Similar or the Same?
Why Biosimilars are not the Solution

Lisa Diependaele, Julian Cockbain, and Sigrid Sterckx

1. Introduction

In the last decades the pharmaceutical industry has undergone a significant evolution: advancements in the field of biotechnology have accelerated the development of drugs that are manufactured from cultures of living cells, drugs which are commonly referred to as "biologics."[1] The development of these drugs has resulted in the introduction of valuable medical treatments, especially for rare diseases, immunological and inflammatory disorders, and cancers. In just a few years' time, biologics have come to represent an important part of the global drug market – about 26% of worldwide pharmaceutical sales in 2017, a percentage that will continue to grow in the coming years (up to 30% in 2022).[2]

The introduction of these new treatments, however, has come at a high price. The annual cost of some biologics exceeds US$250,000 per patient.[3] Furthermore, many of the top revenue-generating drugs are monoclonal antibodies — large and highly complex biologics.[4] These high figures have adverse consequences: public healthcare budgets soar, and certain drugs are unaffordable for many patients.

One of the main reasons new drugs can be sold at such high prices is that they are generally covered by patents, and until those patents expire, originator companies can sell their drugs at a price far above the production price. The temporary patent monopoly allows originator companies to recoup the high costs associated with the development of new drugs — which are typically claimed to be in the billion U.S. dollar range.[5]

In addition to a patent monopoly, originator companies are granted temporary exclusive user rights to the clinical data that need to be submitted to the regulatory authorities.[6] This "data exclusivity" de facto delays the market entry of generic competitors. After these exclusive user rights on the clinical data expire, however, a generic competitor can be allowed to enter the market by demonstrating that its version of the drug is identical (bioequivalent) to the original (reference) product — thus relying on the clinical data that already have been provided by the originator to show that the generic version of the drug will be safe and effective.

Until relatively recently, most drugs were small chemical molecules, Aspirin (acetyl salicylic acid), for example, is a molecule with only twenty-one atoms and a molecular weight of 180 Da. Proving that the generic competitor's version of such a drug is identical to the

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originator's version is quite trivial. Consequently, once the patent and data exclusivity periods have expired, generic competitors' versions of the drug can be rapidly introduced on the market, allowing the sale price of the drug to fall to a fraction of the earlier price.

Biologics, on the other hand, are very large, complex molecules produced by genetically engineered organisms, e.g. bacteria or mammalian cells,[7] and unless a generic version of a biological is produced by the same cell line as the originator's biological, it is extremely unlikely to be chemically identical. As the original biologic's cell line and manufacturing process will be closely guarded as trade secrets, a generic competitor will have no other option than to develop a new cell line.[8] A "generic" biologic may have the same desired functionality as the originator's biologic but will generally only be similar to the original biologic and is therefore referred to as a "biosimilar."

We will argue that the regulatory pathway for biosimilars in the E.U. and the U.S. does not adequately serve the purpose of bringing safe and effective drugs onto the market without undue delay. On the contrary, it has resulted in the allocation of substantial resources to the development of drugs equivalent to those that already exist, and has encouraged unnecessary performance of clinical trials — contrary to the Oviedo Convention and recognized as a violation of important ethical principles guiding the conduct of medical research.

As with traditional generic drugs, the development of biosimilars has been presented as the key solution to decrease prices and increase access to biologic drugs. However, the development process and launch of biosimilars continues to raise significant problems, none of which can easily be addressed. As we will elaborate in Section 2, the development of a biosimilar requires considerable time and resources, and safety concerns necessitate elaborate clinical testing and regulatory review of (candidate-) biosimilars. Furthermore, concerns regarding the substitution and interchangeability of original biologics with biosimilars persist, and the introduction of biosimilars onto the market has not consistently resulted in significant price reductions (see Section 3).

Due to the challenges of the biosimilar development process, originators' biologics have maintained a quasi-monopoly, even after patents and regulatory exclusivities expire. The significant "knowledge gap"[9] between the original biologic's manufacturer and the biosimilar manufacturer has distorted the trade-offs that has traditionally guided both patent protection and regulatory exclusivities: an "enabling disclosure" as key condition to benefit from a monopoly.

We will argue that the regulatory pathway for biosimilars in the E.U. and the U.S. does not adequately serve the purpose of bringing safe and effective drugs onto the market without undue delay.[10] On the contrary, it has resulted in the allocation of substantial resources to the development of drugs equivalent to those that already exist, and has encouraged unnecessary performance of clinical trials — contrary to the Oviedo Convention[11] and recognized as a violation of important ethical principles guiding the conduct of medical research.

Nevertheless, solutions do exist: facilitating the development of a drug that more closely resembles the original product, a "biogeneric." In addition to discussing some of the suggestions that have been made in this regard, we will argue that requiring the deposit of the original biologics' cell line, which at a later stage generic companies can access, can be an effective remedy for some of the major shortcomings of the current situation.

We will proceed by shedding light on the current regulatory framework for biosimilars in the E.U. and the U.S. (Section 2) and will subsequently discuss some of the problems that the development and use of biosimilars have raised (Section 3). In Section 4 we will discuss our proposal to require the deposit of original biologics' cell line and will explain why this does not constitute an unreasonable transgression of originator companies' rights and interests.

2. Regulating Biosimilars

2.1. Regulatory Requirements for Approval

Because a biosimilar can never be identical to the original biologic (reference product), the requirements for bringing a biosimilar to the market are significantly more extensive than those for introducing a traditional small molecule generic on the market.[12] Basically, the biosimilar applicant is required to prove that

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the differences between the candidate-biosimilar and the reference product are not clinically significant.[13]

The first regulatory framework for the approval of biosimilars was developed by the European Medicines Agency (EMA).[14] Already in 2003, the E.U. Directive regulating the approval for medicinal products for human use mandated the EMA to develop principles for the approval of "similar biological medicinal products."[15] The relevant guidelines prescribe how a biosimilar applicant needs to demonstrate the similar nature in terms of quality, safety and efficacy of the candidate-biosimilar.

Overall, a biosimilar application requires the carrying out of elaborate analytical, nonclinical and clinical studies comparing, head-to-head, the biosimilar with the reference product.[16] In addition to a comprehensive analytical data package showing that several key characteristics are the same for the biosimilar and the reference product,[17] preclinical pharmacokinetic (PK) and pharmacodynamics (PD) studies (in animals), clinical comparative PK and PD studies (mostly in healthy volunteers), and comparative clinical efficacy and safety trials (in study populations representative for all indications for which approval is sought) are in most cases required.[18]

The EMA accepts a step-wise approach, meaning that the level of certainty obtained in each phase will guide the specifics and scale of the studies required in subsequent phases.[19] For each deviation from the reference product, additional justifications and data will need to be provided. On the other hand, increased levels of certainty on the absence of clinically meaningful differences may reduce the number and scale of the necessary confirmatory clinical trials.[20]

The U.S. regulatory authority, the Food and Drug Administration (FDA), was rather late in the establishment of a regulatory pathway for biosimilars. Opponents and proponents of an abbreviated pathway long disagreed on the safety of biosimilars and the extent of testing that should be required to allow biosimilars on the market.[21] As a consequence, the Biologics Price Competition and Innovation Act (BPCIA) was only adopted in 2009.[22] This Act created an abbreviated Biological License Application (aBLA) for biologics that are demonstrated to be highly similar to a reference product based upon data derived from analytical studies, animal studies, and clinical studies. Specifically, section 351(k) requires the assessment of immunogenicity, PK and PD via clinical studies that are "sufficient to demonstrate safety, purity, and potency in one or more (…) conditions (…) for which licensure is sought (…)."

The FDA encourages pre-submission consultations and, like the EMA, relies on a step-wise approach.[23] The demonstration of biosimilarity must be based on an elaborate analytical comparability assessment, clinical pharmacology studies to compare the PK and PD characteristics of the candidate-biosimilar and the reference product, and clinical trials to confirm that there are no clinically meaningful differences between both products.[24] However, if initial phases of comparability studies result in higher levels of confidence regarding the similarity of the (candidate-)biosimilar with the reference product, less extensive clinical studies can suffice.[25]

Before the abbreviated pathway for biosimilars was created, the FDA approved some biosimilar versions of first-generation biologics as traditional generic drugs, under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.[26] Such a demonstration of bioequivalence requires head-to-head clinical studies comparing the PK and PD characteristics of the candidate-generic and the reference product. If these studies confirm that the (candidate-)generic delivers the same active ingredient in the same amount and in the same time period as the original drug, the generic applicant may further rely on the safety and efficacy data provided by the originator and will be authorized to enter the market based on this information.[27] Thus, much less preclinical and clinical testing is needed to ensure that the bioequivalent drug is safe and effective. Likewise, in the E.U. the traditional generic approval pathway is still open for biologics, although it is highly unlikely that biosimilars will meet the conditions for being recognized as a "bioequivalent" generic.[28] Consequently, for the most part, biosimilar applicants will have no other option than to take the longer "biosimilar route."

2.2. Data Exclusivity for Biologics

The introduction of data exclusivity dates back to the Hatch-Waxman Act of 1984, which established the regulatory pathway for traditional generics in the U.S., but at the same time offered five years of "data exclusivity" to "new chemical entities."[29] This implies that, for a period of five years following the initial market authorization, generic competitors are not allowed to submit an "abbreviated new drug application" (ANDA) that relies on the clinical data submitted by the originator in support of their applications.[30] Some commentators have argued that this system of market protection has become much more important than traditional patent protection, as the data exclusivity protecting a drug may exist even if patent protection has not been applied for, been granted, or when the relevant patents either expire or are invalidated.[31]

For biologics, the BPCIA has significantly lengthened this system of regulatory protection. For four years, the FDA may not accept any biosimilar appli-

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cations, and, for another eight years, may not grant final approval of such applications, which adds up to twelve years of regulatory protection for the original biologic.[32] In the E.U. no distinct regulatory exclusivity for biologics exists, but the standard period of data exclusivity is much longer than in the U.S. Neither biosimilar nor generic applications can be accepted for eight years after the reference product has been authorized to enter the market and the final regulatory approval relying on the originators' data can only be granted after ten years.[33]

2.3. Biosimilars on the Market

Several biosimilars have reached the market in the last decade. The E.U. remains the frontrunner, with 39 biosimilars authorized and only five applications being refused or withdrawn.[34] The first biosimilars approved by the EMA were rather simple protein therapeutics (first-generation biologics), but since 2013, the EMA has authorized several biosimilar monoclonal antibodies.[35] The FDA has approved nine biosimilars.[36]

Several of the bestselling originator biologics are facing patent expiry before 2020, and approximately eight hundred biosimilars for approximately a hundred reference products are currently under development.[37] Accordingly, it is projected that the biosimilar market will come to represent a 4–10% market share by 2020, worth about US$10–25 billion.[38] Besides the U.S. and the E.U., other countries such as the BRIC nations could prove to be attractive markets for biosimilars and might play an important role in the further development of the biosimilars market as well.[39]

3. The Problems With Biosimilars

3.1 Extrapolation of Indications, Interchangeability and Substitution

Notwithstanding the widespread enthusiasm over the biosimilar market potential, biosimilar drug development raises some important questions and problems. Due to their complex nature, many have questioned the safety of biosimilars, mostly in relation to the risks of unpredictable immune responses.[40] Unexpected adverse responses to biosimilar treatment have not yet been reported,[41] but the overall slow uptake[42] of biosimilars has been attributed to physicians' concerns about patient safety, problems with interchangeability, and a corresponding reluctance to prescribe biosimilars.[43]

An important hurdle for biosimilars is that the demonstration of similar efficacy, safety and potency for one indication does not guarantee that the biosimilar is functionally equivalent for the other indications the original biologic was approved for. The extrapolation of clinical results between different indications can be justified and is sometimes accepted by the regulators, but complex modes of action of biologics involving multiple receptors can necessitate additional comparative clinical studies to ensure that the biosimilar and the original biologic behave alike. Hence, there is no guarantee that a biosimilar will be therapeutically equivalent for all indications.[44] Besides hindering the acceptance of biosimilars, this necessitates additional clinical testing and corresponding financial investments.

Likewise, doubts persist regarding the "interchangeability" and "substitution" of biosimilars.[45] Even when the quality of biosimilars is high, potential differences between biosimilars and original biologics necessitate caution when patients are changed from one product to another.[46] In cases of repeat switching, there are major concerns regarding increased immunogenicity, leading to adverse reactions.[47]

The safety of interchangeability and substitution is not assessed during the EMA approval process and remains subject to the decision of the national authorities. In most E.U. countries, automatic substitution of biosimilars is prohibited.[48] Only recently, have some E.U. countries have taken careful steps towards encouraging interchangeability and accepting substitution, albeit under strict conditions.[49] In the U.S., licensed biosimilars can directly be recognized as "interchangeables" by the FDA — which in the U.S. implies that they can automatically be substituted at the pharmacy level.[50] To be recognized as "interchangeable," the BPCIA requires that a biosimilar must have the same clinical effect as the original biologic for every individual patient and that (repeat) switching does not pose any additional risks.[51] In January 2017 the FDA issued a draft guideline for demonstration interchangeability, but has not yet granted such a status.[52]

In sum, in comparison with traditional small molecule generics, significant scientific, safety-related and regulatory hurdles remain for the recognition and use of biosimilars as *fully equivalent therapeutics.*

3.2 Unnecessary Duplication of Clinical Trials?

Besides the issues hindering the recognition of biosimilars as fully equivalent drugs, the entire biosimilar development process raises some questions as well. Because of the burdens and risks associated with the execution of clinical studies, one could question the fact that in order to develop something that already exists — a particular treatment for a particular (set of) indication(s) — numerous clinical studies are being conducted.

In order to be ethically justified, clinical research must aim at generating knowledge that can contribute

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to improvements in health and well-being. Substantial overlap with proven results, on the other hand, is generally considered to be unethical, as clinical study participants' exposure to risks cannot be justified by the expected benefits of the study results.[53] Therefore, the *unnecessary* duplication of clinical trials is prohibited by the Oviedo Convention[54] and generally recognized as a violation of important ethical principles guiding the conduct of medical research.[55]

Although dosage variation studies are not often required for the clinical testing of biosimilars,[56] the fact that biologics are particularly unpredictable and can set off unforeseen immune responses make it unwise to assume that biosimilar trials are risk-free. Hence, this raises the question to which extent the extensive comparative clinical testing of biosimilars can be justified by the expected benefits.

In sum, it seems likely that price reductions will remain limited and biosimilar development will only bring a marginal benefit to society. Taking into account the fact that clinical trials are never without risk and no new therapeutic or other clinical benefits are realized through these investments, making such significant investments to develop something that already exists seems to be a waste of resources.

3.3 Sufficient Competition?

A recent study of price evolutions in the European Economic Area (EEA) shows that biosimilars are only 7% up to 37% less expensive when comparing prices of biologics in the year before biosimilar market entry with the average prices of the corresponding biosimilars in 2016.[57] A general study of the prices of biosimilars in the U.S. is not available, but projections expect the price of biosimilars to be 10% to 30% lower than the originators' price — an estimate that is confirmed by some preliminary statistics.[58] Clearly, these figures stand in sharp contrast with the average price reductions for traditional generic drugs of 50% up to 80%.[59]

The fact that the introduction of biosimilars on the market has not generally resulted in substantial price reductions is understandable bearing in mind the challenges of the biosimilar development process, but this is problematic from the societal perspective. Whoever pays — the patient, a private insurer or the public health budget — the high cost of biologics (for both originator biologics and biosimilars) contributes to non-affordability, higher premiums, and reductions on other services and public causes.[60] To address the issue of soaring healthcare costs and to make drugs more affordable, encouraging biosimilar market entry and competition has widely been accepted as a pivotal solution to realize substantial cost reductions.[61] However, there are several factors that may prevent biosimilars from behaving on the market like traditional generics.[62]

Firstly, significant price reductions are only possible when there are multiple competitors on the market. This is illustrated by the fact that, for traditional small-molecule drugs, the price reductions realized by one generic competitor on the market will be rather modest but will gradually increase as more competitors enter the market.[63] Without a substantial number of biosimilar competitors on the market, there might not be sufficient competition to ensure that the market price is closer to the actual cost of production and distribution. After all, the goal of the generic industry is maximizing their profits, and as long as the market allows originators and biosimilar competitors to keep the price high, they will do so. Only if price reductions can help them to maximize their profits, will prices drop.

In the biosimilar market, this dynamic seems somewhat disturbed as there appears only to be a weak correlation between biosimilar uptake and price reductions,[64] which might be explained by the fact that biosimilars are not fully equivalent and interchangeable.[65] Nevertheless, even if a lower price is not the most effective way to increase biosimilar uptake,[66] this does not mean that lowering prices should not be aimed at in order to remedy soaring healthcare costs and increase access. The purpose of price competition is not to reduce the originators' market share (by encouraging the use of biosimilars over the original biologic) but to bring prices closer to the actual cost of production and distribution. Even when biosimilar uptake remains relatively low, this can only be realized in a competitive market, for which the presence of sufficient competitors is essential.

Secondly, the costs and risks associated with the biosimilar development process might prevent sufficient competitors from finding their way to the market.[67] The biosimilar development process requires much more time, and comes at a much higher cost, than the

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development of traditional small-molecule generics. For a biosimilar, the development process can take up to eight years instead of three to five years for a traditional small-molecule generic.[68] The costs are estimated to range from US$25 million to US$300 million, compared to US$5-10 million for a traditional small-molecule generic.[69] Hence, in addition to a high regulatory barrier, biosimilar market entry requires significant investments and is not without risks[70] — which might be sufficient to deter traditional generic companies from engaging in the biosimilar development process, especially for specialty drugs.[71] Moreover, the relatively high cost of development will make it easier for originators to keep competitors off the market by setting their prices just low enough to deter competitors.[72]

In sum, it seems likely that price reductions will remain limited and biosimilar development will only bring a marginal benefit to society. Taking into account the fact that clinical trials are never without risk and no new therapeutic or other clinical benefits are realized through these investments, making such significant investments to develop something that already exists seems to be a waste of resources.

4. Overcoming the Barriers: A Biogenerics Proposal

To address the challenges of the biosimilar development process discussed in Section 3 above, many strategies have been suggested, such as a more efficient cell line development process, improving analytical techniques to simplify the characterization of biologics, additional head-to-head studies to tackle interchangeability and substitution issues, and physician and patient education.[73] However, as the problems of biosimilars are predominantly caused by the fact that these therapeutics cannot be recognized as fully equivalent products, we suggest a more effective way to make the entire biosimilar development process less burdensome: the deposit and subsequent disclosure of the original biologics' cell line.

4.1 Disclosing the Cell Line

The most effective way to address the problems and challenges related to the development and marketing of biosimilars is to enable the development of a drug that more closely resembles the original product, a "biogeneric." In order to facilitate this, we propose the establishment of a procedure for the deposit of original biologics' cell lines, which at a later stage generic companies can access. More specifically, we recommend that the cell line be deposited by the originator at the time of the regulatory approval of the original biologic, and that generic companies be allowed access to the deposit at a fixed term of two or three years in advance of the expected expiry date of all applicable patents and regulatory exclusivities.[74] After the "unlock date," generic companies can begin the process of developing a generic version of the original biologic and proceed with their regulatory applications. Nonetheless, as the precise expiration date cannot always be predicted in advance, the final approval of a biogeneric should only be granted if all relevant patents and regulatory exclusivities of the original biologic have expired.

As the entire biologics production process — including the cell line — is traditionally guarded as a valuable trade secret, some may find such an idea unsettling. There are, however, several good reasons to consider it. To begin with, by providing candidate competitors access to the original cell line they are enabled to develop a product that more closely resembles the original biologic than a biosimilar, not least by having been subjected to the same folding mechanism as the original[75] — something which is impossible to achieve through reverse-engineering from the original biologic or reference product. Second, a more limited clinical assessment of the (candidate-)biogeneric may suffice. If the analytical and preclinical comparison of the (candidate-)biogeneric and the reference product result in higher levels of certainty on the likeness of both products, regulators may waive any aspect of the development program that is deemed unnecessary.[76] Even though a candidate competitor will have to (re) develop the entire manufacturing process — encompassing several critical phases which all may influence the end-product[77] — it should be easier and less costly to reach higher levels of certainty at an earlier stage in the development process.

What is more, higher levels of certainty should facilitate the recognition of biogenerics as interchangeable biologics in the U.S. — as lower levels of "residual uncertainty" can impact what additional data and information would be needed and "may lead to a more selective and targeted approach to the clinical studies necessary to demonstrate interchangeability."[78] For the European Union, on the other hand, it is to be recommended that a pathway for demonstrating 'interchangeability' is introduced, mirroring U.S. provisions.[79]

Importantly, providing a prospective generic competitor access to the originator's cell line will not make all other aspects of the development process minor, as our proposal does not require the full disclosure of all the manufacturing process details. The candidate-competitor will have to determine how to ferment and purify the protein and develop a robust process that allows for the manufacture and formulation of the protein on a large-scale.[80] Consequently, allowing generic companies to develop an equivalent biologic

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based on the originator's cell line should not result in a less rigorous regulatory review or quality assessment. No drug development process is risk-free, and for biologics all changes to the manufacturing process can pose significant risks. Even so, by allowing generic companies to work with the same cell line, unnecessary risks may be avoided.[81]

A problem that may arise is the "drifting apart" of different versions (original and generic) of a biologic due to post-approval manufacturing changes, more specifically major changes such as cell line changes, which at times even necessitate additional clinical testing.[82] To ensure that the original biologic and biogeneric can be produced using the same cell line, it could be required that a new deposit is made if the originator changes the cell line. However, if an originator's manufacturing change results in new formulation or process patents, these could delay the use of "cell line B" by (prospective) generic competitors.

Relying on various evergreening strategies, originator companies may significantly push forward the date of expiry of all relevant patents on an original biologic. Especially new formulation and manufacturing patents (sometimes applied for post-approval), can, for an extended time, prevent the use of the same cell line as the original biologic. This problem may be addressed by allowing prospective generic competitors to use a previously deposited cell line ("cell line A") to produce a biogeneric for a previous version of the original biologic, for as long as a new formulation or process patent would prevent the use of "cell line B," deposited after a manufacturing change. As manufacturers of both originator and biogenerics should in no way be prevented from making improvements to their production processes and products, it will indeed be a difficult task for the regulator to ensure that the interchangeability of different versions of a biologic is not negatively affected. While we recognize this is a highly complex issue, it must be emphasized that this problem also may occur in the current system of biosimilar development. If biosimilarity of a competitor's product is established against version A of an original biologic, major manufacturing changes of the latter raise similar concerns and questions.[83]

The cell line development is a critical step in the biosimilar development process,[84] and our proposal aims to moderate the existing scientific and regulatory barriers, as well as reduce the risks and costs involved in the current biosimilar development process. Even though an originator may have improved its manufacturing process and potential profitability since the initial regulatory approval, providing access to the cell line lowers the entry barrier for competition, and increased levels of certainty on the absence of clinically meaningful differences between the original biologic and biogeneric can facilitate a swifter adoption of biogenerics as fully equivalent or interchangeable products.

4.2 Why Mandatory Disclosure Is Necessary

The proposal to provide generic competitors access to the original cell line might seem drastic, but suggestions to disclose some aspects of the biologics production process have been made before. In this context, the most notable contribution to the literature has been made by Price and Rai,[85] who have proposed disclosing the Chemistry, Manufacturing, and Controls (CMC) Section of the original biologic's Biologics License Application (BLA), which contains all crucial information regarding the biologic's production process. More specifically, Price and Rai have recommended a mechanism that offers a compensation as incentive, for example an additional period of market exclusivity or accelerated regulatory approval, to originator companies that are willing to disclose the CMC Sections of their applications.[86] This proposal, however, might turn out to be ineffective to enable the development of biogenerics.[87]

To begin with, physical access to the cell line is essential to enable the development of a fully equivalent biologic. As explained above, if a generic competitor has to develop a new cell line capable of producing a biologic with the same desired functional region, it is unlikely that the copy will be equivalent to the original biologic.[88]

What is more, a voluntary mechanism can only work if it is in the interest of the originator companies, thus if the compensations offered for the disclosure would allow them to make higher profits than they would without participating in such a scheme. Besides the fact that this seems to necessitate very high compensations, this might not even be enough to convince originator companies to deposit the cell line. After all, maintaining a monopoly on the original biologic might always be more profitable than eventually allowing a generic competitor on the market with an equivalent product.

Besides, it seems disproportionate to offer originators yet another additional exclusivity period in addition to patent protection, SPCs and existing regulatory exclusivities, as this implies that further delays to generic market access are acceptable. Moreover, the fact that this would allow the originator to choose between the benefits of the additional protection and the potential benefits of retaining trade secrecy, might in practice turn out as a means for originator companies to optimize their commercial strategies[89] rather than for facilitating biogeneric market entry.

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Therefore, we argue for a mandatory system, for example by making the deposit of the original biologic's cell line a strict condition for the regulatory approval of the original biologic. While it might indeed be impossible to require this for biologics that are already on the market today as such a requirement is difficult to apply retroactively,[90] there is nothing that prevents the regulatory approval procedures from being changed in this regard for future approval applications.

4.3 Why This Is Not Theft: Adequate Compensation and the Public Interest

Our proposal would require originator companies to hand over a physical asset — the cell line — that embodies crucial commercial information which is traditionally protectable as trade secret and therefore often labelled as "proprietary."[91]

Traditionally, trade secrets protect ideas, knowledge, data, and other information with a commercial value against unauthorized disclosure or use, on the condition that reasonable measures to maintain secrecy have been taken. For the FDA, Section 301(j) of the Federal Food, Drug, and Cosmetic Act prohibits revealing the information acquired for a new drug application (NDA), "concerning any method or process which as a trade secret is entitled to protection,"[92] a provision which is deemed to apply to BLAs as well.[93] However, this protection is limited to situations in which there was no prior expectation that the regulators would disclose the information.[94] As a result, by changing legislation, the presumption in this regard can be changed, as long as not retroactively applied.

It has been significantly debated whether or not trade secrets could constitute property[95] — and thus be protected by the Fifth Amendment of the U.S. Constitution — but it has been recognized that requiring the disclosure of commercially valuable information in the context of the regulatory approval process can constitute a taking under U.S. constitutional law, and would need to be adequately compensated.[96] Following one of the leading cases in this regard, *Ruckelhaus v. Monsanto Co.*, requiring a *retroactive* application of any new statutory disclosing requirement would result in constitutional challenges under the takings clause.[97]

For a *prospective* application of a novel disclosure requirement — limited to requiring a cell line deposit for new biologic license applications — it could be argued that some form of compensation is still warranted, as the doctrine of unconstitutional conditions set some limitations on the nature of the conditions the lawmaker may sets for the receipt of a discretionary benefit.[98] In the context of regulatory approval, it has therefore been argued that even a prospective application of a disclosure requirement could fall within the scope of the takings clause, as it gives an applicant no choice but sacrificing its property.[99] However, this does not entail that the government may not set such conditions, merely that a compensation may have to be provided.

The (possible) legal obligation to provide originators a compensation for sharing the cell line they have developed can be said to be already present in the form of data exclusivity for biologics. As has been recognized in the context of the BCPIA, a "collective bargain" such as the provision of some sort of regulatory exclusivity can serve as an adequate replacement for individual compensations.[100] Furthermore, from an ethical perspective, the current compensation received by the originators (10 to 12 years of exclusivity) seems excessive, given the fact that allowing biosimilar applicants to (partially) rely on the originators' clinical test data does not place prospective competitors in a satisfactory position to compete. While it is indeed true that obliging originator companies to deposit the cell line would be a substantial demand,[101] providing an additional compensation for the cell line deposit merely because they *already* benefit from these regulatory exclusivities seems disproportionate.

Regardless of the question of compensation, the legislator should consider mandating a cell line deposit to benefit society as a whole. In addition to the fact that the regulatory approval process could be simplified and potentially duplicative clinical trials avoided, allowing generic companies to use the same cell line should result in more competitors reaching the market and price competition that brings biologics prices closer to their marginal cost, ensuring affordable access to these therapies.[102] What is more, a mandatory depository could guarantee the effective use of compulsory licensing of patented drugs. As it is of pivotal public importance that a state can mandate the production or distribution of a patented drug in case of emergencies, a cell line depository for biologics can guarantee that a biologic can be successfully reproduced.

In this context, it is important to note that obligations to disclose or share commercially valuable information are not extraordinary. Even the BPCIA requires significant levels of disclosure: in order to allow originator companies to assess whether or not a biosimilar manufacturer would infringe any of the originator's patents, the biosimilar applicant is required to fully disclose its manufacturing process details to the originator.[103]

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4.4 Why Not Relying on the Disclosure of the Patent?
Considering that the disclosure of the invention is one of the key conditions for being granted patent protection and benefiting from the corresponding monopoly position,[104] it might seem remarkable to suggest organizing the deposit of a biologic's cell line at the stage of regulatory approval. However, there are several reasons why the deposit can best be organized at the stage of regulatory approval rather than through the patent system.

First, the cell line that could be deposited at the time of the patent application will probably not be the cell line the originator company will eventually use to produce the biologic. In most cases, significant changes will be made by the time the biologic is approved.[105] Besides, requiring an (additional) deposit of the cell line would be very difficult to implement, as such a requirement could constitute a discrimination with regard to the field of technology, which is explicitly prohibited by the TRIPS agreement.

Secondly, the regulatory approval is a hurdle all drugs need to take, both innovative and non-innovative drugs. Applying for a patent, on the other hand, is optional. As biologics cannot simply be reverse-engineered, it is not unlikely that a requiring an (additional) cell line deposit through the patent system might persuade originator companies to refrain from applying for patent protection altogether.[106]

Finally, enabling the development of biogenerics is consistent with the objectives that have been pursued through regulatory "policymaking" before. Since the adoption of the Hatch-Waxman Act of 1984, regulatory approval has often been used as a means to execute or enforce policies meant to stimulate pharmaceutical innovation and competition, such as orphan drug exclusivities and generic exclusivity.[107] Furthermore, as it is the statutory mandate of the FDA and EMA (or any other regulator) to ensure that only safe and effective therapeutics reach the market, facilitating the development and marketing of therapeutics for which concerns regarding switching and interchangeability persist seems to be an aberration. Enabling the development and marketing of biogenerics, on the other hand, is likely to result in higher levels of certainty regarding the safety of those products and lower the risks during development process.

In this context, it is important to note that there may be some advantages to this system for the originator companies as well. For example, the scope of protection of Supplementary Protection Certificates (SPCs)[108] is limited to "the product covered by the authorisation to place the corresponding medical product on the market"[109] and in 2015, the EFTA Court clarified that such protection cannot extend beyond products with "the same active ingredient."[110] Hence, whereas this scope of protection might be too narrow to prevent the market authorization and sale of biosimilar compounds, this will not be the case for biogenerics, and their market access could be additionally delayed by an SPC.

Furthermore, mandating the deposit of the cell line does not leave the originator with no means to protect its investments: Innovative drugs can be patented, and when a cell line has multiple potential uses, originators can still apply for secondary use patents.[111]

While it is quite understandable that private companies, investors and shareholders will want to avoid competition, and will set their prices as high as the market can bear, having a product that cannot be reverse engineered and the resulting quasi-monopoly is just a fortunate coincidence, especially in a highly regulated market for which little alternatives exist. However, as biologics are drugs, and not just any other product on the market, it is unacceptable that originator companies can retain such a powerful position, when patents and regulatory exclusivities expire.

4.5 Trade Secret Monopolies
Generally, trade secrecy has several advantages over patent protection: trade secrets do not expire, do not have to be applied for, and can protect information that would not be patentable.[112] However, as most traditional small-molecule drugs can easily be reverse-engineered, patent protection (or SPCs) and regulatory exclusivities have long been the only means at the disposal of the originator companies to prevent generic competitors from entering the market with a fully equivalent drug. For biologics, on the other hand, originator companies do not have to choose between

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patent protection and trade secrecy: even if the claimed biologic is disclosed in the patent,[113] this will not necessarily enable any meaningful competition.

It is expected that the pharmaceutical research companies will increasingly rely on trade secret protection in addition to patents and regulatory exclusivities, and thus differentiate their strategies.[114] In addition to the fact that several court rulings in the U.S. narrowed the scope of patentability,[115] the passage of the America Invents Act (AIA) in 2011 has somewhat reduced the risks of keeping (parts of) an invention secret, as the AIA has made it impossible to use the "best mode requirement" as a defense for patent infringement and prior use rights have been extended, eliminating the risk for inventors that secret inventions are later patented by someone else.[116] Other considerations that could support this evolution are the fact that obtaining, maintaining and enforcing patents in several countries is increasingly expensive,[117] as well as increased domestic and international policy initiatives strengthening the protection of trade secrets.[118]

Protection against trade secret misappropriation, however, is not as straightforward as the guarantees of a patent monopoly. There is no coherent codification regarding trade secrets, but it is mostly required that reasonable measures have been taken to keep the information secret. Therefore, one of the objections against disclosure of details on the biologics manufacturing process anticipated by Price and Rai[119] is that such a mandatory deposit would make effective trade secret protection impossible, especially on the international level. While it is indeed true that requiring the deposit of the cell line will result in the loss of some commercial secrecy, we must emphasize that we do not argue that originators should simply hand over all confidential information regarding an original biologic's manufacturing process.

Furthermore, in a highly regulated market, the usage of the cell line can easily be limited to the purposes for which its deposit was intended. Access to a cell line could, for example, be made conditional upon (a) approval of a request by the regulator and/or (b) the signature of a contract which prevents the prospective generic competitor from, for example, selling the resulting biogeneric products in foreign markets[120] or reselling the cell line for the development and marketing of medicinal products by third parties. Such contractual or statutory limitations can be effectively enforced by making compliance with these limitations a condition for obtaining regulatory approval, and noncompliant practices can be penalized with a withdrawal of license. Besides, as has been suggested by Price and Rai,[121] it seems unlikely that some coordination between the principal regulators would be impossible.

5. Concluding Remarks

While it is quite understandable that private companies, investors and shareholders will want to avoid competition, and will set their prices as high as the market can bear, having a product that cannot be reverse engineered and the resulting quasi-monopoly is just a fortunate coincidence, especially in a highly regulated market for which little alternatives exist. However, as biologics are drugs, and not just any other product on the market, it is unacceptable that originator companies can retain such a powerful position, when patents and regulatory exclusivities expire.

The biologics production process has allowed originator companies to benefit from patent protection as well as regulatory exclusivities, without being required to give anything significant in return. As a result, the system that should ensure that only safe and effective drugs reach the market has resulted in the allocation of substantial resources towards the development of therapies that already exist. Furthermore, the introduction of biosimilars on the market — and encouraging biosimilar uptake — is meant to increase competition on the market and hence to reduce prices of biologics. The biosimilar development process, however, is a highly inefficient way to realize this goal. Biosimilar uptake might be improved in specific circumstances, but this will always require significant additional investments and the regulatory hurdles will persist. Hence, the focus should be on reducing the gap between original biologics and their generic counterparts rather than building expensive bridges.

Importantly, the aim of our proposal to facilitate the development of biogenerics by requiring the deposit and of the original biologic's cell line, is not to reduce the market share of original biologics, but to enable sufficient and efficient competition in the market, to the benefit of the patient and society as a whole. We hope to have made clear that the current regulatory framework should be critically reviewed so that limitations of biosimilar development can more effectively be addressed. As the drug market changes, we must be willing to adapt the rules to preserve the necessary balances in the system.

Note

The authors have no conflicts to disclose.

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1. Biologics encompass a broad range of different therapeutic classes, such as erythropoietin, growth hormones, interferons, stimulating factors, low molecular weight heparins, insulins, and monoclonal antibodies.
2. See Evaluate Pharma, "World Preview 2017, Outlook to 2022 (10th Edition)," June 2017, *available at* <www.evaluate.com/PharmaWorldPreview2017> (last visited August 2, 2018); Iqvia Institute for Human Data Science, "Medicine

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Use and Spending in the US: A Review of 2017 and Outlook to 2022," April 2018, *available at* <www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1525781125780> (last visited August 2, 2018).

3. A.S. Kesselheim, J. Avorn, and A. Sarpatwari, "The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform," *JAMA* 316, no. 8 (2016): 858–871, at 859.
4. For example, Humira (adalimumab) — one of the top revenue generating drugs — has generated a net revenue of US$14,012 million for 2015, US$16,078 million for 2016, and US$18,427 million for 2017. See AbbVie, "2017 Annual Report on Form 10-K and 2018 Proxy Statement" January 26, 2018, *available at* <https://investors.abbvie.com/static-files/8f8ea49f-4735-404c-be08-2f963441b74d> (last visited September 18, 2018); Other biologics that have generated among the highest global revenues are Avastin (bevacizumab) and Remicade (infliximab). See EvaluatePharma, "World Preview 2014, Outlook to 2020," June 2014, *available at* <http://info.evaluategroup.com/rs/evaluatepharmaltd/images/EP240614.pdf> (last visited September 18, 2018); EvaluatePharma, "World Preview 2017, Outlook to 2022," June 2017, *available at* <http://info.evaluategroup.com/rs/607-YGS-364/images/WP17.pdf> (last visited September 18, 2018); EvaluatePharma, "World Preview 2018, Outlook to 2024," June 2018, *available at* <http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf> (last visited September 18, 2018).
5. The claim that costs of research and development have significantly increased has also been questioned. See D.W. Light and J.R. Lexchin, "Pharmaceutical Research and Development: What Do We Get for All That Money?" *BMJ* 345 (2012): 1-5 and S. Morgan et al., "The Cost of Drug Development: A Systematic Review," *Health Policy* 100, no. 1 (2011): 4–17.
6. In order for a drug to be sold legally, the vendor (or her supplier) must have regulatory approval for it from the regulator of the state or region in which it is sold. In the U.S. this is the Food and Drug Administration (FDA), for the E.U. the European Medicines Agency (EMA) and the national regulatory bodies of the E.U. member states. Such regulatory approval must be applied for with the application being supported by clinical data showing that the drug is (sufficiently) safe and (sufficiently) effective for the purpose for which the drug is to be sold, e.g. to lower the patient's blood pressure.
7. Biologics typically are proteins (such as antibodies) or carbohydrates. Proteins are long, chain-like molecules with the links of the chain being amino acid residues. The biological activity of such compounds results from the way in which the chains fold presenting functional regions capable of interacting with human cells or other targets and provoking or suppressing a desired or undesired activity in the patient's body. As imaginatively described by Price and Rai, "In terms of size and rough complexity, if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet." (W.N. Price and A.K. Rai, "Manufacturing Barriers to Biologics Competition and Innovation," *Iowa Law Review* 101, no. 3 (2016): 1023-1063, at 1026).
8. While, to obtain a patent, the originator may have had to deposit a sample of a cell line capable of producing a biological with the desired functionality, this may not be the cell line it subsequently uses to produce the biological that is put onto the market.
9. P. Declerck, M. Farouk-Rezk, and P.M. Rudd, "Biosimilarity Versus Manufacturing Change: Two Distinct Concepts," *Pharmaceutical Research* 33, no. 2 (2016): 261-268, at 267.
10. We have limited our discussion to the U.S. and the E.U., as those are still the biggest pharmaceutical markets and the regulatory standards in other countries are often comparable to E.U. and U.S. frameworks.
11. "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine," Oviedo, April 4, 1997). ETS No. 164, *available at* <https://rm.coe.int/168007cf98> (last visited September 27, 2018).
12. F. de Mora, "Biosimilar: What It Is Not," *British Journal of Clinical Pharmacology* 80, no. 5 (2015): 949-956, at 951.
13. S.K. Naizi, *Biosimilars and Interchangeable Biologics: Strategic Elements* (Boca Raton, FL: CRC Press, 2015): at 86.
14. Independent of the national regulatory authorities, the EMA is responsible for handling all centralized marketing-authorization applications. Once granted, the centralized marketing authorization is valid in all E.U. Member States as well as in Iceland, Liechtenstein and Norway.
15. Directive 2001/83/EC (consolidated version), Annex 1, Part II.4.
16. See EMA (European Medicines Agency), "Guideline on Similar Biologic Medicinal Products," CHMP/437/04 Rev 1, October 23, 2014, *available at* <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf> (last visited August 2, 2018); A.B. Argawal and A. McBride, "Understanding The Biosimilar Approval And Extrapolation Process—A Case Study Of An Epoetin Biosimilar," *Critical Reviews in Oncology/Hematology* 104 (2016): 98–107, at 99.
17. See A. Beck and J.M. Reichert, "Approval Of The First Biosimilar Antibodies In Europe," *mAbs* 5, no. 5 (2013): 621-623, at 622.
18. Naizi, *supra* note 13, at 81-87.
19. *Id*., at 81-91, 96-97.
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21. For an overview of the debate in the U.S. and the legislative history of the Biologics Price Competition and Innovation Act (BPCIA), see E. Lietzan, K. Hessler Carver, and J. Elikan, "An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009," *Food & Drug Law Journal* 65, no. 4 (2010): 671-818 and J. Wing Yan Tam, "Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation," *The Georgetown Law Journal* 98, no. 2 (2010): 535-565, at 550-552.
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40. Declerck et al., *supra* note 9, at 265.
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42. Studies have indicated that biosimilar uptake differs greatly between therapeutic classes and can be influenced by various factors such as the national pricing system and reimbursement and procurement policies (See Remuzat et al., *supra* note 37, at 3, 7). For example, biosimilar uptake has risen significantly in Norway since the general public reimbursement system was reformed and biologics are now purchased through hospital tenders. See A. Welch, "The Norwegian Biosimilar Phenomenon: From Biosimilar To 'Biogeneric,'" *Biosimilar Development*, July 26, 2016, *available at* <https://www.biosimilardevelopment.com/doc/the-norwegian-biosimilar-phenomenon-from-biosimilar-to-biogeneric-0001> (last visited August 2, 2018).
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49. Olech, *supra* note 24, at S6.
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52. See FDA, "Considerations in Demonstrating Interchangeability With a Reference Product (Guidance for Industry)," Draft Guidance, January 17, 2017; CDER, *supra* note 36; There seems to be the expectation that establishing interchangeability will be a costly process, as the BPCIA introduces a period of 12 to 42 months of market exclusivity for the first biosimilar to be approved as "interchangeable." See Y. Heled, "Regulatory Competitive Shelters," *Ohio State Law Journal* 76, no. 2 (2015): 299-356, at 350.
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54. Article 16 states that research on a person may only be undertaken if there is no alternative of comparable effectiveness and the risks which may be incurred by that person are not disproportionate to the potential benefits of the research.
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69. Notably, the purchase of the reference product for carrying out comparative clinical studies can account for a significant part of the total cost, and while some are optimistic about the evolution of biosimilar development costs, others expect the costs to rise as more complex monoclonal antibodies become the most important targets of biosimilar development. See Rader, *supra* note 68, at 18; Blackstone and Fuhr, *supra* note 67, at 471.
70. There are already several examples of biosimilar applications that have been withdrawn or refused by the regulatory authorities. See EMA, *supra* note 34.
71. Many originator companies have also entered the biosimilars market with biosimilar versions of their competitors' biologics. See Casey, *supra* note 37, at 208; Gupta et al., *supra* note 37, at 24; Some commentators have even described biosimilars as "me-too" drugs instead of generics, as market behavior and marketing strategies for biosimilars generally come closer to the former category than the latter. See McKinsey & Company, "Insights into Pharmaceuticals and Medical Products: Biosimilars seven years on: Where are we and what's next?" *available at* <https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/Pharma%20and%20Medical%20Products/PMP%20NEW/PDFs/Biosimilars%20Seven%20years%20on_White%20Paper.ashx> (last visited August 2, 2018); D.E. Williams, "Biosimilars Are 'Me-Too' Drugs, Not Generics," Health Business Blog, May 11, 2016, *available at* <healthbusinessblog.com/2016/05/11/biosimilars-are-me-too-drugs-not-generics/> (last visited August 2, 2018).
72. QuintilesIMS reports that biosimilar market share correlates negatively with the price reductions offered by the originator after biosimilar entry, which can, on the longer term, result in biosimilars not entering the market at all. See QuintilesIMS, *supra* note 57, at 5; Notably, the anti-trust authorities in the U.K. have recently issued a provisional decision indicting Merck & Co. for restricting competition by biosimilar versions of infliximab by using a discount scheme. See Gov.uk, "CMA issues provisional decision in relation to drug firm's pricing," May 23, 2017, *available at* <https://www.gov.uk/government/news/cma-issues-provisional-decision-in-relation-to-drug-firms-pricing> (last visited August 2, 2018). Another interesting example of how the pricing-policy of originators can result in making biosimilars less attractive is the "rebate trap," which occurs when originators revoke price discounts for the original biologic when a certain percentage of patients switches to a biosimilar, resulting in a total spending increase. See A. Hakim and J.S. Ross, "Viewpoint: Obstacles to the Adoption of Biosimilars for Chronic Diseases," *JAMA* 317, no. 21 (2017): 2163-2164.
73. See J.J.C. Hou et al., "New Frontiers In Cell Line Development: Challenges For Biosimilars," *Journal of Chemical Technology and Biotechnology* 86, no. 7 (2011): 895–904; Moorkens et al., *supra* note 43, at 5-8.
74. Waiting until after the expiry of all relevant patents and regulatory exclusivities, might come too late to ensure the timely introduction of generic competitors on the market. See Price and Rai, *supra* note 7, at 1050.
75. Proteins are long, linear molecules which can fold up in different ways. The same protein, produced by cells of different species, can be folded in a species-specific manner causing differences in activity.
76. Goel and Chance, *supra* note 56.
77. Several types of post-translational modifications may affect protein activity.
78. See Declerck et al., *supra* note 9, at 265-266; Moorkens et al., *supra* note 43, at 3; FDA, *supra* note 52.
79. The lack of recognition of biosimilars as fully equivalent "interchangeable" therapeutics makes it more difficult for physicians, patients, and payers, to allow switching. Hence, the possibility to establish such a status is critical to enable competition.
80. See Y.S. Kim et al., "Biosimilars: Challenges and path forward," *Biotechnology and Bioprocess Engineering* 19, no. 5 (2014): 755–765.
81. This can be illustrated by the fact that for major changes to an original biologic's manufacturing process — such as cell line change — comparative clinical studies to confirm the safety and therapeutic equivalence of the modified product are often required. See Declerck et al., *supra* note 9, at 261. On the other hand, when only minor changes are made to the original biologic's manufacturing and purification process limited quality and analytical studies will often suffice to ensure that the quality, safety and efficacy of the product are not affected. See Weise et al., *supra* note 48, at 3191; Declerck et al., *supra* note 9, at 265.
82. See V. Azevedo et al., "Differentiating Biosimilarity and Comparability in Biotherapeutics," *Clinical Rheumatology* 35, no. 12 (2016): 2877–2886; S. L. Bridges, Jr. et al., "The Science Behind Biosimilars: Entering a New Era of Biologic Therapy," *Arthritis & Rheumatology* 70, no. 3 (2018): 334–344.
83. See I.A. Perez et al., "Ensuring the Consistency of Biosimilars," *Current Pharmaceutical Design* 23, no. 44 (2017): 6733–6738.
84. See J. Yang, "Cell Line and Cell Culture Development for Biosimilar Antibody-Drug Manufacturing," in *Biosimilars of Monoclonal Antibodies*, C. Liu and K. J. Morrow, Eds. (Hoboken, NJ, USA: John Wiley & Sons, Inc., 2016): 397–425.
85. See Price and Rai, *supra* note 7, and W.N. Price, "Regulating Secrecy," *Washington Law Review* 91, no. 4 (2016): 1769-1812, for a parallel discussion of their proposal.
86. *Id*., at 1053.
87. Another preliminary suggestion has been made in a blog article. See DrugBaron, "Biosimilars Are Not Similar Enough: A Proposal For True 'Biogenerics,'" DrugBaron Blog, March 19, 2013, *available at* <www.drugbaron.com/biosimilars-are-not-similar-enough-a-proposal-for-true-biogenerics/> (last visited August 2, 2018); This proposal, however, is incomplete as it is suggested that the originator should license others to make identical biologics. This would allow the originator companies to retain a relatively powerful position as this implies some control over how many competitors there will be, and thus prevent sufficient price competition.

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88. If the entire CMC section is disclosed, also the knowledge on how the biologic can most effectively be produced will also be disclosed. If generic competitors can only access the cell line, the originator can retain the advantages that come with the prior knowledge and experience with the purification and manufacturing process.
89. For example, by making available the cell line of biologics for which similarity and interchangeability might more easily be established — allowing them to benefit from additional exclusivity periods they would have otherwise not enjoyed — and keeping the cell lines of biologics for which the biosimilar market entry would be more challenging (e.g. for very complex molecules or for very rare conditions) undisclosed.
90. This is one of the reasons Price and Rai see a mandatory disclosure mechanism as unfeasible. See Price and Rai, *supra* note 7, at 1054.
91. On the qualification of a physical asset as trade secret see C.M. Holman, "Trade Secret Law: An Increasingly Important Form of IP for Biotechnology," *Biotechnology Law Report* 35, no. 2 (2016): 45-54.
92. 21 U.S. § 331(j).
93. See E. Lietzan, "A New Framework for Assessing Clinical Data Transparency Initiatives," *Marquette Intellectual Property Law Review* 18, no 1 (2014): 33–85, at note 51. The EMA, on the other hand, has always had more discretion in deciding which information can be disclosed, although "commercially confidential information" is mostly redacted before disclosure. See Regulation (EEC) No 2309/93; G. Schneider, "A Transparency Challenge: Can Commercial Confidentiality in Clinical Trials Data Be Overcome?" *European Pharmaceutical Law Review* 2, no. 1 (2018): 3-18.
94. See Lietzan, *supra* note 93, at 56.
95. *Id.*, at 57-59.
96. *Ruckelhaus v. Monsanto Co.*, 467 U.S. 986 (1984).
97. See R. Epstein, "The Constitutional Protection of Trade Secrets and Patents under the Biologics Price Competition and Innovation Act of 2009," *Food and Drug Law Journal* 66, no. 3 (2011): 285-328, at 304. Were cell line deposits to be required for already approved biologics, it would seem that any "taking" would be of the regulatory approval.
98. See G.R. Stone, L.M. Seidman, C.R. Sunstein, M.V. Tushnet, and P.S. Karlan, *Constitutional Law* (New York: Wolters Kluwer Law & Business; 2017): 1760 p., at 1583.
99. See Epstein, *supra* note 97, at 313.
100. *Id.*, at 313.
101. Price, *supra* note 85, at 1804.
102. See Blackstone and Fuhr, *supra* note 67, at 474.
103. See D. Hirsch, "The Riddle of the Mysterious Patent Dance Wrapped in an Enigma: Is the Patent Dance of the BPCIA Optional or Mandatory?" *Fordham Intellectual Property, Media and Entertainment Law Journal* 27, no. 3 (2017): 645–690, at 677-678, explaining how the "patent dance" is necessary to ensure that originators can effectively enforce process patents protecting the original biologics, which would be much more difficult without such a disclosure obligation for biosimilar applicants. Interestingly, the mandatory nature of the patent dance has been challenged by Sandoz Inc. (the generic and biosimilar division of Novartis) when seeking approval for the first biosimilar version of filgrastim. In June 2017, the USSC *did not answer the question whether the patent dance is mandatory or not*, but instead ruled that a mere failure of a biosimilar applicant to disclose manufacturing information to the originator is not an act of artificial infringement and hence the exclusive remedies — injunctive relief and damages — do not apply. See *Sandoz Inc. v. Amgen Inc.*, 582 U. S. _____ (2017), at 15.
104. As an essential component of this exchange, the disclosure of the invention requires "enablement," meaning that a "person skilled in the art" can, based on the information disclosed in the patent, make and use the patented invention.
105. It has been argued that, absent a cell line to allow the enablement of a patented biologic, a biologics patent cannot be valid. See G.N. Mandel, "The Generic Biologics Debate: Industry's Unintended Admission that Biotech Patents Fail Enablement," *Virginia Journal of Law & Technology* 11, no. 8 (2006): 1-25, at 21-24; L.L. Ouellette, "Access to Bio-Knowledge: From Gene Patents to Biomedical Materials," *Stanford Technology Law Review*, N1 (2010): at para 100-103; However, in this context the problem of patent invalidity is also redundant, as the biologic that is actually put onto the market will rarely be identical to the biologic that would be produced by the cell line deposited at the time of the patent application. The patent deposit is required in order to enable the skilled reader to produce a biologic with the required properties, not necessarily the biologic that the patentee subsequently markets.
106. Price and Rai, *supra* note 7, at 1052.
107. 21 U.S.C. §360; 21 U.S.C. §355 (j) (5)(B)(iv)).
108. SPCs can be applied for, to lengthen patent rights for a maximum of five years after patent expiry, as a compensation for the time needed to obtain regulatory approval for medicinal products.
109. Regulation (EC) No 469/2009, article 4.
110. *Pharmaq v. Intervet*, Case E-16/14, Judgement of the Court, 9 April 2015, *available at* <www.eftacourt.int/uploads/tx_nvcases/16_14_Judgment_EN.pdf> (last visited August 2, 2018).
111. For inventive new uses of a cell line or new indications an originator can apply for secondary patents, and in some cases enjoy an extension of the data exclusivity term. However, even when a secondary patent prevents the approval of a biosimilar for a new indication, "off-label" use is still possible, although cautiousness is generally advocated in absence of sufficient proof there are no clinically meaningful differences for that particular indication. See E. Li and E. Lobaina, "Application of the FDA Biosimilar Extrapolation Framework to Make Off-Label Determinations," *Journal of Managed Care & Specialty Pharmacy* 23, no. 12 (2017): 1227–1232; S. Zhao, J.R. Nair, and R.J. Moots, "Biosimilars: From Extrapolation into Off Label Use," *Current Pharmaceutical Design* 23, no. 44 (2018): 6746–6751; For biogenerics, greater levels of certainty regarding functional equivalence with the original product may result in increased off label use, thereby placing originators in a situation similar to the situation for most small molecule drugs today. Without denying that the difficulty to enforce second use patents can be a legitimate concern for originators, the need to address this does not trump the potential benefits of our proposal. Other measures, such as adapting prescription and substitution policies and statutory and contractually limiting the purposes for which the deposited cell line (and resulting biologic product) may be used, can address some concerns in this regard. See *infra* Section 4.5.
112. See B.T. Yeh, "Protection of Trade Secrets: Overview of Current Law and Legislation," Congressional Research Service (CRS) Report Prepared for Members and Committees of Congress, April 22, 2016.
113. In the paradigm case, trade secrecy ends the moment a secret is disclosed, for example in a patent application.
114. Holman, *supra* note 91.
115. One of the most prominent cases in the context of biotechnology is the United States Supreme Court ruling on *Mayo Collaborative Services v. Prometheus Laboratories* in 2012, reaffirming the law-of-nature exception to patentability. See D.S. Almeling, "Seven Reasons Why Trade Secrets Are Increasingly Important," *Berkeley Technology Law Journal* 27, no. 2 (2012): 1091-1117, at 1114.
116. See J. Pooley, "Choosing Between Patents and Trade Secrets, A Discussion Worth Revisiting," IP WatchDog, 2017, <www.ipwatchdog.com/2017/11/01/patents-and-trade-secrets-revisited/id=89641/> (last visited August 2, 2018).
117. See Almeling, *supra* note 115, at 1114.

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118. See K. Linton, "The Importance of Trade Secrets: New Directions in International Trade Policy Making and Empirical Research," *Journal of International Commerce and Economics* 7 (2016): 1-17.
119. Price and Rai, *supra* note 7.
120. In addition, originator companies can apply for patent protection in all the relevant global markets.
121. Price, *supra* note 85, at 1811.

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