No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD. AND THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* GENENTECH, INC. AND BIOGEN IDEC, INC. IN SUPPORT OF PETITIONER

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INTEREST OF *AMICI CURIAE*[1]

Founded in 1976, *Amicus* Genentech, Inc. was the first biotechnology company, and today is a leading manufacturer of biotechnology-derived products ("biologics"). Genentech's growth is mirrored by that of the biotechnology sector of the pharmaceutical industry. In 1989 biologics represented only .5% of the market share for drugs. Today, more than three hundred and fifty biotechnology medicines are in development. See PhRMA, *2004 Survey: Medicines in Development, Biotechnology*, 1 (Oct. 2004); Biotechnology Indus. Org., Biotechnology Industry Facts (2005), *at* http://www.bio.org/speeches/pub/er/statistics.asp. Continuing innovation, product development, and cost containment in biotechnology are critically important both to the pharmaceutical industry and to the American public; and they are at stake in this case.

In order to develop safe, innovative, and effective products, Genentech necessarily undertakes significant commercial risks, involving substantial investments of time, resources, energy and scientific expertise. Specifically, in the past 28 years, Genentech has invested more than $6.4 billion in the research and development of biologics, and has discovered and introduced more than a dozen significant therapies for serious and life-threatening diseases, including cancer, heart disease, stroke and pulmonary disease.

In 1985, for example, Genentech received approval to market the synthetic human growth hormone Protropin®, one of the first biologics manufactured and marketed in the United States. This was followed by approval of Activase®, a human tissue plasminogen activator for use in dissolving

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[1] Letters of consent have been filed with the Clerk. Pursuant to Rule 37.6, *Amicus* states that no counsel for a party authored any part of this brief, and no person or entity other than amicus and its counsel made a monetary contribution to the preparation or submission of this brief.

blood clots in patients suffering from acute myocardial infarction. Since then, Genentech has developed or co-developed and received approval for numerous breakthrough drugs, including Pulmozyme®, the first new therapy for management of cystic fibrosis in 30 years; Herceptin® for treatment of a certain form of metastatic breast cancer; Xolair® for treatment of asthma; and Avastin® for use in treatment of metastatic colorectal cancer. In addition, Genentech has discovered new indications for drugs already approved by the FDA, such as Activase® used in treating acute ischemic stroke.

Amicus Biogen Idec, Inc. was created by the 2003 merger of Biogen, founded in 1978, and IDEC Pharmaceuticals, founded in 1985. In the past 26 years, Biogen Idec has invested more than $3.9 billion in the research and development of biologics, and has discovered more than 7 significant therapies for serious and life-threatening diseases, including multiple sclerosis, cancer, hepatitis B and psoriasis.

In 1986, for example, a Biogen developed product, Intron® A (recombinant interferon alpha-2b), received marketing approval for treatment of hairy cell leukemia. This was followed by the 1989 launch by Biogen's licensee of its hepatitis B vaccine, Engerix®-B. Since then, Biogen Idec has developed or co-developed and received approval for several breakthrough drugs, including Avonex® for treatment of relapsing forms of multiple sclerosis; Rituxan® for treatment of certain forms of B-cell non-Hodgkin's lymphoma (which was co-developed and is co-marketed by Genentech), and Tysabri® for treatment of relapsing forms of multiple sclerosis.

Today, Genentech and Biogen Idec (collectively, "*Amici*") manufacture the majority of the world's protein-based biologics. Because the development and commercial production of each biologic involves an extensive effort to invent, develop, test, and gain federal approval, *Amici* aggressively pursue patents on inventions they make during

this process of discovery and development. *Amici* believe the patent system, including appropriate enforcement of patent rights, is crucial to the continuing development of innovative, life-saving drugs. Yet *Amici* also strongly support a generous and practical reading of the statutory exemption from patent-liability for the testing and evaluation of new drugs as being equally necessary to encourage innovation. *Amici* plainly have a substantial and critical interest in the issue presented here. As leading developers and manufacturers of biologics, *Amici* invest billions of dollars in both preclinical *and* clinical research – *viz.*, in investigating and testing innovative candidate biologics and translating this work into therapeutic medical interventions.

SUMMARY OF ARGUMENT

The issue presented in this case is scope of section 202(e)(1) of the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act"), 35 U.S.C. § 271(e)(1). This provision, also known as the FDA exemption, exempts from infringement the use of a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law" regulating the manufacture, use, or sale of "drugs." *Id.* A biologic is a "drug" within the meaning of the FDA exemption.[2] In the decision below, the Federal Circuit seemingly limited the FDA exemption to the formal process of *clinical* research and testing of drugs for FDA approval that takes place under an Investigational New Drug ("IND") application. It thus improperly excluded from the scope of the

[2] Section 201 of the Federal Food Drug and Cosmetics Act ("FDCA"), 21 U.S.C. § 321(g)(1), defines a "drug" as a product "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man"; and a "biologic" is similarly defined by the Public Health Services Act ("PHSA") as a live cellular product "applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i).

FDA exemption the *preclinical* research that must be performed during the investigation or development of candidate drugs to generate information to support an IND application.

Preclinical testing of a new drug or biologic generates information that is essential to the FDA approval process. The Federal Circuit's limiting construction of the FDA exemption, however, exposes this preclinical research to patent infringement liability. Such liability risks would impinge on the very preclinical testing which the FDA exemption was designed to induce.

The Federal Circuit's position – that the FDA exemption should be narrowly interpreted because it was intended primarily to support FDA approval of generic drugs, an abbreviated process which does not require preclinical research supporting an IND application – has a uniquely harsh impact on the biotechnology sector of the pharmaceutical industry for two reasons. First, for reasons set forth below, there is no such thing as a generic biologic, and no abbreviated approval process for biologics; each and every biologic is a new or "pioneer" drug that must be supported by the full panoply of preclinical and clinical investigation. Further, again as explained below, unlike manufacturers of traditional chemically-synthesized drugs, manufacturers of biologics must demonstrate to the FDA that not only the product, but also the *manufacturing process* is safe and effective. This requires significant additional preclinical research and the use of a broader array of technology in order to provide the FDA with the more extensive information it requires.

Issues that go beyond the question of the scope of the FDA exemption are not raised by the present case. In particular, the question of whether the use of patented "research tools" in the discovery of new drug candidates should be exempted from patent infringement *other* than in situations governed by the FDA exemption is not presented. The present case does

not concern activities done for reasons other than to generate information needed for the FDA drug approval process, and petitioner is not seeking to shield its acts under the uncodified experimental use defense. Accordingly, *Amici* urge the Court to limit its holding to the scope of the FDA exemption.

ARGUMENT

I. INTRODUCTION.

Under the Patent Act, "whoever without authority makes, uses, offers to sell, or sells any patented invention . . . during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). In 1984, however, Congress enacted the Drug Price Competition and Patent Term Restoration Act ("the Hatch-Waxman Act"), which carved out an exemption from that rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs. [*Id.* § 271(e)(1) ("FDA exemption").][3]

Here, the issue presented is what uses of a patented invention are "reasonably related to the development and

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[3] The FDA exemption was created, in part, to respond to the Federal Circuit's determination, in *Roche Products, Inc.* v. *Bolar Pharmaceutical Co.*, 733 F.2d 858 (Fed. Cir. 1984), that testing done by a generic manufacturer to generate information to support approval of its copy of a new drug was not shielded by the common law "experimental use defense" to patent infringement. *Id.* at 862-63. As the Federal Circuit held:

> [d]espite Bolar's argument that its tests are 'true scientific inquiries' to which a literal interpretation of the experimental use exception logically should extend, we hold the experimental use exception to be truly narrow, and we will not expand it under the present circumstances. Bolar's argument that the experimental use rule deserves a broad construction is not justified. [*Id.* at 863.]

submission of information" under a Federal law regulating drugs. A divided panel of the Federal Circuit held that the FDA exemption is "correctly confined . . . to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug*." Pet. App. 13a (quoting *Intermedics, Inc.* v. *Ventritex Inc.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), *aff'd*, 991 F.2d 808 (Fed. Cir. 1993) (table)). The panel observed that the FDA "does not *require* information about drugs other than the compound featured in an Investigational New Drug application," and concluded that the FDA "has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*." *Id.* at 12a (emphases supplied). The court thus seemingly limited the FDA exemption to the human *clinical* research that occurs under an IND application, and denied the exemption to all preclinical research. In so doing, the panel relied heavily on legislative history indicating that "the express objective of the [Hatch-Waxman Act] was to facilitate the immediate entry of safe, effective *generic* drugs." *Id.* (emphasis supplied). Although the court subsequently clarified that the "scope of the safe harbor is not limited to generic drug approval," the court nonetheless found that the legislative history of the Hatch-Waxman Act "inform[ed] the breadth of the statutory text." *Id.* at 36a. See also *id*. at 13a (finding in the "context of this safe harbor" a focus on "facilitating expedited approval of" generic versions of patented drugs "already on the market").[4]

Amici endorse petitioner's and the United States' position that the Federal Circuit's decision erroneously limits the FDA exemption and would complicate the development of innovative drugs in contravention of congressional command

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[4] Judge Newman dissented from the liability determination on the ground that all of the experiments at issue were exempt under either the FDA exemption or the common law experimental use exemption. Pet. App. 35a. As petitioner and the United States have recognized, the common law experimental use exception is not implicated in this case, and is not before this Court.

and intent. The text of the exemption is phrased in broad terms, embracing the "development" of information; and both the legislative history and the purposes of the Hatch-Waxman Act support a generous construction. See Pet. Br. 36-37; U.S. Br. 14-15. Using these traditional tools of statutory construction, the exemption is best interpreted to extend to *all* research intended to generate information that the FDA would require or consider in connection with an IND application. Logically, it also must include the same research performed by the developer of a candidate drug or biologic who elects not to pursue an IND application for that candidate drug or biologic (*e.g.*, because the candidate did not exhibit results in testing that could justify preclinical investigations). As the House Report describing the FDA exemption explained, "[a] party which develops such information but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought." H.R. Rep. No. 98-857, pt. 1, at 45 (1984).

Consistent with the text, structure, and the purposes of the Hatch-Waxman Act, this Court has already made clear that the FDA exemption should be generously interpreted. In *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990), the Court addressed the meaning of the phrase "'a Federal law which regulates the manufacture, use, or sale of drugs.'" *Id.* at 665. Eli Lilly argued that this phrase should be limited to "those individual provisions of federal law that regulate drugs," denying the exemption to medical devices, while Medtronics asserted that the exemption referred to "the entirety of any federal Act . . . at least some of whose provisions regulate drugs," an interpretation that would extend the exemption beyond drugs to medical devices. *Id.* at 665-66. The Court concluded that the FDA exemption broadly exempts from infringement the use of patented inventions to develop and submit information to the FDA under *any* provision of a Federal law regulating drugs. A similarly broad construction

of the reasonable-relationship test incorporated into the FDA exemption is warranted.

Amici write separately to make two points: First, for several reasons, limiting the FDA exemption to human clinical research conducted under an IND application has a particularly harmful impact on the biologics component of the pharmaceutical industry. Second, Congress's considered decision to employ the familiar reasonable-relationship test reflects its intent to accord a generous sweep to the FDA exemption; that test, as applied in numerous areas of law noted *infra*, requires only that the use of the patented invention be reasonably intended to produce information that would be required or considered by the FDA.

II. BIOLOGICS DIFFER FROM CHEMICALLY-SYNTHESIZED DRUGS IN WAYS THAT MAKE APPLICATION OF THE FDA EXEMPTION EVEN MORE CRITICAL TO THEIR DEVELOPMENT AND DEPLOYMENT.

A. Biologics Differ From Chemically-Synthesized Drugs In Ways That Significantly Affect The Regulatory Approval Process And Its Requirements.

Biologics are fundamentally different from traditional chemically-synthesized drugs, sometimes known as "small molecule drugs." The active ingredient of a biologic usually is a large, complex molecule derived from a living organism; a biologic, typically a protein, can be a chain of hundreds of amino acids with a complex three-dimensional structure. As the FDA has explained, biologics are "complex mixtures of molecular species that [are] difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that had the potential to affect many of its characteristics." FDA, *Guidance Concerning Demonstration of Comparability of Human Biological*

Products Including Therapeutic Biotechnology-derived Products (Apr. 1996) ("*Comparability Guidance*"), *available at* http://www.fda.gov/cder/guidance/compare.htm. Thus, unlike chemically-synthesized drugs – the functional characteristics of which generally do not vary significantly – the safety or effectiveness of a biologic cannot be evaluated simply by identifying the physical structure of the active ingredient.

In addition, unlike a chemically-synthesized drug, conclusions about the safety or effectiveness of a biologic cannot be separated from the specific process used to manufacture each biologic. The manufacturing process for a chemically-synthesized drug involves discrete, linear steps that progress predictably. The manufacturing processes for biologics, in contrast, generally use living cells as hosts or miniature factories that create the desired product. The capabilities of these hosts are inherently variable. Biologics include, for example, products such as recombinant DNA-derived therapeutic proteins which are created by inserting a DNA sequence into a living organism that synthesizes the desired protein. As the FDA has stated:

> [b]ecause of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), a *biological product was often defined by its manufacturing process*. . . . FDA recognized that changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself . . . . [FDA, *Comparability Guidance* (emphasis supplied).]

Simply put, each biologic manufacturing process will result in a unique product. Minor differences in a biologic's manufacturing process can have a significant impact on the biologic's clinical attributes, including both its effectiveness and its safety; and manufacturers employ extensively validated manufacturing controls. Thus, even if the physical, chemical, and biological properties of the process and the resulting product are carefully defined or characterized, that

does not ensure clinical or therapeutic equivalence of two biologics produced in different conditions of manufacture. "There is no such thing as a 'me-too' biologic." See Public Information, 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974) ("[A]ll biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rule making. . . . . This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective.").

It is also instructive that to date, no legal regulatory framework is in place in Japan, Europe or the United States that would permit a so-called "generic biologic" to gain regulatory and market approval. While the responsible regulatory agencies in these countries have been wrestling with these issues for some time and have promised that guidelines would be forthcoming, none is persuaded that chemical and biological similarity between innovator products and "biogeneric" copies thereof can effectively be shown. The FDA's regulation of biologics and the application of the FDA exemption to the investigation and development of biologics can only be understood with the unique characteristics of biologics in mind.

B. Because The FDA Requires Manufacturers Of Pioneer Drugs, Including Biologics, To Submit Substantial Preclinical Research In An IND Application, The "Use" Of "Patented Invention[s]" In Such Research Is Protected By The FDA Exemption.

Federal law – specifically, the FDCA and the PHSA – forbids the introduction into commerce of any drug, chemically-synthesized or biologic, unless the Secretary of Health and Human Services has determined the drug is both safe and effective. See 21 U.S.C. § 355(a) & (d) (all drugs);

42 U.S.C. § 262(a)(2)(A) (biologics). To permit the investigation of products not yet found to be safe and effective, Congress exempted from the statutory requirements of safety and effectiveness "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. § 355(i)(1) (all drugs). In addition, Congress authorized the Secretary to promulgate regulations "conditioning such exemption upon . . . the submission to the Secretary . . . of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing." *Id.* § 355(i)(1)(A). See also 42 U.S.C. § 262(a)(3) ("[T]he Secretary shall prescribe requirements under which a biological product undergoing investigation shall be exempt" from the safety, purity and potency requirements of § 262(a)(1) & (2)).

1. *The FDCA Process.*

Pursuant to the FDCA's authorization of investigational uses of unapproved drugs, the Secretary has issued regulations establishing the IND application process. See 21 C.F.R. § 312.20 *et seq*. Those regulations do not require particular studies, but they clearly and expressly anticipate the submission of results from *preclinical* research. Specifically, they require "[a] summary of the pharmacological and toxicological effects of the drug in animals," "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," and provision of the "rationale for the drug or the research study." See *id.* § 312.23(a)(3)(iv), (5)(ii) & (8). It is preclinical studies that generally provide the data and hence the support for these showings. Thus, it is preclinical work that allows the manufacturer to demonstrate that the drug warrants clinical trials, *i.e.*, that the drug does not "represent[] an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. § 355(i)(3)(B)(i); see also *id.* § 355(i)(1)(A). Only if the IND

application is granted can the drug manufacturer proceed to the clinical testing necessary to submit a new drug application ("NDA"). Once the NDA is approved, the drug may be marketed.

What is critical here is that data from preclinical research are routinely submitted to the FDA in IND applications, and are considered by the FDA in its review of an IND application. Thus, the generation of data from preclinical testing of patented inventions is "reasonably related to the development and submission of information under a Federal law which regulates" drugs. 35 U.S.C. § 271(e)(1).

2. *The PHSA Process.*

In contrast to drugs, biologics are subject to the regulatory processes of the PHSA.[5] The PHSA requires the Secretary to establish by regulation requirements for the licensing of biologics. 42 U.S.C. § 262(a)(2) & (3). To obtain approval of a biological license application ("BLA"), the manufacturer must demonstrate that the biologic is safe, pure, and potent. See *id.* § 262(a)(2)(C); 21 C.F.R. § 601.2. The regulatory process for biologics is administered by the FDA Center for Biologics Evaluation and Research ("CBER"). CBER reviews and approves biologics through a process akin to that for chemically-synthesized drugs. See Jeanne M. Novak et al., *The Biological IND, in Biologics Development: A Regulatory Overview* 49-81 (M. Mathieu ed., 2d ed. 1997); see also Suzanne M. Sensabaugh, *A Primer on CBER's Regulatory Review Structure And Process*, 32 Drug Info. J., 1011, 1017-18 (1998).

There is some overlap in the regulation of biologics and drugs; however, the biologics regulatory pathway is more

[5] At the outset of the biotechnology industry, a small number of biologics were evaluated and approved as drugs under the FDCA process. Since that time, nearly every biologic has been evaluated and approved under the PHSA.

extensive and requires more information.[6] For example, a biologics manufacturer seeking approval to begin clinical testing of a new biologic must fulfill all the requirements placed on the manufacturers of new chemically-synthesized drugs; in addition, a biologics manufacturer seeking a BLA must further establish that the facility in which a biologic is manufactured, processed, packed or held meets standards that ensure that the product remains safe, pure, and potent. 21 C.F.R. § 601.2(a); see also *id.* § 601.20(c).

As is the case with chemically-synthesized drugs, a new candidate biologic must be investigated through preclinical development and research before the FDA will approve an IND application which grants the sponsor the legal authorization to evaluate the biologic in clinical investigations. Under the FDA regulations implementing the PHSA, the biologic manufacturer "shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency." *Id.* § 601.2(a). With regard to "products under development," the regulations expressly incorporate sections 505(i) and 520(g) of the FDCA, invoking the Secretary's authority to authorize investigational uses of biologics and to establish the IND application process. *Id.* § 601.21.

As a practical matter, there can be no doubt that a wide range of preclinical research forms an essential part of the FDA's decision to approve an IND application for a biologic. One author explained that "[p]re-clinical development [of a biologic] should include pharmacology and toxicology studies in appropriate animal models" in order to "permit the FDA to assess whether the product is reasonably safe for initial

[6] The PHSA provides that the FDCA "applies to a biological product subject to regulation under [the PHSA], except that a product for which a license has been approved under [PHSA § 351] shall not be required to have an approved application under section [505 of the FDCA]." *See* 42 U.S.C. § 262(j).

testing in humans." Novak, *supra*, at 53. Another author further highlighted the importance and essential "[p]urpose[s] of [p]re-clinical [s]afety [e]valuation" for biologics:

> A primary goal in conducting preclinical studies is to obtain data necessary to initiate clinical trials. The data derived from preclinical studies provide the scientific basis for the development of clinical monitoring parameters and the rational selection of an initial safe starting dose, a dose-escalation scheme, a duration of use, a route of administration, and potential target organs for toxicity.
>
> *Preclinical studies should be designed to answer specific questions.* These answers should provide an understanding of the dose/activity relationship, the relationship of route and scheduling to activity/toxicity, the dose/toxicity relationship, and the risks for toxicity. Often additional studies are designed to help discern a product's mechanism of action, to facilitate future clinical development (i.e., to help ensure that clinical trials are not needlessly interrupted), and to satisfy liability and/or labeling issues. [Joy A. Covagnaro, *Preclinical Safety Assessment of Biological Products in Biologics Development: A Regulatory Overview* 21, 25-26 (M. Mathieu ed., 2d ed. 1977) (emphasis supplied).]

The ideal, this author concluded, is "a dialogue between FDA and industry scientists [that] will take place early in product development." *Id.* at 27.

In addition, because the manufacturing process determines the safety and efficacy of a biologic, the biologics manufacturer must also provide sufficient information "so that CBER can assess the validity and safety of manufacture." Novak, *supra*, at 53. The regulation of the process as well as the product dramatically increases the amount of preclinical investigation that must be done prior to the submission of an IND application. And the breadth of the preclinical work

necessary means that a broader array of technology – *viz*., patented inventions are implicated.

This explains why an IND application submitted to CBER requires a summary of preclinical data, see *id.* at 59-62 (describing investigator's brochure and clinical protocol). And, as noted, the application must also include "adequate information about the pharmacological and toxicological studies performed in animal models or *in vitro* to establish that the investigational product is reasonably safe for the initiation of clinical studies." *Id.* at 59-66 (citing 21 C.F.R. § 312.23(a)(8)). Guidance for this section was issued by the FDA in November 1995, see FDA, *Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-derived Products* (Nov. 1995). That Guidance spells out in detail the extensive preclinical support that the FDA expects to receive and will consider in connection with their evaluation of an IND application for a biologic. See, *e.g.*, *id*. at 10 (explaining that one section of an IND application should contain "a description of the pharmacologic effects and mechanism(s) of actions of the drugs in animals"); *id*. ("[p]resent regulations require an integrated summary of the toxicologic effects of the drug in animals and *in vitro*"); *id*. at 11-13 (describing information required in summary of toxicologic findings of animal studies and in data tabulation, and requiring records to be made available for inspection).

In sum, both legally and practically, manufacturers of biologics conduct substantial preclinical research to satisfy the FDA's requirements for an IND application. Equally to the point, in developing a biologic, a manufacturer will conduct substantial preclinical research not only on the safety or effectiveness of a new biologic, but also on how the biologic can be produced and purified. Information from such research – whether conducted before the IND application is submitted or after the BLA has been approved – must

be retained and made available to the FDA at its request, regardless of whether the steps used to produce or purify the biologic in the preclinical stage ultimately are those used to produce the biologic on a commercial scale. The use of patented inventions in such research should be shielded by the FDA exemption; protection from infringement litigation cannot turn on the success or failure of the research being conducted without having the practical effect of discouraging the research itself. This is why the text does and should protect all uses "reasonably related" to the approval process. Although it may come to pass that some data that is generated by use of a patented invention is not submitted to the FDA with the IND application, or is only submitted later in response to a CBER inquiry, the "use" was nonetheless "reasonably related to the development and submission of information" to the FDA under the FDCA and the PHSA.

C. Interpreting The FDA Exemption Narrowly Due to Congress's Focus On The FDA's Approval Of Generic Drugs Is Particularly Harmful To The Discovery And Development Of Biologics.

As noted above, the Federal Circuit was intent on narrowing the interpretation of the text of the FDA exemption because, in its view, the exemption had to be construed to reflect at least in part Congress's "express objective . . . to facilitate . . . generic drugs." Pet. App. 12a. In so doing, the Federal Circuit resisted the necessary implications of this Court's decision in *Medtronic*, which expressly rejected the notion that the FDA exemption is restricted to generic drugs and held that even medical devices are covered. See 496 U.S. at 665-67, 669 & n.2. Critically, for *Amici*, a narrow focus on generic drugs is uniquely damaging to the biologics sector.

The primary approval route for generic versions of chemically-synthesized drugs is section 505(j) of the FDCA, which authorizes review and approval of abbreviated new drug applications ("ANDAs") based on a demonstration that the generic drug is the "same as" an approved pioneer drug.

If a generic contains the same active ingredient, the same route of administration, the same dosage form, the same strength, and the same bioavailability as an approved drug, the generic may be approved based on the clinical safety and effectiveness data included in that approved drug's NDA.

As explained above, "'there is no such thing as a 'me-too' [generic] biologic.'" See *supra* at 10 (quoting 39 Fed. Reg. at 44641). The FDA has *never* applied an abbreviated approval process to a biologic. Indeed, in 1984, the Agency expressly recognized that the new abbreviated mechanism did not extend to biologics. See Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17951 (Apr. 28, 1992) (the ANDA process is "inapplicable to . . . biological drug products licensed under [the PHSA]").[7] While chemically-synthesized drugs generally have simple chemical structures that can be easily identified and replicated to achieve therapeutic equivalence, this is not true of biologics. Under current scientific testing methods, biologics cannot be shown to be identical to approved drugs due to their complexity and inherent variability. See, *e.g.*, S. Usdin, *CBER's Abbreviated Route*, BioCentury, Apr. 15, 2002, at A6-7 (FDA official concludes that because of safety issues, even the best-characterized biologics require clinical data, and are not suited to an abbreviated approval process). Put in terms of the statutory language, because the ANDA process may be used only when manufacturers show that the new drug is the "same as" – *i.e.*, the bioequivalent of – an approved drug, see

[7] As noted *supra*, for reasons largely of history, a small number of drugs which fulfill the definition of "biological product" under the PHSA (*e.g.*, insulin and human growth hormone) have been approved instead under § 505 of the FDCA. But, the FDA has never treated these products differently from other biologics – that is, the FDA has never used the abbreviated approval process in connection with such a drug.

21 U.S.C. § 355(j)(2)(A)(ii)(I), the ANDA process cannot be utilized in order to seek FDA approval of a biologic.[8]

Accordingly, limiting the scope of the FDA exemption to activities in connection with the abbreviated or generic drug approval process would have a disproportionately harsh impact on the biologics sector of the pharmaceutical industry. Under the strictest interpretation of the exemption (an interpretation, we submit, that should have been effectively foreclosed by *Medtronics*), no use of patented inventions in preclinical and clinical biologics research and development would ever be exempted because a biologic can never be approved through an abbreviated or "generic" application process.

Under the Federal Circuit's somewhat less constrained interpretation of the exemption, uses of a patented invention in connection with clinical trials conducted under an IND application would be protected but uses in connection with preclinical research would not. Such clinical trials may never occur, however, if biologics manufacturers were confronted with claims of patent infringement during the preclinical investigations of a new candidate biologic that the FCA expects to occur. This is because, for the reason set forth *supra*, the developer of a new biologic must employ a diverse and broad range of investigative technologies in conducting such research, some or all of which may be subject to patents. In some instances, it simply will not be economically feasible for a biologics manufacturer to continue the preclinical

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[8] The FDA has authorized certain changes in the manufacturing process to be made by a biologic's experienced manufacturer in an abbreviated application process. *See* FDA, *Comparability Guidance*. Changes to an approved manufacturing process by a manufacturer with complete knowledge of that process and significant historical and experience making and validating the biologic are not remotely analogous, of course, to approving a different manufacturer's biologic – which uses different starting materials and a different process – as safe and effective without product-specific testing.

investigation needed of a candidate biologic if doing so creates substantial licensing costs or other liability.

To this end, the FDA exemption should be interpreted to encourage complete analysis and study of a new drug or biologic in order to generate as much information as possible regarding that product's safety and effectiveness. Indeed, an interpretation that exposes these preclinical investigations of a new drug or biologic to patent liability would run precisely counter to the legislative design of the FDA exemption. The Federal Circuit's constrained view of the scope of the FDA exemption thus contravenes to the reason for its incorporation into the patent statute; namely, to encourage the types of testing that both manufactures and the FDA believe should be done on a new candidate biologic or drug before it is first administered to a human in a clinical setting.

III. CONGRESS'S CHOICE OF THE REASONABLE-RELATIONSHIP TEST MANDATES A RATIONAL-BASIS INTERPRETATION OF THE FDA EXEMPTION.

A. Congress's Decision To Employ The Reasonable-Relationship Test Is Significant.

In law, the reasonable-relationship test is a familiar one, a formulation with connotations of deference to decision makers, whether they are lawmakers or administrators. Congress's use of this typical formulation indicates its intent that the FDA exemption be expansively interpreted.

As petitioner and the United States have already explained, the text, the legislative history, the purposes of the FDA exemption, and this Court's decision in *Medtronics* all support a broad interpretation of the FDA exemption, not only for research actually recited in an application to the FDA, but also for research that was reasonably calculated to result in an application ultimately not submitted. *Amici* will not burden the Court with a repetition of that analysis here. Instead, *Amici* show that this Court's broad construction of the FDA

exemption is amply justified by the congressional decision to employ a reasonable-relationship test – a test with a familiar and generally accepted meaning across the legal spectrum that mandates this result.

The question whether an act or decision is reasonably related to a particular goal frequently recurs in this Court's jurisprudence. The test for whether a search is lawful is whether it is "reasonably related in scope to the circumstances which justified [the stop]." *Terry* v. *Ohio*, 392 U.S. 1, 20 (1968) (*Terry* stop search); see also *New Jersey* v. *T.L.O.*, 469 U.S. 325, 341 (1985) (school search). The test for the lawfulness of restrictions on prisoners' First Amendment rights is whether those restrictions are "reasonably related to legitimate penological interests," see *Turner* v. *Safley*, 482 U.S. 78, 89 (1987); while the test for analogous restrictions on students' rights is whether they are "reasonable related to legitimate pedogogical concerns." See *Hazelwood Sch. Dist.* v. *Kuhlmeier*, 484 U.S. 260, 273 (1988). The test for whether a tax on interstate commerce is lawful is whether that tax is "reasonably related" to the taxpayer's presence or activities in the state. See *Complete Auto Transit, Inc.* v. *Brady*, 430 U.S. 274, 286-87 (1978). And, the test for whether conditions imposed in Spending Clause legislation are constitutional is whether they are "reasonably related" to the purposes of the spending. See *Massachusetts* v. *United States*, 435 U.S. 444, 461-62 (1978) (plurality opinion). There are many further examples. See, *e.g.*, *Hodel* v. *Virginia Surface Mining & Reclamation Ass'n*, 452 U.S. 264, 283 (1987) (legislation does not violate the Equal Protection Clause if the means employed are "reasonably related" to the goals Congress sought to achieve); *City of Monterey* v. *Del Monte Dunes at Monterey Ltd.*, 526 U.S. 687, 703-07 (1999) (property regulation is lawful if "reasonably related" to legitimate public interests); *United Steelworkers of America* v. *Sadlowski*, 457 U.S. 102, 111-12 (1982) (question is whether a union rule that interferes with a member's statutorily

protected interest is "reasonably related to the protection of the organization").

In all these settings, the reasonable-relationship test has a well accepted meaning. It inquires whether there is a "valid, rational connection" between one act or decision and another. *Block* v. *Rutherford*, 468 U.S. 576, 586 (1984). A connection fails the reasonable-relationship test only if it is "arbitrary or irrational." *Turner*, 482 U.S. at 89-90. The question whether the use of a patented invention is "reasonably related" to the "development and submission" of information to the FDA is thus akin to this Court's rational-basis test – that is, a deferential and lenient test that asks only whether the drug manufacturer had a rational basis for believing that the "use" at issue would produce information that would be useful to the FDA in assessing an IND application, an NDA or a BLA.

B. The Question Of The Application (If Any) Of The FDA Exemption To Research Tools Is Premature.

Contrary to the decision of the Federal Circuit, this case does not raise the question whether the FDA exemption covers "research tools." Pet. App. 14a. As petitioner explains, respondent has never asserted that the patented inventions at issue are research tools. Pet. Br. 41-42. The issue simply is not presented here.

Amici submit that the sole inquiry necessary for the Court is whether the acts done by petitioner are shielded under the FDA exemption because they were "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." To the extent that use of a patented invention – whether or not it can be labeled a "research tool"[9] – is to

[9] There also is no established definition or understanding of the term "research tool"; and the FDA, the expert agency that administers and implements the FDCA and the PHSA, has never attempted to develop a

generate such information, such use is shielded by the FDA exemption.

Amici also submit that the concerns expressed by the Federal Circuit in its decision are both unwarranted and premature. We note that even if the exemption were interpreted to cover "research tools," it would shield only those acts done with the "research tool" to generate information reasonably related to the FDA review of a new drug or biologic; the "research tool" patent holder would be able to enforce its patent in all other contexts. Moreover, as Judge Newman observed in dissent below, there are obvious and accepted differences between the use of a substance or device as a tool to study other substances or devices, and the study of the substance or device itself. See Pet. App. 35a. Researchers often pay licensing fees for the former, but generally not for the latter.[10]

In light of the breadth and flexibility of the statutory language and the highly specialized and technical nature of the inquiry, it is likely that any FDA determinations about the meaning of the term "research tool" and the application of the FDA exemption to the use of such tools would receive substantial deference from the courts. See *Chevron U.S.A., Inc.* v. *National Res. Def. Council, Inc.*, 467 U.S. 837, 859-66 (1984). And, although the brief of the United States in response to the Court's invitation strongly supports a generous interpretation of the scope of the FDA exemption, it does not provide the United States' view on whether the FDA exemption applies to research tools, instead stating (correctly)

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regulatory definition. Nor has the FDA ever considered the application of the FDA exemption to research tools or whether or to what extent the use of a research tool is "reasonably related" to the development and submission of information to the FDA.

[10] Indeed, *Amici* are not simply "users" of patented research tools. Instead, both *Amici* have invented, developed, patented and licensed a variety of basic and platform technologies that are properly considered to be "research tools."

that research tools are not implicated here. Indeed, the FDA would likely seek input from all its constituents before making a final judgment on this issue.

For all these reasons, *Amici* respectfully submit that the Court should not prematurely address the application of the FDA exemption to research tools.

CONCLUSION

The decision below should be reversed.

Respectfully submitted,

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