehoon Ghil, Jihyun Han, Kyung Ah Kim & Gillian R Woollett, *Interchangeability for Biologics is a Legal Distinction in the USA, Not a Clinical One*, 36 BIODRUGS 431, 433–34 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9190447/ ("European regulators, in their independent capacities, have observed that all of their biosimilars are already interchangeable by this definition, and as such they can be switched for their reference in the practice of medicine (as opposed to legally substitutable by other than the prescriber, which is not a European Commission decision. The FDA has agreed with this conclusion for the purposes of physician prescribing.").

[72] Pekka Kurki, Leon van Aerts, Elena Wolff-Holz, Thijs Giezen, Venke Skibeli & Martina Weise, *Interchangeability of Biosimilars: A European Perspective*, 31 BIODRUGS 83 (2017), https://pubmed.ncbi.nlm.nih.gov/28120313/.

[73] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (2019), https://www.fda.gov/media/124907/download.

[74] *See Biosimilar Medicines Can be Interchanged*, EUR. MEDS. AGENCY (Sept. 19, 2022), https://www.ema.europa.eu/en/news/biosimilar-medicines-can-be-interchanged.

[75] Thomas M. Herndon, Cristina Ausin, Nina N. Brahme, Sarah J. Schrieber, Michelle Luo, Frances C. Andrada, Carol Kim, Wanjie Sun, Lingjie Zhou, Stella Grosser, Sarah Yim & M. Stacey Ricci, *Safety Outcomes When Switching Between Biosimilars and Reference Biologics: A Systematic Review and Meta-Analysis*, 18 PLOS ONE e0292231, 9 (2023), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10547155/.

[76] OFF. OF MGMT. & BUDGET, BUDGET OF THE U.S. GOVERNMENT—FISCAL YEAR 2025 143 (2024), https://www.whitehouse.gov/wp-content/uploads/2024/03/budget_fy2025.pdf.

[77] *See Contract Year 2025 Medicare Advantage and Part D Final Rule (CMS-4205-F)*, CTRS. FOR MEDICARE & MEDICAID SERVS., (Apr. 4, 2024), https://www.cms.gov/newsroom/fact-sheets/contract-year-2025-medicare-advantage-and-part-d-final-rule-cms-4205-f; *see also* Fed. Reg., Unpublished Rule (to be published Apr. 23, 2024), 42 CFR PART 423—VOLUNTARY MEDICARE PRESCRIPTION DRUG

its amenability to the change.[78] Taken together, these recent evolutions reflect the federal government's shift towards the most current, cumulative science regarding safely switching biosimilars for reference products, enabling increased access and lower costs for patients, without the unnecessary—and arguably unethical—need for clinical switching studies as originally implied by BPCIA, lessening the burden on biosimilar sponsors.

Although it remains to be seen whether these latest executive actions are feasible absent legislative reform, such moves indicate a clear tailwind in the public health policy realm that statutory provisions perceived as overly onerous ought to be dispensed with, in view of the cumulative data and growing scientific consensus regarding switching studies to demonstrate interchangeability, the goal being to drive greater patient access and affordability. This view comports with a Least Burdensome approach.

VII. INSULIN ROLLOVERS AND THE FIRST INTERCHANGEABLE BIOLOGIC MAY HELP LEAST BURDENSOME PRINCIPLES TO ENTER THE REGULATORY MAINSTREAM

Insulins transitioned from regulation as traditional drugs to biologics on March 23, 2020, as part of the BPCIA's "deemed to be a license" provision at Section 7002(e). In a 2019 Draft Guidance,[79] FDA had shifted towards what can be described as a less burdensome approach with respect to biosimilar and interchangeable insulin applications submitted under Section 351(k).[80] Owing to decades of "extensive clinical experience"[81] with insulins, and the "relatively small, structurally uncomplicated and

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BENEFIT § 423.100 at 30832 ("*Maintenance change* means one of the following negative formulary changes with respect to a covered Part D drug: . . . (2) Making any negative formulary changes to a reference product within 90 days of adding a biosimilar biological product other than an interchangeable biological product of that reference product to the same or a lower cost-sharing tier and with the same or less restrictive PA, ST, or QL requirements. [emphasis in original]"), https://www.federalregister.gov/public-inspection/2024-07105/medicare-program-medicare-advantage-and-the-medicare-prescription-drug-benefit-program-for-contract.

[78] *See, e.g.*, Zachary Brennan, *FDA is Ready to Eliminate the Interchangeability Designation for Biosimilars*, ENDPOINTS NEWS (Apr. 15, 2024) (quoting Dr. Sarah Yim, Director, Office of Therapeutic Biologics and Biosimilars, Office of New Drugs, CDER: "But Yim said the shift is necessary now because there are no longer any scientific or clinical reasons to make a difference between 'the two classes of products, because instead of having two different levels of similarity, for example, we don't feel like we can implement that,' Yim said."), https://endpts.com/fda-is-ready-to-eliminate-the-interchangeability-designation-for-biosimilars/.

[79] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, CLINICAL IMMUNOGENICITY CONSIDERATIONS FOR BIOSIMILAR AND INTERCHANGEABLE INSULIN PRODUCTS 1 (2019), https://www.fda.gov/media/133014/download. [hereinafter FDA, CLINICAL IMMUNOGENICITY CONSIDERATIONS].

[80] *Cf.* U.S. FOOD & DRUG ADMIN., CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT, GUIDANCE FOR INDUSTRY 9 (2019), https://www.fda.gov/media/124907/download. ("For biological products that are not intended to be administered to an individual more than once, FDA expects that switching studies would generally not be needed. For products intended to be administered more than once, sponsors are encouraged to meet with FDA to discuss the planned development approach, including any *proposed justification* of why data from a switching study is not needed." [emphasis added]).

[81] FDA, CLINICAL IMMUNOGENICITY CONSIDERATIONS, *supra note* 79, at 5.

well characterized nature"[82] of the molecule itself, FDA stated it had "diminished concerns about the risk of clinical impacts from immunogenicity for currently approved insulin products."[83] As such, FDA decided that "a comparative clinical immunogenicity study generally would be unnecessary to support a demonstration of biosimilarity or interchangeability," provided there was "little or no residual uncertainty regarding risk of clinical impact from immunogenicity."[84] Furthermore, FDA noted that:

> [A]dvances in analytics may allow for extended analytical characterization that affects the extent of other data and information needed to support a demonstration of interchangeability and may in certain circumstances lead to a more selective and targeted approach to clinical studies intended to support . . . interchangeability . . . . [V]ery low residual uncertainty about immunogenicity generally would mean that an applicant would not need to conduct a comparative clinical immunogenicity study, e.g., a switching study, to support licensure . . . so long as the statutory criteria for licensure as an interchangeable are otherwise met.[85]

This is a less burdensome approach to insulin biosimilar sponsors, even as it appears to run close to obviating the black letter legal requirements of BPCIA.[86]

The first interchangeable biologic, Semglee®, an insulin glargine, was approved in the United States on July 28, 2021.[87] By the end of 2022, FDA designated three other biosimilars as interchangeable, including a second insulin glargine.[88] While insulins may appear on the simpler end of the spectrum of molecular complexity, the statutory requirements are the same for all biologics.

As FDA continues to authorize biosimilars and its comfort with reference comparator data sets increases, the agency's need—and requests for—clinical trial data may be reduced in favor of *in vitro*, PK, and pharmacodynamics (PD) data. Experts have described this body of evidence as a "confirmation of sufficient likeness" (CSL) standard.[89] Adoption of this paradigm would align with Least Burdensome principles, reduce development costs of biosimilars, and increase access to needed therapies while decreasing prescription drug costs and comporting with ethical guidelines that human studies have an expectation of furthering knowledge.

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[82] *Id.* at 3.

[83] *Id.* at 5.

[84] *Id.* at 3–4.

[85] *Id.* at 7.

[86] 42 U.S.C. § 262(k)(4).

[87] Press Release, U.S. Food & Drug Admin., FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes, https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes (last updated July 28, 2021).

[88] *E.g.*, Alyssa Billingsly, *What Is an Interchangeable Biosimilar Drug?*, GOODRX HEALTH (Mar. 3, 2023), https://www.goodrx.com/healthcare-access/medication-education/interchangeable-biosimilar-drugs.

[89] Webster, Wong & Woollett, *supra* note 68, at 605–09.

VIII. LEAST BURDENSOME PRINCIPLES—EXPANDING BEYOND CDRH

Currently, FDA's statutory authority only requires that medical device premarket review adhere to Least Burdensome principles. However, this Paper suggests FDA adopt the principle as a matter of scientifically sound—and ethically appropriate—regulatory policy for all medical products it oversees. This Paper has described instances where, in furtherance of public health policy, FDA and the wider federal government have taken steps to lessen sponsor burden in favor of enhanced access and evolving, cumulative scientific and clinical data, and understanding thereof. The Least Burdensome principles lend clear advantages to the agency, sponsors, and patients alike by requiring (and reviewing) no more data than are necessary to reach a regulatory decision and meet statutory requirements. This approach has the potential to enable those same products to reach patients sooner. Unnecessary data generation takes not only additional time to gather and a financial toll to produce, but also raises ethical questions around human experimentation[90] and requires additional time and resources for FDA staff teams to review, without the promise of improvement in the medicines which are ultimately approved. In sum, generation of unnecessary data leads to decreased and delayed access for patients, a higher cost for the products ultimately approved, and strains FDA and sponsor resources that could be better applied to development and authorization of other products.

Least Burdensome principles are more qualitative than quantitative, and appropriate metrics are still in development for evaluating whether the agency is achieving them. Yet, as former FDA Commissioner Scott Gottlieb stated, "[a]pplying the least burdensome concept to medical device regulation has been fundamental to our mission of protecting patients while promoting access to innovations that can help patients improve their health."[91] Under Gottlieb's leadership, 100% of the CDRH staff and CBER staff involved in premarket device submissions review completed a mandatory training on Least Burdensome principles.[92] Furthermore, FDA also has signaled its intent to go independently beyond the mandatory Least Burdensome provisions from the Cures Act and begin implementing an assessment of how much data are minimally necessary to assure safety and effectiveness in all premarket or postmarket settings regarding medical device regulation.[93] While a one-size-fits-all approach for drugs or biologics is likely unworkable, for every drug or biological candidate is different as a scientific and clinical matter, requiring more—or less—supporting data depending on

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[90] *See, e.g.*, World Med. Ass'n, *supra* note 50.

[91] Press Release, U.S. Food & Drug Admin., FDA Statement, Statement from FDA Commissioner Scott Gottlieb, M.D., in Response to GAO Report Regarding FDA's Ongoing Commitment to Employing a Least Burdensome Approach to Device Review (Jan. 16, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-response-gao-report-regarding-fdas-ongoing-commitment.

[92] U.S. FOOD & DRUG ADMIN., REPORT TO CONGRESS, LEAST BURDENSOME TRAINING AUDIT 4 (June 18, 2018),https://fda.report/media/113823/FDA+Report+to+Congress-Least+Burdensome+Training+Audit.pdf.

[93] FDA, THE LEAST BURDENSOME PROVISIONS, *supra* note 7, at 6–7 ("FDA believes, as a matter of policy, that least burdensome principles should be consistently and widely applied to all medical device regulatory activities in the premarket and postmarket settings to remove or reduce unnecessary burdens so that patients can have earlier and continued access to high quality, safe and effective devices.").

myriad factors, explicitly applying such principles across other FDA Centers can achieve the goal of improving bidirectional (that is, for both the FDA Centers and sponsors) efficiency under the auspices of Least Burdensome principles without compromising standards of approval. It is about refining the burden of proof, given that the sponsor must still demonstrate safety and efficacy, thereby ensuring a focus on actionable data, while stakeholders can avoid generating, analyzing, or evaluating superfluous data.

The Least Burdensome approach is consistent with sound FDA regulatory strategy as a whole. Sponsors who seek FDA approval or licensure bring data into a two-way conversation with the agency, and both parties learn from the exchange. The agency can continue to optimize its review procedures in real-time, realizing the principles of Least Burdensome without compromising the gold standard of safety and efficacy. This is not unlike the negotiations which happen in the drug and biologic space for ANDA or biosimilar approval; however, incorporating the Least Burdensome principles directly into the dialogue can streamline the data and review burden on both sides while maintaining the gold standard of review that all stakeholders do and should continue to expect and demand from FDA.

IX. CONCLUSION—ALIGNING LEAST BURDENSOME WITH GLOBAL HARMONIZATION AND REGULATORY RELIANCE

The Pure Food and Drug Act of 1906 first codified the regulatory responsibilities of protecting the nation's supply of food and drugs. Over the last century, FDA and its regulatory forerunners have met a multitude of challenges with flexibility to both safeguard—and improve—the nation's public health. The Least Burdensome provision which guides CDRH decision-making is one more recent step along that pathway, and one that should now be applied to drugs and biologics as well, as a matter of agency policy; a congressional mandate being unnecessary and likely, in and of itself, unduly burdensome. In other words, while the law *requires* that CDRH incorporate Least Burdensome appropriate means of evaluating medical devices, CBER and CDER *may* electively do so, reaping the putative benefits for all stakeholders of its own accord. That FDA currently has the necessary authority to take the Least Burdensome approach across CDER and CBER is key to its timeliness and immediate feasibility.

Furthermore, FDA can continue internal harmonization efforts across Centers to maximize consistency and efficiency. FDA can do so in parallel with global harmonization. Agency initiatives such as Project Orbis,[94] an international collaboration between FDA and other highly regulated nations in the oncology space, created in 2019[95] to accelerate approval for oncology combination therapy, continue to advance those laudable goals. Providing patients with rapid access to potentially life-saving therapies goes hand-in-hand with Least Burdensome principles. Likewise,

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[94] *Project Orbis*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis (last updated Dec. 16, 2024).

[95] Press Release, U.S. Food & Drug Admin., FDA Takes First Action Under New International Collaboration with Australia and Canada Designed to Provide a Framework for Concurrent Review of Cancer Therapies, Approving Treatment for Patients with Endometrial Carcinoma (Sept. 17, 2019), https://www.fda.gov/news-events/press-announcements/fda-takes-first-action-under-new-international-collaboration-australia-and-canada-designed-provide.

the FDA–EMA Parallel Scientific Advice (PSA) Pilot is intended to "avoid unnecessary testing replication or unnecessary diverse testing methodologies."[96] Closer cooperation among like-minded regulatory agencies such as these above and the International Coalition of Medicines Regulatory Authorities (ICRMA) will streamline the regulatory processes even further and ensure the latest and greatest advancements are delivered into the hands of those who need them as rapidly as possible—removing burden while not increasing risk—creating a yet lighter lift for FDA's gold standard of review.

Extending productive initiatives such as Project Orbis, the FDA–EMA PSA Pilot, and ICRMA by inviting like-minded international regulators to collaborate allows for all to approach new technologies through the two-way-street concept of Least Burdensome and build on cumulative scientific and regulatory precedent. This approach will allow for better, more consistent submissions across and between National Medicines Regulatory Authorities, and more timely approvals—and resulting access—for all patients. Science is a shared global language—sound data transcends national borders and supports regulatory reliance. When standards converge, regulators around the world can leverage common data resources while ensuring that safe and effective therapies reach more patients, more quickly.

FDA's leadership towards a least (or less) burdensome approach to drug and biologic regulation has begun—intentionally or not—and should continue within its existing statutory authorities and the well-defined, established rigor of substantial evidence. By focusing on what data is actionable for a given product's safety and efficacy, the agency may empower itself as well as industry to share in the more efficient and timely development of all the medicines that it oversees. What better partnership to promote and protect the public health is there than that?

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[96] EUR. MEDS. AGENCY & U.S. FOOD & DRUG ADMIN., GENERAL PRINCIPLES EMA–FDA PARALLEL SCIENTIFIC ADVICE (HUMAN MEDICINAL PRODUCTS) (July 2021), https://www.fda.gov/media/105211/download.