



# Pharmaceutical Compounding

An essential piece of the  
healthcare reform puzzle

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## **Abstract**

Pharmaceutical compounding plays an invaluable role in our nation's healthcare system. Regulated by both the FDA and state boards of pharmacy, compounding is a science practiced by licensed pharmacists with advanced training in pharmaceutical chemistry who use FDA-approved bulk chemical components to create new compounded drug formulations. Access to safe compounded drugs is crucial because of the growing number of drugs in short supply, the high costs of prescription drugs, and the rapidly accelerating out-of-pocket costs for drugs under insurance plans. Safe and affordable compounded medications can help address our nation's drug shortage by putting competitive pressure on prices and increasing availability and access. In turn, lower drug costs and improved access to needed medications will lead to greater drug adherence for patients. Current law and pending legislative proposals do not directly address the problems of drug shortages and the lack of competition for pharmaceuticals, and in many cases are likely to contribute to these problems. Incumbent drug manufacturers benefit from the status quo and can be counted on to work against pro-competitive reforms. This poses significant challenges for policymakers. Thoughtful action is crucial if we are to succeed in solving the problems of high drug prices and shortages of critically needed medicines. This monograph illuminates these issues and recommends concrete policy initiatives for consideration and implementation.

## About the Author

Mark L. Baum is the Founder and CEO of Imprimis Pharmaceuticals, Inc. Throughout his professional career, he has worked to align his professional interests with his personal values. This commitment led to the founding of Imprimis in 2011 as a way to make safe, affordable, and innovative medicines available to patients who need them. This vision for Imprimis has led to the development of new compounded prescription drugs serving over 500,000 American patients since April 2014. When Martin Shkreli, former CEO of Turing Pharmaceuticals, infamously acquired the marketing rights to the infectious disease drug Daraprim<sup>®</sup> and immediately raised its price by more than 5,000%, Mr. Baum led his team at Imprimis to develop a compounded alternative. Using the same core ingredient as Daraprim<sup>®</sup>, Imprimis combined it with another medication commonly taken with Daraprim<sup>®</sup> and priced it at 99 cents per pill, compared to Turing's cost of \$750 per pill. Since then, Imprimis has safely dispensed more than 10,000 doses, saving individual patients and the U.S. healthcare system more than \$10 million. Imprimis also developed the novel compounded formulations (Droplless<sup>®</sup> and LessDrops<sup>®</sup>) for use following cataract surgery that today are saving the elderly population of America hundreds of millions of dollars per year. Droplless is actually changing the landscape of post-cataract surgery care because it allows many patients to avoid weeks of tedious and expensive post-surgical eye drops. Mr. Baum and Imprimis intend to continue leveraging this record of success by bringing new, affordable compounded drug innovations to market. Mr. Baum firmly believes the result of these efforts will be greater competition in the U.S. prescription pharmaceuticals market, lower consumer prices for certain legacy critical medicines, and greater access to safe, affordable drugs for all Americans.

Aside from his professional interests, Mr. Baum's number one goal in life is to celebrate a 50th year wedding anniversary with his wife, who served in the U.S. Navy as a medical doctor. Mr. Baum is the father of two children and resides in Del Mar, California.

Mr. Baum acknowledges the significant contributions of Bonnie Ortega and Jordann Phillips in researching, organizing and editing this monograph.

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## I. The U.S. Prescription Drug Crisis

The lack of competition for many FDA-approved drugs has resulted in rapid and excessive price increases for numerous critical medicines in the United States. As the already high cost of many drugs continues to grow at an unprecedented rate, the growing number of drugs in short supply also continues to negatively impact patient health. These issues affect not only patients, through higher deductibles and out-of-pocket costs, but hospitals and medical institutions as well.<sup>1</sup> The entire healthcare system faces a prescription drug crisis. Existing policies that have led to the present crisis should be reexamined and new solutions must be considered and adopted.

A considerable part of the \$3.2 trillion U.S. healthcare market consists of prescription drug costs.<sup>2</sup> A study conducted by The Henry J. Kaiser Family Foundation and The *New York Times* in January 2016 found that 20% of working-age Americans with health insurance reported problems paying or an inability to pay medical bills in the past 12 months.<sup>3</sup> This monograph explores how reforming policies concerning compounded prescription drugs may help solve these problems – and improve patient health and quality of life – by increasing access to critical medicines and providing needed competition to many high-priced drugs that may never face competition from generic or other lower cost alternatives.

According to a study published in the *Journal of the American Medical Association*, the prices of 19 branded dermatologic prescription drugs increased an average of 500% between 2009 and 2015 due to drastic price hikes by large pharmaceutical companies Valeant Pharmaceuticals International Inc., GlaxoSmithKline PLC and Novartis AG.<sup>4</sup> These companies and their approach to pricing are not isolated examples. Turing Pharmaceuticals increased the price of the anti-parasitic drug Daraprim<sup>®</sup> 5,000% overnight in August 2015, from \$13.50 per pill to \$750.00 per pill.<sup>5</sup> At a price of \$35,000 per 5 ml vial, H.P. Acthar<sup>®</sup>, a drug produced by Mallinckrodt Pharmaceuticals, was named one of the top five most expensive drugs in the world in 2015, after two price increases totaling 87,000% since 2001.<sup>6,7</sup> Understandably, 2015 was named as “the year of prescription drug price outrage” by the Chicago Tribune.<sup>8</sup>

A Gallup poll in November 2015 showed that 42% of Americans named the cost of healthcare or access to healthcare as the most urgent health problem facing the U.S.<sup>9</sup> The prescription drug pricing crisis is closely connected to America’s drug accessibility problem, and the two problems magnify one another in a vicious circle. Drug supply shortages are difficult to predict, and when they occur they affect not only the availability of medications but also the way

medications are prepared and administered to patients. This in turn affects the quality and safety of patient care.<sup>10</sup> In January 2015, more than 300 drugs were listed by the FDA as being in short supply. Some of these drugs have historically been so scarce that patients have died when their access to needed medications was cut off.<sup>11</sup> As drug shortages increase healthcare costs, making it harder for patients to pay for necessary medications, they correspondingly compromise patient care.<sup>12</sup>

Federal legislation such as Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA) was supposed to have reduced the number of new national drug shortages. But this and other laws have not protected vulnerable patient populations. In particular, patients with acute conditions and the critically ill are increasingly at risk of not receiving the medications they need due to high prices and lack of access.<sup>12,13</sup>

With 77% of Americans reporting that healthcare policy is one of the most important political issues facing the nation, the discussion surrounding drug pricing and accessibility is more pertinent than ever.<sup>14</sup> The attention now being paid to these issues by healthcare policy makers suggests that the U.S. prescription drug price crisis is finally ripe for resolution.

## **II. High Drug Costs That Put Health Out of Reach Can Kill People**

The price of any good drug directly impacts the number of people who can afford it and who are willing to buy it. This basic truism, which is familiar in so many areas of the economy, applies equally to prescription drug prices.

In a society with limited resources, the higher the price of a drug, the less likely that people in need will be able to gain access to it. Two new drugs for the treatment of hepatitis C, Sovaldi<sup>®</sup> and Harvoni<sup>®</sup>, prove this point. The two drugs have virtually cured hepatitis C. But the price of treatment for Sovaldi<sup>®</sup> and Harvoni<sup>®</sup> is tens of thousands of dollars – an amount that is out of reach for most Americans.<sup>15</sup> As a result, only a select few have been able to gain access to these “miracle” drugs.<sup>16</sup> If the prices of these drugs were significantly lower, more people could afford them and thus fewer Americans would still be living with hepatitis C. Price and affordability are directly connected to access, and access to critical medicines is directly linked to the quality of one’s health and life.

Unaffordable prescription drugs also lead to the devastating phenomenon of non-adherence. According to the FDA, “the cost of a drug is a factor causing medication non-adherence – patients can’t afford to fill their prescriptions or decide to take less than the

prescribed dose to make the prescription last longer.”<sup>17</sup> According to Pharmaceutical Research and Manufacturers of America (PhRMA), a lobbying advocacy group for leading pharmaceutical and biotechnology companies, “Not taking medicines as prescribed increases health care costs and exacts a significant human toll.”<sup>18</sup>

A 2003 study showed that more than 20% of adult Medicaid enrollees reported they did not buy necessary prescription drugs because of cost.<sup>19</sup> Medicaid recipients experience the direct connection between cost and access firsthand.

The Centers for Disease Control and Prevention (CDC) estimates non-adherence is the cause of 125,000 deaths per year in the U.S., and 30% to 50% of treatment failures for chronic disease.<sup>20</sup> This highlights the impact of current policies in promoting high costs, unaffordability and diminished access, which ultimately lead to non-adherence. In a January 2011 report regarding medicine adherence, PhRMA stated:

*“Nonadherence to medicines is a major health care cost and quality problem, with numerous studies showing high rates of nonadherence directly related to poor clinical outcomes, high health care costs, and lost productivity. The cost of nonadherence has been estimated at \$100 billion to \$300 billion annually, including costs from avoidable hospitalizations, nursing home admissions, and premature deaths...”*

*Adherence is inversely proportional to the number of times a patient must take their medicine each day. The average adherence rate for treatments taken only once daily is nearly 80 percent, compared to about 50 percent for treatments that must be taken 4 times a day...*

*Other research indicates that 33 to 69 percent of medicine-related hospital admissions are caused by poor adherence, with a resulting estimated cost as high as \$100 billion a year.”<sup>18</sup>*

For policymakers, the cost and affordability of prescription drugs, including FDA-approved brand, compounded, over-the-counter and generic drugs, should be very high on their list of concerns. The FDA’s mission currently does not include any responsibility for the cost of the drugs they regulate, insulating it from the devastating effects high prescription drug prices

have on Americans.<sup>21</sup> Policymakers and regulators should focus their attention on the issues of prescription drug prices and non-adherence, and consider how market forces can be harnessed to drive competition and bring greater access and better health to all Americans.

### **III. Ineffective Policy Solutions to Date**

Following the Turing debacle with Daraprim<sup>®</sup>, a number of congressional hearings investigated and debated the issue of drug pricing. The Congress also created a task force in response to the aggressive pricing of decades-old drugs. At several of the hearings, the FDA was questioned about its lengthy approval times for generic drugs, and about the agency's backlog of more than 3,800 Abbreviated New Drug Applications (ANDAs).<sup>22</sup>

This flurry of recent activity in both the House and the Senate has taken place against the backdrop of legislation that has failed to address the FDA's role in the epidemic of runaway drug prices. When the Food and Drug Administration Safety and Innovation Act was signed into law in 2012, it was meant to reduce the FDA backlog that even then had existed for many years. The stated congressional purpose was to promote innovation, increase patient participation in FDA processes, improve the safety of the drug supply chain, and improve the agency's responses to imminent or existing drug shortages.<sup>23,24</sup> FDASIA also gave the FDA more money to speed up the review and approval time for ANDAs and eliminate the existing backlog of ANDAs.<sup>24,25</sup> Despite the extra \$1 billion in fees the FDA received from the generic drug user fee program authorized by the statute, the pace of approving generic drugs has in fact slowed. This unfortunate fact was highlighted by the Chairman of the Senate Committee on Health, Education, Labor and Pensions in a January 2016 press release.<sup>26</sup> Although the FDA has made notable progress recently in at least reducing the existing backlog of ANDAs, competition in the marketplace continues to be stifled by the large number of open applications in various stages of processing.<sup>26,27</sup>

Fewer approvals for generic drugs has resulted in less competition in the marketplace and higher prices for consumers. Physicians and healthcare industry experts recognize how the lack of competition in the generic drug market contributes to the U.S. drug pricing crisis.<sup>28,29</sup> Patients and their families continue to share heartbreaking stories of how excessive drug price increases are negatively impacting their lives.<sup>29,30</sup>

In the face of this powerful evidence of the negative impact that exorbitant drug prices are having on millions of Americans, the pharmaceutical industry is being called to account. Current and former company executives of Valeant, Retrophin Therapeutics (Retrophin), Turing,

and Mylan have been forced to provide Congress with the details behind their drug pricing tactics and practice of excessive price hikes.<sup>29,30</sup> Despite this political pressure, the industry hasn't flinched. In some cases, the defense of pushback against congressional oversight has been beyond unapologetic. Following questioning at a House Committee on Oversight and Government Reform on February 4, 2016, Martin Shkreli, former CEO of Turing, called his elected representative inquisitors "imbeciles."<sup>31</sup>

In other cases, industry has offered Congress empty promises. At a Senate Special Committee on Aging hearing titled "Valeant Pharmaceuticals' Business Model: the Repercussions for Patients and the Health Care System," held on April 27, 2016, Bill Ackman of Pershing Square Capital Management, a Valeant investor and board member, testified he proposed to Valeant to reduce the cost of Isuprel and Nitropress by 30% in order for hospitals to have access to these two drugs that had seen abrupt and massive price increases.<sup>30,32</sup> But the *New York Times* reported in May 2016 that hospitals were still waiting to receive the discounts promised by Valeant for Nitropress and Isuprel.<sup>33,34</sup>

A June 2016 investor note by Morgan Stanley analyst David Rinsinger called attention to Pfizer's 8.8% second quarter 2016 drug price hikes, which it noted came on the heels of prior sequential six-month increases of 10.4%, 8.5%, 8.8% and 7.4%.<sup>35</sup>

Despite public scolding by legislators and negative media attention, many pharmaceutical executives and their lobbyists remain adamant they will continue to increase prices to maximize profits. Between 2007 and 2015, Mylan CEO Heather Bresch raised the price of its emergency epinephrine delivery device, for which it is the sole supplier, by 461%. During the same period, her total compensation went from \$2,453,456 to \$18,931,068, a 671% increase.<sup>36</sup> On August 24, 2016, she told CNBC that Mylan will not reduce the list price for the drug because "the system incentivizes higher prices ... we're going to continue to run a business, and we're going to continue to meet the supply and demand of what's out there."<sup>37</sup>

While some have proposed that patients be allowed to end-run the U.S. regulatory system by importing drugs from Canada and other countries that maintain price controls, this approach has serious drawbacks. Obtaining pharmaceuticals outside the U.S. system as administered by the FDA under the Federal Food, Drug, and Cosmetic Act (FD&C Act)<sup>38</sup> would raise critical safety concerns. It is understandable that many patients in need of life-saving medications resort to buying cheaper drugs from black market pharmacy rings within the U.S., or to illegally importing drugs from foreign countries.<sup>39</sup> But maintaining the very U.S. policies that

are responsible for the current dysfunctional system of drug price gouging, inaccessibility and shortages which also allow some people to work around the system is hardly a solution to the problem.

Manifestly, legislation currently on the books has not provided a solution to our nation's drug pricing, shortage, and accessibility problems. FDASIA was enacted, in part, to help relieve our country's current drug shortage challenge.<sup>23</sup> The Drug Quality and Security Act (DQSA) of 2013 was signed into law the following year to further respond to this challenge as well as to increase drug safety.<sup>40</sup> The DQSA sought to relieve the growing drug shortage problem by clarifying FDA regulation of state-licensed compounding pharmacies under Section 503A and allowing pharmacies to register with the FDA as "outsourcing facilities" that can compound drugs including those on the FDA drug shortage list.<sup>40</sup> While these enactments may hold the potential to mitigate the drug pricing crisis, existing administration and enforcement of these laws has produced little in the way of positive results.

An article in the May 2016 issue of *Health Affairs*, a well-respected health policy journal, reports on studies of drug shortages for both acute and non-acute care drugs, pre-and post-passage of DQSA and FDASIA.<sup>12</sup> The article observes that the drug shortage challenge has not abated in spite of the passage of these two laws. For non-acute care drugs, there has been a minimal abatement of drug shortages. Most alarmingly, the article reports, for acute care drugs the number of drug shortages and the length of time these shortages have existed has increased significantly. FDASIA, despite generating increased fees for the FDA from industry through user fee programs, has not had any positive effect on access or pricing.<sup>41</sup>

The most significant of the reasons the DQSA has not been successful to date is that there has been little participation in the new Section 503B outsourcing facility program established by the law. Thus far, the FDA's interpretive guidance has authorized only a very narrow formulary of drugs to be made in an outsourcing facility under Section 503B. As a result of this restrictive guidance, less than 1% of those eligible to register with the FDA under Section 503B have done so.<sup>42</sup>

A less restrictive approach to administering the DQSA could bring a greater portion of pharmaceutical compounding into the regulatory fold, allowing the FDA to ensure greater safety for all patients who rely on safe compounded drugs.<sup>43</sup> The FDA is undoubtedly aware of the crisis of sky-high prices for drugs that lack any meaningful competition in the marketplace, but it has shown little interest in addressing it. There are readily available opportunities for the FDA to

authorize competition for decades-old off-patent drugs that are currently offered only by monopoly providers.<sup>44</sup> Currently, because these drugs are not on the FDA's shortage list, even FDA-registered 503B outsourcing facilities may not compound them. For all drugs not on the shortage list, the FDA requires that the compounded version be chemically different from the commercially available drug.<sup>45</sup> This policy of protecting markets for old off-patent drugs only further insulates the monopoly providers from competition.

This is a tragic irony since the DQSA was intended in part to alleviate the drug shortage problem. There is an opportunity for outsourcing facilities to generate needed competition for finished dosage form drugs that have been subject to massive price spikes. Such drugs have effectively become commercially unavailable to millions of patients over the past decade.<sup>46</sup> Yet as the FDA's Janet Woodcock testified before Congress in February 2016, approximately 12% of branded drugs susceptible to having a generic alternative do not, and likely will not, experience competition from such an alternative. This would remain true even if the entire backlog of generic drug applications now before the FDA were eliminated.<sup>47</sup> As a result, as Dr. Woodcock warned, "there will still be problems with drugs that don't have generic competition."

The FDA's slow pace of approval for generic medications contributes significantly to the lack of competition in the pharmaceutical marketplace.<sup>48</sup> FDA Performance Reports to Congress for the Generic Drug User Fee Amendments show that out of the 1,598 new ANDAs submitted in 2014, not a single one was approved.<sup>49</sup> Following a similar trend, only one ANDA out of the 522 original ANDAs submitted in 2015 was approved.<sup>50</sup>

The FDA claimed in March 2016 to have begun prioritizing generic drug ANDA submissions for which there are currently only one existing manufacturer to increase market competition.<sup>51</sup> Unfortunately, the data show that ANDA rejection rates via complete response letters (CRLs) are increasing at a much greater pace than ever.<sup>52</sup> During the fiscal year ending June 16, 2016, with four months left to report, the FDA had already denied approval for 1,030 ANDAs. More than one-third of these denials occurred in late March through June.<sup>53</sup> This escalating trend highlights a noticeable increase in denials from the previous fiscal year. In fiscal 2015, there were a total of 1180 CRLs issued in the entire 12-month period.

Further evidence of the increased rate of denials of generic drug ANDA submissions comes from the most recent data. For the month ending April 16, 2016, the FDA rejected 190 ANDAs – the highest number since fiscal 2013. Those 190 rejections represent a 30% increase over the previous month, when the FDA rejected 147 ANDAs.<sup>52</sup>

The sluggish FDA approval process for generic drugs, in combination with the increased rate of ANDA rejections for generics, is stifling competition in the pharmaceutical marketplace.<sup>52</sup>

Drug compounding in FDA-registered 503B outsourcing facilities can help to alleviate this lack of competition, if the FDA is willing.<sup>54</sup> To address the drug price crisis faced by millions of patients experiencing ever-increasing out-of-pocket expenses, the FDA should amend the definition of “drug shortage” to expressly recognize that economic factors — that is, high prices that put prescription drugs out of reach for ordinary Americans — are effectively creating shortages that are every bit as real as those caused by lack of supply. In addition, the FDA should allow patients access to more generic alternatives, and to compounded drugs made under its current good manufacturing practice (cGMP) standards. These steps will ultimately benefit everyone who relies upon our healthcare system.<sup>46</sup>

#### **IV. Introduction to Compounding**

Pharmaceutical compounding was the original art of making medicine. Historically, most prescriptions were compounded medications and compounding pharmacies existed long before the development of the regulated and complex pharmaceutical industry present today.<sup>55</sup> In fact, well-known pharma companies including Merck, Ely Lilly, Warner-Lambert, and GlaxoSmithKline were founded by compounding pharmacists, and began operations as compounding pharmacies.<sup>56</sup>

Traditionally, prescription medications were produced as compounded formulations by physicians themselves who mixed the medicines they prescribed for their patients.<sup>55</sup> It was not until the late 19<sup>th</sup> century that the roles of doctor and pharmacist were distinguished.<sup>57</sup> In the 1950s and early 1960s, as drugs began to be mass produced, pharmacists began simply to dispense manufactured drugs rather than compound their own formulations.<sup>58</sup>

In the 21st century, modern pharmaceutical compounding is focused on the customized preparation of medicines that are not otherwise commercially available.<sup>59</sup> Compounded medications are made using FDA-approved drugs. The compounding pharmacy typically combines the FDA-approved drugs, changes the dosage or administration method, or modifies their composition in other ways. For example, the compounding pharmacy could remove binding agents due to a patient’s allergies, or combine several drugs to help reduce the number of administrations. Compounding can be used to modify the drug delivery method to create a cream, liquid, or other form – or to add flavoring to make the drug more palatable.<sup>60</sup>

Compounded medications are prescribed by physicians to meet the specific needs of individual patients.<sup>61</sup> In the modern regulatory environment, prescribing a compounded medication comprised of one or more FDA-approved drugs is equivalent to prescribing an FDA-approved drug for “off-label” use – that is, for an application not specifically approved by the FDA. Off-label use of FDA-approved medications, like drug compounding, is commonplace. Physicians routinely prescribe compounded medications or drugs for off-label uses because they believe them to be the best medical options for their patients.<sup>62</sup>

The compounding industry is regulated at both the federal and state levels.<sup>63,64</sup> At the federal level, regulation within the FD&C Act governs the preparation, handling, storage, marketing and distribution of pharmaceutical products.<sup>65,66</sup> In recent years, the FDA has dramatically stepped up its inspection of compounding pharmacies, particularly those involved in higher-risk sterile compounding.<sup>67</sup> State Boards of Pharmacy regulate compounding pharmacy operations as well. These regulations cover compounding processes, safety protocols, purity, sterility, storage, controlled substances, record-keeping and mandates regular facility inspections, among other requirements.<sup>68</sup> In addition, they generally include licensing requirements for pharmacists, pharmacy technicians, and pharmacies. Failure to comply with state regulations can result in a pharmacy being prohibited from operating in that state, financial penalties, and/or additional oversight from the state’s board of pharmacy.<sup>67</sup> Standards set by the United States Pharmacopeia (USP) are mandated by law in most states and integrated into a pharmacy’s daily practices.<sup>69</sup>

Compounded drugs as finished dosages that include FDA-approved ingredients are federally and state regulated and inspected at every step in the supply chain. Beyond federal and state regulation, many compounding pharmacies are members of non-profit industry agencies that require adherence to additional quality guidelines.<sup>62</sup>

The important role that pharmaceutical compounding plays in today’s healthcare system is well-recognized by Congress, the U.S. Supreme Court, the FDA and other healthcare associations. According to *IBISWorld*, an estimated 4,100 compounding pharmacies in the U.S. generated \$8 billion in revenue in 2015.<sup>70</sup> Of the estimated 3.6 billion prescriptions dispensed annually in the U.S., approximately 35 million are for compounded medications.<sup>43</sup> Compounded drug spending represents between 1% and 3% of the \$457 billion prescription drug market, accounting for up to \$13 billion annually.<sup>64,71</sup>

For many years, scientists and physicians have extolled the potential of personalized medicine.<sup>72</sup> In the not-too-distant future, prescription drugs will be tailor-made for an individual patient or for groups of people with specific clinical needs. Today, pharmaceutical compounding is at the forefront of this movement toward personalized medicine. Patients are prescribed compounded drugs for their individual needs, rather than receiving “one size fits all” fixed-dose and mass produced drugs.

For the benefits of personalized medicine to be fully realized, a reasonable and consistent regulatory framework is needed that embraces and drives innovation. The beginnings of such a framework exist today in the regulatory approach to compounded drugs. With compounding, FDA-approved drugs can be offered in new or different dosage forms, various formats, and in combination with other active pharmaceutical ingredients (APIs). Policymakers and industry participants alike should consider how the long-term objectives of current drug policy can be adjusted to encourage the further development of personalized medicine in ways that will benefit Americans and the healthcare system overall.

In the healthcare system as it exists today, compounding is indispensable to physicians, and an absolute requirement for the millions of patients whose unique health needs make them dependent on individualized medications.<sup>43</sup> Additionally, compounded alternatives are crucial during a drug shortage – or when FDA-approved retail drugs are discontinued.<sup>10</sup> Key buyers of compounded drugs include primary care doctors, specialists, emergency and other outpatient care centers, hospitals, and individual patients.<sup>43</sup> Most intravenous drugs given in hospitals and clinics are compounded medications. Virtually every hospital compounds medications.<sup>64</sup>

While compounded drugs are produced from the same FDA-approved active ingredients used in FDA-approved branded pharmaceuticals, they are normally considerably less expensive than the proprietary brands. So long as compounded drugs use FDA-approved ingredients, further FDA approvals are not required, so that a compounded drug is often less expensive than even a generic. The lower cost of compounded drugs, combined with their ability to meet the individual needs of each patient, make them a particularly attractive choice when the only alternative is a drug that historically has had no competition and is excessively priced.

In order to offer a legitimate alternative for high-priced drugs and for drugs in short supply, compounding needs to be executed safely. Safe compounding can provide the American public increased competition and choice, lower costs, greater access and reduced non-adherence.

As noted, recent FDA guidance has interpreted the DQSA very narrowly, limiting the role compounding can play in solving the drug pricing crisis and improving patient health. This FDA action coincides with intense pressure from the pharmaceutical industry. Other voices, however, are also being heard. The American Academy of Ophthalmology (AAO), the world's largest association of eye physicians and surgeons, formally commented on proposed FDA guidance towards compounded medications and took a strong public stand in support of compounding and access to critical drugs. Explaining the importance of physician and patient access to safe compounded drugs, AAO stated in part:

*"We are concerned about the potential adverse impact on patient care that will come with requiring patient specific prescriptions for compounded drugs from 503A facilities if outsourcing facilities are unable to meet all practitioner needs for office-use drugs. With ophthalmology relying heavily on compounded drugs to treat our patients, timely access to critical treatments is extremely important. Many times these drugs are used to treat urgent and emergent conditions and delays in treatment could cause significant and irreparable harm to the patient. Thus, having a supply of these treatments readily available for caring for these patients is essential. ...*

*Proposed policy does nothing to address potential access issues to rarely utilized but nonetheless essential treatments. For these drugs, physicians need avenues of immediate access to meet urgent care needs. In a scenario where an ophthalmologist is caring for a new patient facing an urgent condition, the delays involved in accessing treatments from 503A facilities with a patient specific prescription could cost them their sight. ...*

*We believe that the proposed restriction could prevent the timely access to critical compounded treatments, which could lead to adverse outcomes, including blindness or significant loss of sight. This is especially true for patients facing urgent need of care, as a delay of even a few hours could cost them their sight."<sup>73</sup>*

The July 2016 AAO comment letter to the FDA makes it clear that without access to safe compounded drugs, the healthcare of millions of Americans will be negatively affected.<sup>73</sup>

Despite the tenor of its recent guidance, the FDA's policies toward compounding and the cost savings to patients offered by compounded drugs have not always been unfavorable. In the past, when massive price increases for critical medicines have threatened patient access, the FDA has taken action to protect drug access. This fact was highlighted by U.S. Rep. Earl "Buddy" Carter, himself a licensed pharmacist, at a House Oversight and Government Reform Committee hearing on drug prices in February 2016, at which the principal witness was Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research (CDER).<sup>74</sup>

One particularly notable example of the FDA's past willingness to rely on compounded drugs to ensure continued patient access in the face of exorbitant pricing was discussed at this hearing. When the owner of Makena<sup>®</sup>, a drug administered by OB-GYNs for women at risk for pre-term birth, announced its plans to increase the price from \$15 to \$1,500 per dose, there was outrage among both patients and physicians.<sup>75</sup> The American College of Obstetricians and Gynecologists (ACOG) sharply criticized the move, stating that "the extremely high cost of Makena<sup>®</sup> will hinder access and affordability to this treatment for both insured and uninsured patients."<sup>76</sup>

The FDA responded by announcing that compounding pharmacies could continue to produce 17 $\alpha$ -hydroxyprogesterone, the very drug (branded as Makena<sup>®</sup>) for which the FDA had just granted KV Pharmaceutical Corporation (KV) and its subsidiary Ther-Rx exclusive market control. This FDA action made the drug available to pregnant women at a cost of \$10 - \$20 per dose.<sup>77</sup>

The only limitation on the FDA's embrace of the compounded alternative was that it be produced in a safe manner, of standard quality, and compounded in accordance with appropriate standards for sterile products.<sup>75</sup> The FDA's action was particularly striking because KV's new drug application with the FDA under the Federal Orphan Drug Act had been granted just weeks before it announced the price increase.<sup>78</sup> The FDA's decision to approve Makena<sup>®</sup> as an orphan drug on February 4, 2011, had given KV seven years of market protection for this critical medication. When in March 2011 the FDA decided to allow patients and physicians access to Makena<sup>®</sup>'s compounded alternative, it effectively negated the right it had granted to KV only weeks before. The intended effect of the agency's action, of course, was to protect the

rights of patients to affordable medicine by letting them choose a lower cost compounded alternative.

The FDA's action not only gave pregnant women a lower-cost alternative to Makena<sup>®</sup>, but it also had a salutary effect on the pricing of the branded drug. On April 1, 2011, KV announced that it would drop the price of Makena<sup>®</sup> by 55%. Given the magnitude of the initial price hike, however, cutting the price by more than half did little to appease the physician community. The ACOG stated in a press release:

*“Although this may seem like a relatively significant price reduction, unfortunately it remains a woefully inadequate response ... [We] will continue to collaborate to ensure that this medication is accessible and affordable to every pregnant woman who needs it.”<sup>76</sup>*

ACOG was joined in its condemnation of KV's pricing policy by a host of other physician and medical groups, including the Society for Maternal-Fetal Medicine, the American Academy of Pediatrics, the American College of Osteopathic Obstetricians & Gynecologists, the National Medical Association, the American Academy of Family Physicians, the American College of Nurse-Midwives, and the Association of Women's Health and Obstetric and Neonatal Nurses.

While the Makena<sup>®</sup> example is a case study of how compounding can stimulate price competition for high-priced drugs and protect patient access to much-needed pharmaceuticals, it is also a study in the FDA's inconstant policy toward compounded drugs. In the wake of the agency's decision to allow compounded 17 $\alpha$ -hydroxyprogesterone to compete with Makena<sup>®</sup>, patients and their physicians were highly satisfied with this lower cost, safe alternative. The pharmaceutical industry responded by lobbying the FDA to respect its original decision granting a monopoly to KV, raising questions about the production standards of compounding pharmacies.<sup>79,80</sup> Under pressure, the FDA relented.

The immediate beneficiaries of the FDA's reversal were industry participants KV and AMAG Pharmaceuticals, Makena<sup>®</sup>'s current owner. AMAG reported record sales revenue for Makena<sup>®</sup> of over \$78 million for the second quarter of 2016.<sup>81</sup> As of August 1, 2016, the price of Makena<sup>®</sup> was \$779 per dose.<sup>82</sup>

In retrospect, the Makena<sup>®</sup> case is another example of a drug initially made as a compounded drug whose price skyrocketed once it went through the FDA approval process. It

shows how a compounded alternative can keep runaway prices for monopoly drugs in check. And it illustrates how the FDA's on-again, off-again, embrace of compounding has failed to tap the full potential of compounding to help lower prescription drug prices. The FDA should revisit its prior policy of allowing safe, cGMP compounding of the lower-cost alternative to Makena®; it should also exploit opportunities to provide choice, competition and prescription customization in similar situations.

There are myriad examples of such opportunities to ensure safe access to compounded drugs, in the process saving patients and the health care system billions of dollars each year.

Wet age-related macular degeneration (wet AMD) is a severe, chronic eye disease that causes blurred vision or a blind spot in one's visual field. To treat wet AMD, compounded or repackaged Avastin® (bevacizumab) used off-label at \$50 per dose has been shown to be equivalent to FDA-approved Lucentis® and Eylea® at approximately \$2,000 per dose.<sup>83</sup> AAO states that "all three are safe and effective treatments for wet AMD."<sup>84</sup> A study conducted in 2012 by the Office of the Inspector General for the United States Department of Health and Human Services (HHS) cited in a December 2014 *New York Times* article stated that if patients being treated with Lucentis® were instead given Avastin® during 2011, the federal government would have saved about \$1.4 billion.<sup>85</sup>

According to J. Gregory Rosenthal, a retina specialist in Toledo quoted in the same article: "They keep talking about evidence-based medicine, and they keep pretending the corporate-sponsored research is nonbiased. The evidence says that Avastin® has at least the clinical efficacy of Lucentis® and is perhaps safer."<sup>85</sup>

Presently, however, FDA draft guidance will significantly restrict access to compounded Avastin®. This would include compounded versions made in FDA-regulated outsourcing facilities following cGMP requirements. One should question why the FDA would restrict physician access to a safe and effective treatment for wet AMD that costs patients \$1,950 less per dose. Ned S. Braunstein, MD, Senior Vice President and Head of Regulatory Affairs at Regeneron Pharmaceuticals Inc., the manufacturer of \$2,000-per-dose Eylea®, served as an "industry member" of FDA's Pharmacy Compounding Advisory Committee (PCAC) which recommended the FDA guidance against the use of a compounded alternative that would compete with Eylea®.<sup>86</sup> The FDA should be wary of such striking conflicts of interest. In this case, it should allow cGMP compounding of Avastin® in order to better serve patients and realize the billions of dollars in annual Medicare savings this decision would produce.

Medication used in eye surgery provides another example. Patients undergoing surgery for glaucoma, as well as refractive and corneal surgery patients, rely on a critical medicine called mitomycin. This is an antifibrotic agent used to minimize scarring in the eye. As an off-patent, compounded drug, it was safely and affordably available for decades at \$30 per dose. In 2012, however, based on a new drug application (NDA) with the FDA filed by Mobius Therapeutics LLC, the FDA approved a branded version of mitomycin called Mitosol<sup>®</sup>. Mobius now charges \$359 per kit for Mitosol<sup>®</sup>.<sup>87</sup>

In a press release following FDA approval of his NDA for Mitosol<sup>®</sup>, Ed Timm, CEO of Mobius, stated: “We know all payors look to Medicare’s expertise, and we expect to continue to see broad coverage of Mitosol<sup>®</sup>. We applaud CMS in assuring existing and new Mitosol<sup>®</sup> patients and providers economic security.”<sup>88</sup> One can imagine that like KV, Mobius and its shareholders are elated that Medicare is willing to transfer funds from the public treasury to their corporate coffers through an FDA policy that has taken the lower-cost compounded version of mitomycin off the market, now that Mobius’s “new” drug application has been approved.

Mitomycin is yet another example of an off-patent drug that could be safely made in accordance with cGMP standards in compounding pharmacies and FDA-regulated outsourcing facilities. Since mitomycin prescribed in connection with glaucoma and corneal surgery is paid for by Medicare, the use of the compounded version would also save taxpayers tens of millions of dollars each year.

The current opioid crisis in America provides yet another example highlighting the importance of access to safe compounded medications. A July 2016 *Los Angeles Times* article reported that in 2014, more than 47,000 Americans died from drug overdoses in 2014. Almost 60% of these overdoses were from opioids, including FDA-approved prescription painkillers.<sup>89</sup> One of the critical remedies used in an emergency to treat and reverse effects of opioid overdose is naloxone, an inexpensive compounded drug that was made safely available for many years. Because naloxone works in minutes, it can be a lifesaver.

Notwithstanding that naloxone had long been available as a compounded drug at low cost, the FDA granted market protection to a small number of companies that paid the various FDA fees and successfully gained FDA approval. This effectively took compounded naloxone off the market.

Since this handful of companies gained a shared monopoly over naloxone, demand for the drug has risen dramatically – not because of their marketing efforts or any improvement in

the drug, but as a direct result of the growing number of deaths caused by opioid overdoses. Currently, it is estimated that 130 people per day in the U.S. die from opioid overdose.<sup>90</sup> The FDA rights owners for this formerly low cost compounded drug have taken advantage of the increased need and demand, raising the price of a single dose almost twenty-fold in the last decade.<sup>91</sup> In 2016, Kaléo Pharmaceutical Co., which makes the auto-injector version of the drug, increased the price for a two-pack of the injectors to \$4,500 from the previous \$690.<sup>90</sup>

Americans suffering from opioid addiction and the first responder agencies that often treat them, should not be made to suffer further from federal prescription drug policy that needlessly protects high-priced drugs from competition. Taxpayers who foot the bill for first responders and emergency rooms that use naloxone deserve more affordable access to this emergency remedy. For the benefit of patients and the healthcare system alike, the FDA should permit naloxone to be compounded under cGMP standards in either a compounding pharmacy or an FDA-regulated outsourcing facility.

Yet another drug used in life-threatening situations, and which has seen huge price increases, is epinephrine. Epinephrine is used most commonly to reverse the effects of severe serious reactions, such as anaphylaxis, cardiac arrest, superficial bleeding, and even asthma.<sup>92</sup> For those in anaphylactic shock from a bee sting or from a reaction to some element in nature, access to epinephrine is the difference between life and death.

Epinephrine is inexpensive to produce. The drug is commonly compounded in various finished dosages. It also happens to be on the FDA's drug shortage list.

Epinephrine is the sole active pharmaceutical ingredient in the Epi-Pen<sup>®</sup>, a quick acting syringe "pen" which is exclusively marketed by Mylan N.V., a Netherlands-based global pharmaceutical company. Since Mylan's EpiPen<sup>®</sup> lacks competition, the company has raised the price over 450% since 2004. The price for a pack of two Epi-Pens<sup>®</sup> is now is over \$600, and some buyers such as emergency medical services pay upwards of \$900. Over 3.6 million prescriptions for its injectable version of the drug were written in 2015.<sup>93</sup> At its current sales rate of \$175 million per month, this low-cost drug is generating \$2.1 billion per year in revenue.

Were compounded epinephrine, customized for the individual patients' needs, to be made available in competitive auto-injector form, would the FDA allow access to this lower-cost prescription option for a life-saving drug? Policymakers may soon find out; Imprimis has patents pending on a freeze-dried form of epinephrine which could be offered with a delivery system functionally similar to the Epi-Pen<sup>®</sup>. The company is also planning to repackage, and offer for

physician prescription, FDA-approved epinephrine with commercially available auto-injectors to serve patients in need of an alternative to the EpiPen®.

## **V. Increased Regulation of Compounding to Reduce Risk, and Other Reform Measures**

While drug compounding has made important and unique contributions to the U.S. healthcare system over a period of many decades, the industry encompasses a wide variety of participants. In addition to sophisticated companies whose facilities are regulated and inspected by the FDA as well as by state boards of pharmacy, there are a number of smaller operations that exist outside the FDA's regulatory framework and largely beyond the reach of regular federal and state inspections. In recent years, therefore, Congress has enacted laws that significantly strengthen the regulatory framework governing pharmaceutical compounding.

In 2012, one such small operation, the New England Compounding Center (NECC) -- a family-run business in Framingham, Massachusetts -- was found to have violated both federal and state law by producing drugs in unsafe and unsanitary conditions.<sup>94</sup> The illegal acts of NECC led to a fungal meningitis outbreak linked to the deaths of 64 people.<sup>95</sup> As the company went bankrupt and its principals were prosecuted, the reaction in Congress was swift. Remedial legislation, titled the "Drug Quality and Security Act," was introduced in September and signed into law on November 27, 2013.<sup>40</sup> The new law, which received widespread support from Republicans and Democrats in both the House and Senate, made significant amendments to the FD&C Act and the regulation of compounding.<sup>96</sup>

As enacted, the DQSA clarifies and strengthens the federal regulatory framework governing compounding pharmacies. It was designed to provide safeguards to make compounded medications safer for patients. The Act also gives the FDA broad powers to regulate the pharmaceutical compounding industry, and to improve communications between the FDA and state pharmacy boards.

Of special importance is the law's addition of a new Section 503B to the FD&C Act, which establishes a new, highly-regulated form of entity for the formulation of compounded drugs called an outsourcing facility. Registration as an outsourcing facility is voluntary, and requires that both the facility and the products it compounds be registered with, and regularly inspected by, the FDA.<sup>54</sup> Specifically, outsourcing facilities are subject to cGMP standards and regular FDA inspection, among other requirements.<sup>97</sup>

An outsourcing facility is permitted to compound large quantities of drug formulations in advance of receiving a prescription for an individual patient, thus allowing the practice known as anticipatory compounding. If a compounded drug's ingredients appear on the FDA's drug shortage list or the bulk substances list established by the FDA, outsourcing facilities are also permitted to distribute it nationally.

Other provisions of the DQSA deal specifically with pharmacies. Under Section 503A, a licensed pharmacist must compound a drug for an identified individual patient. The compounding must be pursuant to a valid prescription. Pharmacies may only compound in limited quantities before receipt of a prescription for an individual patient, and are subject to strict limits on anticipatory compounding for distribution, generally based on historical prescription volumes.<sup>97</sup> A pharmacy may distribute a compounded drug interstate only to other states where the pharmacy has a license. Pharmacies that conform to these requirements may be exempt from the provisions of the FD&C Act requiring cGMP compliance, adequate directions for use on labels, and FDA approval before marketing.

Immediately after the 2013 enactment of the DQSA, the prospects for robust implementation of Section 503B, establishing the new category of highly-regulated outsourcing facilities, seemed bright. Former FDA Commissioner Margaret A. Hamburg wrote open letters to "Hospital Purchasers" and state officials – including governors, state boards of pharmacy and health departments – urging them to require the purchase of compounded drugs only from 503B outsourcing facilities. She specifically stated in these letters that compounded drug formulations created in outsourcing facilities are safer because they are subject to cGMP standards, FDA inspections and greater federal oversight.<sup>98,99</sup>

But such high hopes were dashed when the current FDA guidance and policies were announced, discouraging the establishment of 503B outsourcing facilities. Ironically, the FDA's stance is having the effect of encouraging sterile compounding in pharmacies that are overwhelmingly not inspected by the FDA and that do not abide by cGMP requirements.<sup>46</sup> As of June 17, 2016, there were 61 compounding pharmacies registered as 503B facilities<sup>42</sup>, a mere 1% of the total number of compounding pharmacies in the U.S.<sup>43</sup>

Imprimis owns facilities that operate under both Sections 503A<sup>100</sup> and 503B<sup>54</sup> of the FD&C Act. We understand the differences in quality systems and processes required under Title 21 of the Code of Federal Regulations (CFR), parts 210<sup>65</sup> and 211<sup>66</sup>, in addition to USP <797>. We recognize that patient care and access to necessary medications are likely to be

negatively affected by the current FDA guidance and policies, and recommend that the FDA revise their final “interim policy” for sections 503A and 503B.<sup>101</sup> Our specific recommendations are outlined in Section VIII of this monograph, “Proposals for Future Action.”

Encouraging more compounding pharmacies to register as outsourcing facilities and to submit to cGMP production – or to other more rigorous standards safer than those described under the USP – will increase overall drug quality and patient safety and better achieve the objectives cited by the FDA.<sup>102,103</sup>

In addition to more stringent regulation of compounding and legislative protections for the security of the drug supply chain, other legislative and regulatory reforms are underway. Pricing reform, in particular, is a priority within the Centers for Medicare and Medicaid Services (CMS). At a June 2016 Senate Finance Committee hearing, CMS announced plans to initiate a pilot program to evaluate revisions to drug payments under Medicare Part B. The purpose of the revisions is to eliminate current financial incentives to prescribe more expensive drugs instead of their lower-cost equivalents.<sup>104</sup> Currently, Medicare Part B pays physicians and hospital outpatient departments the average sales price of a drug plus 6%. Under the pilot program, physicians will be paid the drug’s average sales price, together with a lower add-on fee of 2.5% and an estimated flat fee of \$16.80.<sup>105</sup>

Such reimbursement reform is sorely needed. As CMS has noted, the current Medicare Part B drug payment methodology can penalize doctors for selecting lower-cost drugs, even when these drugs are as good or better for patients based on the evidence.<sup>105</sup> As a result of the financial penalty for prescribing the most competitively priced drugs, physicians rarely choose an equivalent lower-cost compounded alternative for their patients. A doctor being paid 6% on top of reimbursement of the actual cost of a drug has a powerful incentive to prescribe, for example, the \$2,000 Lucentis<sup>®</sup> instead of \$50 Avastin, despite their generally accepted equivalency.<sup>106</sup>

CMS should revise Medicare reimbursement policy to remove disincentives to prescribe the lower cost option. Future policy should be designed in a way that allows more economical high-quality options for patients. This will not only save Medicare and the healthcare system money, but will also put a greater share of drug reimbursement in the hands of those who actually perform healthcare services.

The Medicare Prescription Drug Price Negotiation Act, The Medicare Prescription Drug Savings and Choice Act and The Medicare Drug Savings Act were first introduced during the

113<sup>th</sup> Congress (2013-14) and reintroduced in the 114<sup>th</sup> Congress (2015-17). Together, these bills would authorize CMS to negotiate directly with pharmaceutical companies on behalf of the Medicare system, and require those companies to provide rebates to low-income Medicare beneficiaries.<sup>107</sup> Were these bills – the collective purpose of which is to reduce prescription drug prices – to become law, Medicare would in principle be incented to buy the best medicines at the lowest cost. While this is the intent of the proposed legislation, it is not clear whether CMS would in fact choose compounded alternatives made from FDA-approved bulk drug ingredients, when these provide the lowest-cost medicines at equivalent high quality. Current Medicare policy does not allow or support this. For this reason, any legislation authorizing Medicare to negotiate lower prices for prescription drugs should specify that CMS shall consider both FDA-approved drugs and safe compounded alternatives. The opportunity this would present for lowering Medicare drug costs is massive.

In 2015, the comprehensive Medicare Access and CHIP Reauthorization Act (MACRA) was signed into law.<sup>108</sup> This legislation, supported by a bipartisan majority and the majority of stakeholders in the healthcare and patient communities, ties CMS payments to physicians and other clinicians under Medicare directly to the cost and quality of patient care. Proposed rules under the law were announced in April 2016, representing the first step in the implementation of MACRA.

MACRA established the Quality Payment Program (QPP), which includes two tracks. The Merit-Based Incentive Payment System (MIPS) calibrates Medicare reimbursement to the delivery of high quality and value-driven patient care measures. Healthcare providers are evaluated according to cost, quality, clinical improvement and advancing care, and the payments they receive from Medicare are based on their results. The Alternative Payment Models (APMs) provide new ways for Medicare to pay health care providers, including lump-sum incentive payments and other financial bonuses. Physicians who qualify to participate under an APM could be exempt from MIPS reporting requirements. Because of the extensive qualification requirements for a health care provider to qualify for payment under an APM, CMS estimates that only 30,000 to 90,000 clinicians will be on the APM track. In contrast, CMS expects 687,000 to 746,000 physicians to be on the MIPS track.<sup>110</sup> In combination, the two tracks that comprise QPP are intended to streamline the number of Medicare payment programs into a new, flexible framework.<sup>110</sup>

MACRA's focus on cost and quality offers significant reason for CMS and healthcare providers to include safe compounded drugs in the mix of options from which they may select.

While CMS has estimated that the law's tying of payments to cost and quality "would have no net effect on overall payments," because positive or negative performance adjustments would be offsetting in the aggregate, the significant performance incentives for physicians have the power to change behavior significantly.<sup>111</sup> If CMS implements MACRA in a way that fairly reimburses physicians who prescribe safe compounded drugs, the law's incentive system will ensure substantial savings for Medicare and the entire healthcare system.

In June 2016, the U.S. House of Representatives majority leadership issued its long-awaited "A Better Way" plan for healthcare reform.<sup>112,113</sup> The document cites NIH Director Francis Collins' testimony that it currently takes about 14 years and \$2 billion or more to get a new drug to market. Notwithstanding this remarkably high cost in time and money, according to Director Collins, "more than 95% of drugs fail during development." The House plan proposes a number of means to cut through the red tape at the FDA, including using biomarkers to streamline the drug approval process.

Whether future legislative enactments will be more fruitful than past efforts at addressing the U.S. prescription drug crisis remains to be seen. Thus far in the 114<sup>th</sup> Congress (2015-17), more than 400 bills focused on improvements to the U.S. healthcare system have been introduced.<sup>112</sup>

## **VI. Regulatory and Commercial Impediments to Compounding**

The availability of safe drug compounding threatens the current pharmaceutical ecosystem in which drug companies enjoy profit windfalls protected from competition by an antiquated regulatory system. Given the billions of dollars at stake, powerful forces are hard at work to maintain the status quo.

With most of its regulated branded and generic drug company community in agreement that competition from compounding must be prevented, the FDA frequently puts the entire compounding industry in a dim light by reprising the NECC tragedy. In contrast, the FDA rarely highlights the tragedies that occur weekly as a result of deaths from FDA-approved drugs.<sup>114</sup> Yet it is a fact that FDA-registered drug manufacturers found to have safety issues and unsanitary conditions make the news regularly.<sup>115</sup> As outlined in this monograph, the answer to this challenge is that both manufactured FDA-approved drugs and compounded drugs can and should be held to the same cGMP or other similar appropriate standards.

The well-organized and well-funded campaign to minimize Americans' access to lower-cost, safe compounded drugs takes advantage of the deficiencies of the current drug regulatory system to achieve market dominance and insulation from competition. The roadblocks thus erected for compounding include regulatory as well as commercial restraints on competition. The following are some of the impediments that prevent Imprimis from fulfilling its vision to deliver customized and other novel medicines to physicians and patients at accessible prices.<sup>116</sup>

#### **A. Impediment: 503A and 503B Restrictions**

The DQSA opened tremendous possibilities for incentivizing greater use of compounded drugs made under a cGMP process. The reality thus far is that the exact opposite is happening. The FDA's approach, manifested through numerous draft guidance documents, has strictly limited what drugs can be made in an FDA-registered, FDA-inspected Section 503B outsourcing facility compliant with cGMP. As a result, more compounding, and in particular more sterile compounding, is being done outside the FDA's regulatory oversight in traditional state-regulated compounding pharmacies according to USP <795> and <797> standards.<sup>117,118</sup> This approach does not take advantage of the opportunity to move more compounding into a cGMP environment. Instead, it protects the pharmaceutical industry from competition and keeps prices for many drugs high, limiting patient access, and ultimately increasing non-adherence. The following is an itemization of the specific problems with the current regulatory approach to the DQSA:

##### *Overly restrictive 503B bulk substance "positive" list.*

First, FDA has issued guidance concerning which FDA-approved bulk drug substances (the "building blocks" used in compounding) may be compounded at Section 503B outsourcing facilities.<sup>119</sup> This guidance limits significantly the types of substances — and thus the types of compounded medications — that a Section 503B facility may compound.<sup>120</sup> By severely limiting what can be compounded in a 503B facility, the FDA is pushing more compounding to 503A facilities that do not have such restrictions.<sup>46</sup>

Second, FDA's draft Section 503B bulk list of substances that may be compounded in an outsourcing facility includes several drug components already found in FDA-approved drugs.<sup>121</sup> This confuses rather than clarifies what an outsourcing facility may do, since other FDA guidelines prohibit 503B facilities from producing a drug that is "essentially a copy of one or more approved drugs." The FDA defines "essentially a copy" to include any drug containing an active pharmaceutical ingredient (API) used in an approved or marketed drug, unless the

compounded drug produces clinical differences for an individual patient.<sup>122</sup> This limitation does not appear in the statute, and has been created out of whole cloth by the agency. It defeats the intent of the DQSA to allow outsourcing facilities to compound marketed drugs experiencing a shortage without individual prescriptions.<sup>45</sup>

In July 2016, the FDA issued further draft guidance for 503A and 503B facilities that adds to its definition of “essentially a copy.” The definition now includes a compounded drug that has the same API, excipients, dosage form and strength, and route of administration as a commercially available or FDA-approved drug.<sup>123-125</sup> Under this latest guidance, each facility is required to document the relevant change to the already-available commercial or approved drug which produces a clinical difference for any given prescription.<sup>126</sup> The FDA considers oral medications essentially a copy if they are within 10% of the dosage strength of a drug that is already on the market, unless there is a clinical difference for an individual patient.<sup>125</sup>

This extra-statutory approach is directly at odds with the idea of compounding drugs in FDA-regulated and inspected 503B outsourcing facilities, according to cGMP standards, to offer an alternative to drugs that command a monopoly price. In their guidance for 503B outsourcing facilities, the FDA explicitly stated: “Other factors such as a lower price are not sufficient to establish that the compounded product is not essentially a copy of the approved drug.”<sup>124</sup> Yet this has not always been the FDA’s approach in the past. As described in Section IV of this monograph, the FDA allowed compounded versions of Makena<sup>®</sup> after the approved drug was considered to be unreasonably expensive and many pregnant women were thus effectively deprived of access.<sup>125</sup>

To be sure, the July 2016 guidelines are described as nonbinding recommendations and do not provide final guidance to compounding facilities. In reality, however, these guidance documents directly limit the breadth of the formularies that compounders are willing to make available to their customers. The FDA has made it clear that, for the foreseeable future, it “does not intend to evaluate” a long list of substances nominated for inclusion on the draft Section 503B bulk list. This makes it especially difficult for outsourcing facilities to understand which drug components may be currently used in compounding.<sup>127</sup>

Third, in important respects the FDA has provided more restrictive guidance to 503B outsourcing facilities, which are required to manufacture to the highest standards and are FDA-registered and inspected, than to 503A facilities which do not manufacture to cGMP standards and are not registered and inspected by the FDA. This has the effect of guaranteeing that

significant amounts of sterile compounding will occur in more lightly-regulated 503A compounding pharmacies, continuing the very situation that existed prior to the passage of the DQSA.

Specifically, the FDA has not authorized 503B facilities to use substances and dietary ingredients that are components of FDA-approved drug products, or are the subject of USP or NF (National Formulary) monographs.<sup>127</sup> In contrast, bulk substances used to compound in 503A facilities are *required* to be components of FDA-approved drugs, or the subject of a USP or NF monograph, or on a list of bulk drugs deemed acceptable for compounding by the FDA.<sup>128,129</sup> If the FDA fully prohibits the use of such substances by 503B outsourcing facilities, it will go far to defeating the statutory intent of the DQSA.

The FDA's restrictive and vague guidance is ensuring more sterile drug compounding in non-cGMP facilities, while limiting patient access to needed medications and ensuring higher consumer prices. Perversely, it even prevents the new category of highly-regulated 503B outsourcing facilities from fully competing with the less-regulated 503A compounding facilities. By contravening the stated goals of the DQSA, the FDA is depriving itself of the opportunity to bring more of the smaller-scale compounding facilities that existed at the time of the NECC tragedy into compliance with cGMP standards under its direct oversight.<sup>46</sup>

*“Clinical need” restriction.*

The FDA's current view, as expressed in former FDA Commissioner Hamburg's letters, is that 503B outsourcing facilities are the preferred avenue for providing compounded drugs, particularly sterile medications.<sup>98,99</sup> Thwarting this objective, however, is the fact that current FDA policy restricts a 503B outsourcing facility to producing medications for which there is a “clinical need,” unless a published shortage exists.<sup>127</sup> In order to determine whether there is a clinical need, the FDA subjects even substances that have been used in compounding for decades to an onerous multi-factor submission that has the direct effect of limiting patient access to critical medications.<sup>46</sup> Specifically, the prescriber must submit the following information:

- A statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat;
- A list of FDA-approved drug products, if any, that address the same medical condition;

- If there are any FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary;
- If the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product;
- A bibliography of safety and efficacy data for the drug product compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature; and
- If there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.<sup>119</sup>

If 503B outsourcing facilities are indeed to become the preferred avenue for providing sterile medications and other compounded drugs, the process of listing those drugs for which there is a clinical need must not be this slow and cumbersome. Until this occurs, substances that have long been used in compounding will be restricted to less-regulated 503A facilities

*“Emergent” Condition Restriction.*

The availability of compounded drugs for office use -- that is, limited quantities maintained by prescribers on their premises -- is especially important to meet emergency, acute care needs. When the DQSA was enacted, this practice was intended to be allowable. Prior to the enactment of the DQSA, FDA was preparing draft guidance under Section 503A regarding compounding for office use. This draft FDA policy permitted compounding in 503A facilities in advance of a patient-specific prescription.

Nonetheless, the FDA has since taken the position that a 503A facility may not compound drugs for office use. The reversal of FDA’s position and its frustration of congressional intent has prompted at least six statements from the Senate and House of Representatives that FDA does not have jurisdiction to prohibit compounding for office-use.<sup>130</sup>

AAO, in its public comments on the FDA’s recent draft guidance concerning compounding, urges the FDA to permit Section 503A compounding pharmacies to compound certain drugs for office use to meet emergency, acute care needs.<sup>73</sup>

The vast majority of states authorize office-use compounding in their state laws.<sup>131,103</sup> In its report accompanying Fiscal Year 2016 appropriations legislation, the U.S. House of Representatives Committee on Appropriations directed the FDA to provide new guidance regarding the compounding of office-use medications by 503A facilities within 90 days of enactment. The report language makes clear the view of Congress that FDA's current guidelines under Section 503A are inconsistent with the DQSA's intent.<sup>13</sup> The FDA has not complied. Instead, on April 15, 2016, it issued its Draft Guidance that explicitly prohibits office-use compounding by 503A facilities.<sup>133</sup>

In response, in June 2016, 49 members of Congress wrote the FDA that its interpretation of Section 503A is unacceptable.<sup>134</sup> In this letter, the members of Congress pointed out that the need for new FDA guidance consistent with congressional intent in the DQSA was reiterated in the committee-passed House of Representatives' Fiscal Year 2017 Report.<sup>131</sup> In addition to the members of Congress who signed this letter, members of the House and Senate of both parties have spoken out regarding the need for compounded drugs in emergent situations.

As U.S. Senator John Boozman has stated, drug compounding is an integral part of the healthcare system because it helps address supply chain gaps and demand spikes, especially in neglected and rural areas. In his words, "Without compounders, patients would suffer from limited access."<sup>135</sup> Imprimis can testify to the accuracy of this statement, based on our real-life experience.

When Imprimis began to offer its compounded alternative to Daraprim<sup>®</sup>, used to treat toxoplasmosis for patients including AIDS populations, leading hospitals and healthcare institutions including Johns Hopkins and UCLA prescribed the compounded alternative to the \$325-per-pill Daraprim<sup>®</sup> (the price after the 50% discount offered strictly to hospitals).<sup>136</sup> Their patient-specific prescriptions were filled at Imprimis' 503A facilities for patients not experiencing immediate urgency to receive their prescriptions.<sup>137</sup> During the acute-care phase of toxoplasmosis treatment, however, the same hospitals could not prescribe the compounded drug, priced at \$0.99 per capsule, but instead were forced to purchase the exorbitantly priced Daraprim<sup>®</sup> pills at \$325 each. This was due entirely to the FDA's current 503A guidance on office use. Unless and until FDA issues clarifying guidance, hospitals will remain unable to keep a reliable stock of Imprimis' drugs and those of other compounders for use in emergency situations and will instead be forced to stock Daraprim<sup>®</sup> at the prevailing price Turing charges.<sup>122</sup>

The FDA should allow responsible 503A facilities to provide help to the most vulnerable patients who suffer from restricted access to emergency medications due to the FDA's own discretionary prohibition of 503A office-use compounding. Current FDA policy against emergent care office-use compounding is hurting patients and making it needlessly expensive and difficult for healthcare institutions, particularly rural, community-based providers, to care for those patients.<sup>46</sup>

### **B. Impediment: Pharma Industry Interest in the Status Quo**

In analyzing the sources of the U.S. prescription drug crisis that has witnessed extraordinary price increases even for older medications that are inexpensive to make, it is important to focus on regulatory policies that limit competition. The current regulatory system – a complex web of laws, regulations, and guidance governing the pharmaceutical supply chain – is an unintentional but powerful source of protection for incumbent drug manufacturers. Global pharmaceutical giants skillfully exploit this complexity, and their own intimacy with the FDA, to prevent competition from compounding. It is, of course, in their interest to do so.

“Big Pharma” has feared the competition that compounding could bring to their industry for many decades. In 2012, the knowing violations of law by the small, family-owned NECC, and the tragic consequences that followed, gave them an opportunity. Since the NECC tragedy, every pharmaceutical industry trade group, along with the outside think tanks and organizations they support, has cited NECC as the reason the FDA should place restrictions on compounding. Collectively, they have lobbied to keep their markets as free as possible of competition from compounded drugs – even for off-patent, well-characterized drugs that were originally brought to market as compounded drugs. These organizations include the American Public Health Association (APHA), the Biotechnology Industry Organization (BIO), the Generic Pharmaceutical Association (GPhA), the Pew Charitable Trusts (Pew), PhRMA, and Trusts for America's Health.<sup>138-140</sup>

Nearly every recent communication to the FDA from these groups has recounted the 64 deaths that resulted from NECC's unlawful behavior. None of this lobbying has mentioned the significantly greater numbers of deaths and injuries caused by FDA-registered drug manufacturers. FDA-approved drugs manufactured by the pharmaceutical industry lead to more than 100 deaths *each day* in the U.S. – far more on a daily basis than were caused by the one-time compounding tragedy of NECC.<sup>141</sup> Nor do these groups ever pause to acknowledge

the unsafe conditions that exist at some FDA-registered manufacturing facilities, even though these are widely reported in the press.

Nothing can excuse the behavior of any irresponsible company that knowingly violates the law and places unsafe drugs, whether manufactured or compounded, into the stream of commerce. Nothing is more important than safety. But it is important to recognize that the purpose of pharmaceutical industry lobbying is not to bring more of the compounding industry under FDA regulation, but to limit the opportunity for compounded drugs to be made in facilities that would be registered and inspected by the FDA, according to the very same high standards of quality and safety that apply to the pharmaceutical industry itself.

Congress, of course, immediately enacted remedial legislation in the wake of the NECC tragedy. The Drug Quality and Security Act opens the way for compounding to be FDA regulated in the same way as the manufacture of the most extravagantly priced branded drugs. But by lobbying against the production of compounded drugs in the very 503B outsourcing facilities established by the DQSA, the pharmaceutical industry gives the lie to its professed concern for regulation that responds to the NECC tragedy. Their true purpose in promoting the NECC example at every turn is to demand new legal prohibitions on compounding in order to protect themselves from competition.

The pharmaceutical industry groups sow fear of compounded drugs because, if compounded drugs were allowed to compete with their products, they would be forced to cut their high prices.

The FDA should take the expressed concerns of the pharmaceutical industry lobby at face value, and address them head on. The lobbyists cite the fact that compounded drugs have no “FDA premarket review for safety, effectiveness and quality.”<sup>140</sup> The FDA, too, has stated it shares this concern. To remedy this problem, the FDA should establish a process for reasonable premarket review for compounded drugs. Such a process would take into account the fact many of the drugs that are now FDA approved were originally made as compounded drugs and safely prescribed, dispensed and used successfully by patients. A common sense approach should provide an abbreviated approval filing process, giving the FDA increased visibility into how a particular compounded drug is made, and how it is used. Issues related to prospective clinical effectiveness should be addressed by physicians choosing to prescribe the compounded medicines for their patients.

The industry lobbyists further cite “risks associated with the administration of unapproved drugs.”<sup>140</sup> No similar concern is expressed over the administration of their own drugs for unapproved off-label uses. The FDA well knows that the pharmaceutical industry profits billions of dollars each year from off-label use of drugs that are unapproved by the FDA for the conditions they are treating. So long as the FDA is willing to allow an approved drug to be used off-label, it should similarly allow a lower-cost compounded version of the same FDA-approved drug to be used off-label.

The result of industry lobbying at the FDA has been directly injurious to patients who are harmed by limited competition and higher prices for prescription drugs. A rational regulatory approach to compounding would foster improvements to patient safety while allowing patients to realize the many benefits compounding can offer. To achieve this, the FDA must recognize the anticompetitive role that pharmaceutical lobbying has played in creating the prescription drug crisis, and free itself from regulatory capture.

### **C. Impediment: Attempts to Justify High Drug Prices**

Many pharmaceutical companies seek to justify their high prices as necessary to pay for risky research for other drugs they own or are developing. In effect, they are arguing that high drug prices are a necessary “tax” imposed on all U.S. consumers when they pay for their prescription medicines. Whereas in other industries the costs of financing risky prototype development that a company hopes will pay off big in the long term are normally borne by the company’s investors, the pharmaceutical industry argues that U.S. consumers must pay high drug prices in order to generate high profits for investors. The industry then promises that these corporate profits will be used to fund high-risk research and development.

While some may agree with the idea of a high price umbrella for life-saving drugs, the logic must be examined for less-essential drugs. There is little reason for a company to invest money in further development of a drug that, due to its artificially high price, is high-margin, competition-free, and generating rich profits. Arguably this company would be acting foolishly to disrupt its artificial government-sanctioned monopoly by altering the product’s current position in the marketplace. To the contrary, it would have a strong incentive to do everything possible to maintain the status quo. This would include joining other beneficiaries of this system to aggressively lobby the government to protect themselves from competition.

As we know, the reality of the current prescription drug market is neatly in accord with this incentive system. When regulators and Congress request that drug manufacturers accused

of profiteering disclose their pricing tactics, they obfuscate by describing the complexities of the drug business and myriad laws that govern it. Under persistent public scrutiny, a company that is riding high on monopoly profits from a decades-old drug while investing little in R&D may invest a small portion of its profits in a modest research program. This allows the company to claim it is in fact using its profits to discover new treatments. As Congress discovered in its investigation of Turing Pharmaceuticals – where the profits so desperately needed for R&D was used to pay for lavish bonuses and parties aboard yachts featuring private fireworks displays<sup>142</sup> – whenever companies claim that altruism is more important than self-interest, it is better to verify than to trust.

For its part, the FDA faces a conflict of interest because of the significant amount of money it generates for its own budget from fees paid by industry for ANDAs and NDAs.<sup>143</sup> Occasionally this conflict rises to the surface in the FDA's own disclosures of its motivations. Recent FDA guidance prohibiting the compounding industry from making essential copies of FDA-approved drugs gives the following as one of the reasons: "Sponsors might also be less likely to seek approval of an ANDA for a generic drug if compounders were permitted to compound drugs that are essentially copies of commercially available drugs without going through the ANDA process."<sup>123</sup> While the FDA indisputably does many good works to protect American consumers, it has a vested interest in maximizing the number of ANDAs and NDAs and the fees they bring in. A regulatory approach that embraces compounding to provide a check on runaway drug prices, while serving the public interest, would not produce the same magnitude of fees.

The FDA's comfort with the current system is thus an impediment to reform. That the current system necessarily results in higher drug prices seems not to be the FDA's concern. In alignment with the pharmaceutical industry, the FDA accepts the argument that the high prices the public pays today are a necessary "tax" for future benefits it hopes will be forthcoming, if not for today's consumers then for others later. In recent guidance, the FDA made its agreement with the industry's talking point explicit. The agency explained that drug companies "may be less likely to invest in and seek approval of innovative, life-saving medications" if they had to compete with less expensive compounded drugs.<sup>123</sup>

Given this statement, and the FDA's duty to protect the patient population they serve, one must ask if the FDA is currently doing everything in its power to ensure companies such as Turing are in fact supporting research with the high prices they charge. The evidence suggests not. In the case of Turing, a highly visible company was selling a 63-year-old drug for which it

had done no development, at a price the entire healthcare community believed to be obscene. It took congressional investigators to discover how the outsized revenues were actually being applied.

Federal policymakers should recognize the perverse incentive effects of current FDA policy that protects markets for pharmaceutical companies such as Turing, while making it difficult for Americans to get the medications they need. Just as drug makers may benefit from the extra “tax” they collect from consumers in the form of higher prices for novel drugs, so too should consumers be recompensed for the higher prices they have paid over many years. Their reward should come not just from the new drugs that hopefully come to market in the future (and which, if they do come, will have their own extra-high prices), but from lower prices for aging, off-patent drugs.

Normally in a well-functioning market, products and technologies do not receive special government protections and monopolies. Nor are there many products that, absent new improvements, get progressively more expensive over time. The FDA-drug approval business is an enormous exception. It is characterized by market protections that last decade after decade – even when patents have long since expired. Many FDA-approved drugs lack any competition. FDA policy vigorously enforces these market protections, with the agency acting to impede any competition, especially from compounded drugs. All of these work in combination to keep prescription drug prices abnormally high.

The FDA mandate is to protect patient safety, which must be interpreted to embrace patient-friendly policy that keeps drug prices – and hence needed medications – within the reach of most Americans. Drug companies should have market-based incentives, not regulatory cocoons, to take risky bets, discover new drugs, and charge reasonable prices the market can bear. The FDA should allow consumers to benefit from the savings that increased competition for old, off-patent drugs will bring.

#### **D. Impediment: Centers for Medicare & Medicaid Services (CMS) Policy**

*CMS payment policies taking insufficient advantage of pharmaceutical compounding*

Medicare and Medicaid combined are the largest purchasers of drugs in the world. Their decisions have enormous consequences for the entire drug industry. Medicare and Medicaid policy on prescription drugs is made by the Centers for Medicare & Medicaid Services (CMS).

Medicare Part A covers medical care and drugs administered in a hospital or similar inpatient setting. Medicare Part B covers the treatment of patients and the administration of drugs in a physician office or the outpatient department of a hospital. Medicare Part D is a voluntary drug benefit program established in 2003.<sup>144</sup> Participants can enroll for Part D benefits through private prescription drug plans (PDP) or through Medicare Advantage plans.<sup>107</sup> In 2014, over 40 million Americans were enrolled in Medicare Part D, representing more than 76% of all Medicare beneficiaries.<sup>145</sup>

The federal government is prohibited by law from negotiating drug prices paid by Medicare.<sup>146</sup> As a result, PDPs negotiate pricing directly with pharmaceutical companies for discounts or rebates. This differs from state Medicaid programs and the U.S. Department of Veterans Affairs' TRICARE military health plan, all of which are permitted to negotiate drug prices. As a result of rising drug costs, a growing number of policymakers believe Medicare should be able to negotiate Part D drug prices. Over 80% of the public supports this.<sup>147</sup>

Part D policy toward compounded drugs is set out in Chapter 6 of the Medicare Prescription Drug Benefit Manual. It provides the following guidance regarding Part D coverage of "Extemporaneous Compounds":

1. Compounded prescription drug products can contain all, some, or no Part D drug product components.
2. Only costs associated with those components that satisfy the definition of a Part D drug are allowable costs under Part D because the *compounded products as a whole do not satisfy the definition of a Part D drug*. As a consequence, claims for compounded prescriptions can consist only of National Drug Codes (NDCs) for FDA-approved prescription drug products.
3. Bulk powders (i.e., active pharmaceutical ingredients for compounding) *do not meet the definition of a Part D drug* and as a result *are not covered by Part D*.
4. Labor costs for mixing a compounded product that has at least one Part D drug component can be included in the dispensing fee. For compounds containing all generic products, the generic cost-sharing is to be applied. If a compound contains any brand products, the Part D sponsor may charge the higher brand name cost-sharing to the entire compound.<sup>148</sup>

As this guidance makes clear, there are ample opportunities for CMS to make greater use of compounding as a means of controlling Part D costs and keeping patient copays low. According to a March 2016 report from HHS, Part D drug costs nearly doubled between 2005 and 2014, increasing from \$9.4 billion in 2005 to \$18.5 billion in 2014.<sup>149</sup>

The same report highlights the similarly rapid growth of drug spending on biologics under Part B, which has grown from 39% to 62% of total spending. Nearly all Part B drug payments go directly to providers as opposed to being packaged with other services. Under Part B, Medicare pays physicians the average sales price of the drug plus an additional 6%.<sup>106</sup> The current Part B payment method does not provide physicians with any incentives to choose the lowest-cost therapy for their patients. Whereas private insurers and Plan D sponsors use value-based cost-savings programs that include tiered copayments, prior authorization, and step therapy, Medicare Part B has not implemented any of these. The result is that the Part B payment program provides a financial incentive for physicians to prescribe more expensive drugs.

A June 2016 study published in *JAMA Ophthalmologist* found that U.S. ophthalmologists continue to prescribe Eylea<sup>®</sup> (aflibercept, manufactured by Regeneron) and Lucentis<sup>®</sup> (ranibizumab, manufactured by Genentech) even though the lower-cost compounded drug, Avastin<sup>®</sup> (bevacizumab, also manufactured by Genentech) has been shown to be equally effective. These drugs, used to treat ophthalmic conditions, represent more than \$6 billion in Medicare Part B costs.<sup>150</sup> For comparison purposes, the per-dose prices of Eylea<sup>®</sup> and Lucentis<sup>®</sup> are \$1,850 and \$1,170, respectively. The per-dose price of compounded Avastin<sup>®</sup> is \$50 per dose.<sup>104</sup> Although repackaged compounded Avastin<sup>®</sup> is not FDA-approved for ophthalmic conditions, it is widely used off-label.<sup>83,151</sup>

There are many such opportunities by which Medicare could take advantage of the cost savings offered by compounded drugs. Whether it is an estrogen cream for which Medicare is currently willing to pay ten times the compounded price, an injection of compounded Avastin<sup>®</sup>, or paying Turing \$750.00 per pill for Daraprim<sup>®</sup> and not pay \$0.99 per pill for a compounded alternative, CMS policy should allow compounded drugs to compete. This will drive significant savings for both the Medicare system and, equally importantly, for Medicare beneficiaries in the form of lower out-of-pocket expenses.

*Inspector General report questioning Part D spending on compounded topical drugs*

In June 2016, the HHS Office of the Inspector General (OIG) reported on an unusual increase in Medicare Part D costs for compounded drugs, particularly topical drugs in New York City. Although Part D spending on compounded drugs in 2015 represented only 0.3% of the overall Part D spending on prescription drugs, the OIG noticed that the rate of increase for compounded drugs was almost four times higher than for Part D prescription drugs overall.

In particular, Part D spending on topical drugs such as creams, gels, and ointments has grown at an average rate of almost 25% per year since 2006, so that by 2015 topical drugs represented nearly half of all compounded drugs paid for under Part D. Moreover, the trend was most pronounced over the last year before the report: between 2014 and 2015, Part D spending on topical drugs grew by 56%. The OIG report questioned whether this unusual increase might be due to fraud, citing several criminal and civil cases of fraudulent practices by physicians, middlemen and compounding pharmacies implicated in kick-back schemes and other prescription abuses. OIG concluded its report by recommending that CMS continue to assess compounded drug trends and that CMS take necessary action where needed to protect the integrity of the Part D program.

In 2014, Express Scripts, the largest pharmacy benefits manager (PBM) in the U.S., noticed a significant increase in its costs for a similar class of medications for the treatment of scars, wrinkles, and pains.<sup>152,153</sup> In response, Express Scripts implemented its “compound management solution” to target or block more than 1,000 bulk ingredients that had experienced significant price increases with no apparent additional clinical benefit. Express Scripts noted that the move was necessary in order to prevent a growing number of schemes developed by some physicians, manufacturers, and pharmacies to charge high prices for low-value alternatives.<sup>154</sup> In 2015, Express Scripts reported that as a result of its compound prescription management solution, there was a nearly 40% decrease in claims, an 80% decrease in spending, and payors achieved a 97% decrease in total plan costs for the compounded drug class.<sup>155</sup> As a result of the initiative taken by Express Scripts and similar actions taken by others, the fraud connected to compounded pain and scar creams has been resolved.

*2014 GAO report finding Medicare Part B policy on compounding is unclear*

In a 2014 report titled “Compounded Drugs: Payment Practices Vary across Public Programs and Private Insurers, and Medicare Part B Policy Should Be Clarified,” the Government Accountability Office (GAO) recommended that “CMS clarify its Medicare Part B

payment policy to either allow or restrict payment for compounded drugs containing bulk substances and align payment practices with this policy.”<sup>144</sup> HHS, of which CMS is a part, disagreed with GAO’s recommendation that clarification of its policy is necessary, or that any further decision about how to handle compounded drugs is required. The disagreement highlights the fact that what FDA believes is clear and logical is not so clear to objective observers outside the agency.

In preparing its report, the GAO studied CMS’s payment policies for Medicare and Medicaid, as well as the payment policies the largest five state Medicaid programs. They also surveyed the policies of private health insurers offering Medicaid and Medicare plans as well as those of private plans.<sup>156,157</sup> In addition, GAO interviewed officials from OptumRx, CVS Caremark and Express Scripts, the three largest PBMs in the U.S., to gain their perspective on their payment practices for compounded drugs in pharmacies.

The report stated that compounded drugs may contain one or more FDA-approved products or may be compounded with bulk drug substances. In this report, “bulk drug” substances were defined as raw powders that are *not* generally FDA-approved. (This terminology appears inaccurate, since when listing examples, the authors included the muscle relaxant, baclofen, and an anticonvulsant drug, gabapentin, both of which are FDA-approved drugs.) The report noted that active ingredients for both FDA-approved products and bulk substances components are generally assigned national drug codes (NDCs).

The report stated that only two of the five insurers and one of the two Medicare Part D-only sponsors did not cover bulk substances under their Part D plans. However, three of the five insurers that offer private health plans, and four out of the five state Medicaid plans, did not allow payment for ingredients they considered bulk drug substances.

One outcome of this policy is that Medicare and Medicaid cover Premarin<sup>®</sup> estrogen cream, which costs \$3,600 per year, but not compounded estrogen cream made with the same FDA-approved active ingredient, which costs \$360 per year.<sup>158</sup> Prior to the FDA approval of Premarin,<sup>®</sup> whose owner significantly raised its price, this estrogen cream was an off-patent low-cost drug. If, following the GAO’s alternative recommendation, CMS were to choose to allow payment for compounded drugs containing bulk substances, Medicare and Medicaid would cover the lower-cost compounded estrogen cream. Patients with co-pays would realize the cost savings along with the entire Medicare and Medicaid system.

GAO investigators found that most of the private insurers, as well as the Medicare and Medicaid programs, paid for compounded drugs administered in an outpatient or physician office setting. Some payors conduct additional claim reviews for compounded medications billed under nonspecific codes to make payment decisions. In those cases, GAO investigators found that claims reviewers would have difficulty obtaining the information they were seeking because the majority of these drugs lack specific billing codes -- a consequence of the ambiguous CMS policy toward compounded drugs.

The GAO also found the CMS national policy for compounded drug payments under Medicare Part B to be unclear. The policy states that in order for Medicare to pay for drugs they must be FDA approved. But since CMS contractors processing Part B claims do not collect information on whether drug ingredients are FDA approved or not, the GAO concluded that Medicare may be paying for ingredients that are not approved by the FDA. The report concluded that, "as a result, CMS may have paid for compounded drugs ... inconsistently with its payment policy."

In practice, Medicare still does not allow payment for compounded drugs made from FDA-approved bulk chemicals – even those made in FDA-registered and FDA-inspected 503B outsourcing facilities. This is so despite the many government reports and analyses highlighting opportunities for savings and increased patient access, were it to do so. However, Medicare will pay for compounded drugs that include finished FDA-approved drugs as "components" of the compounded drug. This policy is best understood as price protection for pharmaceutical companies, because it authorizes payment for the compounded drug only if it includes expensive FDA-approved finished drugs.

The current policy thus exacts a "retail economic toll" in favor of the drug manufacturers. Beyond ensuring that the compounded product will have a higher price than the already-expensive retail product that it incorporates, this policy also risks compromising the quality of the finished compounded product. That is because the branded and generic retail product contains not just the active ingredient the patient needs, but also fillers, excipients, and other materials. Despite the clinical advantages to the patient of avoiding these excess materials, and the budgetary advantages of savings from the use of bulk drug components that are often made in the same exact facilities as the FDA-approved finished drug, Medicare is only willing to pay for the retail branded and generic product components of the compound.

Since Medicare is such a large payer, it would realize billions of dollars in annual savings if it were to take advantage of the opportunity to pay significantly less for compounded drugs. Working with CMS, FDA should put in place sturdy regulations for the use of bulk chemicals in compounded drugs, and then enforce those regulations in the same robust way it does for all drug manufacturers. Doing this would enable Medicare to save enormous sums, merely by agreeing to cover certain compounded drugs in urology, ophthalmology, dermatology, pain management, emergency room medicine, and ear, nose and throat (ENT) medicine, among others.

*CMS policy toward Dropless Therapy: a case study*

Medicare payment policy directly affects a patient's access to medicines, either favorably or adversely. A 2015 policy change affecting Dropless Therapy provides a case study of how CMS reimbursement decisions severely inhibit not only the ability of patients, but of their doctors, to choose the best medication.

Dropless Therapy is used following cataract surgery to eliminate or reduce the need for eye drops. For many patients, particularly the elderly and those with Parkinson's, Alzheimer's, and other age-related infirmities, self-administration of drops creates serious compliance issues. Other patients are unable to accept drops even when administered by others. In lieu of a weeks-long regimen of multiple doses of different drops each day, Dropless Therapy uses a compounded formulation of antibiotic and/or steroid consisting of triamcinolone and moxifloxacin (Tri-Moxi) that is injected into the eye in a single administration. The purpose of the drops, and of Dropless Therapy as an alternative, is postoperative infection prophylaxis and management of inflammation. Both are equally effective, though patient satisfaction is significantly higher with Dropless Therapy.<sup>159</sup>

As with other compounded medications, the cost of Dropless Therapy compares favorably to prescription drops. An economic study conducted by Andrew Chang & Co. LLC for Cataract Surgeons for Improved Eyecare (CSIE) and co-sponsored by Imprimis demonstrated that Dropless Therapy could save Medicare and Medicaid more than \$7.1 billion over the next 10 years, when compared to the cost of post-surgery topical drops. Patients could save an additional \$1.4 billion for out-of-pocket costs for expensive pharmaceutical eye drop co-payments. State governments could save \$124 million in Medicaid payments during the 10-year time period.<sup>160</sup>

Until January 2015, patients paid for Dropless Therapy out-of-pocket which was priced lower than most out-of-pocket costs for co-pays connected to branded eye drops. As a result of a CMS Medicare policy change that month, however, patients were prohibited from choosing and paying for Dropless Therapy. This is not the result of CMS disapproval of Dropless Therapy on medical grounds; to the contrary, CMS claims it is now "covering" Dropless Therapy via the Part B facility bundle fee. Since the amount of this fee was not increased beyond what is already paid for cataract surgery, the result is that physicians and healthcare providers themselves have to pay for it themselves. Medicare continues to pay the full retail cost of the far-more-expensive drops, so no cost savings have been realized by the CMS decision.

Physicians, including many of the nation's leading cataract surgeons and presidents of medical societies, have protested that Dropless Therapy should not be treated as if it were part of the standard cataract procedure, because it is not. The compounded medication is injected after the cataract surgery and serves the identical purpose of the post-surgery drops for which Part D pays in full.

Dr. Richard Lindstrom, a former president of the American Society of Cataract and Refractive Surgeons and current member of its Executive Committee, attending surgeon of Minnesota Eye Consultants, and a member of the Imprimis board of directors, has described the physicians' dilemma succinctly. "The current federal policy against reimbursement for Dropless Therapy has hampered our ability to deliver the best possible care to our patients," he has written. "It is one thing for Medicare not to reimburse for something. But going so far as to tell doctors who participate in Medicare that their patients can't choose to pay either, makes this a Catch-22. This policy seriously interferes with the doctor's duty to prescribe the best possible care, and the patient's right to choose the best care."<sup>161</sup>

CMS should make a straightforward revision to its January 2015 Update of the Hospital Outpatient Prospective Payment System (OPPS) Policy to allow either for reasonable payment for Dropless Therapy by Medicare, or for patients who choose to pay for it themselves. The latter option would still be welcomed by patients, since the full cost of Dropless Therapy is less than the typical patient co-payment for drops under Medicare and most insurance. Either course of action would provide substantial cost savings to Medicare, Medicaid and patients alike. Reform of this policy would also alleviate patients' inability to access Dropless Therapy.<sup>162</sup> There is precedent for such a change; in May 2005, CMS revised its reimbursement policy on

cataract surgery to allow patients to upgrade from a conventional intraocular lens (IOL) to deluxe presbyopia-correcting IOLs, with patients paying the difference.<sup>163</sup>

**E. Impediment: Private insurance, PBMs and state insurance programs see insufficient competition in the market for prescription drugs**

Following the actions Imprimis took in the fall of 2015 to combat the growing practice of extreme price hikes for critical drugs lacking competition, insurers and PBMs have begun embracing compounding as a method to decrease costs. Many believe compounding offers a viable solution to monopolistic drug pricing.<sup>125</sup> Private insurance companies, PBMs, state programs and the government are implementing cost-savings programs, narrowing choices to “preferred formularies” and excluding payments for certain expensive drugs in their fight against price gouging. Express Scripts, Cigna, and Harvard Pilgrim Healthcare Co. have all signed value-based contracts for higher cost drugs that tie drug payments to improved patient outcomes.<sup>164</sup>

Mark Merritt, President and CEO of the Pharmaceutical Care Management Association (PCMA), testified before the U.S. Senate Special Committee on Aging in December 2015 and outlined PCMA’s recommendations to resolve the drug pricing issue.<sup>165,22</sup> PCMA represents PBMs in the U.S. that provide prescription drug plans for more than 266 million Americans with health insurance through sponsors including self-insured employer plans, labor unions, Medicare Part D, Medicaid, the Federal Employees Health Benefits Program (FEHBP), and others. Merritt presented PCMA’s recommendation that policymakers and stakeholders explore ways to enhance competition. PCMA believes that market-based solutions can play an important role in increasing competition and stopping price gouging.

As an example, he cited the partnership between Express Scripts and Imprimis Pharmaceuticals to offer a \$0.99 per pill alternative to Daraprim<sup>®</sup> to treat toxoplasmosis. Imprimis brought its lower-cost drug to market to meet an urgent patient need after Turing increased the price of the branded drug from \$13.50 to \$750.00 per tablet.<sup>166</sup> Both drugs are orally administered and contain the same active pharmaceutical ingredient. In connection with the partnership, Imprimis’ compounded formulation consisting of pyrimethamine and leucovorin was endorsed by the HIV Medicine Association and the Infectious Diseases Society of America.<sup>167</sup>

In his Senate testimony, Merritt also put forward PCMA’s advice that encouraging price competition was likely to be far more effective at reducing drug prices, while still maintaining

supplies, than approaches such as federal price controls on drugs and pharmacy services, legal limits on patient cost sharing, or expanded coverage mandates. Each of these, PCMA believes, risks making drug costs and pharmacy benefits less affordable. Among other recommendations to encourage drug price competition, PCMA listed the following solutions for Congress to consider:

- (a) First, the FDA should compile a list of all drugs and associated indications without patent protection, and without generic or brand substitutes. Policymakers and stakeholders should explore ways to encourage competition for drugs on this list that have proven susceptible to price gouging. Accelerated ANDAs and other means of providing regulatory flexibility, PCMA believes, “would allow more solutions similar to the Express Scripts/Imprimis solution” to the Turing/Daraprim crisis.
- (b) Second, PCMA recommends that laws and regulations be updated to facilitate the initiatives of stakeholders to move to alternative payment methods such as bundled payments, accountable care, comparative effectiveness research (CER), evidence-based medicine (EBM), and value based payments linked to performance. These programs, partly the result of regulatory and market pressure to lower health costs, can be effective means of slowing the increase in specialty drug costs.

Express Scripts, as well as several state programs, have been in the vanguard in the fight against increased drug costs. In a December 2015 report, Express Scripts described its role in ensuring access and affordability for their patients by partnering with Imprimis to offer a lower-cost alternative to Daraprim<sup>®</sup>.<sup>168</sup> Express Scripts also announced plans to introduce its “market events” program in late 2016, designed to allow rapid response to excessive drug price increases. This program, which focuses especially on older drugs that are overpriced, helps move patients to more affordable alternatives.<sup>169,170</sup>

BlueCross and BlueShield of Vermont’s *Step Therapy Program* encourages their doctors to try less expensive drugs before using the most expensive branded ones.<sup>171</sup> Imprimis’ alternative to Daraprim<sup>®</sup> is one of the lower-cost medications mandated through their program.<sup>172</sup> In June 2016, the Governor of Vermont signed legislation to fine drug companies that hike drug prices abruptly and refuse to disclose the reasons behind the increases.<sup>173</sup> Vermont is not alone in its effort to reduce price gouging: 13 additional states, including New York,<sup>174</sup> California,<sup>175</sup> Ohio,<sup>176</sup> Massachusetts,<sup>177</sup> and Virginia,<sup>178</sup> have already introduced or passed similar legislation related to drug pricing transparency.

## VII. Imprimis Principles and Values: Imprimis Cares®

Imprimis is committed to serving unmet needs in the marketplace and providing drug accessibility through its proprietary formulations and Imprimis Cares® program.<sup>179</sup> Under Imprimis Cares®, the company owns, markets and dispenses a portfolio of lower-cost compounded therapeutic alternatives to higher-priced FDA-approved drugs in several therapeutic areas, including ophthalmology, urology, and infectious diseases.<sup>180</sup>

As a further demonstration of its principles and values, Imprimis aims to provide physicians and patients with visibility into the pricing of their compounded formulations. This is in stark contrast to other pharmaceutical companies in the industry that lack transparency regarding their pricing tactics.<sup>181,182</sup>

With its formulations for Dropless Therapy and alternatives to Daraprim®, in addition to many other low-cost alternative medications, Imprimis has demonstrated that its approach to compounding can make a meaningful contribution to easing the impact of our nation's current drug pricing, drug shortage and drug accessibility problems while making patient safety the highest priority.

Imprimis' highest value is patient safety. Imprimis' formulations contain only FDA-approved APIs, and the company consistently maintains an intense focus on quality control. By providing more safe compounded drugs, Imprimis has provided healthy competition in the marketplace that has significantly benefited patients.

The benefits of safe, lower-cost compounded drugs on competition were amply illustrated in 2015 when Imprimis introduced its compounded alternative to Daraprim®.<sup>183,184</sup> The drug's patent had expired in 1953, and there had been no further research and development on it since then.<sup>185</sup> Yet its manufacturer, Turing Pharmaceuticals, was charging \$750.00 per pill. Thanks to Imprimis, patients who were previously unable to access their medication due to this astronomical price gained a much-needed alternative.<sup>186</sup> Imprimis was able bring its Daraprim® alternative to market quickly and cost-effectively because compounding is not subject to the time and expense of clinical studies and FDA approval.<sup>187</sup> Despite not requiring FDA approval, the fact that the Daraprim® alternative from Imprimis contains only FDA-approved APIs led Dr. Steve Miller, Senior Vice President and Chief Medical Officer of Express Scripts, to deem it "safe, high quality and extremely cost-effective." Based on this assessment, Express Scripts – the largest pharmacy benefit management (PBM) organization in the United

States – partnered with Imprimis to make the company’s low-cost compounded therapeutic alternative available to its millions of patients.<sup>166</sup>

In each of its therapeutic areas, Imprimis is committed to providing high-quality formulations to physicians and patients that meet or exceed U.S. Pharmacopeia (USP) <795> and <797> requirements.<sup>117,118</sup> On a risk-adjusted basis, for certain sterile formulations, Imprimis has voluntarily adopted cGMP practices even in its 503A compounding pharmacies. Imprimis’ pharmacies are accredited by the Pharmacy Compounding Accreditation Board (PCAB) and are licensed to ship to all 50 states. Operating under the regulatory framework of the federal DQSA and state pharmacy laws, quality assurance is of the utmost importance to the company.<sup>188</sup> Imprimis has invested \$5M in creating its state of the art New Jersey facility to be registered with the FDA as a 503B outsourcing facility and is committed to cGMP standards, the same manufacturing standards to which FDA-approved drugs are held, to ensure public confidence in quality and patient safety for compounded drugs.<sup>189</sup>

### **VIII. Proposals for Future Action**

Americans must reflect on whether the current healthcare system is working. They must examine whether critical drugs are accessible and affordable, for both themselves and the people they know. The public needs to question whether or not they are satisfied with their out-of-pocket costs for prescription drugs and the recent increases in health insurance premiums caused in significant part by higher drug prices.

The healthcare regulatory environment in the U.S., which leads the world in many ways, has not kept up with developments in the marketplace. Prescription drug manufacturers are increasingly able to game the system to take advantage of an artificial dearth of competition. This not only harshly affects American patients in need of life-saving medications, but also hurts taxpayers and the overall U.S. economy, which could deploy these resources more efficiently to other national needs.

Even as the largest prescription drug companies continue to reap the benefits of stringent FDA and CMS regulation that protects them from competition in the U.S., they routinely obtain the APIs and chemicals used in their drugs from operations in China, India and other countries with lighter regulation. As a result, not a few U.S.-based manufacturers of these APIs and chemicals have shut down their U.S. operations and never reopened. In the process,

thousands of Americans lost their jobs. These closures have also contributed to the nation's growing drug shortage.<sup>67</sup>

When companies re-open overseas, there is necessarily less FDA oversight over the production of chemical components and final dosages of many critical drugs sold to U.S. patients.<sup>190</sup> For some critical APIs, the FDA has effectively been forced to allow the import of critical medicines even from manufacturing plants known to be less safe. One must ask what policymakers have learned and what has changed since the Congress and the executive branch expressed public outrage at the predatory pricing tactics of former Turing CEO Martin Shkreli or the investors and executives at Valeant. Now as before, the regulatory policies that have given rise to these exploitative opportunities need to be reformed.

In fact, despite the outrage, recent FDA draft guidance has clearly spelled out how the agency intends to protect companies including Turing and Valeant by insulating their old, off-patent drugs from competition from companies like Imprimis that can offer patients safe compounded formulations at lower cost. Turing and Valeant exploited FDA policy, treating patients as pawns, and yet the latest FDA guidance seeks to protect them. One might ask why our regulatory system can be so impervious to change. The public should not be reduced to powerless victims at the hands of lobbying organizations that successfully tweak the rules to protect the interests of the Turings and Valeants of the pharmaceutical industry.

In this untenable situation that begs for reform, the potential value that safe, FDA-regulated compounding can drive in the marketplace can be a key weapon in the fight for lower prescription drug prices and greater access to critically needed drugs. Policymakers and regulators will require a deeper understanding of the way that compounded drugs are produced, the needs of physicians and health care providers for compounded medications, and the many circumstances in which compounded alternatives meet or exceed branded pharmaceuticals in safety, quality, efficacy and patient satisfaction. Such deeper insight will be necessary to accurately appraise the contrary claims of the incumbent drug manufacturers that do not wish to see competition from compounding. If policy were revised to create greater access to safe compounded drugs, patients and private and public payors would experience massive savings. A safe, lower-cost alternative to an expensive drug is an attractive option and deserves the attention of the public and policymakers alike. Access and affordability very often mean the difference between life and death.

The following recommendations set out concrete action items for policymakers to consider in order to achieve greater patient access to medicines while lowering costs. The competition that implementation of these recommendations will produce will not only reduce prescription drug prices, but also help refocus the pharmaceutical industry on finding novel, life-saving drugs instead of monopolizing old, off-patent ones.

#### **A. Make more APIs in the U.S.**

It should be a national priority to re-establish domestic production of the bulk ingredients used in our finished form drugs.

As of July of 2016, approximately 80% of all bulk drug chemicals used in FDA-approved drugs and compounded medications are made outside of the U.S.<sup>191</sup> Americans are now reliant on drugs produced under FDA exemptions for certain Chinese factories that have a history of poor quality controls.<sup>191</sup> Putting aside the economic cost to the U.S. from losing these jobs, this is a terrible situation from a safety perspective. The FDA does not test imported ingredients, and instead relies on the companies themselves to ensure they meet American standards. Erin Fox, Pharm.D., director of the University of Utah Drug Information Service, sums it up: “There is no transparency. We just have to take FDA’s word that they think it’s OK.”

According to the FDA, although it is the drug manufacturers themselves who are responsible for the testing when products are exempt from its import bans because of shortage concerns, the companies “are often asked to perform additional testing, hire independent auditors, or take other steps.”<sup>192</sup> This is hardly the equivalent of arm’s length FDA regulation in the U.S. Moreover, drug companies that import their components “aren’t required to disclose to the public where they get their ingredients.”<sup>191</sup>

For these reasons, Congress and the executive branch should adopt policies to encourage chemical and API production domestically. In addition, CMS should adopt reimbursement policies that support payment for drugs manufactured in the U.S., including compounded drugs. This policy would ensure that the FDA is actually inspecting more of the drug supply administered to U.S. patients, and ensuring compliance with cGMP. Ultimately, such a policy would go far to preventing the import of potentially dangerous foreign chemicals for use in FDA-approved drugs.

If the FDA is concerned about compounding from FDA-approved bulk ingredients made in FDA-registered and inspected plants, perhaps it is because the agency does not fully trust the

manufacturers of the APIs. Manufacturing bulk ingredients in the U.S. will ensure the high quality of these ingredients by giving the FDA direct access to the plants where they are made. This will not only allay FDA concerns about compounding from bulk drug ingredients, but also improve the quality of the entire U.S. drug supply chain.

### **B. Implement transparency in the drug supply and dispensing chains.**

Every drug that Imprimis produces and dispenses is made in the U.S., in facilities that are inspected by the FDA and state pharmacy boards. Imprimis is extremely careful about what we buy and use to produce our finished formulations. This is not dissimilar from the common sense approach most consumers take when they shop for groceries. They look for healthy and safe ingredients, with a bias towards things produced locally. The same level of common sense should apply to APIs used in the drugs that we put into our bodies. However, presently, there is very little transparency to the consumer when it comes to the drug supply chain.

When Americans buy a vehicle, there is a sticker on the windshield of the car that makes clear in plain English where the parts of the vehicle are manufactured, assembled and the related costs of each component assembly. This transparency allows consumers to choose to buy cars that are made in America or elsewhere, as they see fit. At a time where we know that 80% of the APIs in the drugs we use are made outside of the U.S., often in plants in China and India, with poor inspection histories, why should the public not have complete transparency as to the supply chain of the drugs we critically rely on. This would relate to the components and final production of the prescription drug.

In addition to production information transparency, FDA should begin to grade plants that produce APIs. I suggest an A, B, C and F grading. This can be connected to plant inspections, Form 483s and Warning Letters. "A" could be issued to plants with clean or near clean inspections. "B" could be issued to plants with minor corrective actions required. "C" could be issued to plants with more significant corrective actions required. And "F" would be for plants that failed inspection or that failed to take corrective actions connected to past inspections. Consumers should have access to these plant inspection grades when they purchase and consume a prescription drug.

Imprimis does something that I do not believe any drug company does. When we dispense a sterile drug, we include the actual sterility tests for the lot number of the drug. Our belief is that consumers need to know that we did our job and tested for sterility and that the drug they have been shipped is sterile. Why shouldn't other drug companies provide

consumers with this information – such as sterility, potency, endotoxin, exotoxin and other related testing – all in the form of a simple checkbox format. This information is readily available and would only involve simple packaging changes. Consumers should feel confident that what they are buying is safe – not just because it is “FDA Approved”, but because a series of steps have been taken to ensure safety and those steps have been disclosed to the consumer on the packaging of the product they are buying.

Lastly, consumers should know who is getting what percentage of the list price of the drug they are purchasing. There are many bodies that “feed” off of an average wholesale price (AWP) of a drug. When a consumer learns that a drug has a list price of \$600, it doesn’t necessarily mean that the drug company is getting all of that money. Some percentage may go to a pharmacy benefit manager or a wholesaler. Others in the chain may get rebates or make spreads based on discounts offered by the drug manufacturer. A simple table that makes clear the average estimated percentage or range of percentages of the AWP that the various parties involved in the dispensing of the drug receive is important and readily available information that would provide important disclosure to the American public.

The upshot of the above proposed transparency is that consumers will have access to information that is readily available and that will allow them to make better decisions. More disclosure will also act as a strong silent force to get drug companies to buy more APIs and make more finished drugs in places with a history of better safety and greater access to reasonable inspection by the FDA.

### **C. Define drug shortages to include shortages due to economic factors.**

The term “drug shortage” should be defined more broadly to encompass economic factors.<sup>46</sup> In communities across America, patients are unable to pay for their necessary medications due to excessive drug prices. With no feasible way to obtain their medications, these patients find themselves in circumstances identical to those who need a drug that is in “short supply” as currently defined by the FDA. This is particularly true for the growing number of Americans who have high-deductible drug benefits.<sup>3</sup> Defining “drug shortage” to include economic factors – particularly in the case of drugs that have no generic competition and that are off-patent – would allow cGMP compounded production of these drugs in FDA-registered outsourcing facilities. This is a market-based way to lower the cost of high-priced drugs and to help those in need, without resorting to drug imports or price controls.<sup>193</sup>

#### **D. Create billing codes for compounded drug prescriptions.**

As the 2014 GAO report highlighted, the absence of specific standard billing codes for compounded drugs prevents Medicare from identifying compounded drugs administered in an outpatient or physician office setting. This lack of specific billing codes is challenging for payors, both public and private. The “track and trace” sections of the DQSA were based on a real need for the national government to collect data on all prescription drugs. Unfortunately, lacking billing codes, compounded drugs are among the least tracked and traced drugs Americans use. Congress should insist on new billing codes and a related payment convention for compounded drugs. The most efficient way to do this is to identify compounded drugs by their constituent NDC codes, such as private insurance currently does, and use clinical need and pricing methodologies developed for compounding by companies such as Focus Script, LLC. A strategy to identify compounded drug prescriptions and efficiently scrutinize them is an important step in realizing the potential economic gains compounding has to offer.

#### **E. Allow market-based solutions to control prices.**

Market-based solutions should be the preferred choice in the reform of drug pricing. Experience has demonstrated that price controls, while offering temporary relief to patients, can disrupt supply and lead to drug shortages. Similarly, overly aggressive insurance coverage mandates and legislated payment restrictions can lead to unwanted premium hikes, market participants dropping out, and other unintended consequences. The partnership between Imprimis and the largest PBM in the U.S. to solve the Daraprim<sup>®</sup> crisis demonstrated how two organizations with a common goal can work together to quickly create a viable solution for patients unnecessarily bearing the burden of U.S. drug price gouging.

As noted in a March 2016 article, “Drug Compounding: Cause and Cure for High Drug Prices?”:

*“At a time when many lawmakers are calling for radical costs controls, the Daraprim<sup>®</sup> incident has revealed how traditional market mechanisms and the creative employment of existing pharmacy practices, such as compounding, may serve as effective checks and balances. This is an important consideration as our society confronts the challenge of structuring suitable drug pricing reforms, which inevitably involve difficult trade-offs between innovation, patient need, and cost.”<sup>194</sup>*

Compounding may play an even larger role in health reform through a positive and respectful relationship with the FDA and CMS. Mutual cooperation between compounding companies and public and private payors, working constructively with these regulators, will ensure the best outcomes for the patients being served.

#### **F. Encourage compounded drug production according to cGMP.**

Healthcare policy should encourage all drug makers, including compounding companies, to adopt the safest and highest quality manufacturing standards. These standards, referred to as cGMP are reflected in Title 21 of the CFR Parts 210 and 211.<sup>65,66</sup>

Presently, the FDA has adopted an “all or nothing” policy for FDA-registered outsourcing facilities or pharmacies. The agency’s current view is that if anything in a facility should be made to cGMP standards, such as a sterile drug, then everything in the facility must be made in accordance with cGMP. Since many compounding pharmacies need to make drugs such as diaper rash creams and other low risk formulations, they refrain from registering with the FDA and instead remain as state-licensed compounding pharmacies. As a result, they are free to make their formulations according to lower safety standards.

The FDA should mandate cGMP regulation for compounding facilities using a risk-based approach. For example, in the preceding example, FDA should allow for the use of a U.S. Pharmacopeia <795> standard for the diaper rash cream, and a cGMP standard for the riskier sterile formulation such as an eye drop. Federal policy should encourage rather than discourage more cGMP production, regardless of the setting in which the drug is produced – in an FDA-registered outsourcing facility or in a state licensed pharmacy.

Current policy seems in conflict with what is referred to as the “Hamburg Principle.” The Hamburg Principle encourages adoption of cGMP for all drugs produced in the U.S. It is named for a January 8, 2014 letter from former FDA Commissioner Margaret Hamburg encouraging purchasers of compounded drugs to choose to buy from FDA-registered outsourcing facilities. Among her reasons was that outsourcing facilities produce drugs according to cGMP.<sup>98,99</sup> A policy that effectively penalizes a compounding pharmacy for adopting cGMP for only those drugs that require it and not for those that are non-sterile or otherwise classified as lower risk drugs is manifestly unwise. It should be amended to instead encourage cGMP production of compounded formulations wherever practicable.

### **G. Allow Medicare to pay for compounded drugs made from bulk drug ingredients.**

All APIs used to make compounded drugs are FDA-approved and have been manufactured in FDA-inspected cGMP manufacturing facilities – under the same regulatory framework as branded drugs.<sup>195,196</sup> These ingredients are supplied to the compounding facility in bulk to be made and dispensed as compounded medications.

As previously noted, however, Medicare Part D does not cover APIs for compounded drugs because they do not meet its definition of a Part D drug, which must be a finished drug product that itself is FDA-approved. Yet if a branded FDA-approved drug is used in the compounding process, Medicare does cover it – both the cost of the branded drug, and the compounding labor costs.

The current policy benefits large pharmaceutical companies selling FDA-approved drugs to compounding pharmacies for use as components in compounded drugs. As explained previously, the use of finished drugs as components in compounded drugs does not benefit patients, because the correct active ingredients for compounded drugs are the FDA-approved bulk substances made in FDA-registered and FDA-inspected manufacturing facilities. By mandating the use of non-optimal components in compounded drugs for the Medicare market, current policy succeeds only in putting money in the pockets of the drug manufacturers.

The current CMS policy also shortchanges the Medicare program, which is denied the savings from compounded drugs made with lower-cost bulk drug ingredients. Across the federal government, payors including CMS, the Department of Veterans Affairs, and the Department of Defense should rationalize their coverage of compounded drugs to take advantage of the cost savings that would be obtained through paying for compounded drugs made properly from bulk chemicals.

### **H. Recognize the link between drug prices and patient health.**

Imprimis serves patients each day whom are negatively affected by the high cost of their medicines. High prices and accessibility issues determine whether or not a prescription gets filled.

Compounders can safely make lower-cost copies of some highly priced FDA-approved drugs. However, recent draft FDA guidance preventing compounding of “essential copies” of FDA approved drugs and makes it clear that, “factors such as a lower price, are not sufficient to establish that the compounded drug product is not essentially a copy of the commercially

available drug product.”<sup>123</sup> While the guidance does imply that price can be a consideration, denies a link between drug prices and patient health that often provides a compelling rationale for prescribing a compounded formulation instead of a commercially available drug.

In the aforementioned draft guidance minimizing considerations of patient cost, the FDA quotes the House-Senate Conference Report from the FDA Modernization Act of 1997 in support of its rationale.<sup>197</sup> This law provides a broad exemption for drug compounding subject to several conditions, including that the compounded drug is not “essentially a copy” of a commercially available drug product. Both law and the Conference Report accompanying it, however, support a different interpretation of “essentially a copy” than the FDA has advanced. The Conference Report specifically states that whether there is “a significant difference” between a compounded drug and a commercially available product is dependent on the circumstances of its use by an individual patient. The Conference Report specifically states that whether a compounded drug produces a “significant difference” for a patient shall be “determined by the prescribing practitioner.” Moreover, the conferees expressly directed FDA to “accord great deference to the licensee’s judgement.”<sup>197</sup>

As an example of the rare instance where the prescribing physician’s judgement should not be accorded deference, the Conference report cited a physician who prescribes a compounded alternative because he “is receiving financial remuneration or other incentives to write prescriptions for compounded products.” This is a very different framework than the one that the FDA has adopted. It is especially ironic the FDA would cite this passage, given that the Medicare system through 6% payment incentives to doctors for prescribing higher-priced drugs, is in effect providing financial remuneration to write prescriptions for higher-priced non-compounded choices.<sup>106</sup> Through its Imprimis Cares<sup>®</sup> program, Imprimis offers lower-cost compounded drugs as alternatives to high priced FDA-approved drugs, and they do so without inducements of any kind. Imprimis believes in conducting business in this way because they, along with the prescribers with whom they work, always keep the best interests of their patients in mind. Additionally, these practices are consistent with and at the core of the mission, vision and values of Imprimis’ ethical approach to participating in the pharmaceutical industry.

The U.S. prescription drug crisis is all about the link between drug prices and patient health. When a safe, high-quality alternative to an off-patent, multi-decades old, FDA-approved drug – particularly if that drug began its commercial life as a compounded drug – the FDA should not protect this drug from lower-priced compounded competition. The interests of patients, the imperative that essential medications be affordable and available, and the directive

in federal law that the FDA defer to the prescribing physician's judgment all militate to the conclusion that FDA policy should be revised so that it no longer protects markets for drug makers that make critical medicines unaffordable and inaccessible.

FDA policy should be on the side of affordability and access for Americans rather than the profits of the pharmaceutical industrial complex.

**I. Keep the physician-patient relationship sacrosanct.**

Physicians should always have the final say on the treatment their patients need. Those choices are influenced by factors including side-effects, dosage or strength, and costs incurred by the patient. Because the physician is always in the best position to judge a patient's specific needs, which drug to prescribe should never be decided by the FDA or any other government agency. Physicians must not have their armamentarium limited to FDA-approved retail drugs when the same active ingredients – used in those commercially available drugs may be individualized and tailored to best treat their patients.

**J. Allow Medicare patients the right to pay for prescription medicines that Medicare does not cover.**

The U.S. prescription drug crisis has received significant media coverage and spurred U.S. legislators and regulators to action. Nonetheless, there has been little noticeable effect on actual drug prices in the market, which continue to escalate. Just as it is apparent drug prices will continue to increase, it is equally clear that meaningful reforms – if they are coming at all – will require time to implement. For this reason, current policies toward compounded drugs should be reexamined as a means of making affordable, quality healthcare for all Americans an urgent priority.

An example from the Imprimis experience illustrates one way that compounded medications can provide immediate relief from escalating drug costs. In April 2014, Imprimis introduced its Dropless Therapy compounded formulations, used to prevent infection and inflammation after cataract surgery. Since then, these formulations have been successfully used by the nation's leading ophthalmologists following over 300,000 cataract surgeries in the U.S. Until January 2015, Medicare was silent to cataract surgery patients paying out-of-pocket for Dropless Therapy at a price far less than they paid for the eye drops that are the alternative means of preventing infection and inflammation after cataract surgery. This resulted in significant saving for patients, providers, and Medicare. Since then, however, CMS policy has

not only prevented Medicare reimbursement, but also prevented patients from paying for the drugs themselves. Now, Dropless Therapy is used only when the physician or provider pays the full cost on behalf of the patient – from the providers' fees.

Not surprisingly, the effect of this policy change has been to severely restrict patients' access to Dropless Therapy, particularly for those in society who are most in need of an alternative to the highly priced conventional eye drops. This policy change prevents Medicare from realizing the significant cost savings from allowing patient choice of Dropless Therapy or any other alternative to legacy eye drop therapies. Patients, physicians and the U.S. healthcare system will benefit from a common-sense revision to Medicare policy that would at least allow those patients who choose Dropless Therapy to pay for it themselves, relieving their physicians of this burden.

In the case of Dropless Therapy, CMS could make this policy change itself, without need of legislation. Were it to do so, physicians who deem Dropless Therapy to be better for their patients would no longer have a disincentive to do so. Patients who choose Dropless Therapy would gladly pay for it, because the full price is less than the *copayment* for conventional eye drops under Medicare and most health insurance.

More broadly, in order to extend this common-sense reform to all cases in which direct patient payment would be less costly than the patient's required copayment for an equivalent alternative, Congress should amend Section 1834 of the Social Security Act to state as follows:

*In the case of any drug for which Medicare covers all or part of the cost through Part B or Part D, and for which the patient is responsible for a copayment, the patient shall be entitled, in lieu of such Part B or Part D coverage, to pay a lesser amount than the copayment directly to the provider of the drug, if the provider is willing to accept such payment in full satisfaction of the cost. This patient protection shall extend to compounded drugs from bulk ingredients used in FDA-approved products prescribed as substitutes for, or medical equivalents of, the specific drug for which Medicare covers all or part of the cost through Part B or Part D.*

Physicians know what is best for their patients. They should not face financial disincentives to prescribing the best medication. This one small policy change could substantially reduce healthcare costs while improving the lives of millions of patients by providing access to safe, high-quality, lower-cost compounded drugs.

### **K. Get Medicare Parts B and D in sync.**

In its administration of Medicare, CMS makes decisions that affect the overall cost of the program. Yet CMS executes its responsibilities in a way that often obscures opportunities for savings in one part of Medicare through more modest expenditures in another part. Different groups within the business operations staff of CMS are responsible for Part B and Part D. The result is that the overall cost of Medicare's separate parts is unnecessarily high.

CMS should change its approach to reimbursement decision making in Parts B and D, so these separate parts of the program managed to maximize cost efficiencies in both. Currently, there is apparently no meaningful effort to reconcile reimbursement decisions in the two programs, and the related benefits to patients.

The goal of integrating Part B and Part D reimbursement decisions should be to provide Medicare beneficiaries with the best clinical options while, at the same time, allowing Medicare to incent payment for the lowest cost option.

An example will illustrate. Presently, if a new \$500 drug that may be administered in a Medicare Part B setting, such as a hospital or outpatient facility, can therapeutically displace the need for a \$5,000 drug traditionally paid for through Part D, there is no way for Medicare to capture the benefit. Medicare Part B is measured only against itself. So if CMS decides that Medicare will cover the new \$500 drug, this will be a net cost to Part B. The vastly higher savings realized in Part D are not netted against it. The CMS managers of the Part B benefits see only \$500 in higher costs, not the overall Medicare savings of \$4,500.

Imprimis has direct experience with this conundrum. As noted previously, a study by Andrew Chang & Co. LLC has demonstrated the billions of dollars in cost savings that would accrue to Medicare if CMS were to cover compounded Dropless Therapy, which can therapeutically displace the far costlier drop therapy that CMS already pays for under Part D. Dropless Therapy currently receives no payment from Medicare, but is included in CPT Code 66984, the cataract surgery bundle fee under Medicare Part B. This means the cataract surgery fee does not increase even when Dropless Therapy is added to the bundle. Worse, in July 2016, CMS issued its proposed 2017 payment rate regulation for hospital outpatient departments and ambulatory surgery centers. It discloses that the new bundled fee for cataract surgery in the ambulatory center setting is expected to be reduced from \$976.17 to \$964.88.<sup>198</sup>

The lack of any reimbursement for Dropless Therapy naturally inhibits its use. Meanwhile, the far more expensive topical drops continue to be covered under Part D.

In a situation where there is a net savings to Medicare overall, CMS should ensure that its managers who make reimbursement decisions for Part B know the benefits that may accrue elsewhere in Part D. This common-sense reform would save Medicare billions.

#### **L. Increase consumer access to cGMP compounded drugs.**

Current FDA policy provides a perverse incentive for a compounding company to operate as a 503A compounding pharmacy rather than a 503B outsourcing facility. That is because 503A facilities can compound a wider range of products by using more APIs, while at the same time being subject to less FDA regulation.

The FDA should begin by placing all drugs permitted to be compounded by 503A compounding pharmacies, including components of approved drug products and substances subject to a USP/NF monograph, on an inclusive list of drugs that may be compounded by a 503B outsourcing facility. The FDA and the PCAC could then, over time, refine the list by removing substances as inappropriate for compounding in a 503B environment. This list would be subject to public comment as statutorily required. In the interim, it would permit the FDA's preferred outsourcing facilities to expand the availability of higher quality compounded drugs to patients and facilities that need them.

Additionally, the FDA should work to finalize the Section 503B bulk list to provide clarity for outsourcing facilities in regard to which drugs they can and cannot produce.

Finally, the FDA should re-evaluate its approach to office-use compounding for 503A compounding pharmacies and permit office use compounding for acute and emergent care conditions such as toxoplasmosis, interstitial cystitis, and infantile spasms and seizures, as determined by the healthcare provider.

#### **M. Provide reasonable FDA oversight of compounded drugs.**

The FDA has both an Office of Generic Drugs<sup>199</sup> and an Office of New Drugs<sup>200</sup> to guarantee the public has access to safe and effective medications for both generic and innovator drugs. The FDA should consider creating an Office of Compounded Drugs or changing the Office of Generic Drugs to become the "Office of Generic and Compounded Drugs" to ensure all compounding companies are reasonably inspected and held to the highest

safety standards, that they are given consistent treatment during FDA inspection, and that they receive further guidance regarding regulatory matters.

While some in the compounding industry are wary of the FDA in light of its recent actions to restrict the use of compounding, the objective of the industry and policymakers alike should be to improve public access to safe compounded drugs. The only way this will happen is for industry to embrace the FDA as a partner and do everything possible to increase the safety profile of compounded drugs. This may involve creating a more customized scale of quality standards that are appropriate certain compounded drugs and dosage forms – which may incorporate critical aspects of cGMP and exclude others that are less relevant for the specific drug. Viewing the FDA as a partner is the best way to increase the quality of drugs produced by compounding facilities, and in turn provide Americans with safer, lower cost compounded drugs.

#### **N. Stop protecting markets for old, off-patent drugs.**

Similarly, to when a brand-name drug goes off-patent and an equivalent generic drugs is immediately permitted by the FDA, the FDA should allow drugs that have been off-patent for a period of more than 10 years to be compounded in 503B outsourcing facilities.<sup>201</sup>

The Hatch-Watchman Act (HWA) intended to bring about competition for off-patent or weakly patented drugs, while still protecting the inventors of new drugs. The law, however, has been only partially successful in incentivizing generic competitors to enter the marketplace.<sup>202</sup> A consequence of the HWA is a legacy of protected markets for old off-patent drugs that have small, overlooked markets. These are precisely the drugs that companies such as Valeant, Turing, and Retrophin have pounced upon. Properly interpreting Section 503B of the DQSA to permit outsourcing facilities to compound these old, off-patent and well-characterized drugs that do not have generic competitors can create needed competition by making safe copies of these drugs to cGMP standards.

#### **O. Provide new FDA approval pathways for compounded drugs.**

Many drug companies, including those that make compounded drugs, are supportive of submission to a reasonable FDA approval process. Currently, however, the requirements for FDA approval of a drug are not universal across drug classes, dosage forms and therapeutic areas.

For example, to demonstrate efficacy for Imprimis' Dropless Therapy compounded formulations, used to prevent infection and inflammation after cataract surgery, current FDA

procedures would require more than 100,000 patients to demonstrate statistical significance between the active drug and a placebo, at a cost likely to exceed \$1 billion, even though Dropless Therapy has been used successfully in more than 300,000 cases. Other manufacturers of drugs to prevent infection and inflammation post-cataract surgery face similar financial hurdles in winning FDA approval. As a result, even most FDA-approved drugs have not demonstrated efficacy in the “standard of care” therapy for infection and inflammation post-cataract surgery. Instead, they are used off-label, such as Vigamox<sup>®</sup> for prophylaxis of postoperative endophthalmitis.<sup>203</sup>

The fact there is no economically feasible pathway for drugs used following cataract surgery – whether compounded or manufactured – to undergo clinical trials affects compounded drugs differently. Imprimis continues to make its Dropless Therapy from FDA-approved drug components. But competitors that, like Imprimis, have not undergone clinical trials to establish the efficacy of their off-label use for infection and inflammation post-cataract surgery are able to claim they are “FDA approved.” Dropless Therapy, the compounded alternative, is in this odd framework “non-FDA-approved.” All parties, including patients, ophthalmologists and Imprimis, would prefer to take their drugs through a reasonable FDA approval process if one existed. Such a process would utilize the clinical experience of patients and physicians. Were this the case, Imprimis would apply for FDA approval of Dropless Therapy.

In the past, Congress and the FDA have taken steps to encourage FDA approval of innovation, particularly with respect to drugs for orphan diseases.<sup>204</sup> Similarly, in the case of compounded drugs used for rare, but devastating, conditions such as endophthalmitis, the FDA could be encouraged to develop *more* “custom clinical pathways” for FDA approval for non-orphan diseases. These would be scaled to the overall market opportunity for the proposed drug. The product of such a policy would be more FDA-approved drugs through an affordable process, administered on a risk-adjusted basis. The cost savings resulting from these custom clinical pathways could be passed on to patients in the form of competition in the market from new, accessible, and affordable FDA-approved drugs.

## **IX. Conclusion: Compounding is Not the Only Solution**

Drug compounding is only part of the solution to the challenges facing our healthcare system. It is not a panacea but rather an important part of a well-functioning healthcare marketplace that Congress and the next president can tap to ensure competition and keep many drug prices in check.<sup>205</sup>

There are several additional, complementary ways to address our national drug pricing crisis.

The FDA should further expedite the approval process for generic drugs. Currently, under normal review, the FDA strives to take action on an application within 10 months of submission.<sup>206</sup> The statistics from 2014-2015 demonstrate that this goal is not being met.<sup>49,50</sup>

Particularly during times of medical urgency, it is crucial the FDA further expedite the ANDA approval process for generic drugs. For these urgently needed drugs, the FDA's goal is to take action on an application within six months of submission.<sup>206</sup> Forcing desperately ill patients to wait half a year does not convey a sense of urgency. Particularly considering the additional delays most applications encounter, the current approach to approving urgently needed generic drugs is failing.

Well-established drugs that are now routinely used for off-label purposes should be given a fast track submission process within the FDA. The efficacy of these drugs is ordinarily established via physician and patient experiences, and such drugs have a known safety profile. A shorter-form "ANDA-light" process and related fee structure would be helpful for compounded drugs. Historically, the FDA only approves a drug and deems it as safe and effective for the specific condition it was tested to treat.<sup>207</sup> For this reason, physicians often prescribe medications off-label to treat patients in ways that have not been specifically approved by the FDA if the treatment is medically appropriate for the patient.<sup>207</sup> This state of affairs means that pharmaceutical companies are not likely to seek FDA approval for a new drug indication for an existing medicine, given the costly and time-consuming FDA approval process.<sup>62</sup> To provide the best possible care for patients, well-known drugs, including compounded drugs, that are currently being prescribed off-label should be permitted to gain FDA approval via a more timely and less costly submission process.

The drug compounding industry holds patient safety in a place of paramount importance, just as pharmaceutical manufacturers do. The continued need for stringent safety regulation of all producers of prescription drugs remains clear. The recent enactment of the DQSA has strengthened that regulation for compounded drugs. Moreover, it has provided a pathway for compounding companies to voluntarily submit to the highest level of FDA regulation and inspection, and to produce compounded drugs at the same cGMP standards as all FDA-approved drugs. The DQSA was passed in the wake of the NECC tragedy, which highlighted the risks of a small, unsupervised operation able to produce drugs unsafely in knowing violation

of the law. And while the NECC example is representative of neither the pharmaceutical industry nor the compounding industry, we must keep in mind that more than 2,400 patient deaths per week are caused by adverse reactions to FDA-approved medications.<sup>114</sup> The challenge for safety regulation is not compounding or drug manufacturing *per se*, but rather ensuring that prescription drugs, however and wherever produced, follow a rational, reliable, and up-to-date set of rules that apply equally to branded, generic, over-the-counter and compounded drugs.

The current system does not fit this description. Each year, 125,000 Americans die from non-adherence, the direct result of high drug costs.<sup>26</sup> Patient safety must be understood to encompass access to affordable medicine. A shortage of drugs priced within reach of the average American is no less a shortage than one produced by lack of supply, and should be treated as such. Currently, even compounding companies such as Imprimis that produce compounded medications in FDA-registered and FDA-inspected facilities to the highest cGMP standards are in most cases not allowed to compete, and the objective of rational safety regulation is not being met.

Federal and state drug regulatory policy must refocus its priorities on those things that are most important: taking care of patients, putting safety first, and addressing the nation's growing drug shortage, drug pricing, and drug accessibility problems. Safe and effective compounding of necessary medications, by serving as the pin to burst the drug pricing bubble that has negatively affected the health and well-being of far too many Americans for too long, can be a critical part of these needed reforms.

*The proverbial "bottom line" is that when Martin Shkreli called members of Congress "imbeciles" in the spring of 2016, he was not necessarily hurling his vitriol at individual elected officials who were confronting him. He was evidencing, in a crystal clear diction, his disrespect and disdain for the American people he sought to fleece through his drug pricing policies and his entire business model. Shkreli is but one example of the many pharmaceutical executives and companies that betrayed the inherent social contract between the American pharmaceutical industry and Americans that bestowed on it so many unusual privileges. It is now up to the American people, our elected leaders and those who are charged with the important work of government agencies to prove Shkreli and the many others like him wrong. Drug and healthcare policy must now encourage competition and work to the advantage of consumers. We are not imbeciles; nor are we lemmings.*

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