Mass Torts
American Bar Association Section of Litigation
Mass Torts Litigation Committee
Volume 5, No. 2, Spring 2007

Defending Biologics: How the Unique Attributes of Biological Products Invite Different Approaches to Litigation[1]

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At first glance, one would not expect the defense of a biological product in a product liability matter to be any different from that of a traditional small molecule pharmaceutical product.[2] Yet, having defended both small molecule pharmaceuticals and biologicals in product liability actions, distinct differences in litigation themes and theories have become apparent. These differences initially surprised us and may be a surprise others as well. The unique attributes of a biological product's development, manufacturing, and biological mode of action render such products particularly unsuitable for mass tort litigation.

Biologics Are Different From Small Molecule Drugs

Although biologics, like other drug products, are used to treat, prevent or cure diseases, they differ significantly from chemically synthesized drugs. See 21 U.S.C. §321(g)(1) and 42 U.S.C. §262(i); *see generally* "Frequently Asked Questions About Therapeutic Biological Products, available at http://www.fda.gov/cder/biologics/qa.htm. Pharmaceutical products are often synthesized from purified materials using chemical processes. They tend to contain one or at most a few active drug ingredients, each of which is small and simple on a molecular scales, and each of which has an exact structure that is precisely identifiable through final product testing. The active ingredients in a pharmaceutical product are generally mixed with known inactive ingredients. The pharmacologic activity of the product as a whole can be well-characterized; that is, the active and inactive components of the product are, by and large, readily identifiable and distinguishable. As a result of the chemical nature of drugs, their ingestion introduces into the body a foreign synthetic chemical to perform a function or task that the body often is not able to do otherwise.

Biologics, on the other hand, are manufactured from living cells, and their production depends upon cellular metabolic activity. They contain many constituent molecules, these ingredients are comparatively complex in structure and large in size, and they are readily recognized by the body's immune system. Many biologics are intended to replicate or mimic naturally-occurring proteins. These products are often intended to work within the immune system or other complex bodily systems. They are often prescribed "simply" to replace a naturally occurring protein that is otherwise deficient or malfunctioning within the patient. In essence, biologics most frequently provide patients with essential proteins that their bodies can no longer produce as a result of some underlying disease or physiological process. Like naturally occurring human proteins, biologics are complex, three dimensional structures, with sites of activity that are often impossible to identify through conventional analytical techniques.

Continued on page 3...

Published in Mass Torts Litigation Newsletter of the Section of Litigation's Committee on Mass Torts Litigation, Volume 5, No. 2, Spring 2007.

Defending Biologics *continued from page 1...*

Unique Defense Opportunities Posed By The Unique Attributes of Biologics

Although both biologics and small molecule drugs are used to treat, prevent or cure diseases, defending a biological product presents several unique opportunities.

The Story Behind the Biologic

The invention and development of biological products often involve issues of science and medicine that strike some as inherently interesting, on the edge of a new frontier, or perhaps even a window into the secrets of human life. The vocabulary and concepts that surround biological products are thus distinct from that of small molecule drug therapy.

The process generally begins when a protein is discovered in living material. A gene is isolated and the DNA code of the gene is used to direct test cells to produce the exact protein needed. Experiments are conducted to determine if the cells, called a "line," can produce the protein commercially. Once identified, the genetic make-up of the cell line is altered to allow the cell to express the desired gene. The cell line, in turn, is cloned and perpetuated, to ensure a ready source of the proposed therapeutic protein.

The discovery of a therapeutic protein, its manufacturing process, and the subsequent clinical studies allows the sponsor of such a product to tell a fascinating story. While the development of small molecule drugs is equally significant, the chemical processes that led to its discovery, and the industrial chemistry that constitutes the manufacturing process for such products, may not provide the same opportunities for gaining the attention of a judge or jury. There is an invaluable opportunity to educate the jury and the court, and to humanize the sponsor of a biological product. At the same time, such a compelling story also teaches the jury, from the outset, how the product works—which is a central component of any defense.

The development of biological products offers a level of evocative detail and fascination that is not present in most other products cases; the opportunity to tell this story to further the defense of the case and to help educate the jury should be embraced.

Individualized Nature of Injuries Undermine Causation Theories

Given the nature of biological products and the diseases that these products treat, potential side effects tend to be patient-specific. How a biologic product works within an individual's immune system is unique to each patient, and it is virtually impossible to predict or precisely identify the exact systems that may be impacted. Thus there will be variation from plaintiff to plaintiff. Also, given the systemic effects of biologics, the side effects that may arise are often many steps removed from the point of action. Simply put, a complicated cascade of events has to occur to be able to establish causation.

Given the nature of biological products and the diseases that these products treat, potential side effects tend to be patient-specific. How a biologic product works within an individual's immune system is unique to each patient, and it is virtually impossible to predict or precisely identify the exact systems that may be impacted. Thus there will be variation from plaintiff to plaintiff.

In contrast, and speaking only in generalities, the movement of a small molecule drug within the body may be more identifiable, predictable, and uniform from patient to patient. Common clusters of adverse events may arise for a small molecule drug, while the reported events for a biological product may be more diverse and infrequent. As a result, causation may be significantly more difficult to establish for a biological product.

For this reason, alternative litigation approaches can be taken to force the causation issue upfront. Bifurcation on causation is one such approach. By forcing issues such as causation early, defendants can accomplish a number of things. For example, and most obviously, it can reduce the cost of litigation. If the initial discovery period is limited to causation issues only, the preliminary document production is restricted considerably, saving much time and expense. Expert costs also are reduced because only causation experts have to be retained during the bifurcated discovery period. Another less obvious benefit of bifurcation is it affords an opportunity to educate the plaintiff's counsel on the significant causation hurdle he or she will have to overcome in light of the nature of biologics. And, by forcing the causation issue early through bifurcation, the plaintiffs are obliged to address the medical issues first, before having an opportunity to create irrelevant side shows to distract the key causation issue.

Bifurcation on the issue of causation is a tactic that has been successful in a number of cases involving the biological product, Enbrel®.[3] Federal district courts in Texas, South Carolina, and Louisiana have ruled that plaintiffs must present evidence of a causal relationship between their injuries and Enbrel® before the litigation would be permitted to proceed to full discovery.[4] In addition, a state trial court in New Jersey came to the same conclusion in the case of *Cerchio, et al. v. Amgen Inc., et al.*, No. L-2857-04 (N.J. Super. Law Div.). Furthermore, another federal district court, in *Pompey v. Immunex Corp., et al.*, Docket No. 2:04-CV-03357 (E.D. La.), approved the parties' Rule 26(f) proposed scheduling order, which set forth an agreed-upon bifurcated discovery schedule. None of the plaintiffs in those cases was able to produce a causation expert during the prescribed

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time period, leading to the entry of summary judgment or voluntary dismissals in those cases.

Theories of Defect

Although traditional theories of liability are generally asserted in product liability cases involving biologics, the chances of succeeding on a design defect claim are low. Particularly for biologics that are intended to replicate endogenous proteins, it is difficult to place blame on a manufacturer for the precise design of the product.

On the other hand, a biological product has the potential to be vulnerable to a manufacturing defect claim. Because biologics are made in cultures from living organisms, rather than synthesized from purified materials, they can react to the slightest changes in temperature and light. Thus the slightest variation in the manufacturing process can affect biologics. The manufacturing process itself is also extremely complex and sensitive. For example, some have speculated that reports of antibody-mediated Pure Red Cell Aplasia (PRCA) in European patients taking Eprex®, an epoetin alfa product, may have been related to a change in the manufacturing of the product by its sponsor, Johnson & Johnson.[5]

No Generic and Few "Me too" Biologics

Because the production of a biologic depends on the metabolic activities of living cells, each step in the process—the cloning of the cell line, the media used to culture and sustain the line, the fermentation and purification processes, and the formulation, fill and finish processes—dictate the product's safety, purity, and potency. As many have stated, in an oversimplified manner, "the product is the process." That is, each sponsor's process yields a unique product, and no amount of end product testing can confirm that one sponsor's biological product is identical to, or interchangeable with, another sponsor's product.

In contrast, most small molecule drugs can be replicated using varied and distinct manufacturing processes. Thus, under the existing generic drug scheme, a sponsor can gain marketing approval in the United States by showing that its drug is the same as an approved "pioneer."[6] "Sameness" is generally based on showing that the proposed generic drug has the same active ingredient, dosage form, route of administration, strength, and bioavailability as the approved pioneer. See 21 U.S.C. §355(j). This system pertains only to drugs approved under a new drug application. Id. It does not apply to biological products licensed under the separate regime administered under the federal Public Health Service Act. 42 U.S.C. §262.

By showing "sameness" to the pioneer product, a sponsor is permitted to obtain marketing approval based on the safety and effectiveness data developed by the pioneer manufacturer. Once approved, a generic drug is considered by FDA to be fully substitutable for the pioneer. Generic drugs have increased competitive pressures in various drug classes. As a result, there is often an overlay of aggressive promotion of small molecule drugs, which may tend to complicate the litigation.

In addition to drug classes being crowded with generics, for many major diseases and conditions, numerous drug companies will have their own analogues of small molecule drugs to treat those conditions. Thus, a patient and the patient's physician, when deciding on how to treat a particular disease, may very well have a fairly large number of small molecule drugs to choose from to treat that condition. As a result, patients in traditional pharmaceutical litigation may conclude that they did not necessarily have to take the drug at issue, as opposed to another "mee too" drug in the class. There usually is not clear evidence as to why a plaintiff should use one drug over any other. Plaintiffs frequently tout another manufacturer's product as safer (until they sue that manufacturer).

In stark contrast, with biologics the number of choices to treat any given disease condition are fewer. In some instances, there is only one choice. Additionally, there are currently no "generic biologics," and most biological products tend to have a special niche with few, if any, competitors.

The lack of generic biologics has two identifiable effects on litigation. First, this absence of competing products seems to explain an interesting phenomenon that has occurred in every biological product case in which we have been involved—the plaintiffs' fondness for the product. Biological products are typically prescribed for very serious diseases, and patients tend to realize that biological products are replenishing something essential that their bodies are not producing.

Second, the lack of generic biologics also results in litigation with fewer potential parties. Whereas generic manufacturers may be joined in a traditional pharmaceutical product liability action, there is no such threat in biologic litigation.

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These distinctions have the potential to impact litigation involving biologics in various ways. First, because of the limited number of alternative therapies available for certain debilitating diseases, it should be easier to explain to the jury why the potential benefits associated with a particular biologic justified the potential risks associated with the product. This argument can be particularly helpful to learned intermediary, informed consent and assumption of risk defenses. Also, because the number of similar products in a class is smaller, the risk of multi-defendant litigation is also reduced.

Biologics Tend to Have More Comprehensive Warnings

Because of the potentially diverse responses to biologics, the warnings that accompany these products tend to be lengthy and varied. Given the unpredictability of how a particular biological product may impact a patient's immune system, it may be difficult to weigh one adverse event over another, or predict whether one will be more pronounced in any particular population. Labeling thus tends to report what was observed, without drawing conclusions of causation, mechanism of action, or precautions that may help to minimize the potential for or otherwise mitigate the occurrence of an event.

The open-ended nature of biological product labeling, particularly with respect to adverse events and warnings, tends to support a learned intermediary defense. Despite recent efforts by FDA to streamline the labeling of drugs and biological products, it remains essential for sponsors of biological products to continue to make their labeling as comprehensive as possible, particularly where it is impossible to draw clear editorial lines among reported events.

Regulatory Interplay

Coordination with FDA Lawyers

As one would expect coordination with lawyers who were and are involved in the regulatory side of biological product development and approval has proven to be particularly helpful. Such coordination helps facilitate various defenses, including, for example, structuring a preemption defense. Even more, early involvement of regulatory counsel—prior to the emergence of litigation—can allow a sponsor to develop an agency record to bolster defense strategies, including a preemption defense.

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Historically, and relative to small molecule drugs, the level of communication between a sponsor and FDA on the development, study, and review of a biological product has been high. As a result, there may be many more regulatory documents to be mined for potential defenses. For example, telephone contact reports may document FDA's participation and direction in the drafting of warnings for a specific biological product. Similarly, regulatory documents may support a causation defense to the extent that FDA itself may have expressed uncertainty about the biological pathway of the product. FDA lawyers, with direct knowledge of the regulatory process for the particular drug at issue, can thus be invaluable as they can help the trial attorneys navigate through the file.

Unique Opportunities for Regulatory Experts

While the same general types of experts are typically retained in litigation involving biological products and small molecule drugs, there are fewer potential experts with true expertise in the biological arena. And, given the relatively young age of biologics, it may be possible to retain experts who were actually involved with the biologic at issue in litigation. An expert with actual first-hand knowledge of the FDA review process for the product at issue can certainly be helpful.

Related Expert Issues

Also, because there is generally less of a commercial overlay with biological products, our experience has been that medical experts are more willing to become involved in the litigation than they are in pharmaceutical litigation. Further, because almost all therapeutic proteins are breakthrough products, many physicians have an allegiance to the science and are more likely to become involved, even if it means rendering a causation opinion that is adverse to their patients' litigation position. Having a treating physician rebut a causation opinion is always ideal in a pharmaceutical product liability case.

The Science Should Remain the Primary Focus

Because of the scientific issues in litigation involving biologics, the approach to documents may also be somewhat different. In traditional pharmaceutical cases plaintiffs typically look for the "smoking gun" to show that someone within a pharmaceutical company continued to develop a drug knowing about a particular adverse event. The chances of such a document in the regulatory file or corporate documents for a biologic are much less. This is because much less is known about the product. As a result, smaller document review teams may be utilized, and the core resources of the defense team can be focused on the science-related issues, which tend to be the most critical with biologics. Indeed, it has been our experience that large discovery teams have not proven to be necessary in many of the biological product liability cases. In essence, biological product liability litigation tends to be more medically and expert—as opposed to document—driven. Therefore, documents and protecting against the smoking gun should not be the driver of the defense; the science should remain the primary focus.

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Biological Product Liability Litigation Is Not Well-Suited for Mass Tort Designation

While the attributes of biologics permit creative approaches to litigation, those same characteristics render biological product litigation particularly ill-suited for mass tort designation. As an initial matter, the number of cases tend to be more limited than litigation involving small molecule drugs. And, as noted above, the number of parties involved in cases tends to be much more limited due to the lack of generics. Further, there is great variation in the molecular structure of the biologics within a particular class. Also as a result of the nature of biological products, there tends to be variation in the injuries claimed by the various plaintiffs. The lack of common alleged injuries also weighs against mass tort designation.

To our knowledge, there has not been a mass tort designation involving a biological therapeutic protein product. In one recent example of a court seeking mass tort designation for a biological product, the Honorable Carol E. Higbee of New Jersey's Superior Court, filed an application to the Supreme Court of New Jersey, seeking to designate the biologic Enbrel®, as a mass tort along with three other products—one other biologic, Remicade®, and two small molecule drugs, Celebrex® and Vioxx®. At the time, Judge Higbee already presided over the Vioxx® cases, which at that time had recently been designated as a mass tort. The theory behind this attempt was that all of these products are prescribed to treat arthritis.

The manufacturers of Enbrel® filed an objection to the application to designate Enbrel® as a mass tort. These defendants were able to utilize some of the unique attributes of biological products, as described above, to argue that not a single factor set forth in the New Jersey Mass Tort Guidelines (Directive #11-03)[7] weighed in favor of mass tort designation. For example, the litigation did not involve large numbers of parties and there was not the threat of generic drugs being added to the cases. Even more importantly, there were limited common issues among the seven then-pending Enbrel®, and virtually no common issues among the Enbrel® cases and cases involving the other products. The products are prescribed to treat different types of arthritis, have different regulatory histories, different molecule structures and different mechanisms of action. Although an opinion was not issued with the denial, the Supreme Court of New Jersey properly determined that the Enbrel® litigation did not warrant a mass tort designation. This successful avoidance of mass tort designation illustrates that there is a sufficient basis to object to any future attempt to designate litigation involving a biologic as a mass tort.

Conclusion

Counsel defending biological products should consider the defense opportunities posed by the unique attributes of biological products. In doing so, non-traditional litigation strategies can be utilized, often leading to the early disposition of cases. Further, the distinctive properties of biologics can serve as a basis for arguing against mass tort designation should such a situation arise.

Endnotes continued on page 15...

Published in Mass Torts Litigation Newsletter of the Section of Litigation's Committee on Mass Torts Litigation, Volume 5, No. 2, Spring 2007.

Defending Biologics *continued from page 6...*

Endnotes

1 Although we use the general term "biologics" throughout this document, our focus is on therapeutic proteins, which are laboratory-engineered proteins for pharmaceutical use. Many therapeutic proteins are manufactured by recombinant DNA technology "genetic engineering." FDA defines "biological products" to include toxins, antitoxins, and analogous products with immune effects. See 21 C.F.R. §600.3(h).

2 Enbrel® is a prescription biological product first approved by FDA on November 2, 1998, to treat rheumatoid arthritis in patients who had an inadequate response to other medications. *See* Approvals, available at www.fda.gov/cder/biologics/biologics_table.htm. Enbrel® has since been approved for additional indications, including polyarticular juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. *Id.* The rheumatoid arthritis indication has also been expanded, to include use for reduction in signs and symptoms and delaying structural damage in patients with moderately to severely active rheumatoid arthritis, including those who had not previously failed with a DMARD. *Id.* Use of Enbrel® has also been approved for this indication in combination with methotrexate in patients who did not respond to methotrexate alone. *Id.*

3 *See Hahn v. Amgen Inc., et al.*, Action No. 4:03-CV-855-Y (N.D. Tex.); *Parker, et al. v. Amgen Inc., et al.*, No. 4:02-CV-3286 (D.S.C.); *Diamond, et al. v. Immunex Corp., et al.*, Docket No. 2:03-CV-564 (W.D. La.).

4 N. Casadevall et al., "Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoetin," 346 *New Engl. J. Med.* 469-475 (Feb. 14, 2002); Adam Feuerstein, "Popular Anemia Drug Comes Down with Ailment," *TheStreet.com* (Feb. 14, 2002), at http://www.thestreet.com/tech/adamfeuerstein/10009126.html.

6 *See generally* 21 U.S.C. §355(j), codifying Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the "Hatch-Waxman Amendments").

7 Mass Torts- Guidelines and Criteria for Designation, Directive 11-03 (October 27, 2003), available at: www.judiciary.state.nj.us/directive/civil/dir_11_03.pdf.

Bellwether Plaintiffs *continued from page 12...*

Endnotes

1 *In re Chevron U.S.A., Inc.*, 109 F.3d 1016, 1019 (5th Cir. 1997).

2 *See In re Vioxx Products Liability Litigation*, __ F.R.D. __, 2006 WL 3391432 (E.D. La. Nov. 22, 2006); *In re: Welding Fume Products Liability Litigation*, 2006 WL 1173960 (N.D. Ohio April 5, 2006); *In re: Guidant Corp. Implantable Defibrillators Products Liability Litigation*, 2006 WL 409200 (D. Minn. Jan 31, 2006).

3 *See In re: Guidant Defibrillators Products Liability Litigation*, 2006 WL 905344 (D. Minn. March 23, 2006).

4 As a third alternative, the court can simply order the parties to identify a specified number of bellwethers.

5 *In re Chevron U.S.A., Inc.*, 109 F.3d 1016, 1019 (5th Cir. 1997).

6 *See* 2 L. of Toxic Torts § 20:14 (2005).

7 *In re Chevron*, 109 F.3d at 1020.

8 For a detailed discussion of the interaction between due process concerns and bellwether trials applying to non-bellwethers, *see* R. Barton, *Utilizing Statistics and Bellwether Trials in Mass Torts: What do the Constitution and Federal Rules of Civil Procedure Permit?* 8 Wm. & Mary Bill Rts. J. 199 (1999).

9 The due process concerns addressed by the Fifth Circuit in *In re Chevron* may go unrecognized by state court judges unfamiliar with mass tort management. The desire to decide issues of general liability or causation applicable to all claimants through the use of bellwethers is common and understandable, but counsel must work to educate judges of the pitfalls of such case management techniques.

10 *See generally* A. Rudlin and C. Graham, *Toxic Torts: A Primer*, 17 SPG Nat. Resoures & Env't. 210, 258 (2003).

11 439 U.S. 322, 327 (1979) (holding that offensive use of collateral estoppel did not violate defendant's Seventh Amendment right to trial). The requirements of collateral estoppel in a particular jurisdiction must also be satisfied. For example, in the Tenth Circuit the application of collateral estoppel requires: "(1) the issue previously decided is identical with the one presented in the action in question, (2) the prior action has been finally adjudicated on the merits, (3) the party against whom the doctrine is invoked was a party, or in privity with a party, to the prior adjudication, and (4) the party against whom the doctrine is raised had a full and fair opportunity to litigate the issue in the prior action." *See Dodge v. Cotter Corp.*, 203 F.3d 1190, 1198 (10th Cir. 2000).

12 *In re TMI Litigation*, 193 F.3d at 725-726.

13 For a discussion of the distinctions between "mature" and "immature" torts, see Frances E. McGovern, *Resolving Mature Mass Torts Litigation*, 69 B.U.L.Rev. 659 (1989).

Published in Mass Torts Litigation Newsletter of the Section of Litigation's Committee on Mass Torts Litigation, Volume 5, No. 2, Spring 2007.