The Case for Disclosure of Biologics Manufacturing Information

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I. Introduction: Why Biologics Are So Expensive and Why That Is Unlikely to Change

Biologic pharmaceuticals (biologics) are an increasingly important class of drugs and among the most commercially-successful biomedical products on the U.S. and worldwide market.[1] They are also among the most expensive.[2] With many biologics going off exclusivity, hope was that prices would drop once cheaper versions of these products enter the market, same as with generic versions of small molecule drugs.[3] In a previous article, "Follow-On Biologics Are Set Up to Fail,"[4] I explained why the United States does not have, and is unlikely to have, competitively robust[5] biologics markets and why, as a result, biologics markets are unlikely to see price-drops like those observed in generic drug markets. That conclusion, I believe, still holds even after the issuance, in May 2019, of the Food and Drug Administration's (FDA) much-anticipated guidance on approval of interchangeable biosimilar products.[6]

Since the late 1990s and early 2000s, the brand-name pharmaceutical industry[7]—with its lobbying spearheads, the Biotechnology Innovation Organization (BIO) and the Pharmaceutical Research and Manufacturers of America (PhRMA) and its many allies in Congress, state legislatures, and state and federal administrations — has been highly successful in undercutting the emergence of competition in biologics markets in the United States.[8] Primary among these successes are the enactment of the Biologics Price Competition and Innovation Act (BPCIA),[9] an Industry-favorable[10] pathway for the approval of follow-on biologics,[11] and (2) the application to biologics of the prohibition to disclose regulatory filings — including manufacturing information — to third parties in perpetuity.[12] When combined with protections afforded to biologics under the Patent Act, BPCIA and the prohibition on disclosure of biologics manufacturing information have created a uniquely powerful trifecta of intellectual property (IP) protections that make entry barriers to biologics markets extremely high.

The trifecta of IP protections of original biologics consists, first, of numerous — sometimes whole portfolios — of primary patents and, frequently, secondary patents that last long after the primary patents covering the product have expired.[13] Second, approved biologics benefit from an unprecedented period of twelve to 12.5 years of market exclusivity as well as four to 4.5 years of data exclusivity under BPCIA.[14] And third, biologics know-how, including the details of the process of manufacturing the product, are protected, practically in perpetuity, as trade secrets, under the FDA's confidentiality policies.[15] This triple-whammy of exclusivities affords biologics unusually long periods of exclusivity and guarantees that the barriers for entry into biologics markets remain high, sometimes for decades after a biologic was launched.[16]

As a result, the picture of competition in biologics markets has been and continues to be grim. The first approval of a follow-on biologic in the United States took place in 2015, almost ten years after the first approval in Europe and nearly twenty years since the emergence of the debate regarding how to evaluate and approve follow-on biologics in the United States.[17] Since then, as of the time of writing this arti-

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cle, a total of twenty-one follow-on products (deemed biosimilar to a total of nine original products) have been approved in the United States[18] (as compared with Europe's sixty-three[19]); only ten of these products (deemed biosimilar to a total of seven original products) actually cleared all hurdles to make it to the market;[20] and none of these products has been approved as interchangeable.[21] Moreover, as predicted by commentators, biologics markets, whether in original or follow-on products, are dominated by "a few subsidiaries of big pharma, a handful of established multinational generic manufacturers and the dominant large-cap biotech companies"[22] who keep prices high while being protected by high entry barriers and only minimal competition with one another.

Given all of this, arguably, *the regulatory and legal ecosystem of biologics itself is anti-competitive*.[23] Thus, one must not be overly heartened by the number of biosimilar applications pending at the FDA and the emergence of *some* competition in certain biologics markets.[24] One also should not take the mere emergence of such competition to be a sign of BPCIA's success nor be impressed by sales figures — high as they may be — of a few approved follow-on biologics, as sales figures are poor indicators of competition and are more telling of medical need and desperation of patients.[25] The goal has never been merely to have *some* competition in biologics markets. Rather, it is to have *sufficient competition to drive biologics prices down significantly*.

Even with the issuance of the FDA's interchangeability guidance,[26] there is little reason to believe competition in biologics markets in the United States is going to significantly improve.[27] To be sure, certain biologics markets are sufficiently lucrative to incentivize follow-on entry of a few or even a handful of sophisticated and financially well-backed companies.[28] Yet, competition in most biologics markets is and will likely remain more akin to the competition in markets in which a few large companies promote their "me too" versions of certain drugs[29] rather than to competition in markets that have seen the entry of true generics.[30] As a result, while a few exceptions may exist where competition drives the price of certain biologics below the typical 10-30% markdown,[31] the prices of most biologics will likely remain high. Therefore, from a public health standpoint, follow-on biologics are, and will in all likelihood continue to be, a limited phenomenon, providing only few, expensive options for payors, prescribers, and patients.

To make biologics markets in the United States truly competitive, a significant change must occur. This article calls for such a change to the legal and regulatory regime that dictates how follow-on biologics are evaluated and approved by FDA. Specifically, this article makes the case for legislation that would allow — possibly require — the FDA to share original biologics manufacturing information with follow-on biologics developers, enabling them to recreate the process of making the biologics they seek to imitate.

Part II of this article discusses the current regime of approval of follow-on biologics in the United States and explains in further detail why a paradigm shift is necessary if biologics markets are to become truly competitive. Part III explores ways of instigating such a shift by making original biologics' manufacturing information available to follow-on product developers as a potentially effective way of instilling competition into biologics markets. It lays down possible legal paths of doing so and addresses potential problems and critiques, arriving at the conclusion that making original biologics' manufacturing information available to follow-on product developers is legal, practicable, and advisable.

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II. The Current Model of Competition in Biologics Markets and Why it Does Not Work

The paradigm of increasing access to biologics seeks to emulate the success of the Hatch-Waxman Act[32] in opening drug markets to competition. That paradigm assumes that access to pharmaceuticals would

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increase once their prices drop; that prices would drop once competing follow-on products enter the market; that follow-on products will enter the market if their development can be incentivized; and that such development can be incentivized if follow-on manufacturers are allowed to rely on data submitted by the original product developer without having to make the same investment in developing the same data. That way, follow-on product developers can enter lucrative product markets without having to invest in redeveloping the data necessary to obtain FDA approval — essentially, the product — from scratch. The more data follow-on product developers can rely on, the greater their savings. And the greater their savings, the cheaper their products can be. In a nutshell: allowing follow-on product developers to rely on previously developed data to obtain FDA approval for their copycat follow-on products incentivizes them to enter drug markets, thereby bringing competition into such markets and, with it, much hoped-for price drops. One underlying assumption lies, however, at the heart of this paradigm and is necessary for all of this to work: that the original product and its follow-on version be sufficiently alike to serve as an acceptable substitute for each other.

In order to determine whether a follow-on product may substitute an original product, the FDA must determine whether the two products are sufficiently alike to make the substitution of one with the other clinically acceptable. To establish such clinical equivalence in the context of small-molecule drugs, the Hatch-Waxman Act requires that (1) the active pharmaceutical ingredient (API) in the follow-on product be chemically the same as the API in the original product,[33] (2) the two products have the same route of administration, dosage form, and strength,[34] and (3) the follow-on product is expected to have the same therapeutic effect as the original product when administered to patients.[35] Follow-on product developers are, in most cases, able to meet these requirements relatively easily, with a modest financial investment,[36] and without having to directly observe information from prior regulatory filings. Once the abovementioned requirements (1)-(3) are met, the Hatch-Waxman Act gives the FDA the authority to approve a follow-on product based on the assumption that if the original product was proven clinically safe and effective, and the two products are the same, then the follow-on product is expected to be *equally* safe and effective. In this way, the Hatch-Waxman Act makes it possible to establish clinical equivalence, and it does so while dispensing with the need to disclose or directly use data submitted as part of earlier FDA filings. Unfortunately, this elegant pathway for determining clinical equivalence of small-molecule drugs does not work for biologics.

Biologics are highly complex in both structure and composition,[37] and, at least presently, cannot be fully and precisely characterized in the same manner and to the same extent as small-molecule drugs.[38] As a result, under current scientific methods, it is very difficult and sometimes even impossible to establish that a follow-on biologic is the same as the original reference product that it seeks to imitate.[39] That is why Industry proponents have often argued that when it comes to biologics "the process [of making the product] is the product."[40] Hence, it is broadly accepted that short of meticulously replicating the process of making a biologic under the same conditions and using the same cell line, it would be very difficult and sometimes impossible to guarantee identity or even near identity between an original biologic and its follow-on version(s).[41]

But making biologics typically involves dozens if not hundreds of steps as well as many standards and techniques developed in-house and a highly specific (and potentially proprietary) progenitor cell line.[42] Reverse engineering or recreating all of these essential components — the cell line, techniques, and multitude of processes — for any specific biologic simply cannot be done without access to a product's manufacturing information.

The manufacturing information of biologics is an integral part of biologics license applications (BLAs) submitted to the FDA by original product developers seeking marketing approval for their biologics.[43] However, although the FDA is in possession of biologics' manufacturing information, the agency is prohibited from making that information available to follow-on biologics developers.[44] The laws prohibiting the disclosure of manufacturing information reflect an acceptance of the Industry's position that information submitted to the FDA in connection with product applications is proprietary and, as such, is not to be disclosed to third parties.[45] These laws further dictate that the FDA could not even compare the process of making an original biologic with the process of making follow-on products as part of its *internal* review of follow-on biologics marketing applications, without disclosing any of the information to follow-on applicants.[46]

Developers of follow-on biologics therefore find themselves in a difficult position. On the one hand, they have no access — not even indirect — to original biologics' manufacturing information, which would make it possible for them to create their own versions of the original biologics they seek to imitate. On the other hand, current scientific methods of character-

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ization and comparison of biologics do not enable them to establish identity of their follow-on versions of original biologics with the original products they seek to imitate.

As a result, developers of follow-on biologics are unable to follow a path similar to the one laid down in the Hatch-Waxman Act because they cannot establish that their products are identical to the original biologics they seek to imitate.[47] They must therefore attempt to recreate as close an imitation as possible of the original product and then establish its *clinical comparability* (rather than chemical identity) to the original biologic. They do so by first creating their own cell line and putting it through such purification and fermentation processes that the final product is as much like the original product as possible in its structure and composition, all the while refining their processes to try to conform their product to the original.[48] Next, they must attempt to recreate the clinical results of the original biologic using their own product by testing it on animals and, ultimately, human subjects.[49] If they also seek FDA recognition that their follow-on product and the original product are interchangeable, follow-on product developers must further carry out a "switching study"[50] on human subjects that would establish that the follow-on product "can be expected to produce the same clinical result as the [original] product in any given patient; and … the risk … of alternating or switching between use of the [follow-on] product and the [original] product is not greater than the risk of using the [original] product without such alternation or switch."[51] The exact nature and extent of the actual necessary comparisons between the follow-on biologic and the original product is decided on a case by case basis by follow-on product developers in consultation with the FDA.[52]

The resulting framework of evaluation and approval of follow-on biologics is detrimental to the emergence of competition in biologics markets. Without access to original biologics' manufacturing information, follow-on biologics developers are forced to partake in a sort of regulatory or scientific "hide-and-seek"[53] in which they try to fashion a follow-on product sufficiently akin to the original product so as to produce comparable clinical results in human patients, yet without being able to conclusively compare the two products or their manufacturing processes.[54] The necessary product-specific comparisons are therefore complicated, uncertain, and involve a much larger investment of resources than establishing bioequivalence under the Hatch-Waxman Act.

Developing a follow-on biologic is estimated to cost in the range of $100-250 million and even more for monoclonal antibody products, considerably more than the $1-5 million for a typical generic drug.[55] It takes eight to ten years, which is, again, significantly longer than the three to five years it takes to develop a generic drug.[56] And it is riskier, not just because of the scientific and clinical uncertainties attendant to the limitations of comparing the products and inability to compare the manufacturing processes,[57] but also because the regulatory and legal environment is still very much in flux and will likely remain so for the foreseeable future.[58]

If the market for an original biologic is lucrative enough, a determined and sufficiently sophisticated developer of follow-on biologics may endeavor to make the significant upfront investment necessary in order to traverse these scientific, regulatory, and legal hurdles. Indeed, for multibillion-dollar products, the current framework might even create enough financial incentives for several developers of follow-on biologics to try to enter the market, potentially leading

[T]he emerging regulatory reality of having to put follow-on biologics through expensive and prolonged testing — including on human subjects — is both socially wasteful and unethical. Developers of follow-on products must invest considerable resources only to try to recreate a product that already exists and is available on the market. Especially problematic in this respect is that in order to do so, follow-on biologics are required to undergo "switching studies" that potentially expose human subjects to the risk of significant harm only to confirm that a follow-on product is not more dangerous or less efficacious than an already-approved product.

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to significant price competition and increased access. However, for biologics whose market value might not provide clear opportunity to recoup the necessary initial investment, the current regulatory framework provides a smaller incentive to enter the market, leaving such markets with little or no price competition. With a few exceptions, this is, indeed, the situation in most U.S. biologics markets to date. Market entry of follow-on products is infrequent and results in only minimal price competition.[59]

Even more troubling, however, is that the emerging regulatory reality of having to put follow-on biologics through expensive and prolonged testing — including on human subjects — is both socially wasteful and unethical. Developers of follow-on products must invest considerable resources — resources that, arguably, would have been better spent on other research and development (R&D) projects — only to try to recreate a product that already exists and is available on the market.[60] Especially[61] problematic in this respect is the fact that in order to do so, follow-on biologics are required to undergo studies, including "switching studies," that potentially expose human subjects to the risk of significant harm only to confirm that a follow-on product is not more dangerous or less efficacious than an already-approved product.[62]

To recapitulate, without access to original biologics manufacturing information, in all but a few biologics markets, follow-on biologics do and will continue to lack the competitive edge necessary to drive down biologics prices to levels seen in generic drug markets.[63] This lack of access to manufacturing information also wastes limited societal R&D resources and unnecessarily exposes human subjects to a risk of bodily harm. All of this could change by making biologics manufacturing information available to follow-on product developers.

III. Making Biologics Manufacturing Information Available to Follow-On Developers

The proprietary and confidential status of regulatory filings, including manufacturing information, has, at least thus far, been a reality of pharmaceutical regulation. Yet, it is not a foregone conclusion.[64] Indeed, at least once, in the Federal Pesticide Act (FPA),[65] Congress had allowed public access to regulatory filings — *including manufacturing information* — made as part of applications for marketing approval of products subject to federal government regulation. In so doing, Congress effectively rejected the pesticide industry position — which is virtually identical to the contemporary pharmaceutical Industry position — that disclosure of information contained in regulatory filings is an unconstitutional taking of proprietary information under the Fifth Amendment.[66] Despite vehement opposition mounted by the pesticide industry, the measure passed a constitutional challenge and is in force to this day.[67]

A. Making Regulatory Submissions Publicly Available Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)

Enacted in 1978, the FPA amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[68] Under FIFRA, pesticides must be registered with the Environmental Protection Agency (EPA) prior to their sale in interstate commerce.[69] Receiving marketing approval for an original product under FIFRA typically requires submission of data to the EPA to demonstrate the safety and benefits of the particular pesticide product.[70] The FPA amendments to FIFRA created a ten-year exclusivity period, that could be waived at will, for information submitted by manufacturers of original pesticide products where the data pertains to a new active ingredient or a new use of a known ingredient.[71] This ten-year data exclusivity period is then followed by an additional five-year "mandatory compensation period," during which the EPA may consider previously submitted data in connection with new product applications "only if the [secondary] applicant has made an offer to compensate the original data submitter…"[72] If the parties cannot agree on the compensation amount, either party may initiate an arbitration proceeding with the Federal Mediation and Conciliation Service, the results of which are binding and not subject to judicial review, absent exceptional circumstances.[73] FPA further provides that an original product developer who refuses to participate in negotiations or in the arbitration proceeding with follow-on product developers who wish to use data contained in the original developer's regulatory filings forfeits its claim for compensation.[74]

Most significantly for the present discussion, under FPA, after expiration of the ten-year data exclusivity period and subsequent five-year mandatory compensation period, the data contained in original pesticide developers' regulatory filings becomes freely available for EPA to use in evaluating follow-on applications *and to disclose to qualified parties who request such data* without any need to receive the permission of the original product developer or offer compensation for the data, regardless of whether it includes trade secrets.[75] Importantly, however, the disclosed health, safety, and environmental data that EPA may use and disclose excludes information that would reveal "manufacturing or quality control processes," inert ingredients added to a product, and methods of testing

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or measuring their quantity *unless* the EPA has first determined that such disclosure "is necessary to protect against an unreasonable risk of injury to health or the environment."[76] The EPA also may not disclose information submitted by original pesticide product developers to any foreign or multinational pesticides companies without the consent of the data developer.[77] Finally, FPA made all of these arrangements applicable retroactively, namely to data submitted to the EPA after December 31, 1969.[78]

The legislative history of FIFRA and the FPA is instructive for the context of biologics. Originally, the 1947 version of FIFRA did not allow nor prohibit the disclosure of information relating to pesticide products.[79] During the early 1970s, several key processes and developments took place that eventually resulted in the institution of FIFRA's data protection framework. Among these were the ongoing increased use of pesticides in agriculture and concerns about their potential harmful effects on human and animal health[80] and the establishment of the EPA and its charge with the administration of FIFRA instead of the Department of Agriculture.[81] Another significant development was the amendment of FIFRA in 1972 so as to require a showing that pesticide products seeking marketing approval would not "cause unreasonable adverse effects on the environment."[82] All of these factors resulted in heightened requirements for scientific data regarding pesticide products as a condition for the grant of marketing approval by the EPA.[83] The need to collect such data, in turn, imposed increased financial burdens on developers of pesticide products who were now required to invest substantial resources in complying with the EPA's newly imposed data requirements.[84]

With the heightened data requirements posed by the EPA under FIFRA and the resultant increasing financial burdens, developers of original pesticide products became less and less tolerant of USDA (and later EPA) practices involving the disclosure and use of such data in connection with evaluation of follow-on product marketing applications.[85] Concerned with free-riding by follow-on product developers, original pesticide product developers sought to curb these practices or at least limit them in such a way that would minimize their exposure to financial loss owing to the sharing of data about their products. A heated public policy debate ensued, which epitomized all of the key elements we have been seeing in the debate regarding the confidentiality of FDA regulatory filings.[86]

On one side of the debate were proponents of developers of original pesticide products who advocated for stronger protection of information submitted to the EPA in connection with applications for registration of pesticide products.[87] Much like the Pharmaceutical Industry, the National Agriculture Chemical Association, for example, argued that EPA use of data submitted by original pesticide product developers in connection with an earlier application as part of its review of subsequent applications undermined incentives for the development of new pesticides and constituted a taking under the Fifth Amendment.[88] Proponents of original pesticide product developers sought complete prohibition of disclosure and use of any information they deemed proprietary (including safety, health, and environmental data), or, at the very least, the institution of long exclusivity periods during which the EPA would not be allowed to use and disclose previously submitted data.[89]

On the other side were those who favored access and who advocated for little or no exclusivity in the data submitted to the EPA. Among them were proponents of public access to information as well as those concerned over what they saw as a potentially wasteful and unjustified extension of monopolies via the institution of "quasi-patents" in addition to patent protections in pesticide products.[90]

Particularly relevant to the present discussion regarding biologics was the debate surrounding the length of the proposed exclusivity period under FPA, during which EPA would not be allowed to disclose or rely on information from earlier filings. Proponents of original product developers advocated for a ten-year data exclusivity, yet their pro-access opponents objected to the institution of any exclusivity period or would accept, at most, only a reasonable compensation requirement for disclosure of regulatory filings to follow-on product developers.[91] Others preferred a "middle-ground" of five years of exclusivity followed by an additional period of five years during which a compensation requirement would apply.[92]

Eventually, in 1978, Congress amended FIFRA by enacting the FPA, which revised FIFRA's data-consideration and data-disclosure provisions and instituted FIFRA's current regime.[93]

Despite its long, ten-year exclusivity period, five-year mandatory compensation period, and limitations on the type of data that could be disclosed by the EPA to third-parties, FPA failed to satisfy developers of original pesticide products as an acceptable compromise. Stepping up their decade long campaign against the use and disclosure of regulatory filings data, the original pesticide products industry challenged the constitutionality of FPA's data use and disclosure arrangements as a violation of the Fifth Amendment.[94] Specifically, the pesticide industry argued that (1) FPA effected a "taking" of original pesticide product developers' proprietary information without just compensation,[95] (2) the use of information was for private rather

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than a public purpose,[96] and (3) FPA's arbitration scheme abrogated original pesticide product developers' due process rights and constituted an unconstitutional delegation of judicial power.[97] The United States Supreme Court addressed these claims in the landmark 1984 case of *Ruckelshaus v. Monsanto*.

The *Ruckelshaus* Court rejected virtually all the claims raised by the original pesticide products industry and held that FPA's data use and disclosure provisions did not violate the Fifth Amendment with respect to data submitted prior to October 22, 1972, or after September 30, 1978.[98] The Court began by acknowledging that data such as that which is submitted by original pesticide product developers to the EPA as part of applications for marketing approval of pesticide products may indeed contain proprietary information and that such information is subject to the protection of the Taking Clause.[99] The Court then recited certain tenets of its takings law, including that there is not "any set formula for determining when justice and fairness require that economic injuries caused by public action must be deemed compensable taking" and that such inquiry is "essentially an ad hoc, factual inquiry" and should take under consideration such factors as "the character of the governmental action, its economic impact, and its interference with reasonable investment-backed expectations."[100]

Proceeding to the taking inquiry itself, the *Ruckelshaus* Court then held that the original pesticide product developers had no reasonable investment-backed expectation that data submitted to the EPA subsequent to FPA would be kept in confidence and not used by EPA or disclosed to qualified third-parties.[101] The Supreme Court explained:

> If, despite the data-consideration and data-disclosure provisions in the statute, [an original pesticide product developer] choose[s] to submit the requisite data in order to receive a registration, it can hardly argue that its reasonable investment-backed expectations are disturbed when EPA acts to use or disclose the data in a manner that was authorized by law at the time of the submission.[102]

The Court reasoned that the federal government's ability to regulate the marketing and use of pesticides cannot be challenged by the original pesticide products industry and that such government regulation is "the burden[] we all must bear in exchange for 'the advantage of living and doing business in a civilized community.'"[103] The Court emphasized that "[t]his is particularly true in an area, such as pesticide sale and use, that has long been the source of public concern and the subject of government regulation" and so, given the legitimate government interest in regulating that area of technology, "as long as [original pesticide product developers are] aware of the conditions under which the data are submitted, and the conditions are rationally related to a legitimate Government interest, a voluntary submission of data by an applicant in exchange for the economic advantages of a registration can hardly be called a taking."[104]

Furthermore, the Supreme Court held that absent *an express promise* developers of original pesticide products did not even have reasonable investment-backed expectations that the EPA will not use or disclose data they submitted before the enactment of FPA which was subject to the general provisions of the Trade Secrets Act.[105] The Supreme Court explained:

> In an industry that long has been the focus of great public concern and significant government regulation, the possibility was substantial that the Federal Government, which had thus far taken no position on disclosure of health, safety, and environmental data concerning pesticides, upon focusing on the issue, would find disclosure to be in the public interest.

Thus, held the Supreme Court, in the absence of *express statutory language* promising that information contained in regulatory filings will be kept confidential, the Trade Secrets Act "provides no basis for a reasonable investment-backed expectation that data submitted to EPA would remain confidential" and it "cannot be construed as any sort of assurance against internal agency use of submitted data during consideration of the application of a subsequent applicant for registration.[106]

The *Ruckelshaus* Court further ruled that even if the disclosure and use of proprietary information by the EPA were to constitute a taking for Fifth Amendment purposes, it would still be for "public use" and therefore permissible. The Supreme Court rebuked the view that "public use" only exists where the property taken by the government is put to use for the general public, warned that "[t]he role of the courts in second-guessing the legislature's judgment of what constitutes a public use is extremely narrow"[107] and ruled that "[s]o long as the taking has a conceivable public character, 'the means by which it will be attained is . . . for Congress to determine.'"[108] Applying these principles to FPA, the Supreme Court upheld FPA's arrangements as directed to "public use" while giving recognition to FPA's underlying rationale:

> [T]he public purpose behind the data-consideration provisions [of FPA] is clear from the leg-

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> islative history. Congress believed that the provisions would **eliminate costly duplication of research and streamline the registration process**, making new end-use products available to consumers more quickly. Allowing applicants for [follow-on products] to use **data already accumulated by others, rather than forcing them to go through the time-consuming process of repeating the research, would eliminate a significant barrier to entry into the pesticide market**, thereby **allowing greater competition among producers of end-use products**. Such a procompetitive purpose is well within the police power of Congress.[109]

Thus, held the Supreme Court, any taking that may occur as a result of EPA use and public disclosure of data submitted by original pesticide product developers would be a taking for public use.[110]

Finally, the *Ruckelshaus* Court rejected the claim that takings affected by FPA — to the extent such takings were to take place — will be unconstitutional for lack of just compensation. The Court held that FPA created an arbitration proceeding aimed at providing for just compensation in cases of taking and that, even in cases in which such compensation was unavailable, original pesticide product developer were still able to sue the government in the Court of Federal Claims under the Tucker Act.[111] Thus, the Court concluded, the challenge to the constitutionality of FPA's arbitration and compensation scheme was not ripe.[112] In conclusion, the Supreme Court held that there was "no constitutional infirmity in the challenged provisions of FIFRA."[113]

Notably, the *Ruckelshaus* Court did not fail to recognize the substantial investment of time and resources necessary in order to develop an original pesticide products; that such investment makes the data produced by original pesticide product developers potentially highly valuable; and that such data "contai[n] or relate to trade secrets ... and Confidential, commercial information."[114] Nor has the Court shied away from recognizing that EPA's disclosure of data that constitutes a trade secret and the use of such data by follow-on pesticide product developers would destroy the trade secret owner's property interest in the data.[115] Nonetheless, the Supreme Court upheld the constitutionality of FPA, setting an important precedent and, potentially, clearing the path for additional similar regimes.

The effect FPA and the subsequent *Ruckelshaus* decision may have had on innovation is difficult to assess. The literature examining pesticide markets and innovation during the 1970s and 1980s shows that increase in the regulatory costs imposed on the pesticide industry (from 14% to 47% of total research spending) accompanied by an increase in development time (from seven to eleven years) caused a sharp decrease in the number of new pesticide product registrations[116] for minor crops (from sixty-two between 1972-76 to just fifteen over the 1985-89 period).[117] At the same time, the literature also shows that during that same period there was almost no change in the number of new pesticide product registrations for major crops, that there was consistent growth in investment in pesticide R&D, and that there was a marked improvement in the safety of pesticides products.[118] Moreover, the reported decrease in the number of new product registrations had occurred almost entirely in the *early and mid*-1970s, well before the enactment of FPA, and is therefore more likely to be the result of increased regulatory stringency subsequent to the establishment of the EPA in 1972 rather than of FPA's data sharing arrangements and *Ruckelshaus*.[119] Thus, to the extent that FPA and *Ruckelshaus* had any effect on innovation, that effect is not readily discernable from the literature.[120] The lack of a clearly observable dampening effect of FPA and *Ruckelshaus* on pesticide innovation may indicate that incentives for innovation were still sufficient even after FPA and *Ruckelshaus*

Making original biologics manufacturing information available to follow-on product developers will significantly lower the resources necessary to develop follow-on biologics and enter biologics markets with follow-on products. That, in turn, is expected to lower the existing high entry barriers to these markets, increase the number of potential competitors who will have the resources to enter such markets, and lead to increased competition, which — given a critical number of competitors — will, ultimately, lower biologics prices.

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and that implementing similar arrangements in other regulated industries might not undermine incentives for innovation. Which brings us back to biologics.

B. The Case for Making Biologics Manufacturing Information Available to Follow-On Applicants

Pesticides and biologics have much in common. Most relevant to the current discussion is that both require significant investment of resources in R&D before they can be brought to market; both are subject to federal regulation under specialized bodies of law and by expert federal agencies; both are required to meet certain standards before they are allowed to enter the market; both are the subject of exclusivities that are meant to incentivize innovation; and both pose high entry barriers, leading to a tendency for market concentration and its attendant ills.[121] When combined with the teachings of *Ruckelshaus v. Monsanto*, these commonalities suggest that implementing in biologics information disclosure rules similar to those enacted under the FPA may serve to alleviate many if not all of the problems discussed earlier.

Making original biologics manufacturing information available to follow-on product developers will significantly lower the resources necessary to develop follow-on biologics and enter biologics markets with follow-on products. That, in turn, is expected to lower the existing high entry barriers to these markets, increase the number of potential competitors who will have the resources to enter such markets, and lead to increased competition, which — given a critical number of competitors — will, ultimately, lower biologics prices.[122]

Disclosure of manufacturing information to follow-on biologics developers will minimize the waste of limited societal R&D resources that are currently spent on efforts to imitate original biologics and make it possible to divert such resources to potentially more meritorious avenues of research.

And, last but not least, sharing manufacturing information with follow-on biologics developers will contribute to patient health and safety and avoid the ethical quagmire of requiring comparability studies. First, sharing manufacturing information will make comparability studies — especially "switching studies"[123] — mostly if not entirely unnecessary, thereby eliminating the health and safety risks for human subjects participating in such studies. Second, the sharing of manufacturing information will also ensure that the safety, efficacy, and purity profiles of original biologics and their follow-on versions are as close to each other as possible, thus eliminating unnecessary health and safety risks that comparability studies might not have detected sufficiently early due to study design limitations.[124] And third, eliminating the need for comparability studies will do away with the very real concern that comparability studies are unjustified, and therefore unethical, because their true purpose is not to create a new product that would benefit patients but to *recreate an existing product via reverse engineering,* using human subjects as mere fodder for a regulatory method whose purpose is to avoid compromising the property interests of original biologics developers.[125]

In short, making original biologics manufacturing information available to follow-on biologics developers would be an efficient and effective way of bringing significant price-competition to biologics markets *and* safeguarding patient (including test subjects) health and safety without undermining or doing away with the BPCIA framework in its entirety. I therefore propose to change the laws pertaining to the regulation of biologics to allow for the disclosure of original biologics manufacturing information to follow-on biologics developers, upon follow-on developers' request,[126] subsequent to the expiration of BPCIA's four to 4.5-year data exclusivity period. The following section discusses the legal feasibility and specific ways of doing so.

C. Pathways for Making Biologics Manufacturing Information Available to Follow-On Applicants

Making original biologics manufacturing information[127] available to follow-on product developers can be achieved in numerous ways. The most preferable way would be for Congress to enact a statute that explicitly grants the FDA the authority to disclose biologics manufacturing information to follow-on product developers. Such a law could take the form of a standalone section, an amendment to BPCIA, the Food, Drug and Cosmetics Act (FDCA),[128] the Public Health Service Act (PHSA),[129] or any combination of these options.[130]

Another way would be for Congress to institute direct disclosure of original biologics manufacturing information to follow-on biologics developers (rather than through the FDA). This course of action, however, is less preferable because of its potential for abuse and for causing friction between the parties.[131] Should congress choose to take this path, it may rely on and expand BPCIA's *existing* requirement that follow-on biologics developers disclose *their* manufacturing information to original biologics developers as part of the Act's patent dispute resolution framework (a.k.a. "patent dance").[132] Doing so, however, would require Congress to construct the measure such that the disclosure of original biologics manufacturing information is not limited to the patent dance framework and/or to situations in which the parties are engaged in a patent dispute.

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Congressional legislation effecting disclosure of original biologics manufacturing information may be tailored broadly — e.g., allowing the FDA to use any information in its possession however it deems necessary to promote the public health. Or it may be structured narrowly — e.g., granting the FDA the authority to give specific parties access to original biologics' manufacturing information when safety considerations or the public health require it,[133] and subject to commitment to keep the information in confidence and not further share it with additional third parties and/or entities with operations outside of the United States.[134] Such a statute may also apply retroactively to filings made prior to its enactment.[135]

Disclosure of original biologics manufacturing information to follow-on product developers could also, at least hypothetically, be achieved through FDA regulation if Congress were to amend FDCA Section 301(j) so as to limit its applicability to original biologics manufacturing information. Section 301(j), which is made applicable to biologics under PHSA Section 351(j),[136] prohibits "using by any person to his own advantage, or revealing ... any information acquired under authority ... of this title concerning any method or process which as a trade secret is entitled to protection."[137] Indeed, FDA regulations clearly reflect the FDA's reading of Section 301(j) as precluding the agency from disclosing information contained in regulatory filings in general and biologics manufacturing information in particular.[138]

Should Congress limit the applicability of FDCA Section 301(j) to biologics manufacturing information, FDA should find ample authority to create a regulatory pathway for the sharing of original biologics manufacturing information. PHSA grants the Secretary of Health and Human Services the authority to "establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses."[139] This broad authority gives the FDA the power to promulgate regulations as it deems necessary to implement BPCIA. BPCIA, in turn, grants the FDA (through the Secretary of HHS) the specific authority to approve applications for follow-on biologics based on a determination that a follow-on biologic is biosimilar to or interchangeable with an original biologic.[140] BPCIA deems two products biosimilar if they are (1) "highly similar ... notwithstanding minor differences in clinically inactive components" and (2) have "no clinically meaningful differences ... in terms of [their] safety, purity, and potency."[141] Thus, BPCIA gives the FDA the power to promulgate whatever regulations it deems necessary to facilitate its evaluation of whether a follow-on biologic and an original biologic are "highly similar" and have "no clinically meaningful differences ... in terms of [their] safety, purity, and potency." This, I contend, may include the power to share previous regulatory filings made in connection with applications for original biologics, including manufacturing information, with follow-on product developers.

[T]he problem with biologics markets is not that they are prone to abuse through regulatory loopholes but that they are constructed in such a way that is itself non- and even anti-competitive. To bring price competition to biologics markets, it is necessary to make a significant change to the paradigm of how FDA evaluates and approves follow-on biologics by giving follow-on developers access to original biologics manufacturing information. Unfortunately, it does not seem like we have reached the point where there is enough political will to make this kind of change. But that point may be fast coming.

Furthermore, PHSA instructs the FDA (again, through the Secretary) to approve applications for biologics only "on the basis of a demonstration that ... the [biologic] is safe, pure, and potent."[142] Reading this statutory language in conjunction with BPCIA therefore obligates the FDA to approve a follow-on biologic only if it is convinced that the follow-on product and original biologic are "highly similar" and have "no clinically meaningful differences ... in terms of [their] safety, purity, and potency."[143] As discussed earlier, the ability to compare follow-on biologics to the original biologics they seek to imitate without having access to the original biologics' manufacturing information is highly limited. Accordingly, if FDA

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is to uphold PHSA's instruction that it approves only follow-on biologics that are sufficiently safe, effective, and pure, then — FDCA Section 301(j) aside — the law *requires* that FDA has the power to disclose original biologics manufacturing information to follow-on biologics developers where such disclosure is necessary to meet the FDA's standards of safety, efficacy, and purity. Indeed, expecting the FDA to ensure that follow-on biologics are sufficiently safe, effective, and pure without disclosing the original biologics' manufacturing information *or even using it internally* as part of its evaluation of follow-on biologics applications is, arguably, asking FDA to perform its statutory duties with one hand tied behind its back while being blindfolded.

Moreover, even in cases where comparability of follow-on biologics with original biologics may be established without disclosure of the original biologics' manufacturing information, because of the inherent limitations of current comparison techniques, the safety and efficacy of follow-on biologics would be further ensured if follow-on biologics developers had access to the original biologics' manufacturing information. This, together with FDA's duties and powers under PHSA and BPCIA, as well as the FDA's core mission — to "protect[] the public health by ensuring the safety, efficacy, and security of … drugs, biological products, and medical devices"[144] — lead to the conclusion that but for FDCA Section 301(j) FDA would have the authority to share original biologics manufacturing information with follow-on product developers to the extent necessary to ensure the safety, efficacy, and purity of follow-on biologics.

BPCIA itself is silent about the issue of sharing and use of information from original biologics regulatory filings and how FDA may choose to implement its authorities under the statute in this regard.[145] Rather, BPCIA only determines what information FDA *may* consider in evaluating follow-on biologics applications.[146] The statutory language, however, does not foreclose the consideration of additional categories of information (e.g., manufacturing information) nor does it prohibit the disclosure of original biologics manufacturing information for the purpose of follow-on products evaluation. To the contrary, BPCIA expressly states that a follow-on biologic application "may include any additional information in support of the application."[147] Therefore, BPCIA itself does not preclude the FDA from use and disclosure of regulatory filings, including original biologics manufacturing information. If anything, BPCIA's open ended language regarding the types of information that follow-on applicants may submit and FDA may consider can be read as an invitation for the FDA to share manufacturing information with follow-on product developers and use such information as part of its evaluation of follow-on biologics.[148]

The discussion now turns to the question of why has Congress not incorporated into BPCIA a pathway for the disclosure of original biologics manufacturing information from its inception and what is the likelihood of Congress doing so in the future?

D. Politics, Political Economy, and Plausibility

With a few exceptions, legislative processes are notoriously slow and exceedingly difficult to traverse. Passing a legislative measure requires forming political alliances sufficient to chaperone the measure through all the necessary procedural hurdles in both chambers of Congress, passing it through (at least) two up-or-down votes, and then getting it past the president — a Herculean feat in the best of times, let alone in this particular day and age. And all of this is without even considering the expected opposition from the Industry, which employs one of the strongest lobbies in Congress and which is known for its lavish and ongoing financial support of numerous members of Congress.[149] Indeed, the influence exerted by the Industry over Congress is responsible for what many view as Congress's long history of over-attentiveness to the Industry's concerns, not to say capitulation to its demands, and too little concern for public access.[150]

Congress's highly favorable attitude toward the Industry may explain why in all the legislative debates that preceded the enactment of BPCIA, the option of making original biologics manufacturing information available to follow-on developers was not even on the table. It is difficult to believe that the drafters of BPCIA and competing bills[151] — including those who are not known as Industry-advocates — were oblivious of the FIFRA regime. A more likely explanation is that the idea of sharing manufacturing information was such a non-starter with industry proponents that pro-access drafters who wanted their bills to be considered seriously as a possible platform for legislative discussions never dared including it in their proposals. It may be telling that the only measure that came even close to such a proposal was an amendment to the BPCIA bill introduced by Senator Bernie Sanders (I-VT) that would have created an arrangement akin to the FIFRA mandatory compensation arrangement under which a follow-on applicant would have access to clinical data submitted by an original product applicant.[152] Yet, even that rather limited proposal was summarily dismissed without any record of it ever actually being given consideration.

No doubt, some things have changed since the enactment of BPCIA. Over the last few years, the

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cost of healthcare in general and pharmaceuticals particularly have become a centerstage issue in the public debate. And while the Industry still has many powerful friends in Congress, an increasing number of Members of Congress are willing to speak out for access and against Industry interests.[153] Still, at this point and in this political landscape, it is difficult to see Congress passing legislation that would make significant changes to the way we regulate biologics. A primary reason for that is that the movement to curb drug prices assumes that prices remain high mostly due to foul play by pharmaceutical companies, drug distributors, and possibly other actors involved in the production and sale of pharmaceuticals. That movement seems to assume that if we just closed all the loopholes that allow for such foul play, the pricing problem would resolve itself through competition. The resultant legislative efforts, therefore, have been rather narrow in that they have focused on eliminating unfair Industry practices.[154]

However, as explained above, the problem with biologics markets is not that they are through regulatory loopholes that could be "fixed" but that they are constructed in such a way that is itself non- and even anti-competitive. To bring price competition to biologics markets, it is necessary to make a significant change to *the paradigm* of how FDA evaluates and approves follow-on biologics by giving follow-on developers access to original biologics manufacturing information. Unfortunately, it does not seem like we have reached the point where there is enough political will to make this kind of change. But that point may be fast coming.

The ongoing, continuing growth of government expenditure on medicines in general and biologics in particular might instigate further shift in Congress's attitude toward the drug pricing problem, driving it to examine the underlying regimes themselves. If and when that shift occurs, Congress may, eventually, consider amending BPCIA and/or FDCA Section 301(j) to allow FDA to disclose to follow-on biologics developers the manufacturing information of the original biologics they seek to imitate. And when it does, the ball will move to the FDA's court for implementation.

To facilitate the disclosure of original biologics manufacturing information, the FDA will probably need to promulgate new regulations via a notice-and-comment process, which will, no doubt, be prolonged and marked by significant Industry opposition. It is highly likely that the promulgation process and issuance of a rule that would affect the disclosure of original biologics manufacturing information to follow-on product developers will also prompt the Industry to legally challenge the regulation, possibly as an unconstitutional taking. As discussed below, the likelihood of success of such a legal challenge in enjoining the FDA rule is not high and the challenge is unlikely to result in the court striking it down.[155] And yet, given the FDA's conservative, even timid record when it comes to biologics regulation,[156] Congress ought to draft the legislation enabling and instructing the FDA to disclose original biologics manufacturing information in explicit and specific terms.

E. Possible Shortfalls, Pitfalls, and (Industry) Critique

1. undermining incentives for innovation in biologics

The primary concern in making changes to regulatory schemes involving innovative products, like biologics, is that such changes might upset a balance struck between incentives for innovation and the public interest in access to the fruits of such innovation. As its name suggests, the Biologics Price Competition and Innovation Act sought to strike such a balance. Thus, the concern is that changes made to the BPCIA framework, especially as they pertain to rights in/to the products of innovative efforts, might detract from and undermine BPCIA's incentives for investment in original biologics R&D.

The overall landscape of incentives for innovation in the area of biologics, however, indicates that such concerns would be unfounded. As mentioned earlier, original biologics currently enjoy a uniquely powerful array of intellectual property protections, including patents, a twelve-year market exclusivity, a four-year data exclusivity, and trade secret protection of manufacturing information and testing data, practically in perpetuity.[157] It is this array of protections that is responsible, in large part, to the poor state of price competition in biologics markets. Indeed, if anything, the area of biologics suffers from over-protection for innovation,[158] which is evidenced by original biologics manufacturers' ability to charge super-competitive prices for their products long after the expiration of the primary patents and market exclusivities covering these products, and certainly long after the manufacturers have recouped their R&D costs.[159]

Furthermore, biologics markets are *the most lucrative pharmaceutical markets in history*.[160] The cost of developing original biologics is a highly fraught issue with estimates ranging dramatically.[161] Yet, even the highest estimates that are advanced by Industry-funded organizations and researchers[162] make clear that once a company has secured the resources necessary to develop an original biologic, recouping such investment is not particularly risky.[163]

Moreover, under BPCIA, exclusivity in original biologics is assured, at a minimum, for twelve-years

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subsequent to the approval of an original biologic by FDA.[164] That period of exclusivity — also the subject of much controversy[165] — was devised to serve in lieu of patents and was based on the Industry's own estimates of the length of time it would take developers of original biologics to recoup their investment in a typical biologic.[166] In other words, BPCIA already includes *the Industry's own preferred mechanism* for maintaining sufficient incentives for innovation in biologics: the twelve-year market exclusivity. Making manufacturing information available to follow-on biologics developers is not going to change that.[167] Accordingly, by the Industry's own logic, the indefinite protection of manufacturing information is not only unnecessary, but also excessive.

As a side, the excess of incentives for innovation currently afforded to original biologics developers — with its harmful consequences for competition in biologics markets — is unlikely to be fully resolved even if manufacturing information were made available to follow-on product developers. Without the indefinite confidentiality of manufacturing information, original biologics developers are still going to benefit from (1) BPCIA's twelve-year market exclusivity,[168] (2) BPCIA's four-year data exclusivity,[169] (3) BPCIA's additional six months of exclusivity for putting their products through pediatric studies,[170] and (4) whatever patent protection is available in the original active ingredient(s), processes of making them, and methods of using them.[171] Making manufacturing information available to follow-on biologics developers may, however, alleviate some of the negative effects of the overprotection afforded to original biologics by bringing *a measure* of price competition to *some* biologics markets.

2. UNCONSTITUTIONALITY

The Industry's longstanding position has been that its submissions to the FDA in connection with product marketing applications contain proprietary and confidential information and that sharing such information with third parties or using it for the purpose of comparing original and follow-on products would constitute a per se violation of the Fifth Amendment's Taking Clause.[172] Indeed, it was the Industry's successful assertion of this position that dissuaded the FDA from attempting to develop a *regulatory* pathway for the approval of follow-on biologics based on its existing authorities, eventually drove Congress to step in, and resulted in the legislative efforts that led to the enactment of BPCIA.[173]

However, the Industry's position is significantly challenged, if not wholly belied, by the Supreme Court's decision in *Ruckelshaus*. Under *Ruckelshaus*, "[i]f an individual discloses his trade secret to others who are under no obligation to protect the confidentiality of the information, or otherwise publicly discloses the secret, his property right is extinguished."[174] Thus, should Congress authorize the FDA to disclose original biologics manufacturing information to follow-on biologics developers, then — even assuming portions of the information qualify as proprietary — subsequent voluntary submission of such information to the FDA by original biologics developers will extinguish any property rights in that information, precluding the possibility of a taking.[175] As plainly stated by the *Ruckelshaus* Court, "as long as [original product developers are] aware of the conditions under which the data are submitted, and the conditions are rationally related to a legitimate Government interest, a voluntary submission of data by an applicant in exchange for the economic advantages of a registration can hardly be called a taking."[176]

As also made clear by *Ruckelshaus*, a law allowing disclosure of regulatory filings information to third parties does not constitute per se taking under Supreme Court taking jurisprudence.[177] Importantly, the *Ruckelshaus* Court did not view *even the retroactive application of such a law*, namely applying the law to regulatory filings made *before* the new law went into effect, as constituting a per se taking.[178]

And yet, all of this is not to say that disclosure of manufacturing information to follow-on biologics developers could *never* constitute a taking. Under well-established Supreme Court takings law, the determination of whether a taking occurs is an "ad-hoc, factual inquiry" that requires consideration of "the character of the governmental action, its economic impact, and its interference with reasonable investment-backed expectations."[179] As discussed earlier, making original biologics manufacturing information available to follow-on biologics developers will achieve a variety of public policy goals — improving access to life-saving medicines, preventing waste in allocation of research funds, foregoing the need for unethical research, and more — without interfering with original biologics developers' patent and BPCIA exclusivity rights. It would, however, potentially diminish or completely destroy the value of trade secrets contained in such information and significantly compromise the ability of original product developers to maintain a monopolistic market position in their products past the expiration of their 12-12.5-year market exclusivity, thus undermining projected profits from original products past that point.

The Industry has argued that such consequences would interfere with original biologics developers' reasonable investment-backed expectations that regulatory filings be kept confidential in perpetuity.[180]

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That position is not without merit. Section 301(j) of FDCA, prohibits "using by any person to his own advantage … or revealing … any information acquired under authority … of this title concerning any method or process which as a trade secret is entitled to protection."[181] Arguably, the language of Section 301(j), which under PHSA also applies to the approval of biologics,[182] may be read as a prohibition on FDA employees to disclose proprietary information contained in regulatory filings. Furthermore, FDA regulations explicitly reflect the agency's policy of not disclosing information contained in regulatory filings in general and biologics manufacturing information in particular.[183] These provisions and policies could have, indeed, created reasonable expectations among original biologics developers that their regulatory filings be kept confidential.[184] However, there is also merit in the view that it would be unreasonable to expect Congress and the FDA to *never* reconsider the current arrangements dictating the non-disclosure of regulatory filings pertaining to original biologics.

First, as explained by the *Ruckelshaus* Court, that the law provides general protection to trade secrets — e.g., under the Trade Secrets Act,[185] the Defend Trade Secrets Act,[186] and PHSA Section 301(j) — "is not a guarantee of confidentiality to submitters of data, and, *absent an express promise*, [a submitter of data has] no reasonable, investment-backed expectation that its information would remain inviolate in the hands of [the agency]."[187] Like pre-1972 FIFRA, BPCIA is silent with respect to the possibility of disclosure of information from regulatory filings to follow-on applicants, which, under *Ruckelshaus*, may deem unreasonable expectations that such information would remain undisclosed forever.[188] Similarly, FDA policies prohibiting the disclosure of information contained in regulatory submissions also, arguably, do not meet the *Ruckelshaus* "express promise" standard because they are not made in a statute.[189]

Second, as further explained by the *Ruckelshaus* Court, in regulated industries, where the statute is silent, applicants should expect that regulatory filings might be disclosed.[190] Much like the pesticide industry in the 1970s, the pharmaceutical industry nowadays is "the focus of great public concern and significant government regulation," which the *Ruckelshaus* Court viewed as cause enough for putting product applicants on notice that the government might, "upon focusing on the issue … find disclosure to be in the public interest."[191] Indeed, arguably, the *Ruckelshaus* decision *itself* puts original biologics developers on notice that the federal government might eventually decide to disclose information from regulatory filings to follow-on applicants, rendering unreasonable any expectations that such information be kept secret in perpetuity.

And third, the Industry's position cuts against current transparency trends in Europe and at FDA itself.[192] These trends should, at the very least, raise questions among original biologics developers regarding the future of policies involving the confidentiality of regulatory filings. That, in turn, could call into question the reasonableness of reliance on such policies.

To summarize: the question of reasonableness of original biologics developers' expectations that manufacturing information contained in regulatory filings be kept confidential in perpetuity does not have a conclusive answer and is unlikely to have one unless and until a federal court decides it as part of its ad-hoc factual inquiry into the takings question. If the Industry is found to have not had reasonable investment backed expectations that manufacturing information be kept confidential in perpetuity by the FDA, then under Supreme Court Fifth Amendment jurisprudence there can be no taking. For the purpose of the present discussion, however, let us assume that a federal court may indeed find reasonable the Industry's expectations that biologics manufacturing information be kept confidential in perpetuity.

In such a case, a court deciding the question of taking must still also consider "the character of the governmental action [and] its economic impact" before it can make a determination of whether there is a taking under the Fifth Amendment.[193] Given careful consideration by legislators and/or FDA regulators of the pros and cons of disclosure of original biologics manufacturing information and a carefully worded legislative and/or regulatory measure, it is possible that a court considering the question of a taking will conclude there was none *regardless* of any reasonable investment-backed expectations to the contrary. And so, yet again, let us assume for the purpose of the present discussion that after consideration of all relevant circumstances, the court finds that a Fifth Amendment taking indeed took place, what then? As made clear in *Ruckelshaus*, such a determination still does not mean that the taking cannot proceed but simply that it must be followed by "just compensation."[194]

Supreme Court jurisprudence holds that "The Fifth Amendment does not require that compensation precede the taking" and that "an individual claiming that the United States has taken his property can seek just compensation under the Tucker Act."[195] Accordingly, a legislative and/or regulatory measure that would give follow-on biologics developers access to original biologics manufacturing information and that would constitute a taking under the Fifth Amendment will

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not necessarily have to include a means of compensating original biologics developers for the loss of their trade secrets. Rather, it would enable them to seek such compensation by suing the federal government in the Court of Federal Claims under the Tucker Act. Or, at least that would have been the case had BPCIA not already provided just compensation.

As discussed earlier, BPCIA includes a uniquely long market exclusivity period that embodies the Industry's own preferred mechanism for enabling original biologics developers to recoup their R&D investment.[196] This 12-12.5-year market exclusivity *is* the compensation — which some would say is more than just[197] — afforded by Congress to original biologics developers for the opening of biologics markets to price competition.[198] Indeed, the intended quid-pro-quo that BPCIA meant to achieve is evident in the Act's very name — the Biologics *Price Competition* and Innovation Act — which juxtaposes price competition with incentives for innovation; the exclusivity regime instituted under BPCIA with the opening of biologics markets to price competition.

In sum, Congressional legislation that would make it possible for FDA to disclose original biologics manufacturing information to follow-on product developers might or might not constitute a taking under the Fifth Amendment. Either way, such legislation will not be unconstitutional.

3. DISCLOSURE OF MANUFACTURING INFORMATION MIGHT NOT BE ENOUGH

As discussed earlier, biologics can be difficult to make and even more so to replicate.[199] Indeed, even original biologics manufacturers who have all the resources to replicate *their own* products sometimes have a hard time doing so in different batches of the same product.[200] And in some cases, making a biologic requires not just meticulously following its manufacturing "recipe" but also the use of a highly specific (and proprietary) cell line, as well as application of other standards. In short: there may be cases where original biologics manufacturing information alone might not be enough for follow-on product developers to make close enough imitations of the original products they seek to imitate.

In such cases, it may be necessary to require original biologics developers to share with follow-on applicants any progenitor cell lines necessary to create a copy of the original biologic. Such sharing may be done either directly — with the original manufacturer giving a sample of the cell line to the follow-on developer — or indirectly — by depositing a sample with the FDA, which will share it with qualified follow-on developers.

At a first glance, requiring that original biologics developers share not only information but also *tangible objects* in their possession might seem problematic. The constituting principle, however, is the same: after the expiration of BPCIA's four to 4.5-year data exclusivity period, follow-on biologics developers should be able to have access to whatever knowledge and materials are necessary in order to create the truest replica possible of the original biologic. The physical nature of the cell line also should not significantly change the taking analysis since cell lines are easy and inexpensive to propagate and because sharing a sample from a cell line will neither destroy its value nor deny its owner the ability to use it (or at least the portions of the cell line that it retains in its possession).[201] Indeed, sample depositing and sharing requirements are nothing new in federal law and have been incorporated not only into patent law — with the express intent to make such samples available to third parties[202] — but also into food and drug law.[203]

To conclude this part: disclosure of original biologics manufacturing information is not only feasible but is also *advisable*.

Conclusion

As biologics continue to grow in prevalence and importance, despite the enactment of BPCIA in 2010, their prices remain high. The recent issuance of the FDA Interchangeability Guidance is unlikely to change this reality for most biologics, even after BPCIA's twelve to 12.5-year market exclusivity and primary patents covering such biologics have expired. To bring significant, Hatch-Waxman-like price competition to biologics markets, a shift in the paradigm of approval of follow-on biologics is necessary.

This article proposes such a change: the disclosure by FDA of original biologics manufacturing information to follow-on biologics developers seeking to create their own versions of the original products. Granting follow-on biologics developers access to original biologics manufacturing information will not only bring significant price competition to biologics markets but will also prevent social waste of limited R&D resources, circumvent the need to carry out potentially unethical comparability studies, and advance public health and safety. The disclosure of original biologics manufacturing information is also unlikely to undermine the strong incentives for innovation in the area of biologics. Nor will it run against the Fifth Amendment to the Constitution.

The idea of disclosing original biologics manufacturing information to follow-on biologics developers may seem radical to some, but that is because players in the area of pharmaceutical regulation have grown

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accustomed to the idea that regulatory filings are and will always remain confidential. As discussed in this article, that perspective is belied by the regulatory and commercial reality in the area of pesticides. The other alternative — one which many will find even less appetizing and which the United States seems to be unavoidably moving towards — is direct price control.

Note

The author has nothing to declare.

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References

1. *See* IQVIA Institute for Human Data Science, *Medicine Use and Spending in the U.S.* (2018): at 11, *available at* <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1536097777009> (last visited November 11, 2019; access requested) ("Biologics grew by 12.6% in 2017, averaging 11.2% for the last five years as a variety of biologic treatments for autoimmune disorders, immunology and cancer came to the market"); IQVIA Institute for Human Data Science, *2018 and Beyond: Outlook and Turning Points* (2018): at 20, *available at* <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/2018-and-beyond-outlook-and-turning-points.pdf> (last visited November 11, 2019) ("With the total market for biotech medicines reaching $168 billion across developed markets in 2016 …"); EvaluatePharma, *World Preview 2017, Outlook to 2022* (2017): at 6, *available at* <http://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf> (last visited November 11, 2019) ("Biologics to contribute 52% of the Top 100 product sales by 2022"); E. A. Blackstone and J. P. Fuhr, Jr., "The Economics of Biosimilars," *American Health & Drug Benefits*, September 2013 (2013): at 469 ("The average daily cost of a biologic in the United States is $45 compared with only $2 for chemical (small-molecule) drugs").
2. Six out of the top-ten best-selling pharmaceuticals in 2017 were biologics: Humira (adalimumab), Rituxan (rituximab), Herceptin (trastuzumab), Avastin (bevacizumab), Remicade (infliximab), and Enbrel (etanercept). L. Urquhart, "Market Watch: Top Drugs and Companies by Sales in 2017," *Nature Reviews Drug Discovery* 17 (2018): 232. The annual price per patient of Humira in the U.S. in early 2018 was $38,000. *See* D. Hakim, "Humira's Best-Selling Drug Formula: Start at a High Price. Go Higher," *New York Times*, January 6, 2018, *available at* <https://www.nytimes.com/2018/01/06/business/humira-drug-prices.html> (last visited November 11, 2019). The annual price per patient of Rituxan in the U.S. in 2017 was $36,663 and of Remicade was $44,973. *See* J. Schmier et al., "Costs of Providing Infusion Therapy for Rheumatoid Arthritis in a Hospital-based Infusion Center Setting," *Clinical Therapy* 39 (August 2017): 8. The annual price per patient of Herceptin in the U.S. in 2017 was $74,500. *See* D. Beasley, "Roche Combo of Breast Cancer Drugs Shows Modest Benefit," *Reuters*, June 5, 2017. The annual price per patient of Avastin in the U.S. in early 2018 was $158, 456. *See* I.Hernandez et al., "Pricing of Monoclonal Antibody Therapies: Higher if Used for Cancer?" *American Journal of Managed Care* 24 (February 2018): 2. The annual price per patient of Enbrel in the U.S. in 2017 was $40,422. *See* Institute for Clinical and Economic Review (April 2017), *available at* <www.icer-review.org> (last visited November 11, 2019).
3. *See* N. Courage and A. Parsons, "The Comparability Conundrum: Biosimilars in the United States, Europe and Canada," *Food & Drug Law Journal* 66 (2011): 203 ("Billions of dollars' worth of biologics are going off patent in the next decade. The end of patent protection on blockbuster biologics opens the door for other companies that would like to get a slice of this lucrative market with their own versions of biologics"); IQVIA Institute for Human Data Science, *Medicines Use and Spending in the U.S.* (2017): at 34, *available at* <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicines-use-and-spending-in-the-us.pdf> (last visited November 11, 2019; access requested) ("The impact of patent expiries has been relatively unchanged for the past three years but is expected to increase sharply … The largest group of original biologics facing biosimilar competition are expected in 2019, including the largest selling branded medicine in 2017, adalimumab (Humira)"); IQVIA Institute for Human Data Science, *Advancing Biosimilar Sustainability in Europe* (2018): at 4, *available at* <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/advancing-biosimilar-sustainability-in-europe.pdf> (last visited November 11, 2019; access requested) ("As more original biologic patents expire, a large and diverse group of manufacturers – 184 in total globally – are investing in the development and commercialization of biosimilars"); IQVIA Institute for Human Data Science, *2018 and Beyond: Outlook and Turning Points* (2018): at 10, *available at* <https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/2018-and-beyond-outlook-and-turning-points.pdf> (last visited November 11, 2019; access requested) ("The next five years from 2018 to 2022 will see: [p]atent expiry impact will be 37% larger than the prior five years, including both small molecule and biologics; the peak year of impact is expected to be 2020 when spending on brands that no longer have exclusivity will be reduced by over $30 billion across the ten developed markets").
4. Y. Heled, "Follow-On Biologics Are Set Up to Fail," *University of Illinois Law Review Online* 113 (2018).
5. By "truly competitive" and "competitively robust" biologics markets I mean levels of competition sufficient to drive down the cost of biologics (and follow-on versions thereof) significantly for payors and patient-consumers, well beyond the 15-30% price drops currently typical of biologics markets subsequent to the entry of follow-on products. *See, e.g.*, W. N. Price II, "Regulating Secrecy," *Washington Law Review* 91(2016): 1769, 1798 (discussing the high costs of developing biosimilars and that "biologics are expected to remain much more expensive, with drops of only 20–30 percent in price once competitive biosimilars enter the market"); J. D. Rockoff, "Knockoffs of Biotech Drugs Bring Paltry Savings," *Wall Street Journal*, May 5, 2016, *available at* <http://www.wsj.com/articles/knockoffs-of-biotech-drugs-bring-paltry-savings-1462458209> (last visited November 11, 2019) (Both Zarxio and Inflectra are sold at a 15% discount from the biologic price."); M. A. Carrier and C. J. Minniti III, "Biologics: The New Antitrust Frontier," *University of Illinois Law Review* 2018 (2018): 1, at 10 ("But while the entry of multiple small-molecule generics results in significant price erosion (50% with 2 generics and 75% with at least 6), we predict that the reductions may be more modest given attempts to recoup biosimilar development costs, which greatly exceed those incurred by generics."). For comparison, in the context of small-molecule drugs, significant price drops of more than 70% are typical subsequent to the entry of five or more generic products into a specific drug market. *See* Food & Drug Admin., "Generic Competition and Drug Prices," *avail-*

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able at <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm129385.htm> (last visited November 11, 2019).

6. *See* Food and Drug Administration, *Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry* (2019), *available at* <https://www.fda.gov/media/124907/download> [FDA Interchangeability Guidance]. The FDA Interchangeability Guidance, while clarifying how follow-on biologics developers may seek approval of their products as interchangeable with original biologics, does not change the underlying regulatory and commercial realities of biologics markets, which are described in detail later in this article. *See infra* notes 37-63 and accompanying text. Thus, the Guidance is unlikely to result in significant price competition in all but the few, most lucrative biologics markets. *See infra* discussion in the paragraph following note 58.
7. The brand-name pharmaceutical industry (Industry or Pharmaceutical Industry, for short) includes the brand-name pharmaceutical and biopharmaceutical industries, their various, numerous official and unofficial lobbying arms under the leadership of the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Innovation Organization (BIO), industry-funded patient groups, researchers, research institutions, medical salespersons, and more. Notably, when it comes to biologics the traditional lines between brand-name and follow-on/generic parts of the industry are not as clear as they are in the small-molecule context. Still, with a few notable exceptions, it is possible to speak of efforts led by and on behalf of the brand-name biopharmaceutical industry, which are opposed to the interests of those parts of the industry that are focused on bringing follow-on biologics to market.
8. Like in my previous article, while this article focuses on the Industry's efforts in the United States, it is important to recognize that these efforts are not limited to this country alone and that local efforts are part of larger, well-coordinated strategies aimed at limiting follow-on biologics as a regulatory and commercial phenomenon worldwide. *See* Heled, *supra* note 4, at 113 n.7.
9. *Biologics Price Competition and Innovation Act of 2009*, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119 (2010). BPCIA was enacted as Title VII, Subtitle A of the Affordable Care Act. *Patient Protection and Affordable Care Act*, Pub. L. No. 111-148, 124 Stat. 119, 804–21 (2010).
10. *See* Heled *supra* note 4, at 115-19.
11. The term "follow-on biologics," as it is used in this article, includes all different kinds of biopharmaceutical products that are developed and marketed so as to imitate, in whole or in part, original biologics and to benefit from scientific, clinical, and commercial information developed in connection with such original biologics without having to invest the resources that would have been necessary in order to gather that information independently. As such, the term "follow-on biologics" includes biosimilars, interchangeable biosimilars (a.k.a. interchangeables), biobetters, and any subclass within these product classes.
12. *See infra* notes 136-138 and accompanying text.
13. *See, e.g.*, A. Chatterji et al., *The Follow-On Biologics Market: Enter at Your Own Risk* (2011): at 7, *available at* <https://papers.ssrn.com/sol3/Delivery.cfm/SSRN_ID1969973_code405577.pdf?abstractid=1969973&mirid=1> (last visited November 11, 2019) (while small molecules are typically covered by 8-10 patents, biologics typically have up to 50-70 patents covering the product's methods of use and manufacturing process); C. Koons, "This Shield of Patents Protects the World's Best-Selling Drug," *Bloomberg Businessweek*, September 7, 2017. The phenomenon of the multitude of overlapping patents covering a specific technology or product has come to be known as a "patent thicket." *See* C. Shapiro, "Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting," in A. B. Jaffe et al., eds., *Innovation Policy and the Economy* (2001): at 119, 120, *available at* <http://faculty.haas.berkeley.edu/shapiro/thicket.pdf> (defining a patent thicket as a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology).
14. Under BPCIA, original biologics developers benefit from a twelve-year market exclusivity period during which the FDA may not approve applications for follow-on products seeking to imitate the original biologic. 42 U.S.C. § 262(k)(7)(A). In addition, BPCIA creates a four-year data exclusivity period during which the FDA is not allowed to receive applications for follow on products that seek to imitate the original biologics. Both these market and data exclusivity periods may then be *supplemented* by an additional period of six months of exclusivity for putting the original biologic through additional clinical studies in pediatric populations, bringing the market and data exclusivity period to a total of 12.5 and 4.5 years respectively. 42 U.S.C. § 262(m)(2)(A). For further discussion of these and other exclusivities available in original biologics, *see also* discussion *infra* notes 168-171 and accompanying text.
15. *See infra* note 183 and accompanying text; Price, *supra* note 5, at 1797.
16. *See, e.g.*, Price, *supra* note 5, at 1792 and note 122; 1797 and notes 149–52; 1798 and note 153 (discussing the exclusivity in the product Premarin that has lasted for more than seventy years); B. Mixter, "Administration Works on Increasing Rx Competition Due to Spending Concerns," *Bloomberg Law, Pharmaceutical Law & Industry Report*, April 15, 2015 (quoting Richard G. Frank, Assistant Secretary for Planning and Evaluation at the Department of Health and Human Services).
17. *See* U.S. Food & Drug Admin., "Drugs@FDA: FDA Approved Drug Products – Approval Date(s) and History, Letters, Labels, Reviews for BLA 125553," *available at* <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125553> (last visited April 3, 2018) [hereinafter Zarxio Approval] (citing the approval date of Zarxio as March 6, 2015).
18. *See* Food & Drug Admin., "Biosimilar Product Information," *available at* <https://www.fda.gov/drugs/biosimilars/biosimilar-product-information> (last visited July 18, 2019).
19. An additional five biosimilar market authorization applications were either rejected or withdrawn post-approval. European Meds. Agency, Medicines Search page, *available at* <https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar> (last visited November 11, 2019). *But see* J. J. Darrow, "Biosimilar Approvals and the BPCIA: Too Soon to Give Up," *Health Affairs Blog*, July 19, 2019, *available at* <https://www.healthaffairs.org/do/10.1377/hblog20190718.722161/full/> (last visited November 11, 2019) (arguing that the comparison with approvals in Europe is better explained not by BPCIA but by regulatory delay in promulgating a pathway for evaluation and approval of biosimilars).
20. As of July 18, 2019, searches for biosimilar products available for purchase in goodrx.com and planetdrugsdirect.com indicate that only the following products are currently marketed and available in the United States: Zarxio (Filgrastim-sndz), Inflectra (Infliximab-dyyb), Erelzi (Etanercept-szzs), Renflexis (Infliximab-abda), Retacrit (epoetin alfa-epbx), Fulphila (pegfilgrastim-jmdb), Nivestym (filgrastim-aafi), and Udenyca (pegfilgrastim-cbqv). In addition, on July 18, 2019, Amgen and Allergan's announced that they are launching two other biosimilars: Mvasi (Bevacizumab-awwb) and Kanjinti (Trastuzumab-anns). *See* Amgen, *Amgen And Allergan's MVASI (bevacizumab-awwb) And KANJINTI (trastuzumab-anns) Now Available in the United* States, Press Release, July 18, 2019, *available at* <http://investors.amgen.com/news-releases/news-release-details/amgen-and-allergans-mvasitm-bevacizumab-awwb-and-kanjintitm/> (last visited November 11, 2019).
21. *See* Food & Drug Admin., "Ctr. for Drug Evaluation and Research, List of Licensed Biological Products with (1) Ref-

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erence Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date," June 28, 2019, *available at* <https://www.fda.gov/media/89589/download> (last visited November 11, 2019; hereinafter "Purple Book").

22. *See* Editorial, "Building a Wall Against Biosimilars," *Nature Biotechnology* 31 (2013): 264, 264; *see also* Fed. Trade Comm'n, "Emerging Health Care Issues: Follow-On Biologic Drug Competition," (2009): iii-iv.
23. *See also Building a Wall Against Biosimilars supra* note 22, at 264 (making the similar argument that biosimilars markets are not "molded" to foster a reality where "better products do better, and equivalent products compete on price."); P. Atteberry et al., "Biologics Are Natural Monopolies (Part 1): Why Biosimilars Do Not Create Effective Competition," *Health Affairs Blog*, April 15, 2019, *available at* <https://www.healthaffairs.org/do/10.1377/hblog20190405.396631/full/> (last visited November 11, 2019). *But cf.* Darrow, *supra* note 19 (arguing that anti-competitiveness is not a hallmark of biologics as such; bringing two examples of sharp price drops subsequent to biosimilars' market entry in Europe).
24. As of December 2018, about a dozen biosimilar applications were pending approval at FDA. M. Levin, *Approved and Pending Biosimilar Applications*, *available at* <https://www.mintz.com/sites/default/files/media/documents/2018-12-12/Biosimilar-Chart-2018-12-12-.pdf> (last visited November 11, 2019).
25. *See also* Y. Heled, "Biosimilars Are a Distraction," *Health Affairs Blog*, April 8, 2019, *available at* <https://www.healthaffairs.org/do/10.1377/hblog20190328.523018/full/> (November 11 2019).
26. *See supra* note 6.
27. *See id.* and *infra* Part II.
28. *See also* Fed. Trade Comm'n, *supra* note 22, at iii–iv.
29. *See* U.S. Cong., Office of Tech. Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards, OTA-H-522* (1993): at 7, *available at* <ota.fas.org/reports/9336.pdf> (last visited November 11, 2019) (defining "me too" drugs).
30. The hallmark of generic pharmaceutical products is their fungibility with the product they seek to imitate. This quality, once recognized by the FDA, allows for replacement of the original product with its follow-on version at the pharmacy level and often — depending on state substitution laws — without involvement of the prescribing physician. Follow-on biologics that are not approved by the FDA as interchangeable, however, cannot be similarly replaced by pharmacists, and so the competitive challenge they pose to original biologics is more akin to the kind of competition posed by "me-too" drugs, namely standalone pharmaceutical products that are indicated for the same disease or condition but are not clinically fungible. Examples of me-too drugs include the numerous cholesterol-lowering drugs that followed lovastatin (atorvastatin, fluvastatin, pitavastatin, simvastatin, pravastatin, and rosuvastatin) and hypertension drugs that followed captopril (benazepril, zofenopril, perindopril, trandolapril, enalapril, lisinopril, and ramipril). Pharmaceutical companies typically develop "me-too" drugs where the potential market for a certain condition is sufficiently lucrative to support more than one product.

    Notably, the Federal Trade Commission had reached a similar conclusion as early as 2009 (pre-BPCIA). *See* "Emerging Health Care Issues," *supra* note 22, at iii ("competition from FOB drug entry is likely to resemble brand-to-brand competition, rather than brand-to-generic drug competition."). *See also* T. Woodage, "Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization," *Stanford Technology Law Review* (2012): at 9 (predicting that "as currently structured, BPCIA is not likely to result in the dramatic reductions in healthcare costs").
31. *See infra* note 59.
32. *Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984*, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2012)).
33. 21 U.S.C. § 355(j)(2)(ii) (2017).
34. 21 U.S.C. § 355(j)(2)(iii) (2017).
35. 21 U.S.C. § 355(j)(2)(iv) (2017).
36. *See* Federal Trade Commission, *Emerging Health Care Issues: Follow-On Biologic Drug Competition* (2009): at iii (estimating the product development costs for small-molecule generic drugs is $1-5 million) [FTC 2009 Report], *available at* <https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf> (last visited November 11, 2019).
37. With some exceptions (e.g., human growth hormone and insulin), biologics are typically very large molecules with complex three-dimensional (and, possibly, quaternary) structures and appendages (e.g., oligosaccharide chains) that are very difficult to precisely characterize using current scientific methods. Moreover, at least some biologics consist of not a single API but a *collection or mixture* of structurally-related variations of a certain therapeutically-active molecule in a certain ratio between the different variations. *See*, e.g., M. Chhina, U.S. Food & Drug Admin., *Overview of Biological Products* (2013): 8, *available at* <https://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM356666.pdf> (discussing how the structure of small molecules are known, yet in biological products the "[s]tructure may or may not be completely defined or known"); U.S. Food & Drug Admin., *Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* (2015): 7, *available at* <https://www.fda.gov/downloads/drugs/guidances/ucm291134.pdf> (last visited November 11, 2019) ("Using multiple, relevant, state-of-the-art methods can help define tertiary protein structure and, to varying extents, quaternary structure and can add to the body of information supporting biosimilarity. At the same time, a protein's three-dimensional conformation can often be difficult to define precisely using current physicochemical analytical technology.").
38. *See, e.g.*, H. Dahodwala and S.T. Sharfstein, *Biosimilars: Imitation Games*, 8 ACS Med. Chem. Lett. 690, 691 (2017).
39. This reality is evident in the fact that since the enactment of BPCIA in 2010 through the time of writing of this article — over nine years — no follow-on biologics developer has attempted to seek approval for its biosimilar product as interchangeable with an already-approved original biologic. This is not due to a legal impossibility to do so. Even in the absence of specific guidance, BPCIA has granted the FDA authority to approve follow-on biosimilar products as interchangeable with existing products and follow-on product developers were free to file their applications for such approval at least since the enactment of BPCIA, in March 2010. That no follow-on biologics developer has done so since 2010 is, at least in part, due to the fact that follow-on product developers have been unable to establish identity or near-identity of their follow-on products to the original biologics they seek to imitate, as is done in small-molecule drugs under the Hatch-Waxman Act. At least as late as May 2015, the FDA's position was that "[a]t this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability … given the statutory standard for interchangeability and the sequential nature of that assessment." Food & Drug Admin., *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; Guidance for Industry* (May 2015): at 7, *available at* <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>.
40. *See* D. M. Gitter, "Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-on Biologics in the United States," *Florida State University Law Review* 35 (2008): 555, 561 n.21 (describing "the maxim that, for biopharmaceuticals, the 'process is the product.'"); K. Hessler Carver et al., "An Unofficial Legislative History of the Biologics Price Competition and

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Innovation Act of 2009," *Food & Drug Law* Journal 65 (2010): 671, 708-09 (describing the Industry's position on "[w]hether the process is the product").

41. *See* Price, *supra* note 5, at 1975 notes 134–36*; see also* W. N. Price II and A. K. Rai, "Are Trade Secrets Delaying Biosimilars," *Science* 348 (2015): 188, 189 (describing attempts of follow-on biologics makers to imitate original products as "rang[ing] from merely expensive to nearly impossible and creat[ing] much of the cost barrier for biosimilar entrants"); L. Tzeng, "Follow-On Biologics, Data Exclusivity, and the FDA," *Berkeley Technology Law Journal* 25 (2010): 135, 138 and note 23 (emphasis added) ("The complexity of the biologic molecules, production in living organisms, *and sensitivity of end-product structure to changes in the manufacturing process* render exact [follow-on biologic] replication nearly impossible.").
42. *See* Gitter *supra* note 40, at 561 note 21.
43. 21 C.F.R. § 601.2(a) (requiring "[a] full description of manufacturing methods ... [and] sample(s) representative of the product for introduction or delivery for introduction into interstate commerce.
44. *See infra* notes 136-138 and accompanying text.
45. *See*, e.g., Carver et al., *supra* note 40, at 698–99, 698 note 218, 699 notes 218–25, 700 notes 232-37, 701 note 271 (arguing, for example, that FDA reference to biologics manufacturing information submitted in earlier products' marketing applications raises "insurmountable legal obstacles" and describing the Industry's efforts to assert and enforce that position; describing Industry's successful efforts to foreclose FDA utilization of data contained in earlier regulatory filings for the approval of follow-on biologics); E. L. Korwek, "Towards Understanding the "Generic" Debate about Biologics," *Journal of Biolaw & Business* 7 (2004): 1, 5 (discussing the argument by the Biotechnology Industry Association (BIO) that the FDA's reliance on "innovator information essentially involves misappropriation of the innovator's trade secret and confidential business information, which is not permitted under the Takings Clause of the Fifth Amendment"); Letter from Robert A. Long, Jr., Partner, Covington & Burling, to Food & Drug Admin. 4–5, 8–10, 15–17 (July 13, 2005), *available at* <https://web.archive.org/web/20170211011252/http://www.fda.gov/ohrms/dockets/dockets/03p0176/03p-0176-c000003-01-vol3.pdf> (last visited November 11, 2019) (Docket Nos. 2004P-0171/CP and 2003P-0176/CP) (arguing that the Trade Secrets Act prohibits a government employee from disclosing trade secrets discovered "in the course of his employment or official duties," that the Food, Drug & Cosmetics Act (FDCA) prohibits any person from "using to [their] own advantage, or revealing . . . any information . . . concerning any method or process, which, as a trade secret, is entitled to protection," and that the Takings Clause and FDA policies "clearly support[s] innovators' reasonable, investment-backed expectation that trade secret data submitted to FDA would not be used in follow-on approvals").
46. *See also* Carver et al., *supra* note 40, at 699 and notes 219–25 (discussing how the Industry's assertion of its position that regulatory submissions made in connection with BLAs are proprietary and confidential successfully dissuaded the FDA from attempting to develop a regulatory pathway for the approval of generic biologics based on its existing authorities under FDCA and the Public Health Service Act).
47. As mentioned earlier, a few exceptions to this general rule exist in relatively small and well characterized biologics such as human growth hormone and insulin.
48. *See* 42 U.S.C. § 262(k)(2)(A)(I)(aa) (requiring that applications for marketing approval of follow-on biologics include "analytical studies that demonstrate that the [follow-on] product is highly similar to the reference product notwithstanding minor differences in clinically inactive components".). *See also* Price *supra* note 5, at 1796-1797.
49. *See* 42 U.S.C. § 262(k)(2)(A)(I)(bb)-(cc) (requiring that applications for marketing approval of follow-on biologics include animal studies and "a clinical study or studies ... that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the [original] product is licensed and intended to be used").
50. According to the FDA Interchangeability Guidance, a "switching study" is a clinical study or studies used to determine the impact of alternating or switching between a proposed interchangeable biologic and the original product it seeks to imitate. *See* FDA Interchangeability Guidance *supra* note 6 at 5, note 12 and 9-14.
51. 42 U.S.C. § 262(k)(4).
52. *See* Food & Drug Admin., *Scientific Considerations in Demonstrating Biosimilarity with a Reference Product; Guidance for Industry* (April 2017): 7, 10-12 (discussing a case-by-case approach wherein the sponsor of a follow-on biologic uses a "stepwise approach to developing the data and information needed to support a demonstration of biosimilarity," yet also arguing that the first step should be to compare structural and functional characterization, before beginning in-vitro and animal studies); FDA Interchangeability Guidance *supra* note 6; H. Koyfman, "Biosimilarity and Interchangeability in the Biologics Price Competition and Innovation Act of 2009 and FDA's 2012 Draft Guidance for Industry," *Biotechnology Law Report* 32 (2013): 238, 246 (stating FDA's stepwise approach does not describe what differences in structure would require heightened animal or clinical studies, and further proposing a step-by-step approach using scientific literature to determine what amount of structural difference might affect the biologic); *Building a Wall Against Biosimilars*, *supra* note 22, at 264.
53. *See also* Dahodwala and Sharfstein, *supra* note 38, at 692 (describing the development of follow-on biologics as a game).
54. *See* Price and Rai, *supra* note 41, at 189.
55. *See*, e.g., FTC 2009 Report *supra* note 36, at iii; E. A. Blackstone et al., "The Economics of Biosimilars," *American Health & Drug Benefits* 6 (2013): 469, 471.
56. *Id.* Interestingly, the estimated development time of follow-on biologics is not much shorter than the time it takes to develop an original biologic. *See* R. F. Beall et al., *Nature Biotechnology* 37 (2019): 708, 709 (finding that the median total premarket development time for new biologics approved by the FDA between 2007 and 2016 was 10.6 or 12.4 years).
57. *See*, e.g., *Scientific Considerations in Demonstrating Biosimilarity*, *supra* note 52, at 7, 10–12 (discussing FDA's guidance on the "stepwise approach"); *see also* J. Paradise, "The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the United States Healthcare System," *American Journal of Law & Medicine* 41, no. 1 (2015): 49, 68 (describing the task of determining that two biologic products are similar and the regulatory process thereof as complicated and uncertain).
58. *See supra* discussion following note 8. To illustrate, the protracted legal battle surrounding the approval and launch of the first biosimilar approved in the United States, Zarxio (Filgrastim-sndz), has been ongoing at least since October 2014 and included, thus far, at least six rounds of litigation, including three before the Court of Appeals for the Federal Circuit and one before the United States Supreme Court, and raised numerous novel legal questions, *e.g.,* whether BPCIA's patent dispute resolution scheme (a.k.a. "patent dance") is mandatory or optional, the preemption of state causes of action in light of BPCIA, as well as more mundane issues like patent claim construction, patent infringement, and more. *See* Amgen, Inc. v. Sandoz, Inc., No. 14-cv-04741, 2015 WL 1264756 (N.D. Cal. Mar. 19, 2015); Amgen, Inc. v. Sandoz, Inc., 794 F.3d 1347 (Fed. Cir. 2015) (affirming in part, vacating in part, remanding); Sandoz, Inc. v. Amgen, Inc., 137 S.Ct. 1664 (2017) (reversing in part, vacating in part); Amgen, Inc. v. Sandoz, Inc., 877 F.3d 1315 (Fed. Cir. 2017) (on remand, affirming); Amgen Inc. v. Sandoz Inc., 295 F. Supp. 3d 1062 (N.D. Cal. 2017) (granting Sandoz's motion for summary judgment of noninfringement of U.S. Patent No. 8,940,878); and Amgen Inc. v. Sandoz Inc., 923 F.3d 1023 (Fed. Cir. 2019) (affirming), in which, most

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recently, on June 7, 2019, Amgen filed a Petition for En Banc Rehearing that may result in yet another round of litigation.

59. *See*, e.g., FTC 2009 Report at v; F. Megerlin et al., "Biosimilars and the European Experience: Implications for the United States," *Health Affairs* 32 (2013): 1083. *See also* A. Sarpatwari et al., "Competition and Price among Brand-Name Drugs in the Same Class: A Systematic Review of the Evidence," *PLoS Medicine* 16 (2019): e1002872, *available at* <https://doi.org/10.1371/journal.pmed.1002872> (last visited November 11, 2019) (finding that brand-brand competition — the kind that takes place when non-interchangeable biosimilars enters the market — does not result in lower drug prices absent additional structural reforms).
This low likelihood of price competition in most biologics markets is further compounded by the fact that, to begin with, the number of companies that have the manufacturing capacity, expertise, and financial resources necessary to overcome the high entry barriers imposed on follow-on biologics is relatively small. According to some estimates, there would be significantly fewer such companies, globally, as compared to generic drug manufacturers worldwide. *See*, e.g., T. Woodage, "Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization," *Stanford Technology Law Review* (2012): 9, 18; P. Jones Harbour, Comm'r, Fed. Trade Comm'n, *The Competitive Implications of Generic Biologics* 18 (June 14, 2007) *available at* <https://www.ftc.gov/sites/default/files/documents/public_statements/competitive-implications-generic-biologics/070614genbio_0.pdf> (last visited November 11, 2019).
60. *See also* R. G. Bone, "A New Look at Trade Secret Law: Doctrine in Search of Justification," California Law Rev. 86 (1998): 241, 266-70 (discussing the inefficiencies and waste created by trade secrecy in general); Price and Rai, *supra* note 41, at 1048-49 (also discussing the additional negative implications of non-disclosure to innovation).
61. *See also* F.-X. Frapaise, "The End of Phase 3 Clinical Trials in Biosimilars Development?" *BioDrugs* 32 (2018): 319 (proposing a more resource-conservative approach to comparing follow-on biologics with original products which "may be more appropriate than 600- to 1000-patient, phase 3 trials in assessing biosimilarity and therapeutic equivalence").
62. *See*, e.g., C. J. Webster and G. R. Woollett, "Comment on 'The End of Phase 3 Clinical Trials in Biosimilars Development?'" *BioDrugs* 32 (2018): 519 (arguing that clinical studies in humans done for the mere purpose of comparing clinical safety and efficacy of a biosimilar with an original biologic are unethical); *see also* discussion *infra* notes 123-125 and accompanying text.
This same concern seems to have been recognized in a proposed amendment to the BPCIA bill that was filed by Senator Bernie Sanders (I-VT), although the solution proposed by the amendment would have been insufficient to make "switching studies" unnecessary. *See* 155 Cong. Rec. S12164, 12258 (2009) (amendment S.A. 2858 to S.A. 2786 of Sen. Sanders to the Patient Protection and Affordable Care Act, H.R. 3590) [Sanders Amendment] (proposing to add an "Ethical Pathway for the Approval and Licensure of Generic Pharmaceutical Products").
63. *See also* Price, *supra* note 5, at 1770, 1777, 1784–1793 (making the observation that, despite BPCIA, biologics are "wildly expensive and look to stay that way" and concluding that the lack of competition in biologics markets is attributable to the combination of trade secrecy and FDA regulation).
64. *See*, e.g., Letter from John C. Yoo, Professor, University of California to Senator Orrin G. Hatch, Chairman, Committee on the Judiciary, Oct. 21, 2004, *available at* <https://www.regulations.gov/document?D=FDA-2003-P-0003-0027> (last visited November 11, 2019) (arguing, prior to the enactment of BPCIA, that FDA use of regulatory filings does not constitute a taking under the Fifth Amendment and that FDA may do so with respect to past filings made in connection with BLAs); Letter from Robert A. Long, Jr., Partner, Covington & Burling to Food and Drug Administration, Division of Docekts Management (HFA-305), July 13, 2005, *available at* <https://www.regulations.gov/document?D=FDA-2012-P-0317-0001> (last visited November 11, 2019) (Exhibit 44) (arguing that FDA use of regulatory filings made in connection with applications for approval of biological products would constitute a taking under the Fifth Amendment); R. A. Epstein, "The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009," *Food & Drug Law Journal* 66 (2011): 285 (making a similar argument to that of Long's Letter post BPCIA). *See also* Carver et al., *supra* note 40, at 698 note 218 ("The threshold question whether FDA could lawfully approve a biosimilar product on the basis of trade secrets and confidential commercial information owned and submitted by another applicant were explored in submissions to FDA as well as Congress, and discussed in a hearing before the Senate Judiciary Committee. The question was never resolved.").
65. *Federal Pesticide Act of 1978*, Pub. L. No. 95-396, 92 Stat. 819 (codified at 7 U.S.C. §§ 136–136w-8).
66. *Federal Pesticide Control Act of 1971: Hearings Before the H. Comm. on Agric., Statement of Richard A. Wellman, Vice President and General Manager, Process Chemicals Division of Union Carbide Corp., New York, N.Y.*, 92d Cong. 170, 331 (1971) (arguing, on behalf of original pesticide product developers, that "it is unfair to the company that developed ... information to allow other people to use that information to secure registration of their own" and proposing that "data in support of applications for registration made public pursuant to law shall not, without the permission of the registrant, be considered by the [EPA] in support of any other application."). As is evident from FPA, that position and proposal was, eventually, rejected by Congress.
67. *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1006–07 (1984) (holding that EPA's consideration or disclosure of data submitted by an original product developer to the agency did not constitute an unconstitutional taking regardless of whether such data included trade secrets so long as parties submitting such data were on notice that the agency might disclose the data so prior to submitting its data); *Union Carbide Agric. Prods. Co. v. Costle*, 632 F.2d 1014, 1017 (2d Cir. 1980) (reversing a temporary restraining order against the implementation of FPA).
68. *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)*, ch. 125, 61 Stat. 163 (1947) (codified as amended at 7 U.S.C. §§ 136–136w-8 (2012)).
69. 7 U.S.C. § 136a(a).
70. *Id.* In the context of FIFRA, the safety and benefits of a product are considered under the title of "unreasonable adverse effects on the environment," which is defined as "(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food.... [including] the risks and benefits of public health pesticides separate from the risks and benefits of other pesticides. In weighing any regulatory action concerning a public health pesticide under this subchapter, the Administrator shall weigh any risks of the pesticide against the health risks such as the diseases transmitted by the vector to be controlled by the pesticide." 7 U.S.C. § 136(bb).
71. 7 U.S.C. § 136a(c)(1)(F)(i). *See also* Envtl. Prot. Agency Office of Pesticide Programs, Questions and Answers–Exclusive Use Data Protection for Minor Use Registrations 2 (2014), *available at* <http://www.epa.gov/pesticides/minoruse/exclusive-use-questions.pdf, *archived at* <http://perma.cc/BXM9-UMSM> (last visited December 16, 2019).
In 1998, Congress added to FIFRA an option to extend the ten-year data exclusivity period by one year for every three new "minor uses" approved by the EPA for the original pesticide product. 7 U.S.C. § 136a(c)(1)(F)(ii). Notably, such

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extension is only available up to three times in each pesticide product (up to a total of thirteen years of data exclusivity) and cannot be granted for "minor uses" registered more than seven years after the onset of the ten-year data exclusivity period. *Id.* To prevent abuse of such extensions, FIFRA instructs the EPA to grant one-year extensions only after consulting with the Secretary of Agriculture and subject to a determination that certain public policy considerations are applicable. *See* 7 U.S.C. § 136a(c)(1)(F)(ii)(I)–(IV). These considerations are: "(I) there are insufficient efficacious alternative registered pesticides available for the use [in a particular crop]; (II) the alternatives to the minor use pesticide pose greater risks to the environment or human health; (III) the minor use pesticide plays or will play a significant part in managing pest resistance; or (IV) the minor use pesticide plays or will play a significant part in an integrated pest management program.". *Id.*

72. 7 U.S.C. § 136a(c)(1)(F)(iii). This subsection further creates an elaborate scheme for resolution of disputes regarding the amount of the compensation, including a mandatory arbitration between the parties in case of a dispute. *Id.* Notably, disagreement between the parties regarding the compensation will not delay registration by the EPA. *Id.*
73. *Id.*
74. *Id.*
75. FIFRA §§ 10(d)(1)(A)–(C); 7 U.S.C. §§ 136a(c)(1)(F)(iv), 136h(d).
76. 7 U.S.C. § 136h(d)(1).
77. 7 U.S.C. § 136h(g).
78. 7 U.S.C. § 136a(c)(1)(F)(iii).
79. *See* Union Carbide, 632 F.2d at 1016 ("As enacted in 1947, FIFRA did not specifically prohibit the USDA from publicly disclosing submitted data or from using data supplied by one applicant to determine whether to register a pesticide offered subsequently by another.").
80. *See Federal Pesticide Control Act of 1971: Hearings Before the H. Comm. on Agric.*, *supra* note 66 at 170 (Statement of W.B. Ennis, Jr., Chief of Crops Protection Research Breach, U.S. Dep't of Agric.) ("Since 1940 we have witnessed agricultural changes . . . . This has come about primarily because of . . . control of damaging weeds, diseases, insects, and other pests and parasites.").
    The concerns that underlie FIFRA's data protection framework are highly similar to those that guide the regulation of biologics, including human and animal health, conservation of societal resources, and access to technologically innovative products.
81. *See* "Reorganization Plan No. 3 of 1970," *Federal Register* 35(October 6, 1970): 15,623; *Union Carbide*, 632 F.2d at 1016 ("The United States Department of Agriculture (USDA) administered the registration program from 1947 until 1970, when EPA assumed that responsibility.").
82. *Federal Environmental Pesticide Control Act of 1972*, Pub. L. No. 92-516, §§ 3(c)(5)(C)–(D), 86. Stat. 973, 980–81.
83. *See Union Carbide*, 632 F.2d at 1016 ("This costly research and lengthy development process produce data that define the peculiar characteristics of the pesticide submitted for registration . . . [and] must be submitted to obtain registration.").
84. *Id.*; *Federal Pesticide Control Act of 1971: Hearings Before the H. Comm. on Agric. supra* note 66 at 331 (statement of Richard H. Wellman, Vice President, Process Chems. Div. of Unio Carbide Corp.) (arguing that newer and higher regulatory barriers were being placed before the original pesticide product developers and that the cost of developing the necessary data in support of product marketing applications was heavy).
85. *See Union Carbide*, 632 F.2d at 1016 ("[I]t appears that the USDA made no public disclosures of data but did make use of data on hand in evaluating later applications.").
86. *See*, e.g., H.R. Rep. No. 95-663, at 41–42, 58 (1977) (describing the dispute surrounding the definition of proprietary information).
87. *Federal Pesticide Control Act of 1971: Hearings Before the H. Comm. on Agric. supra* note 66 at 331.
88. *Id.*; *see also* H.R. Rep. No. 95-663, at 41–42, 58.
89. *See* H.R. Rep. No. 95-663, at 41 (reasoning provided by Rep. Thone for his proposal of a ten-year period of data exclusivity).
90. *See* H.R. Rep. No. 92-511, at 69, 72 (1971) (remarks of Reps. Foley & Dow); S. Rep. No. 92-970 at 12–13 (1972) (letter from the Attorney General); H.R. Rep. No. 95-663, at 41, 53–54 (1977) (reasoning provided by Rep. Fithian for his proposal to provide appropriate compensation in lieu of data exclusivity; letter from the EPA expressing preference for compensation of product developers for use of their data over exclusivity in such data).
91. *See*, e.g., H.R. Rep. No. 95-663, at 41–43, 58.
92. *Id.*
93. *Federal Pesticide Act of 1978*, Pub. L. No. 95-396, 92 Stat. 819 (codified at 7 U.S.C. §§ 136–136w-8).
94. United States Const. Amend. V ("nor shall [any person] ... be deprived of ... property, without due process of law; nor shall private property be taken for public use, without just compensation.").
95. *Ruckelshaus*, 467 U.S. at 987, 998-99.
96. *Ruckelshaus*, 467 U.S. at 990, 999.
97. *Id.*; *see also Union Carbide*, 632 F.2d at 1017.
98. *Ruckelshaus*, 467 U.S. at 987. The Supreme Court held that the data submitted between October 22, 1972 and September 30, 1978 was subject to another set of amendments to FIFRA that were in force prior to the enactment of FPA and that allowed a data submitter to protect its trade secrets from internal use by EPA by designating relevant data as trade secrets at the time of submission, provided that the EPA agreed with the designation. *Id.*, at 1010-11. The *Ruckelshaus* Court viewed these arrangements as creating an explicit guarantee of "an extensive measure of confidentiality and exclusive use ... [which] formed the basis of a reasonable investment-backed expectation." *Id.*, at 1011.
99. *Id.*, at 1001–1004.
100. *Id.*, at 1005 (internal citation marks omitted).
101. *Id.*, at 1005–06.
102. *Id.*, at 1006–07.
103. *Id.*, at 1007.
104. *Id.*, at 1007–08.
105. *See id.*, at 1009–14 (discussing data submitted between October 22, 1972 and September 30, 1978).
106. *Id.*, at 1008–09. The Supreme Court recognized, however, that this was not the case with respect to data submitted between October 22, 1972 and September 30, 1978. *See id.*, at 1013–14.
107. *Id.*
108. *Id.*, at 1014 (citations omitted).
109. *Ruckelshaus*, 467 U.S. at 1014–15 (emphases added).
110. *Id.*, at 1016.
111. *Id.*, at 1016–19.
112. *Id.*, at 1019.
113. *Id.*, at 1020.
114. *Id.*, at 998 (quoting the district court opinion; brackets in origin).
115. *Id.*, at 1011.
116. Note that the data is for registrations rather than applications for new pesticide products.
117. The economic literature that analyzes the regulation of pesticides in the 1970s and 1980s focuses more on the effect that EPA regulation generally had on the pesticide industry rather than on any specific episode or event during that period. *See, e.g.*, M. Ollinger and J. Fernandez-Cornejo, "Innovation and Regulation in the Pesticide Industry," *Agricultural & Resource Economics Review* 27 (1998) (reviewing the literature): 15, 15.
118. *Id.*, at 15, Table 1 at 16, and 24-25 (finding that increase in regulatory stringency caused a decline in number of new product registrations but increased product safety); M. Ollinger and J. Fernandez-Cornejo, "Regulation, Innovation, and Market Structure in the U.S. Pesticide Industry," at 2, 7-8 Table 3, and 14 Table 4 (1995) [Ollinger 1995], *available at* <https://naldc.nal.usda.gov/download/CAT11121165/PDF> (last visited November 11, 2019). The same authors have also reported

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that increased regulatory costs correlate with a decrease in the number of firms in the industry (with a stronger negative impact on the number of smaller firms) and increase in foreign-based firm expansion. *See* M. Ollinger and J. Fernandez-Cornejo, "Sunk Costs and Regulation in the U.S. Pesticide Industry," *International Journal of Industrial Organization* 16 (1998): 139.

119. Of further note in regard to a possible connection between the decrease in pesticide product registration and FPA is the potentially "intervening" factor of EPA's imposition in 1982 of additional testing requirements that further increased regulatory stringency. *See id.* (Ollinger, 1995), at 5 and 7 note 8.
120. Notably, the literature does recognize the debate surrounding the sharing of data by EPA and its resolution in FPA. *See id.* (Ollinger, 1995), at 5.
121. *See also* Ollinger and Fernandez-Cornejo, *supra* note 117, at 17 (highlighting additional similarities of the pesticide and pharmaceutical industries).
122. *See also* Price, *supra* note 5, at 1804, note 189, 1804-1808 and Price and Rai, *supra* note 41, at 1053 (making a proposal to publicly disclose the Chemistry and Manufacturing Controls section of New Drug Applications (NDAs) and BLAs upon approval of original biologics; discussing the advantages of trade secret disclosure in the context of regulated industries in general).
123. *See supra* note 51 and accompanying text.
124. *See also* Price *supra* note 5, at 1798.
125. *See also supra* note 62 and accompanying text.
126. While voluntary disclosure by original biologics developers would have achieved the same goals, given the structure of incentives in the area of biologics, it cannot be expected and must, therefore, be mandated by a legislative or regulatory measure. Another possibility is disclosure only in cases where an original biologic developer is unable to meet market demand, fails to maintain quality control of its products, and/or is found to have broken the law somehow in a way that limits access to its products. *See also* Price, *supra* note 5, at 1808-10. This option, however, is also too limited as it will make instances of disclosure too rare to alleviate the competitive ills that plague most biologics markets, including ones that are not affected by original product developers' misconduct.
127. For the purpose of this proposal, "manufacturing information" includes whatever information knowledge *and materials* necessary to create the most accurate replica of an original biologic as approved by the FDA. For further discussion of the possible need and legal feasibility of sharing the progenitor cell line, *see* discussion *infra* Part III.D.3.
128. *Federal Food, Drug, and Cosmetic Act of 1938*, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified at 21 U.S.C. § 301 et seq.).
129. Public Health Service Act of 1944, Pub. L. No. 78-410, 58 Stat. 682 (1944) (codified at 42 U.S.C. § 201 et seq.).
130. Congress has nearly unlimited discretion in determining the scope of disclosure under the statute. *See Ruckelshaus*, 467 U.S. at 1016 ("It is enough for us to state that the optimum amount of disclosure to the public is for Congress, not the courts, to decide, and that the statute embodies Congress' judgment on that question.").
131. The abuse of FDA Risk Evaluation and Mitigation Strategy (REMS) policies by brand-name pharmaceutical companies refusing to sell samples of their products to follow-on developers serves as both a lesson and warning against the institution of direct, unmediated dealings between original and follow-on pharmaceutical developers. *See, e.g.*, Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on New Policies to Reduce the Ability of Brand Drug Makers to Use REMS Programs as a Way to Block Timely Generic Drug Entry, Helping Promote Competition and Access* (May 31, 2018), *available at* <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-policies-reduce-ability-brand-drug-makers-use-rems> (last visited November 11, 2019).
132. 42 U.S.C. § 262(l)(2)(A) ("the [follow-on product] applicant ... shall provide to the [original biologic developer] ... the process or processes used to manufacture the biological product"). For further discussion of the patent dance framework, *see infra* note 172.
133. This would be similar to FPA's grant of authority to EPA to share original pesticide manufacturing information with follow-on developers only when such disclosure "is necessary to protect against an unreasonable risk of injury to health or the environment." *See supra* note 76 and accompanying text.
134. A narrow tailoring of the disclosure arrangement and its close tying to the goal of bringing price competition to biologics markets in the United States would stem challenges to the constitutionality of the measure as effectuating destruction of all economically beneficial uses of trade secrets embodied in manufacturing information disclosed to follow-on developers. *See* Yoo, *supra* note 173, at 36 ("unless government regulation completely deprives property of its entire value, courts will not find a *per se* taking to have occurred"). It may also address other concerns having to do with protection afforded to original biologics in foreign pharmaceutical markets as well as with potential challenges to *Ruckelshaus* itself. For further insight into what such a challenge might entail, s*ee* Epstein, *supra* note 64, at 304-313.
135. *See* discussion *infra* note 178 and accompanying text.
136. 42 U.S.C. § 262(j) ("The Federal Food, Drug, and Cosmetic Act ... applies to a biological product subject to regulation under this section").
137. 21 U.S.C. § 331(j).
138. *See* 21 C.F.R. § 60.151(f) ("The following data and information in biological product file are not available for public disclosure ... (1) manufacturing methods or processes, including quality control procedures.... (3) Quantitative or semiquantitative formulas."); 21 C.F.R. § 20.61(c) ("Data and information submitted or divulged to the Food and Drug Administration which fall within the definition of a trade secret or confidential commercial or financial information are not available for public disclosure.").
139. 42 U.S.C. § 262(a)(2)(A).
Notably, some biologics have traditionally been regulated and approved via the regulatory pathway reserved for small molecule drugs under FDCA. The FDA is expected to transition at least some of these products — e.g., insulin and human growth hormone — to regulation and licensure as biologics under PHSA. *See Statement from FDA Commissioner Scott Gottlieb, M.D., on New Actions Advancing the Agency's Biosimilars Policy Framework*, December 11, 2018, *available at* <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-actions-advancing-agencys-biosimilars-policy> (last visited November 11, 2019) [Gottlieb Statement]. The FDA's set of authorities under FDCA make the discussion in this part also applicable, *mutatis mutandis*, to such biologics.
140. 42 U.S.C. § 262(k)(3)(A), & (4).
141. 42 U.S.C. §§ 262(i).
142. 42 U.S.C. §§ 262(a)(2)(C)(I).
143. 42 U.S.C. §§ 262(i).
144. FDA Mission, *available at* <https://www.fda.gov/about-fda/what-we-do#mission> (last visited November 13, 2019).
145. *But see* Epstein, *supra* note 64, at 293-94 (in an Industry funded article, taking the opposite position that BPCIA precludes FDA consideration of information filed in original biologics regulatory filings as part of its evaluation of follow-on products marketing applications). Epstein's position, however, is based on his very narrow interpretation of Section 351(k)(3) that is not mandated by the statutory language.
146. 42 U.S.C. § 262(k)(2). BPCIA lists categories of "required information" under subsection (k)(2)(i) but then gives the FDA the authority to "determine, in [its] discretion," that some of the categories of information required under subsection (k)(2)(i) are "unnecessary." *Id.*

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147. 42 U.S.C. § 262(k)(2)(iii)(II). Notably, BPCIA does list "publicly-available information with respect to the reference product or another biological product" as an example of such "additional information" and even *requires* that such information be submitted to FDA by follow-on product applicants. 42 U.S.C. § 262(k)(2)(iii)(I)-(II). However, the statutory language is open and does not preclude other kinds of information.
148. Notably, Professor John Yoo has taken a similar position with respect to FDA's authority to create a pathway for approval of generic biologics even before the enactment of BPCIA. *See generally* Yoo *supra* note 173, and especially at 41-43 (arguing that FDCA Section 301(j) does not preclude FDA's broad authority to create a pathway for approval of generic biologics and that "FDA's decisions in this area should be based purely on policy considerations, and should not be deterred by Fifth Amendment concerns.").
149. *See, e.g.,* M. M. Mello, "What Makes Ensuring Access to Affordable Prescription Drugs the Hardest Problem in Health Policy?" *Minnesota Law Review* 102 (2018): 2273, 2301 (citing to Ctr. For Responsive Pols. Top Industries), *available at* <https://www.opensecrets.org/lobby/top.php?showYear=2019&indexType=i> (last visited November 12, 2019) (acknowledging that the pharmaceutical industry alone has already spent over $155 million on lobbying this year and spent $283 million on lobbying in 2018, which was far in excess of any other lobbying group and was worth almost twice as much as the insurance industry lobbying group in second place).
150. *See, e.g.,* L.E. Sekerka and L. Benishek, "Thick as Thieves? Big Pharma Wields Its Power With the Help of Government Regulation," *Emory Corporate Governance and Accountability Review* 5 (2018): 113, 124-25; C. McGreal, "How Big Pharma's Money – and Its Politicians – Feed the US Opioid Crisis," *The Guardian*, October 19, 2017, *available at* <https://www.theguardian.com/us-news/2017/oct/19/big-pharma-money-lobbying-us-opioid-crisis> (last visited November 13, 2019) (discussing how the vast majority of politicians on the federal level have received donations from pharmaceutical companies and how Industry money influences Congress's legislative agenda); Heled, *supra* note 4, at 116-119 (discussing the highly Industry-favorable lean of BPCIA).
151. *E.g.,* Affordable Health Care for America Act, H.R. 3962, 111th Cong. §§ 2575–77 (2009); Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009); Pathway for Biosimilars Act, H.R. 1548, 111th Cong.; Pathway for Biosimilars Act, H.R. 5629, 110th Cong. (2008); Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007); Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007); Patient Protection and Innovation Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. (2007).
152. *See* Sanders Amendment *supra* note 62. The Sanders Amendment does not mention manufacturing information.
153. For example, House Judiciary Chairman Jerrold Nadler (D-NY) and Subcommittee on Antitrust, Commercial, and Administrative Law Chairman David N. Cicilline (D-RI) released a joint statement about addressing the "bully tactics" adopted by large brand prescription drug companies, while House Judiciary Ranking Member Doug Collins (R-GA) and Subcommittee on Antitrust, Commercial, and Administrative Law Ranking Member Jim Sensenbrenner (R-WI) released a joint statement thanking Chairman Nadler and Subcommittee Chairman Cicilline and reaffirming their interest in continuing to "work[] together to promote competition and decrease pharmaceutical costs." Press Release, Congressman Jerry Nadler, House Judiciary Unanimously Passes Bipartisan Bills to Lower Prescription Drug Prices (April 30, 2019), *available at* <https://nadler.house.gov/news/documentsingle.aspx?DocumentID=393903> (last visited November 13, 2019). Senator Chuck Grassley (R-IA), Chairman of the Senate Finance Committee, has also sought to address concerns regarding rising prescription drug costs through hearings and bipartisan proposals. News Release, Sen. Chuck Grassley, Grassley Op-ed: Pharma execs should stop grandstanding and work to lower prescription prices (February 26, 2019), *available at* <https://www.grassley.senate.gov/news/news-releases/grassley-op-ed-pharma-execs-should-stop-grandstanding-and-work-lower-prescription> (last visited November 13, 2019).
154. *See, e.g.*, We PAID (Protect American Investment in Drugs) Act of 2019, S. 2387, 116th Cong. (2019) (establishing a process for calculating a "reasonable" drug price); Efficiency and Transparency in Petitions Act, S. 660, 116th Cong. (2019) (amending requirements in the citizen petition process to prevent abuse by brand-name drug manufacturers); Accelerated Drug Approval for Prescription Therapies (ADAPT) Act, S. 658, 116th Cong. (2019) (creating an accelerated approval pathway for drugs that are legally approved in other countries); Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, S. 340, 116th Cong. (2019) (aimed at preventing abuse of risk evaluation and mitigation strategies (REMS) by creating a pathway for follow-on product manufacturers to purchase original product samples); Prescription Drug Price Relief Act, S. 102, 116th Cong. (2019) (terminating government-granted monopolies for drug manufacturers that charge excessive drug prices exceeding the median price in other countries); Prescription Drug Price Transparency Act, H.R. 1035, 116th Cong. (2019) (adding pharmacy benefits manager standards for the Medicare prescription drug program and the Medicare Advantage program to increase transparency of payment methods to pharmacies); and Bringing Low-Cost Options and Competition while Keeping incentives for New Generics (BLOCKING) Act of 2019, H.R. 938, 116th Cong. (2019) (seeking to prevent abuse of the Hatch-Waxman Act's 180-day generic exclusivity period).
155. *See* discussion *infra* Part III.E.2.
156. *See, e.g.,* Letter from John. C. Yoo, *supra* note 64, at 2 and note 1. *See also generally* Carver (describing FDA hesitancy as one of the leading causes for the delay in the institution of a regulatory pathway for approval of follow-on biologics).
157. *See supra* notes 13-16 and accompanying text.
158. *See, e.g.,* M.A. Lemley, "Intellectual Property Rights and Standard-Setting Organizations," *California Law Review* 90 (2002) ("while IP rights sometimes promote innovation, at other times they can actually impede it. This is particularly true in industries where innovation is cumulative, because granting strong IP rights to initial innovators restricts the options available to improvers."); *White v. Samsung Elecs. Am., Inc.*, 989 F.2d 1512, 1513 (9th Cir. 1992) (Kozinski, J., dissenting) ("Overprotecting intellectual property is as harmful as underprotecting it ... Overprotection stifles the very creative forces it's supposed to nurture.").
Price and Rai have proposed to incentivize a voluntary disclosure of original biologics manufacturing information with additional exclusivities. See Price and Rai, *supra* note 41, at 1053. For the reasons discussed herein, however, creating yet another exclusivity for biologics would be ill-advised as it will further exacerbate the existing overprotection afforded to original biologics, compounding the negative effects on innovation and competition caused by existing overprotection.
159. *See, e.g.,* Heled *supra* note 4, at 129-130 (describing the case of Amgen's twenty-three years of monopoly in its filgrastim product, Neupogen).
160. *See, e.g.,* Gottlieb Statement *supra* note 139 ("the life science industry realizes one of the highest rates of investment in research and development – almost 19 percent of revenues, on average."); Atteberry et al., *supra* note 23 (discussing the profitability of biologics; bringing Humira as an example).
161. Estimates range from several hundreds of millions of dollars to $2.6 billion per product. *See, e.g.,* J.A. DiMasi and H.G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different," *Managerial and Decision Economics* 28 (2007): 469, 469 (estimating the cost of development of a new biologic at $559 million); J. Avorn, "The $2.6 Billion Pill - Meth-

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odologic and Policy Considerations," *New England Journal of Medicine* 372, no. 20 (2015): 1877, 1877-78 (challenging the estimates by the Tufts Center for the Study of Drug Development by noting that the Tufts estimates did not account for large public subsidies provided to pharmaceutical companies or development costs incurred by the public, did not disclose the compounds being studied, and assumed that capital costs amounted to half of the total drug development costs); C. M. Ho, "Drugged Out: How Cognitive Bias Hurts Drug Innovation," *San Diego Law Review* 51 (2014): 419, 448-57 (challenging the calculation that the "*average* cost to develop every drug exceeds $1 billion").

162. *See, e.g.,* Press Release, *Tufts Ctr. for the Study of Drug. Dev., Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion*, November 18, 2014, *available at* <https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5ac66adc758d46b001a996d6/1522952924498/pr-coststudy.pdf> (last visited November 13, 2019) (calculating $2,558 million based on an estimated $1,395 million in capital and $1,163 million in time costs). Notably, the 2014 estimate is significantly higher from an earlier estimated cost of $802 million to develop a new drug made by researchers in the same Industry funded research institute in 2000. *See* J. A. DiMasi et al., "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 155, 166.
163. Even if one were to accept the estimates of $1.2-2.6 billion as true, the sales figures of many if not most original biologics make such numbers pale in comparison. *See, e.g.,* A. Philippidis, "Top 15 Best-Selling Drugs of 2018," *Genetic Engineering & Biotechnology News* March 11, 2019 (reporting the sales figures of top selling original biologics as ranging between $5.908-19.936 billion *annually*).
164. 42 U.S.C. § 262(k)(7).
165. *See, e.g.,* H.C. Grabowski, "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition," *Nature Reviews Drug Discovery* 7 (2008): 479, 486 (arguing that 12.9-16.2 years of market exclusivity in original biologics are necessary to recoup the investment in an original biologic's R&D); FTC 2009 Report at v-vii (arguing against any additional exclusivity for original biologics; disputing the estimates put forward by the Industry that relied on Grabowski); *Biologics and Biosimilars: Balancing Incentives for Innovation: Hearing Before the H. Subcomm. on Courts and Competition Policy of the H. Comm. on the Judiciary*, 111th Cong. 17 n.3 (2009) (statement of Bruce A. Leicher); A. M. Brill, *Proper Duration of Data Exclusivity for Generic Biologics: A Critique* (2008): 7, 8 & 11, *archived at* <http://perma.cc/ S825-8DVQ> (last visited November 13, 2019); L. J. Kotlikoff, *Stimulating Innovation in the Biologics Industry: A Balanced Approach to Marketing Exclusivity* (2008): 6, *available at* <https://pdfs.semanticscholar.org/ac5a/60467ecb61f49496bccd70df446d5dc825a8.pdf> , *archived at* <http://perma.cc/3TSM-8ZNG> (both last visited November 13, 2019).
166. *See, e.g.,* Grabowski, *supra* note 165, at 486; *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. 161–76 (2007) (statement of Henry Grabowski); Biotech Indus. Org. (BIO), A Follow-On Biologics Regime Without Strong Data Exclusivity will Stifle the Development of New Medicines 4, *available at* <https://www.bio.org/sites/default/files/FOBSData_exclusivity_20070926_0.pdf>, *archived at* <http://perma.cc/S59R-P77J> (both last visited November 13, 2019) ("[A] 14-year period of data exclusivity serves essentially as an insurance policy that provides the innovator with some certainty of protection … ."); H. Grabowski et al., *Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques*, Duke University Department of Economics, Working Paper No. 2008-10, 2008): at 4, *available at* <http://public.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf>, *archived at* <http://perma.cc/C7FA-FN85> (both last visited November 13, 2019) (arguing that the purpose of the market exclusivity for original biologics developers is to provide them "with an 'insurance policy' against the potential failings of patent protection for biologics"); H. Grabowski and J. DiMasi, *Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff's White Paper*, Duke University Department of Economics, Working Paper No. 2009-02, 2009): at 408, *available at* <http://public.econ.duke.edu/Papers//PDF/FinalDraft2_5_09.pdf>, *archived at* <http://perma.cc/9EGX-ZFP9> (both last visited November 13, 2019).
167. Notably, original biologics developers' exclusivity in their products is further ensured internationally by similar extra-patent exclusivity arrangements such as the ones instituted under BPCIA as well as by foreign patents covering the original biologics. For further discussion of international implications of disclosure of original products' manufacturing information, *see* Price, *supra* note 5, at 1811.
168. 42 U.S.C. § 262(k)(7)(A).
169. 42 U.S.C. § 262(k)(7)(B).
170. 42 U.S.C. § 262(m)(2)(A). *See also* discussion *supra* note 14.
171. Notably, patents covering original biologics and methods involved in the manufacturing of biologics are notoriously narrow and practically never disclose enough information to enable reproduction of biologics' entire manufacturing processes by competitors. *See, e.g.,* D. Karshtedt, "Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement," *Hastings Science & Technology Law Journal* 3 (2011): 135-37; G.N. Mandel, "The Generic Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement," *VAJLT* 11 (2006): 8; Price and Rai, *supra* note 41, at 1050-53 (arguing that patents are unsuitable for prompting sufficiently full disclosure of original biologics manufacturing information). Disclosure of manufacturing information to the FDA as part of an original BLA, on the other hand, is complete and includes all the details necessary to accurately recreate the full process of manufacturing an original biologic.
172. U.S. Const. Amend. V ("nor shall private property be taken for public use, without just compensation."). *See, e.g.,* Letter from Robert A. Long, *supra* note 45 at 2; H. Carver et al., *supra* note 40, at 698 (expressing the view that "approve[al of] BLAs in reliance on preclinical and clinical safety and effectiveness data submitted in other BLAs … in the view of the authors, [is] inconsistent with … the Federal Trade Secrets Act, FDCA section 301(j), and the U.S. Constitution."); Epstein, *supra* note 64, at 299-300; *see also supra* note 45.
Notably, this position appears to be inconsistent with BPCIA's similar, "opposite requirement" that follow-on biologics applicants disclose *their* manufacturing information *directly* to original biologics developers so that the later could assess whether and to what extent follow-on applicants infringe any patents covering the original biologic. *See* 42 U.S.C. 262(l)(2)(A) ("the [follow-on biologic] applicant (A) shall provide the [original biologic developer] a copy of the application submitted to the Secretary … and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application."). Ultimately, the Supreme Court determined that doing so was optional for makers of follow-on biologics. *See Sandoz Inc. v. Amgen Inc.*, 137 S.Ct. 1664, 1674 (2017) (affirming that makers of a follow-on biologics cannot be forced by injunction to engage in "patent dance" under 42 U.S.C. § 262(l)(2)(A)). Yet, that holding was a surprise for many and did not reflect the intention of BPCIA's drafters, who sought to impose participation in BPCIA's "patent dance" on makers of follow-on biologics. *See* Heled, *supra* note 4, at 119 n.37.
Interestingly, in an Industry funded research, Prof. Richard Epstein has expressed the opinion that BPCIA's arrangements constitute a taking *even without FDA consideration or disclosure of regulatory filings made in connection with original biologics marketing applications*. *See* Epstein, *supra* note 64, at 294, 296, 300 ("even indirect reliance on the data in the prior

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application constitutes a taking" and "FDA's reliance the prior finding of safety, purity and potency in approving a biosimilar application appropriates the underlying trade secrets for the benefit of the biosimilar applicant. That partial loss of exclusive property rights in trade secrets thus triggers the application of the Takings Clause just as if the agency were accessing or releasing the data.").

173. *See* The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary, S. Hrg. 108-635 at 134 (June 23, 2004) (statement of Lester M. Crawford, Acting Commissioner of Food and Drugs), *available at* <https://www.govinfo.gov/content/pkg/CHRG-108shrg96196/pdf/CHRG-108shrg96196.pdf> (last visited November 13, 2019) ("we do not believe such authority exists for follow-on biologics application under section 351 of the PHS Act that relies on the prior approval of the biological product or on data submitted by another sponsor."); Carver et al., *supra* note 40, at 698-99. *See also* J. C. Yoo, "Takings Issues in the Approval of Generic Biologics," *Food & Drug Law Journal* 60 (2005): 33, 34 note 10 (in an article funded by the generic industry, criticizing the FDA's reluctance to create a regulatory pathway for approval of generic biologics as unwarranted).
174. *Ruckelshaus*, 467 U.S. at 1002.
175. Arguably, such a change in the law would also render unreasonable any expectations that regulatory filings made subsequent to the law's going into effect would be kept confidential. *See also* Letter from John C. Yoo, *supra* note 64, at 6).
176. *Ruckelshaus*, 467 U.S. at 1007.
177. The Ruckelshaus Court did not consider the disclosure of regulatory filings by EPA to be per se taking and further emphasized that "this Court has generally been unable to develop any set formula for determining when justice and fairness require that economic injuries caused by public action must be deemed a compensable taking ... The inquiry into whether a taking has occurred is essentially an ad hoc factual inquiry." *Ruckelshaus*, 467 U.S. at 1005. *See also* Letter from John A. Yoo, *supra* note 64, at 3-4.
178. *Ruckelshaus*, 467 U.S. at 987 (holding that FPA's data use and disclosure provisions did not violate the Fifth Amendment with respect to data submitted prior to October 22, 1972).
179. *Id.*, at 1005 (internal citation marks omitted); *see also Penn Cent. Transp. Co. v. City of New York*, 438 U.S. 104, 124, 98 S. Ct. 2646, 2659, 57 L. Ed. 2d 631 (1978) ("A 'taking' may more readily be found when the interference with property can be characterized as a physical invasion by government ... than when interference arises from some public program adjusting the benefits and burdens of economic life to promote the common good. Government hardly could go on if to some extent values incident to property could not be diminished without paying for every such change in the general law.").
180. *See, e.g.,* Letter from Robert A. Long, *supra* note 45.
181. 21 U.S.C. § 331(j).
182. *See* 42 U.S.C. § 262(j) ("The Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] ... applies to a biological product subject to regulation under this section").
183. *See* 21 C.F.R. § 60.151(f) ("The following data and information in biological product file are not available for public disclosure ... (1) manufacturing methods or processes, including quality control procedures ... (3) Quantitative or semiquantitative formulas."); 21 C.F.R. § 20.61(c) ("Data and information submitted or divulged to the Food and Drug Administration which fall within the definition of a trade secret or confidential commercial or financial information are not available for public disclosure.").
184. *See* Letter from Robert A. Long, *supra* note 45.
185. 18 U.S.C. 1905.
186. Pub. L. 114–153, 130 Stat. 376 (2016) (codified at 18 U.S.C. § 1836, *et seq.*).
187. *Ruckelshaus*, 467 U.S. at 1008.
188. Notably, Prof. John Yoo has expressed the view that PHSA Section 301(j) similarly does not provide an express enough promise, under *Ruckelshaus*, not to disclose trade secrets in the specific context of approval of follow-on biologics. *See* Letter from John C. Yoo, *supra* note 64, at 9. *But see* Epstein, *supra* note 64, at 293 (arguing that BPCIA's reference to "publicly available information" creates such an explicit promise).
189. *See also* Letter from John C. Yoo, *supra* note 64, at 10.
190. *Id.*, at 1008-09.
191. *Id. See also* Letter from John C. Yoo, *supra* note 64, at 6-7 ("Statutory silence in a heavily regulated industry, the Court found ... places applicants on notice that they cannot form reasonable investment-backed expectations that submitted data will not be used by the agency in the future.").
192. *See, e.g.,* J. M. Sharfstein et al., "Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products," *Journal of Law, Medicine & Ethics* 45, no. 2, Suppl. (2017): 7-23; P. Doshi, "FDA to Begin Releasing Clinical Study Reports in Pilot Programme," 390 *BMJ* (2018): k294.
193. *Ruckelshaus*, 467 U.S. at 1005.
194. *Ruckelshaus*, 467 U.S. at 1016-19.
195. *Id.*, at 1016. Under the Tucker Act, "The United States Court of Federal Claims shall have jurisdiction to render judgment upon any claim against the United States founded either upon the Constitution, or any Act of Congress or any regulation of an executive department, or upon any express or implied contract with the United States, or for liquidated or unliquidated damages in cases not sounding in tort." 28 U.S.C. § 1491.
196. *See supra* notes 164-166 and accompanying text.
197. *See supra* note 165 and accompanying text.
198. *See also* Epstein *supra* note 64 at 315 and 324 (making a similar point, viewing BPCIA's "special protections ... to innovators ... as the "quid pro quo" for removing at year 12 the innovator's otherwise permanent right to prevent competitors from benefitting from the government's use of those trade secrets" but disagreeing that BPCIA's scheme would allow for FDA disclosure of trade secrets to follow-on biologics developers).
199. *See supra* notes 37-42 and accompanying text.
200. *See, e.g.,* A. G. Vulto and O. A. Jacquez, "The Process Defines the Product: What Really Matters in Biosimilar Design and Production?" *Rheumatology* 56 (August 2017): iv14, iv23 (noting that the manufacturing complexity of biologics can have a negative impact on batch-to-batch consistency); J. Gonçalves et al., "Biosimilar Monoclonal Antibodies: Preclinical and Clinical Development Aspects," *Clinical & Experimental Rheumatology* 34, no. 4 (2016): 698, 698 (there are "unavoidable differences between even subsequent batches of the same product"); S. Louët, "Lessons from Eprex for Biogeneric Firms," *Nature Biotechnology* 21 (2003): 956 (describing how small changes in the manufacturing process of the biologic Eprex caused severe immunogenic responses in patients); M. M. C. van Beers and M. Bardor, "Minimizing Immunogenicity of Biopharmaceuticals by Controlling Critical Quality Attributes of Proteins," *Biotechnology Journal* 7 (2012): 1473.
201. *See Lucas v. S.C. Coastal Council*, 505 U.S. 1003, 112 S. Ct. 2886, 120 L. Ed. 2d 798 (1992). The taking analysis would have changed had the purported taking pertained to real property. *Id.*, at 1015.
202. *See, e.g.,* 37 C.F.R. §§ 1.801 et seq. (2003) (requiring samples to be deposited with the USPTO).
203. *See, e.g.,* 21 C.F.R. § 80.21 et seq. (2018) (requiring a request for certification by the FDA of a batch of color additives to be accompanied by a sample).

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