MEDICAL DEVICES: THE BEGINNINGS
Part 1 - The Rise of Regulations
DEAR CLIENT

If you find that researching the many changes in FDA regulations of medical devices can be a time-consuming and often frustrating task, our cover story is for you. “Medical Devices: The Beginnings” is part one of a two-part series that investigates the evolution of the regulation of devices from the time they were not regulated (pre-1976) up through the 1990 amendments and to the present. Look for part two in our September issue.

Adverse event reports are something every pharmaceutical and medical device company deals with every day. In “There Is An App For That: Adverse Event Reports and the Sentinel Initiative,” we update you on this FDA initiative, as well as an interesting app that allows you to report an adverse report to the FDA from your smart phone.

The multitude of challenges facing pharmaceutical companies after the economic downturn has forced many to reinvent themselves and how they do business. “Collaboration: Part of the Pharmaceutical Industry’s ‘New Normal’” identifies some of the unique challenges facing the industry and explores how companies are relying on collaboration with other stakeholders as an innovative way to meet those challenges and identify and develop new therapies.

Rounding out this issue is a 50-state survey of product liability laws regarding design defect.

We hope you find this issue useful in addressing concerns you face every day.
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Fall 1937 ... somewhere in Tennessee ...

Little Barbara had always been a rather sickly child. You name the current popular sickness and she caught it. Three other children from town had missed church that Sunday complaining of a sore throat, so her parents knew it was only a matter of time before she had the same malady. But she was an obedient youngster and would do her best to gargle with saltwater and take whatever medicine the family had available, although she sometimes had difficulty taking pills. And the powders tasted just awful. Barb’s mother, however, had heard about a new liquid medicine that worked quickly and tasted like raspberries. And she set out that morning determined – no matter the cost – to bring this new miracle drug home.

Nobody but Almighty God and I can know what I have been through these past few days. I have been familiar with death in the years since I received my M.D. from Tulane University School of Medicine with the rest of my class of 1911. Covington County has been my home. I have practiced here for years. Any doctor who has practiced more than a quarter of a century has seen his share of death.
But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony.

(Letter by Dr. A.S. Calhoun, October 22, 1937)

Thankfully, Barbara did not take that elixir. The county’s country doctor had a habit – really more of a ritual – of religiously reading the local paper on the front porch every evening while he allowed the stench of the day, and of his sick patients, to slowly waft off him in the breeze. While annoying as all heck to his wife who just as religiously prepared dinner at the same time every evening, knowing it would remain cooling as he read, this little habit saved that county untold heartbreak. For one evening, while the wife stamped her feet and glowered at him through the window as he turned the newspaper pages, the country doctor stiffened, literally jumped off the porch and raced back to the office. When his dumbfounded spouse went to retrieve the discarded paper, she found the announcement from the AMA warning of the deadly ramifications of taking Elixir Sulfanilamide.

You may be wondering what the above stories have to do with medical devices. It is a rather interesting tale – one that begins over 30 years before the 1937 Elixir Sulfanilamide Disaster.

I. PURE FOOD AND DRUGS ACT OF 1906

Enacted in 1906, the “Wiley Act” was intended to “prevent the manufacture, sale or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines and liquors, and for regulating traffic therein, and for other purposes.” The Act defined the word “drug” to “include all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use, and any substance or mixture of substances intended to be used for the cure, mitigation or prevention of disease of either man or other animals.” The term “device” did not appear in the Act, but the definition of “drug” was broad enough to allow just about anything to be characterized as a drug. For example, prior to the enactment of the FDCA, the Second Circuit held that gauze bandages were “drugs” covered by the 1906 Act. This began a rather long practice of classifying as drug items no one considered in common parlance to be a drug. But the practice allowed regulation, and courts considered regulation essential to the protection of the public health.

Interestingly, the 1906 Act contained no provision requiring some sort of government approval or clearance in any manner before a drug could be marketed. The Act did set out, however, that no person could manufacture or sell any “adulterated” or “misbranded” drug; doing so was a misdemeanor and would subject the miscreant to fines and potential imprisonment (not to exceed one year). A drug would be considered adulterated

- FIRST: If, when a drug is sold under or by a name recognized in the United States Pharmacopoeia or National Formulary, it differs from the standard of strength, quality or purity, as determined by the test laid down in
the United States Pharmacopoeia or National Formulary official at the time of investigation: Provided, that no drug defined in the United States Pharmacopoeia or National Formulary shall be deemed to be adulterated under this provision if the standard of strength, quality or purity be plainly stated upon the bottle, box or other container thereof, although the standard may differ from that determined by the test laid down in the United States Pharmacopoeia or National Formulary.

- SECOND: If its strength or purity falls below the professed standard or quality under which it is sold. And it would be considered misbranded if “the package or label of which shall bear any statement, design or device regarding such article, or the ingredients or substances contained therein which shall be false or misleading in any particular.”

II. FEDERAL FOOD, DRUG AND COSMETIC ACT OF 1938

Eventually, the 1906 Act ran its course after several amendments, and Congress began crafting a more substantial bill. “By 1917, fraudulent medical devices, such as nose straighteners, height-stretching machines and heated rubber applicators advertised as a cure for prostate gland disorders, began flooding the market. It was clear to the FDA that the law should be expanded to include agency authority over medical devices. In its annual report to Congress that year, the FDA stated that the 1906 act “has its serious limitations … which render it difficult to control … fraudulent mechanical devices used for therapeutic purposes.” One of those limitations was that the 1906 Act did not specifically define “devices,” so items that clearly were devices had to be defined as drugs just so they could be regulated. But “calling a medical device a drug, claimed a U.S. senator from Missouri at the time, was like ‘calling a sheep’s tail a leg.’”

And so the bickering began as to how best to address this conundrum in the new Act. In an early 1934 version of the Act, a definition of “device” remained absent, but the term “drug” was defined to include “all substances, preparations and devices intended for use in the cure, mitigation, treatment or prevention of disease in man or other animals …” This was on purpose as noted by the bill’s introducer, Senator Copeland, when discussing the 1906 Act that he hoped to fix: The present law defines drugs as substances or mixtures or substances intended to be used for the cure, mitigation or prevention of disease. This narrow definition permits escape from legal control of all therapeutic or curative devices like electric belts, for example. It also permits the escape of preparations which are intended to alter the structure or some function of the body, as for example, preparations intended to reduce excessive weight. There are many worthless and some dangerous devices and preparations falling within these classifications. [This bill] contains ample authority to control them.

But this bit of wordsmithing did not sit well with the good Senator Clark from Missouri, who later countered: If the devices ought to be outlawed, they ought to be outlawed, and I have no objection to that; but to maintain that a purely mechanical device is a drug and to be treated as a drug in law and in logic and in lexicography is a palpable absurdity, in my opinion.

Others agreed and, in order to quell the rising debate, an amendment was suggested to simply add a definition for “device.” That was done, agreed to without debate, and without further ado, the bill now had a “parallel definition” for devices. The bill still, however, was missing a few details: We have found nothing in the legislative history of the Act indicating that the Congressional purpose in providing a separate definition of “devices” was anything other than to avoid the incongruity of classifying such things as electric belts as “drugs.” There was at the
time no practical significance to the distinction between “drugs” and “devices,” for the operative provisions of the bill (e.g., the provision barring the introduction into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded) applied identically to both. The bill, as late as August 1937, included no section relating to “new drugs,” and no requirement that any products covered by the bill be submitted to the government for prior approval before their introduction into interstate commerce.15

That changed, however, in 1937 because of the Elixir Sulfanilamide tragedy discussed at the beginning of this article. But it changed only for drugs – not devices. Spurred on by the deaths of nearly 100 men, women and children, new bills were introduced that included prior approval provisions for “new drugs,” but “the term ‘new drug’ was used ... without any attention to the fact that the distinction between ‘drug’ and ‘device’ had thus for the first time become important.”16

Upon enactment in 1938, for the first time regulations explicitly applied to drugs – new drugs – that did not apply to devices. Also of significance was the inclusion in the definition of “drug” that it “does not include devices or their components, parts or accessories.”17

So thus continued the practice of classifying medical devices as drugs in order to deem them subject to regulation. In 1968 the Second Circuit, noting the classification of devices to be “exclusionary,” held that AMP’s new products for ligating blood vessels – an applicator, nylon ligature loop and nylon locking disk – were drugs.18 A year later, the United States Supreme Court determined that antibiotic sensitivity discs – which never came in contact with an actual patient – were drugs.19 Much like the Second Circuit, the High Court likewise referred to the device classification as an “exception” and affirmed that devices should be limited to such things as “electric belts, quack diagnostic scales and therapeutic lamps, as well as bathroom weight scales, shoulder braces, air conditioning units and crutches.”20

One wonders what the Missouri senator would have thought of these legal gymnastics. Perhaps he would have suggested yet again: if you want to regulate devices, just regulate devices.

Finally, that happened.

III. MEDICAL DEVICE AMENDMENTS ACT OF 1976

As history shows, sometimes tragedies ensue before action occurs. The FDA notes that “during 1972 and 1973, pacemaker failures were reported. And in 1975, hearings took place on problems that had been reported with the Dalkon Shield intrauterine device, which caused thousands of reported injuries. Those two incidents helped underscore the need for the Medical Device Amendments, enacted in 1976.”21 The MDA created a classification scheme for devices that correlated in general to the level of risk and the concomitant level of FDA regulatory oversight (e.g., Class I, Class II and Class III), and gave the FDA authority over device development, marketing and post-marketing activities. As President Ford said when signing it into law, “The Medical Device Amendments of 1976 eliminate the

Also of significance was the inclusion in the definition of “drug” that it “does not include devices or their components, parts or accessories.”
processes. Whether a device falls under the parameters of the 510(k) paradigm, the PMA process or neither depends on its classification. And classifications are mutually exclusive – a device is either I, II or (never “and”) III.

If Class I, the device is not subject to any sort of pre-approval process, but simply falls under what are known as “general controls.” General controls apply to all medical devices, but they are the only controls that apply to Class I devices. They are the basics, governing such things as adulteration, misbranding, device registration and listing, and good manufacturing practices. Essentially, if determined to be a Class I device, the FDA has decided that it needs only general controls to assure itself of the safety and effectiveness of the device. Of interest, “when initially classifying devices, the FDCA requires that the least restrictive classification must first be considered, and only when the device in question cannot meet the definition of a less restrictive class can more restrictive classifications be considered.”

The Class II devices fall under the 510(k) system. In order to equalize competition with respect to pre-amendment devices that could continue being marketed as “grandfathered” until the FDA classified them, Congress said that new devices that were “substantially equivalent” (SE) to a pre-amendment device also could be legally marketed. But nowhere was the term “substantially equivalent” defined – until 1986 when the FDA issued a Guidance addressing the matter. Although a lot of attention has been paid to the SE term, legislative history makes clear that Congress’s intent was to base the SE determination on another SE finding: safety and effectiveness. Class II devices are those that require a few more standards, or performance standards, in addition to general controls, in order for the FDA to be satisfied that the device is safe and effective.

Lastly, the Class III devices require approval of a Premarket Approval Application (PMA) before they may be legally marketed. These are devices that are “intended to
Although a lot of attention has been paid to the SE term, legislative history makes clear that Congress’s intent was to base the SE determination on another SE finding: safety and effectiveness.

IV. SAFE MEDICAL DEVICES ACT OF 1990

Per the FDA, the “Safe Medical Devices Act (SMDA) was passed in 1990, and represents the first reform of medical device law since the 1976 amendments. This law modified the amendments to give the public greater protection against dangerous medical devices.”32 And how did it accomplish that? These are just a few ways:

- The SMDA formally memorialized the FDA’s methods for determining substantial equivalence as had been set out in the 1986 Guidance.
- Substantial equivalence was actually defined and included safety and effectiveness.
- Any marketed device could be a predicate – not just a pre-amendment device.
- Regulation of Class II devices was enhanced with the use of performance standards and special controls.
- Special controls can be such things as specific labeling requirements or FDA Guidances.
- Mandatory event reporting for certain events, such as death.
- Mandatory post-market surveillance for certain devices.

V. CONCLUSION... FOR NOW

For now, our story pauses. But the tale continues with more on the SMDA, FDAMA in 1997, MDUFMA in 2002, FDAAA and MDUFA II in 2007, and more. Stay tuned.

2. Id. at Sec. 6 (emphasis added).

3. Id. at 829 (noting products must be classified according to Congressional purpose, which here “was, very clearly, to keep inadequately tested medical and related products which might cause widespread danger to human life out of interstate commerce.”).


5. 21 U.S. Food and Drug Administration, “Medical Device and Radiological Health Regulations Come of Age,” FDA Consumer Magazine, January-February 2006. Available at http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/MedicalDeviceandRadiologicalHealthRegulationsComeofAge/default.htm. The premarket regulation of devices again was delayed in 1962 with the aftermath of the thalidomide disaster in Europe. While the 1962 Amendments specifically allowed FDA to regulate some devices as drugs (i.e., sutures and contact lenses), the majority remained unregulated.

By Kari Sutherland
In products liability cases, plaintiffs often allege that the product was defectively designed and inherently dangerous. In pharmaceutical and medical device cases, the design defects claim usually plays second fiddle to the warnings claim, but design defect can still be a winning claim for the plaintiff. Therefore, knowledge of the applicable state law for design defect is critical.

The test for whether a product is inherently dangerous has evolved in recent years from the “consumer expectations test” to the “risk-utility test.” Although products liability scholars have advocated for the explicit use of the risk-utility test,¹ many states have yet to adopt the new standard.

Under the traditional consumer expectations test, the seller of a product is liable if the product is in a defective condition such that it renders the product unreasonably dangerous to the consumer.² This standard allows a jury to infer the existence of a defect if the product fails to meet reasonable expectations of consumers.³

The consumer expectations test prevailed as the standard for design defect claims until the 1980s.⁴ At that time, a view arose among products liability scholars that the consumer expectations test was both indefensible in theory and unworkable in practice.⁵ The scholars advocated instead for a newly
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emerged theory that balanced the benefits of using a product as designed with the risks of harm associated with the design, known as the risk-utility test. This article surveys the current state of law across the 50 states to demonstrate which states have adopted the risk-utility test and which states remain committed to the consumer expectations test. The survey includes whether the state requires a plaintiff to demonstrate that a feasible alternative product design would have prevented plaintiff’s harm at a reasonable cost.

CONSUMER EXPECTATIONS TEST

ARKANSAS:

INDIANA:

KANSAS:

MARYLAND:
- Generally, consumer expectation test. Halliday v. Sturm, Ruger & Company, Inc., 792 A.2d 1145, 1152 (Md. 2002). However, when a product malfunctions, Maryland courts utilize the in risk/utility test. See 792 A.2d at 1153.

NEBRASKA:

NEW HAMPSHIRE:

NORTH DAKOTA:
- Consumer expectations test. N.D. Cent. Code § 28-01.301(4).
- Requirement of feasible alternative design? Has not been addressed in North Dakota.

OKLAHOMA:

OREGON:
• Consumer expectations test, generally. Risk-utility may be required when the jury is “unequipped,” either by general background or facts supplied, to decide whether a product failed to perform as safely as an ordinary consumer would have expected. In this situation, additional evidence about the ordinary consumer’s expectations is necessary. That evidence may consist of a risk-utility balance. McCathern v. Toyota Motor Corp., 23 P.3d 320, 331 n.15 (2001).
• Requirement of feasible alternative design? Generally no. But maybe when the risk-utility analysis is applied. McCathern v. Toyota Motor Corp., 23 P.3d 320, 331 (2001) (Recognizing that evidence that the magnitude of the product’s risk outweighs its utility is often demonstrated by proving that a safer design alternative was both practicable and feasible.)

RHODE ISLAND:
• Consumer expectation test. Austin v. Lincoln Equip. Assoc., Inc., 888 F.2d 934 (1st Cir. 1989).

TENNESSEE:

UTAH:

VERMONT:
• Consumer expectations test. See Zaleske v. Joyce, 133 Vt. 150,
The test for whether a product is inherently dangerous has evolved in recent years from the “consumer expectations test” to the “risk-utility test.”

155, 333 A.2d 110, 113-114 (1975) (Adopting 402A); See also Farnham v. Bombardier, Inc., 161 Vt. 619, 620, 640 A.2d 47, 48 (1994) (Product is defective if it is not “safe for normal handling and consumption.”).

- Requirement of feasible alternative design? Undetermined. It appears no showing is required, but the issue has not been directly addressed. See Manning v. Goodyear Tire & Rubber Co., 2005 Vt. Super. LEXIS 126, fn. 6 (July 20, 2005) (“The adoption of a reasonable alternative design standard based on risk-utility analysis has moved this area of law away from § 402A’s strict liability standard toward negligence. The Vermont Supreme Court has considered this view but has not necessarily adopted it.” (citations omitted)).

WISCONSIN:

WYOMING:
- Consumer expectations test. “A prima facie case that a product was defective and that the defect existed when it left the manufacturer’s control is made by proof in the absence of abnormal use or reasonable secondary causes the product failed ‘to perform in the manner reasonable to be expected in light of [its] nature and intended function.’” Sims v. General Motors Corp., 751 P.2d 357, 364-65 (Wyo. 1988) (emphasis added).

RISK-UTILITY TEST

ALABAMA:

COLORADO:
- Requirement of feasible alternative design? No. See Armentrout v. FMC Corporation, 842 P.2d 175, 185 n.11 (Colo. 1992).

GEORGIA:

IDAHO:

KENTUCKY:
LOUISIANA:
• Requirement of feasible alternative design? Yes. See LSA-R.S. 9:2800.56.

MASSACHUSETTS:

MICHIGAN:

MINNESOTA:
• Requirement of feasible alternative design? Yes. Wagner v. Hesston Corp., 450 F.3d 756, 760 (8th Cir. 2006).

NEW JERSEY:

NEW MEXICO:

NEW YORK:
NORTH CAROLINA:
- Requirement of feasible alternative design? No, as long as the claim is based on the second theory of liability, which provides that “at the time the product left the control of the manufacturer, the design or formulation of the product was so unreasonable that a reasonable person, aware of the relevant facts, would not use or consume a product of this design.” N.C. Gen. Stat. § 99B-6(a).

OHIO:

PENNSYLVANIA:

SOUTH CAROLINA:

TEXAS:
COURTS CAN APPLY EITHER TEST

ALASKA:
• Courts recognize the consumer expectation test and risk-utility analysis. General Motors Corp. v. Farnsworth, 965 P.2d 1209, 1220 (Alaska 1998).

ARIZONA:
• Requirement of feasible alternative design? It is unclear under Arizona law.

CALIFORNIA:
• Courts apply either the consumer expectations test or risk-utility analysis. Soule v. General Motors Corp., 882 P.2d 298, 308-09 (Cal. 1994).

CONNECTICUT:
• Courts apply a “modified consumer expectations test” where if the ordinary consumer would not be able to form his or her own expectation of the safety of a given product based on everyday experience, the risks and utilities are then considered. See Potter v. Chicago Pneumatic Tool Co., 694 A.2d 1319, 1330 (Conn. 1997).

FLORIDA:

HAWAII:
• Courts recognize the consumer expectations test, the risk-utility analysis and the latent danger test. See Acoba v. General Tire, Inc., 92 Haw. 1, 17, 986 P.2d 288 (Haw. 1999).
• Requirement of feasible alternative design? Undetermined. It appears no showing is required, but the issue has not been directly addressed.

MISSISSIPPI:
• Courts require that a product must pass both a risk-utility and consumer expectations test. See Glenn v. Overhead Door Corp., 935 So.2d 1074, 1081 (Miss. Ct. App. 2006).

WASHINGTON:
• Courts can apply either the risk-utility analysis or consumer expectations test. See Soproni v. Polygon Apartment Partners, 137 Wash. 2d 319, 326-27, 971 P.2d 500, 504-05 (1999).

UNCLEAR WHICH TEST APPLIES

DELAWARE:
• It is unclear whether Delaware courts employ either test. Delaware has never adopted strict liability, declaring it to be “impermissible judicial legislation.” Cline v. Prowler Industries, Inc., 418 A.2d 968, 974 (Del. 1980). “A product defect may take the form of a design defect, where an entire product line is designed improperly, or a manufacturing defect, where a product line is properly designed but a particular item was manufactured improperly.” Smith v. Daimlerchrysler Corp., No. 94C-12-002-JEB, 2002 Del. Super. LEXIS 434, at *4 (Del. Super. Ct. Nov. 20, 2002).
• Requirement of feasible alternative design? Undetermined. However, in Delaware, a product is “defective in design where it is not reasonably fit for its intended purpose and where the
design has created a risk of harm which is so probable that an ordinary prudent person, acting as the product’s manufacturer, would pursue a different available design to substantially lessen the probability of harm.” See Allen v. IBM, No. 94-264-LON, 1997 U.S. Dist. LEXIS 8016, 139 (D. Del. May 19, 1997).

MISSOURI:
• “Missouri courts have consistently refused to impose any ‘judicial definition [of unreasonably dangerous] whether derived from consumer expectations, risk-utility or otherwise.’” Sappington v. Skyjack, Inc., 512 F.3d 440 (8th Cir. 2008).

NEVADA:
• It is not clear whether Nevada applies the risk-utility analysis or the consumer expectations test.

SOUTH DAKOTA:
• “It is unclear whether South Dakota has adopted, or would adopt, the so-called ‘risk-utility test,’ in addition to the consumer expectations test of section 402A, for determining the existence of a defective condition.” Robinson v. S.D. Brandtjen & Kluge, Inc., 500 F.3d 691, 698 n.2 (8th Cir. 2007).
• Requirement of feasible alternative design? Has not been addressed in South Dakota.

VIRGINIA:
• Product defective if it “fails to satisfy applicable industry standards, applicable government standards or reasonable consumer expectations.” See Redman v. John D. Brush & Co.,
111 F.3d 1174, 1177 (4th Cir. 1997).

- Requirement of feasible alternative design? Yes. See *Tunnell v. Ford Motor Co.*, 385 F. Supp. 2d 582, 583 (W.D. Va. 2005) (“To satisfy his burden a plaintiff must do more than merely demonstrate that a proposed alternative design would make the product ‘safer’ than it currently is.”)

NEITHER TEST APPLIES

**IOWA:**

- Iowa adopted Sections 1 and 2 of the Restatement (Third) of Torts: Product Liability. Iowa’s standard for design defect cases focuses on if “the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design, and the omission of the alternative design renders the product not reasonably safe.” *See Wright v. Brooke Group Ltd.*, 652 N.W.2d 159, 169-170 (Iowa 2002).

**MAINE:**


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1 The Restatement (Third) of Torts: Products Liability (1998) has abolished the consumer expectations test and exclusively adopted the risk-utility test. 2 [www.law.cornell.edu/wex/consumer_expectations_test](http://www.law.cornell.edu/wex/consumer_expectations_test) 3 Id. 4 Douglas A. Kysar, *The Expectations of Consumers*, 103 Colum. L. Rev. 1700 (2003). 5 Id. 6 Id.
“We try never to forget that medicine is for the people... How can we bring the best of medicine to each and every person? We cannot rest until the way has been found with our help to bring our finest achievements to everyone.”

George Merck’s call to action is as true today as it was 64 years ago. Like other business sectors, the multitude of challenges facing pharmaceutical companies has led some to conclude that there is a crisis requiring systemic change. Ultimately, the means for delivering to patients the pharmaceutical industry’s “finest achievements to everyone” will hinge, in large part, on collaboration.

THE PHARMACEUTICAL INDUSTRY’S GRAND CHALLENGE

Wholesale changes in healthcare legislation, expiring patents, expanded regulatory scrutiny and a recent trend of potential mergers, acquisitions and drug portfolio divestitures, compounded by a still-lagging economy, are all forcing industry change. Perhaps the most significant precipitating change is the industry’s grand challenge: Identifying innovative solutions to improve the productivity of new drug research and development.
The facts present a stark research and development landscape: Nearly 86% of all prescriptions written in the U.S. are for generic drugs. Depending on the study cited, the average cost to develop a new pharmaceutical drug ranges from $1.8 to $4 billion. In 2013, R&D spending was estimated at just over $51 billion, with total R&D as a percentage of total sales at 17.8%. Only two in 10 marketed drugs return revenues that meet or exceed research and development costs.

Yet the pharmaceutical sector has suffered less than others. An aging population, rising incidence of chronic diseases, opportunities in emerging markets, technological advancements, production innovation and impending positive impacts from healthcare reform extending insurance coverage are all contributing to the industry’s growth despite these circumstances.

In 2012, pharmaceuticals generated $959 billion in total revenue, with the Americas contributing the largest share at $417.6 billion. In 2013, the pharmaceutical industry accounted for 810,000 direct jobs and nearly 3.4 million indirect jobs. Currently, there are 400 medicines in development, with 70% of those considered potential first-in-class medicines.

The era of me-too and blockbuster drugs may be ending, and a seismic shift to focusing on discovery research and early translational medicine is underfoot. As part of that change, a growing consensus suggests that developing true breakthrough medicines will first require a complete understanding of human disease biology. However, the scope and breadth of deciphering the most complex and challenging disease states, for which few or no effective treatment options are available, is simply enormous.

Consequently, now more than ever, collaboration and open-source drug discovery may prove to be the key to deciphering complex and widespread disease states in ways that can result in truly breakthrough medicines.

THE FOUNDATION OF COLLABORATION

To be sure, collaboration is not new to drug discovery and development. After Alexander Fleming’s 1928 discovery of penicillin, more than 1,000 scientists from 40 laboratories needed another 10 years before bringing it to market,
As a result, today’s pharmaceutical and larger life sciences industry has evolved into an ever-growing, interdisciplinary R&D ecosystem.

and Henry Kaplan’s oncology breakthroughs of the 1950s harnessed disparate disciplines including medicine, physics and statistics.17 Explosive industry growth in the 1980s led to widespread adoption of strategic alliances — “Kissingeresque marriages of convenience” — as industry stakeholders recognized that no one company could take on the challenge alone.18

Moreover, groundbreaking federal legislation fostered both collaboration and transparency. The 1980 Bayh-Dole Act laid the foundation for public-private collaboration by permitting universities and other nonprofits to retain patent rights secured from government-funded grants.19 The 1997 Food and Drug Administration Modernization Act mandated registration of most clinical trials involving developing pharmaceutical therapies by establishing an online database — ClinicalTrials.gov — providing public access to information about trials, outcomes and adverse events.20 In addition to key legislation, in 2005 the International Committee of Medical Journal Editors implemented a requirement that clinical trials be registered on ClinicalTrials.gov as a condition to publication.21

As a result, today’s pharmaceutical and larger life sciences industry has evolved into an ever-growing, interdisciplinary R&D ecosystem.22 Constituents of this thriving ecosystem are academic research institutions, venture capitalists, startup companies, clinical research organizations, nonprofit foundations, business incubators, and forward-thinking local and state government leaders and are at the center of truly thriving hubs and industry.23 However, generating cutting-edge scientific breakthroughs requires collaboration through reliance on the various ecosystem members.24

COLLABORATION IN PRACTICE

Generally, successful models of collaboration take at least two broad forms implemented at various stages in the drug discovery and development process: (1) sharing data and basic scientific understanding and (2) developing focused, strategic alliances within the R&D ecosystem.

Transparency Through Data-Sharing Pre-clinical collaboration. One of the most exciting alliances created to date is the Accelerating Medicines Partnership (“AMP”), a pre-competitive public-private partnership. Announced in February 2014, the AMP is a five-year cost-sharing pact between the NIH and 10 major rival pharmaceutical manufacturers.25 Focusing on early-stage pre-competitive research, the AMP collaborators will use $230 million in NIH funding, coupled with sharing
Sometimes called bioclusters, corporate mini-labs entail academic and industry experts working side by side to harness the combined expertise of each.

Academic-Industry Collaboration.

Viewed as the United States’ linchpin to securing its lead in innovation and global competitiveness, the Bayh-Dole Act continues to foster innovative and indispensable alliances by harnessing the strengths of academic and industry stakeholders “to identify breakthroughs in basic research that may translate into clinical development opportunities...”

Traditional, widely used academic industry partnerships fall into several broad models: (1) companies providing unrestricted research support, permitting the academic partner to operate independently; (2) a principal investigator or several principal investigators from the same institution are retained by an industry partner to research a specific problem; and (3) fee-for-service research, in which a company identifies a problem and the solution, contracting out related projects to one or more academic partners. However, a number of innovative and increasingly implemented partnership models have emerged, including corporate venture capital, bioclusters and academic drug discovery centers.

EMERGING MODELS OF ACADEMIC INDUSTRY COLLABORATION

Corporate Venture Capital.

While private capital has become a mainstay in fostering and supporting life science startups, corporate venture capital (“CVC”) funds established by pharmaceutical companies have proven successful new initiatives, with CVC funds involving 18% of all deals between 2010 and 2011. For example, the Boehringer Ingelheim Venture Fund (“BIVF”) is a private equity fund created to invest in biotech and startup companies that provide groundbreaking therapeutic approaches.
BIVF focused on companies from the beginning to enable their likelihood of success, and established U.S. offices in Cambridge, Massachusetts, and Fremont, California.36

**Corporate Mini-labs.**

Sometimes called bioclusters, corporate mini-labs entail academic and industry experts working side-by-side to harness the combined expertise of each. For example, Pfizer’s Centers for Therapeutic Innovation (“CTI”), started in 2010 and now located in Boston, San Francisco, San Diego and New York, are characterized by an “open innovation model that puts Pfizer scientists in the lab with academic investigators, where they share their understanding of target biology and translational medicine expertise.”37 Similarly, Johnson & Johnson’s Innovation Centers – in Boston, San Francisco, London and Shanghai – represent “a new approach to partnering aimed at advancing early-stage innovation to collaborate with scientists and entrepreneurs at universities, academic institutes and startup biotech companies to accelerate cutting-edge science into healthcare solutions.”38

**Academic Drug Discovery Centers.**

Similar to the pharmaceutical model, academic drug discovery centers undertake most of the elements of drug discovery by collaborating across various disciplines within an academic institution and other external entities, such as a contract research organization.39 For example, the Alabama Drug Discovery Alliance (“ADDA”) is a collaboration
between the Southern Research Institute (a Birmingham, Alabama-based CRO) and The University of Alabama at Birmingham’s (“UAB”) School of Medicine, Center for Clinical and Translational Science and Comprehensive Cancer Center. The ADDA’s objective is to facilitate drug discovery and development by utilizing the resources that exist at UAB and Southern Research.40 Similarly, the recently established Emory Institute for Drug Development (“EIDD”) provides “organization, facilities and resources to translate academic drug discovery into clinical candidates.”41

CONCLUSION

Collaboration is now an integral part of the pharmaceutical industry’s new normal. Although collaboration “represents a significant departure from the traditional lengthy and linear process of target discovery to eventual drug development,”42 its continued adoption will be vital to successfully crossing the Valley of Death – the “translational gap between drug discovery and clinical development” – in 21st-Century drug development. Sixty-four years later, George Merck’s call for patient-focused drug development justifies the change, just as one leading industry consultant observed: “Collaborating to better comprehend [the] … etiology [of poorly understood diseases] serves the interests of both patients and industry.”43

13 Paul, et al., p. 213.
14 Paul, et al., p. 213.
15 PhRMA 2014 Pharmaceutical Profile, p. 53.
17 Munos, p. 534.
20 Mello, et al., p. 1651.
21 Mello, et al., p. 1651.
22 PhRMA 2014 Pharmaceutical Profile, p. 29.
23 PhRMA 2014 Pharmaceutical Profile, p. 29.
24 PhRMA 2014 Pharmaceutical Profile, pp. 32, 53.
25 Monica Langley & Jonathan D. Rockoff.
26 Monica Langley & Jonathan D. Rockoff.
27 Monica Langley & Jonathan D. Rockoff.
29 Mello, et al., p. 1651.
32 Christopher-Paul Milne & Ashley Malins, pp. 3-4.
33 Christopher-Paul Milne & Ashley Malins, pp. 16-19.
34 Christopher-Paul Milne & Ashley Malins, p. 16.
39 Christopher-Paul Milne & Ashley Malins, pp. 18-19.
40 http://www.uab.edu/medicine/rdpartner/about.Adda.
41 http://eidd.emory.edu/.
43 Munos, p. 535.
In drug or medical device lawsuits, plaintiffs’ attorneys will often try to gain an advantage in the litigation by looking at a manufacturer’s post-market reporting of adverse events. No matter how well-intentioned or diligent a manufacturer may be, plaintiffs’ counsel will inevitably argue that a manufacturer failed to timely report a particular report or that they overlooked a key safety signal. These arguments often gain traction given the tremendous number of adverse event reports any given manufacturer may receive and the allegation that many adverse events are under or partially reported. To compound the problem, following up on an initial report that may contain little information can sometimes be a fruitless venture.

This dynamic is only part of a broader problem. Every year the FDA receives more than 600,000 adverse event reports pertaining to marketed drugs and biological products and approximately 300,000 reports regarding medical devices.\textsuperscript{1} The reporting of these events can be voluntary. Consequently, an expansive and efficient surveillance of adverse events is nearly impossible. Recognizing these problems, Congress passed the Food and Drug Administration Amendments Act (FDAAA) of 2007, which required the FDA \textsuperscript{2} to collaborate with public, academic and private entities to develop methods for obtaining access
Recognizing these problems, Congress passed the Food and Drug Administration Amendments Act (FDAAA) of 2007, which required the FDA “to collaborate with public, academic and private entities to develop methods for obtaining access to disparate data sources and to validate means of linking and analyzing safety data from multiple sources.”

This collaborative effort is now known as the Sentinel Initiative. Pro Te Solutio first considered the Sentinel Initiative in January 2010 – just as Sentinel was about to launch. At the time, there was a great deal of uncertainty about what this project would ultimately look like and how it would structure its vast data-collecting apparatus. Now, more than four years later, the Sentinel Initiative is making deliberate strides toward meeting its intended purpose.

In August 2011, the FDA issued a report to Congress on the status of the Sentinel Initiative. Here, the FDA set forth its vision for this program, promising that it “will serve as an active surveillance system to monitor the safety of marketed medical products.” The FDA boasted that “significant progress” had been made and that the Agency was “committed to continuing this ambitious pace during the coming years.” Specifically, the FDA claimed that they had exceeded Congress’s goal of being able to access data from 25 million patients by July 2010.

In this report, the FDA also explained why they had opted to execute the Sentinel Initiative through a distributed system as opposed to a centralized approach to collecting data. In a distributed system, “personally identifiable information would remain with its data holders in its local environment, protected by existing firewalls and managed by those most familiar with the data.” This approach enhances patient privacy by keeping data localized within an already protected system and enables the owners of the data to perform their own analyses, which only enhances their interpretative value.

Within this model, the FDA envisioned three categories of activities focused on safety signals: signal generation, signal refinement and signal evaluation. The FDA defines a safety signal as a “concern about an excess of adverse events compared to what is expected to be associated with a product’s use.” These signals may be derived from “the product’s clinical development program, postmarket studies of a product or postmarket adverse event reports submitted to FDA’s spontaneous reporting systems.” However, in order to effectively monitor the products it regulates, the FDA must be able to identify and filter out false positive safety signals. To accomplish this task, the Sentinel Initiative employs “signal refinement,” a process in which the FDA “further evaluates a safety signal for which there is already some evidence of a concern, either based on data from the clinical development program, postmarket studies or adverse event reports, or due to a theoretical safety concern related to the type of medical product or the class that the medical product is in.”

A key component to the initial implementation of the Sentinel Initiative is Mini-Sentinel, a pilot project sponsored by the FDA. Mini-Sentinel is designed to provide the FDA with three core capabilities: “1) work through the ‘nuts and bolts’ of designing safety assessments using multiple existing
electronic healthcare data systems; 2) develop and evaluate scientific methods to increase the precision of active safety surveillance efforts; and 3) identify and address barriers and challenges to building a practical, accurate and timely system for active safety surveillance.”

Mini-Sentinel operates through a distributed database and common data model. According to Mini-Sentinel’s website, “The Mini-Sentinel Distributed Data model gives Data Partners complete autonomy over access to and use of data in their possession. This distributed approach is achieved by using a standardized data structure referred to as the Mini-Sentinel Common Data Model. Data Partners transform their data locally according to the Common Data Model, which enables them to execute standardized computer programs that run identically at each Data Partner site. The combined collection of datasets across all Data Partner sites is known as the Mini-Sentinel Distributed Database.”

Mini-Sentinel would not be possible without the more than 20 collaborating institutions that collectively are putting into practice the Sentinel Initiative. By July 2012, 18 of these partner organizations together had data on more than 160 million people, covering 3.5 billion dispensings from over 85 million unique patients. These figures far exceed Congress’s goal of the Sentinel Initiative being able to access data from 100 million patients by July 2012. Significantly, Mini-Sentinel contains data going back more than 10 years, which greatly enhances its ability to detect and evaluate safety signals that pertain to more chronic adverse events. This initial success garnered Mini-Sentinel a 35% increase in last year’s funding.

One writer recently noted some of the practical applications that are emerging from the FDA’s new-found data gathering capacity: “Having such a large data set gives the FDA a new way to quickly detect, analyze and evaluate the risks posed by drugs. In presentations, Mini-Sentinel staffers have demonstrated how they can dig into the database to show hospital visits for acute myocardial infarction stratified by age and sex.” Given its unexpected growth and the vast amount of data under its domain, Mini-Sentinel will likely evolve into a vital tool to not only identify safety signals, but to
A key component to the initial implementation of the Sentinel Initiative is Mini-Sentinel, a pilot project sponsored by the FDA.

Mini-Sentinel is not the only new initiative for enhancing the FDA’s post-market surveillance capabilities. The FDA, in conjunction with Epidemico and Boston Children’s Hospital, has developed MedWatcher, a free app that allows anyone to report an adverse event from their smartphone or tablet. According to MedWatcher’s website (where you can also report an adverse event), “MedWatcher is a free mobile app and web app that allows users to learn about side effects of drugs, medical devices and vaccines, and to easily report adverse events to the FDA. MedWatcher strives to increase transparency around medical products and to improve the safety profile of drugs, devices and vaccines.”

The app is remarkably simple and easy to use. You must first register by providing your name and email address. Once logged in, the user can search for specific drugs, vaccines or medical devices, and then follow specific products to see other user reports.

Reporting an adverse event through the app is intuitive and can be done quickly. MedWatcher asks what other medications or medical products were in use at the time of the adverse event, why the patient was prescribed the drug and the date of the event. It then asks for a description of the event and for the user to select from a list the different outcomes they attribute to the event. The app also allows a user to submit a photo with their report. After a report is submitted, MedWatcher will then forward that report to the appropriate FDA reporting system once they have processed, formatted and approved the report.

With any such reporting system, patient privacy is a concern. According to their website, all personally identifiable information is kept private and confidential. “When we publish a MedWatcher report, we remove the reporter and/or patient’s personally identifiable information. We also remove any information provided in the adverse event description that may further identify a person (e.g. name of hospital). Only age, gender and home state are included in published reports.”

MedWatcher touts the ability to share information across the community of its users as the key advantage to reporting events through their program as opposed to directly reporting it to the FDA. Additionally, they claim that “submitting the reports we receive via MedWatcher to the FDA enables the FDA to link our reported adverse events to the high volume of reports they have received directly, which in turn will raise red flags faster.”

While it is difficult to say how prevalent the use of MedWatcher is among consumers, there is no doubt that it is a powerful tool that enables users of medical products to almost effortlessly report an adverse event. By promoting its use, drug and medical device companies could easily demonstrate their commitment to maximizing the scope of post-market surveillance and the degree to which consumers can gain access to information covering a range of events that relate to specific products.

The ubiquitous use of apps on smartphones and tablets, coupled with the faster-than-expected progress of the Sentinel Initiative, suggests that regulatory oversight of medical products has entered a new era defined by an ever-increasing amount of data. This data deluge is both a blessing and a curse – a blessing in the sense that more events from more patients are catalogued, and a curse in that false positive safety signals are increasingly common and a challenge to
efficiently identify and filter out. On balance, though, drug and medical device companies – not to mention consumers – will benefit in the long term from a more complete sight-picture of the overall safety and effectiveness of their products.

2 Id. p. 1.
3 Id. p. 4.
4 Id.
5 Id.
6 Id. p. 5.
7 Id.
8 Id.
9 Id.
10 Id.
19 Epidemico describes itself as a “health data collection and analytics company” that’s a “spinoff from Boston Children’s Hospital, Harvard Medical School, and MIT.” See <http://www.epidemico.com/>. Last accessed May 6, 2014.
21 Users can select from the following outcomes: non-serious, other serious, hospitalization, disability/permanent damage, birth defect, life-threatening, death.
23 Id.
24 Id.

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