

2013

## Bringing Dormant GRAS(E) to Bloom: Reviving the GRASE Concept for Drugs

Emily Pulchalski

Follow this and additional works at: <http://scholarship.law.umn.edu/mjlst>

---

### Recommended Citation

Emily Pulchalski, *Bringing Dormant GRAS(E) to Bloom: Reviving the GRASE Concept for Drugs*, 14 MINN. J.L. SCI. & TECH. 493 (2013).

Available at: <http://scholarship.law.umn.edu/mjlst/vol14/iss1/11>

*The Minnesota Journal of Law, Science & Technology* is published by the University of Minnesota Libraries Publishing.

## Note

### Bringing Dormant GRAS(E) to Bloom: Reviving the GRASE Concept for Drugs

*Emily Puchalski\**

#### INTRODUCTION

The cost of getting a new drug to market was estimated at \$802 million in 2003, and more recent estimates have placed the cost at \$1.3 billion and \$1.7 billion.<sup>1</sup> Notwithstanding debates concerning the accuracy of these figures, it is clear that there is a high and increasing cost associated with getting a drug to market.<sup>2</sup> Making the commercial drug development process even more difficult, the time from initial development to use of a drug for patient treatment can be fifteen years.<sup>3</sup> In addition, of the compounds discovered as potential drugs, only approximately one in every ten thousand will actually end up as “an approved drug for sale.”<sup>4</sup> This expensive and time-intensive process produces many undesirable side effects including a low incentive to develop drugs for diseases primarily affecting the poor, difficulty in offering affordable drugs to countries of lower- and middle-income levels, drug-access problems, and competition from foreign countries with quicker ap-

---

© 2013 Emily Puchalski

\* J.D. Candidate (2013), University of Minnesota Law School. The author would like to thank Professor Ralph Hall for the idea for this Note and the staff and editors of the *Journal* for all their hard work and dedication.

1. Roger Collier, *Drug Development Cost Estimates Hard to Swallow*, 180 *CANADIAN MED. ASS'N J.* 279, 279 (2009) (estimates in U.S. dollars).

2. See, e.g., *id.* (“Most experts agree that the cost of research and development in the drug industry — the cost of clinical trials in particular — is rising significantly.”).

3. PHARMA, *DRUG DISCOVERY AND DEVELOPMENT: UNDERSTANDING THE R&D PROCESS* 1 (2007), available at [http://www.phrma.org/sites/default/files/159/rd\\_brochure\\_022307.pdf](http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf).

4. Omudhome Ogbu, *Why Drugs Cost So Much*, *MEDICINE.NET*, <http://www.medicinenet.com/script/main/art.asp?articlekey=18892> (last visited Sept. 28, 2012).

proval processes.<sup>5</sup> Such policy concerns have elicited calls for a reformation of the drug-approval system.<sup>6</sup>

Like most complex problems, one fix-it-all solution does not exist. However, a partial solution may be buried deep in the statutory text of the Food, Drug, and Cosmetic Act (“the Act”).<sup>7</sup> Section 321(p)(1)<sup>8</sup> of the Act contains an exemption that could avoid much of the costly research and development and approval processes. Application of § 321(p)(1) could save certain drugs from the costs associated with the New Drug Application (NDA) required by the Food and Drug Administration (FDA) to get a new drug to market. The statutory provision applies to drugs that are “generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed.”<sup>9</sup> Drugs falling within this provision have been referred to as “generally recognized as safe and effective,” or GRASE for short.<sup>10</sup> Thus, drugs that have been shown to be safe and effective through either scientific experimentation or through actual usage could avoid the NDA process.<sup>11</sup> Due to the fact that many drugs, once discovered, can be found applicable for other purposes and the fact that some drugs are

---

5. Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 BIOSOCIETIES 34, 46–47 (2011), available at <http://www.palgrave-journals.com/biosoc/journal/v6/n1/pdf/biosoc201040a.pdf>; Andrew Pollack, *Medical Treatment, Out of Reach*, N.Y. TIMES, Feb. 10, 2011, at B1 (“Now, executives of device companies say the F.D.A. has gone too far in flexing its regulatory muscle, and they worry that a slower, tougher approval process in a weakened economy could chill investments and cripple innovation. In addition, they say that American patients are being deprived of the latest technology because companies routinely seek approval for new devices in Europe first.”).

6. See, e.g., Thomas J. Philipson & Eric Sun, *Quantifying High Cost of Caution May Speed Drug Approval Process*, INVESTORS.COM (June 14, 2010, 6:48 PM), <http://news.investors.com/ibd-editorials-perspective/061410-537266-quantifying-high-cost-of-caution-may-speed-drug-approval-process.htm> (discussing issues associated with providing the sick with access to potentially life-saving drugs and calling for a revolutionary change in FDA’s approval timing process).

7. 21 U.S.C. §§ 301–399 (2006).

8. This Note uses the United States Code statutory citation system and not the parallel citation system of the Act.

9. 21 U.S.C. § 321 (2006).

10. James T. O’Reilly, *GRAS ROOTS: How to Advocate for and Defend “General Recognition” of Safety for Food Ingredients and Drugs*, FDLI MONOGRAPH SERIES, Dec. 2009, at 1, 6.

11. 21 U.S.C. § 321(p)(1) (2006).

based off of products used for centuries safely, the GRASE provision provides a mechanism to get these kinds of drugs to market quicker, as much of the lengthy safety and efficacy studies required for an NDA are not necessary for drugs of this nature.<sup>12</sup>

Despite the potential cost and time-saving benefits of GRASE, the standard for getting a drug designated as GRASE has been set so high that the provision has fallen out of use.<sup>13</sup> Today, the chances of getting a drug classified as GRASE can be equated with the chances of winning the lottery. Knowledge of the bleak prospects of obtaining GRASE status has dissuaded drug manufacturers from even attempting to gain GRASE status.<sup>14</sup> Although the Act has the GRASE provision as a by-

---

12. See, e.g., Alistair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618, 618 (2006) (discussing how “[t]he high cost of drug development favors risk-averse drug-development strategies such as creating new formulations, combining already approved agents, and making subtle chemical changes . . .”).

13. See, e.g., JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13:33 (3rd ed. 2011) (“Drug GRASE claims are very difficult to win over FDA’s objections. An absence of published peer journal articles about a compound ‘is proof that the requisite general recognition does not exist.’”); see also JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13:34 (3rd ed. 2011) (“As the stringency of the NDA review process increased over time, the drug makers’ efforts to escape ‘new drug’ status also increased. GRASE remained a definition toward which courts showed great deference; guided by the Supreme Court’s attitude of deferential acceptance, federal judges declined to overturn FDA decisions about ‘general recognition’ despite some sophisticated arguments of well-prepared challengers. Some, like the Chief Judge of the First Circuit, remarked with surprise *that the general recognition ‘exception’ from new drug status ‘is not an exception at all.’* The FDA has rarely lost GRASE disputes, but did lose one jury case where the opinions of the government’s experts did not outweigh those of the claimant’s experts.”) (emphasis added) (footnotes omitted); JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION § 13:44 (3rd ed. 2011) (“Although the Supreme Court had recognized a narrow exception from the stringent requirement that a drug reach GRASE status through adequate and well controlled studies, the so-called ‘exception’ is so narrow as to be unachievable by virtually all drug products today. Exception is taken from the Court’s comment that ‘in some cases general recognition that a drug is efficacious might be made without the kind of scientific support necessary to obtain approval of a NDA.’ Finding this Holy Grail is so elusive, in light of the FDA’s preference for tangible data, that one should not lightly attempt to claim exemption.”) (footnotes omitted).

14. See RICHARD R. ABOOD, PHARMACY PRACTICE AND THE LAW 73 (6th ed. 2010) (discussing how even if a drug has been on the market without FDA approval for a long period of time, if FDA decides that the drug must be subjected to FDA approval, despite the existence of the GRASE provision in the Act, the FDA “will not GRASE a product,” forcing the drug to comply with the NDA process despite its long-term safe use).

pass for drugs having certain indicia of safety and efficacy, its disuse has essentially deleted the provision from the Act. The current GRASE system is broken and needs fixing, because for all intents and purposes there is no functioning GRASE system. A change to the current GRASE system could introduce a means for certain drugs to get to market through a quicker and less expensive process without losing assurances of the drugs' safety and efficacy.

This Note examines the GRASE designation for drugs. Part I of this Note will describe the history of the Act's GRASE provision. Part II of this Note presents previous proposals for lowering the cost and time requirements of FDA's drug-approval process. Finally, this Note concludes that the GRASE concept should be revived for drugs, and a GRASE Notification System should be implemented because this system could lower the cost associated with drug development.

#### I. BACKGROUND: THE HISTORICAL DEVELOPMENT AND APPLICATION OF GRASE TO DRUGS

To get a new drug to market, the drug must comply with the NDA process; however, the Act provides the GRASE provision as an alternative process for getting the drug to market provided that the requisite showings can be made. Meeting the requirements for achieving GRASE status, in fact, means that the drug is no longer considered to fit the statutory definition of a "new drug."<sup>15</sup> The common sense meaning of a "new drug" does not align perfectly with FDA's statutory definition of a "new drug." Employing the common understanding of the word "new" would lead to defining a new drug as a drug that has recently come into existence. However, this is not the meaning of a "new drug" for FDA purposes.<sup>16</sup> To understand the meaning of "new drug," it is important to recognize that FDA approves a drug for a particular use; the Agency does not issue general approvals for drugs.<sup>17</sup> The particular use for which a drug is approved is referred to as an indication; an example would be the

---

15. Kurt R. Karst, *Marketed Unapproved Drugs—Past, Present and Future?*, FDALAWBLOG.NET (Feb. 2007), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/files/marketed\\_unapproved\\_drugs\\_feb\\_07.pdf](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/files/marketed_unapproved_drugs_feb_07.pdf).

16. 21 C.F.R. § 310.3(h) (2011).

17. Omudhome Ogbru, *Indications for Drugs (Uses), Approved vs. Non-Approved*, MEDICINE.NET, <http://www.medicinenet.com/script/main/art.asp?articlekey=20732> (last visited Sept. 27, 2012).

use of a drug for the treatment of a specific disease.<sup>18</sup> Thus, a drug with an indication for treatment of one disease would be a “new drug” when used to treat a different disease.<sup>19</sup> Other ways of being classified as a “new drug” for FDA purposes include:

- (1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be an active substance or a menstruum, excipient, carrier, coating, or other component.
- (2) The newness for a drug use of a combination of two or more substances, none of which is a new drug.
- (3) The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug. . . .
- (5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.<sup>20</sup>

In addition, manufacturers can only market drugs for indications approved by FDA.<sup>21</sup> Ultimately, the importance of having a drug approved for different indications relates to the ability of the manufacturers to promote the drug for the treatment of different diseases.<sup>22</sup>

To fully understand how the GRASE provision could help get certain drugs to market quickly without the loss of safety and efficacy assurances, the complex regulatory environment in which the GRASE provision operates must be explored. First, a historical inquiry into the GRASE provision including both case law and legislative history interpreting GRASE will be discussed. Next, the parallel “generally recognized as safe” (GRAS) concept for food additives will be introduced as a vehicle for comparison to GRASE. Finally, various solutions that have been proposed as a means of lowering drug development costs will be introduced.

---

18. See, e.g., *id.* (“The Food and Drug Administration (FDA) classifies indications for drugs in the United States. Indications for drugs can be classified in two categories: (1) FDA-approved, also called labeled indications, and (2) Non FDA-approved, also called off-label indications.”).

19. See, e.g., Martin S. Lipsky & Lisa K. Sharp, *From Idea to Market: The Drug Approval Process*, 14 J. AM. BOARD FAM. PRAC. 362, 366 (2001) (discussing that in order to promote a drug’s use for a new indication, the manufacturer must file a supplemental NDA application with FDA which includes the requirement that the manufacturer perform a phase 4 clinical study).

20. 21 C.F.R. § 310.3(h).

21. Ogburn, *supra* note 17.

22. *Id.*

## A. HOW THE GRASE CONCEPT FOR DRUGS ENTERED THE ACT

The GRASE concept for drugs is enumerated in 21 U.S.C. § 321(p)(1), which defines “new drugs”:

(p) The term “new drug” means—

(1) Any drug ... the composition of which is such that such drug is not *generally recognized*, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, *as safe and effective* for use under the conditions prescribed, recommended, or suggested in the labeling thereof ....<sup>23</sup>

The “new drug” concept was not in the original 1906 Food and Drug Act.<sup>24</sup> Its inclusion came in response to the tragic deaths of over one hundred people who had taken a drug known as Elixir Sulfanilamide in 1937.<sup>25</sup> Before the drug was marketed the flavor of the drug was tested while its effect on human patients was not studied.<sup>26</sup> Thus, the 1906 Act’s failure to require a showing of drug safety before its manufacture and sale was recognized as a shortcoming only after users of the Elixir Sulfanilamide died.<sup>27</sup> The Secretary of the Department of Agriculture, further illuminating the problem, pointed to the existence of scientific literature establishing the hazards of diethylene glycol, an element of Elixir Sulfanilamide, in addition to the fact that the toxicity of the Elixir could have been shown in “a few simple and inexpensive tests on experimental animals.”<sup>28</sup>

The tragedy prompted the Secretary of Agriculture’s proposal that a premarket safety approval system for “new drugs” be added to the Act.<sup>29</sup> Then, in 1938, the Act, which contained

---

23. See 21 U.S.C. § 321(p) (2006) (emphasis added).

24. Jay M. Zitter, *What is “New Drug” Within Meaning of § 201(p) of Federal, Food, Drug, and Cosmetic Act (21 U.S.C.A. § 321(p))*, 133 A.L.R. FED. 229, 241–42 (1996).

25. *Id.*; Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG., June 1981, at 18, available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>.

26. Letter of Transmittal of H.A. Wallace, Sec’y of Dept. of Agric., reprinted in CHARLES WESLEY DUNN, FEDERAL FOOD, DRUG, AND COSMETIC ACT: A STATEMENT OF ITS LEGISLATIVE RECORD 1317 (1987) [hereinafter Letter of Transmittal].

27. See *id.* (discussing how the current Act did not require safety testing and proposing changes for this lack of pre-market safety testing).

28. *Id.*

29. Frederick H. Degnan, *Rethinking the Applicability and Usefulness of the GRAS Concept*, 46 FOOD DRUG COSM. L.J. 553, 556 n.16 (1991); Letter of

the new drug concept and the GRASE concept, was enacted.<sup>30</sup> The Act was amended again in 1962 to include a requirement of establishing drug effectiveness; this change was also instituted after a drug-related tragedy.<sup>31</sup> Currently, the Act “sets up a scheme whereby any drug that is not a pre-existing accepted product must show proof of general acknowledgment by experts in the field as to its safety and effectiveness (GRASE),”<sup>32</sup> and if this could not be shown then the product would be considered a “new drug.”<sup>33</sup>

Because the amendments establishing the current drug approval requirements were instituted at different times, questions arose as to how drugs in use before the amendments should be treated.<sup>34</sup> This “grandfathering problem” has effectively produced different classifications of drugs.<sup>35</sup> One class includes pre-1938 drugs, which are those that were in use before FDA required premarket safety approval.<sup>36</sup> Pre-1938 drugs were grandfathered into approval when the 1938 amendment was enacted.<sup>37</sup> A second group of drugs are those that came after the 1938 amendment but before the 1962 amendment, and thus were not required to show effectiveness data in order to get FDA approval.<sup>38</sup> Some drugs in the second group were not grandfathered into approval and were instead studied by FDA for effectiveness while remaining on the market.<sup>39</sup> Finally, a third group of drugs are those that came after both amendments and thus were subject to both premarket approval and

---

Transmittal, *supra* note 26, at 1326.

30. Ballentine, *supra* note 25, at 18.

31. *Milestones in Food and Drug Law History*, FDA.GOV, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm081229.htm> (last updated Feb. 9, 2009). The tragedy was associated with thalidomide: “Thalidomide, a new sleeping pill, is found to have caused birth defects in thousands of babies born in western Europe. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, arouse public support for stronger drug regulation.” *Id.*

32. Zitter, *supra* note 24, at 242.

33. *Id.*

34. O’Reilly, *supra* note 10, at 6–7.

35. See Zitter, *supra* note 24, at 242.

36. *Id.*

37. *Id.*

38. KURT R. KARST, MARKETED UNAPPROVED DRUGS—OVERVIEW AND FDA ENFORCEMENT POLICIES 2 (2006), available at <http://www.hpm.com/pdf/MARKETED%20UNAPPROVED%20DRUGS-%20OVERVIEW.pdf>

39. *Id.*



the effectiveness requirement. This Note focuses on the third category. Although the GRASE concept could hypothetically be applied to pre-1938 drugs “that have not changed content or label claims in 70 years,” such drugs “are a very small subset of today’s marketed drugs.”<sup>40</sup>

If found to be a “new drug,” the drug’s manufacturer must file a NDA with the FDA,<sup>41</sup> which must be approved before the drug can be marketed.<sup>42</sup> Being deemed a “new drug” creates “responsibility [for] the company seeking to market a drug to test it and submit evidence that it is safe and effective. [Then, a] team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the sponsor’s NDA containing the data and proposed labeling.”<sup>43</sup> A “new drug” classification, thus, thrusts a product into the expensive FDA approval processes and the attendant research and development requirements the approval process entails.<sup>44</sup>

Because a GRASE classification exempts a drug from filing the costly, time-consuming, and research-intensive NDA, “regulations have expanded [the GRASE concept] to mean that the requisite recognition has to be based on substantial evidence of adequate and well-controlled scientific, medical, and clinical investigations, not mere anecdotal evidence or testimonials.”<sup>45</sup> Many of the rules regarding the applicability of GRASE to drugs have come out of case law.<sup>46</sup>

## B. APPLICATIONS OF THE GRASE CONCEPT BY COURTS

Cases dealing with a contested GRASE drug often result when a manufacturer markets a drug that it believes to be

---

40. O’Reilly, *supra* note 10, at 6.

41. NDA applications are governed largely by 21 U.S.C. § 355 (2006).

42. *Id.*

43. *How Drugs Are Developed and Approved*, FDA.GOV, <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm> (last visited Sept. 28, 2012).

44. *See, e.g.*, Zitter, *supra* note 24, at 242 (“If it is found that a product is a ‘new drug,’ a New Drug Application must be filed, and unless there is effective approval of the application, the FDCA, in 21 USCS § 355, prohibits its introduction into interstate commerce. Accordingly, the definition of GRASE is quite significant . . .”).

45. *Id.* (citing 21 C.F.R. § 314.111(a)(5)(ii) (2011)).

46. *See, e.g., id.* at 242–46 (discussing how different cases have changed the understanding of GRASE as applied to drugs).

GRASE, and FDA challenges the GRASE classification.<sup>47</sup> These cases necessarily involve the testimony of dueling medical experts opining that the drug either does or does not satisfy the general recognition requirements of safety and efficacy.<sup>48</sup>

In 1958, the first case concerning the GRASE status of a drug was decided in *Merritt Corp. v. Folsom*.<sup>49</sup> In the case, Merrit attempted to prevent FDA from a seizure action against its drug Clarimycin Anti-Biotic Acne Lotion by contending that the drug was GRASE, and thus not a new drug requiring an NDA and FDA approval before being marketed.<sup>50</sup> Merrit provided the court with medical affidavits about the general recognition among medical experts that its product was safe for the treatment of acne, while FDA provided medical affidavits to the contrary.<sup>51</sup> The court found that the drug was not GRASE and stated:

Where there is a genuine difference of medical opinion among the experts on the question of whether a drug is generally recognized as safe for the treatment of a particular disease, it must be concluded that the drug is not *generally* recognized as safe for use in the treatment of that disease.<sup>52</sup>

In 1959, a similar approach to establishing that a drug was GRASE was applied by the U.S. District Court for the District of New Jersey.<sup>53</sup> There the court concluded that “a difference of opinion between experts established that a drug did not have the general recognition of safety required to take it outside the

---

47. *See id.* (discussing FDA challenging the GRASE status of drugs).

48. Zitter, *supra* note 24, at 242; 21 U.S.C. § 321(p)(1) (2006).

49. Degnan, *supra* note 29, at 573 (citing *Merritt Corp. v. Folsom*, 165 F. Supp. 418 (D.D.C. 1958)).

50. *Id.* (citing *Merritt Corp.*, 165 F. Supp. at 421).

51. *See Merritt Corp.*, 165 F. Supp. at 420 (“When viewed in the light most favorable to it, plaintiff’s medical affidavits assert that topical neomycin sulfate is generally recognized by experts as safe in the treatment of acne, even when used over prolonged periods of time. Defendant’s medical affidavits assert that topical neomycin sulfate is not generally recognized as safe by experts in the treatment of acne, because it has been shown to produce sensitization and cross-sensitization to streptomycin, an antibiotic valuable in the treatment of serious disease conditions. In addition, that use of neomycin sulfate for the treatment of acne is a new use for neomycin sulfate both because it has not been generally used for such a disease before and also because prolonged administration, which is required in an acne treatment, is a new method of utilizing the drug.”).

52. *Id.* at 421.

53. Degnan, *supra* note 29, at 573 (citing *United States v. Trim Reducing Aid Cigarettes*, 178 F. Supp. 847 (D.N.J. 1959)).

statutory definition of a new drug.”<sup>54</sup>

In regard to what must be shown to establish recognition by qualified experts, as required in 21 U.S.C. § 321(p)(1), courts have ruled “that unanimity among experts is not necessary to show that a substance is, in fact, GRAS.”<sup>55</sup> The relevant expert testimony “focus[es] on what the colleagues of the testifying expert know about the product; their awareness, recognition, and acceptance is central to the debate.”<sup>56</sup> The scientific experts must establish that the proposed dosage and usage of the drug are recognized generally in the medical community as safe.<sup>57</sup>

These developments have led ultimately to FDA needing only to show the existence of a reasonable number of qualified experts that question safety and efficacy for new drug status to be established.<sup>58</sup> Further reducing FDA’s burden for establishing a contested product as a “new drug,” the requisite qualified experts can be scientists within the Agency.<sup>59</sup> Overall, deferential standards have made it easy for FDA to combat GRASE drug claims.<sup>60</sup>

In consideration of the evidence necessary to establish the safety requirement for GRASE status, courts have held that there must be at least as much safety evidence to get a GRASE

---

54. *Id.*

55. *Id.* at 574 (citing *United States v. An Article of Drug . . . “Furrestrol,”* 294 F. Supp. 1307, 1311 (N.D. Ga. 1968)).

56. O’REILLY, *supra* note 13, § 13:32.

57. *See* 21 U.S.C. § 321(p) (2006) (“Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective *for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .*”) (emphasis added); O’Reilly, *supra* note 10, at 4 (discussing the term “safe” is defined by FDA rules as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use).

58. Zitter, *supra* note 24, at 242.

59. O’Reilly, *supra* note 10, at 8 (discussing how the FDA has been given “almost absolute power over awarding GRASE status or new drug status”). This is further complicated by the culture within FDA which effectively embraces hesitant approval and the fact that FDA’s approval for certain drugs comes much later than the drug gets approved in other, similarly situated, countries. *See* Henry I. Miller, *Is the FDA Innovative?*, DEFINING IDEAS (Nov. 22, 2011), <http://www.hoover.org/publications/defining-ideas/article/100081> (discussing FDA’s risk-averse approach to drug approval decisions).

60. *See, e.g.,* O’Reilly, *supra* note 10, at 8 (discussing how the U.S. Supreme Court gave FDA almost absolute powers over awarding GRASE status or new drug status).

designation for a drug as would be needed to achieve the safety requirement for a “new drug.”<sup>61</sup> It is important to remember that when considering safety, what must be proven is not the overall safety of the drug, but the safety of the drug for the particular use for which it is being offered.<sup>62</sup> In addition, the type of evidence that must be produced has to be “public and available to the scientific community.”<sup>63</sup> These studies are indispensable for proving GRASE status because the presence or absence of peer reviewed articles can serve as a proxy for the existence of general recognition of safety and/or efficacy.<sup>64</sup>

The requirements for establishing GRASE status favor FDA by making it easy for the Agency to prove disagreement among experts and by placing a high burden on petitioners for providing adequate safety evidence.<sup>65</sup> This deference to FDA is furthered by other regulations and court decisions. Notably, “a change in the target use of the product, a change in the formula, its dilution, the duration of treatment, or even the repackaging of the product” have been deemed sufficient for establishing that a drug should be considered a statutory new drug and accordingly subjected to the NDA approval process.<sup>66</sup> In addition, a combination of two FDA approved drugs is considered a new drug.<sup>67</sup> Also helping FDA prevail in GRASE cases is that courts defer to the Agency in the name of achieving the public health

---

61. Degnan, *supra* note 29, at 574 (citing *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 609 (1973); *Weinberger v. Bentex Pharmaceuticals Inc.*, 412 U.S. 645, 652 (1973); and *United States v. Trim Reducing Aid Cigarettes*, 178 F. Supp. 847, 921 (D.N.J. 1959)).

62. 21 U.S.C. § 321(p)(1) (2006).

63. *Id.* (citing *United States v. An Article of Drug . . . Bentex Ulcerine*, 469 F.2d 875, 880 (5th Cir. 1972), cert. denied, 412 U.S. 938 (1973) (“Certainly it is not unreasonable that if a drug is generally recognized safe and effective, one would find in medical literature over a period of years support for this premise from wide experimentation and study.”). *See also* *Bentex*, 412 F.2d at 652; *Colchicine*, 442 F. Supp. 1263, 1242–43; *United States v. Consolidated Midland Corp.*, 603 F.2d 215 (2d Cir.1979); *United States v. An Article of Drug . . . “Mykocert”*, 345 F. Supp. 571, 574 (N.D. Ill. 1972)).

64. *See* O'REILLY, *supra* note 13, § 13:33 (citing *U.S. v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692 (D. Md. 2001)).

65. *See, e.g.*, ABOOD, *supra* note 14, at 73 (explaining that even if a drug manufacturer can show that its product meets the general recognition of safety and efficacy requirements of GRASE, FDA will still require safety and efficacy to be proved via an NDA and courts will defer to FDA and not disrupt its conclusion).

66. Zitter, *supra* note 24, at 242.

67. *Id.*

and consumer protection goals of the Act.<sup>68</sup>

All of these factors together force the conclusion that FDA's opposition to a GRASE status application makes obtaining GRASE status virtually impossible.<sup>69</sup> This pro-FDA environment has led to drug manufacturers basically abandoning the GRASE designation,<sup>70</sup> which raises the question of how the incentives of drug manufacturing are being affected.

However, despite judicial deference to FDA, drug companies can still use GRASE for some over-the-counter drug products.<sup>71</sup> This use relies on 21 C.F.R. § 330, which provides for the publication of "Over-the-Counter (OTC) Monographs," that consist of an index of drugs along with usages in medical treatments.<sup>72</sup> Drug ingredients listed in an OTC Monograph are recognized by FDA to be GRASE.<sup>73</sup> The argument that follows is that the industry could create an OTC drug that complied with the specifications and would still be GRASE.<sup>74</sup> Also, if the company wanted to use the drug in a manner different from the monograph, there is a process for seeking FDA's approval of this, which could allow for more GRASE uses.<sup>75</sup> Another use for the industry would be to "take a product that has been [NDA] approved, and which has had sufficient experience on the market and extensive published literature, and submit a citizen petition to change its Monograph status to general recognition."<sup>76</sup> However, in practice, this use is not often invoked.<sup>77</sup> Although OTC drugs may still be able to use the GRASE provision, this Note focuses on prescription drugs.

---

68. See, e.g., Zitter, *supra* note 24, at 242-43.

69. O'REILLY, *supra* note 13, § 13:33.

70. See, e.g., O'Reilly, *supra* note 10, at 8 ("Weinberger v. Hynson, Westcott & Dunning, gave FDA almost absolute powers over awarding GRASE status or new drug status.") (footnote omitted). Thus, manufacturers have no incentive to attempt to classify a product as GRASE because if FDA disagrees, the agency will most probably win. This will result in seizure actions, litigation, and time and money lost with the final result of having to go through the NDA process, which the manufacturer could just do in the first place.

71. *Id.* at 6.

72. *Id.*

73. *Id.*

74. *Id.*

75. *Id.*

76. *Id.*

77. *Id.*

## C. APPLICATIONS OF THE GRAS(E) CONCEPT IN OTHER AREAS OF FDA JURISDICTION

GRAS, a standard similar to GRASE, applies to food additives.<sup>78</sup> The original interpretation of what GRAS meant for food additives was based on the GRASE standard for drugs.<sup>79</sup> If a food additive qualifies as GRAS then it is not subject to pre-market review and approval that is required for new food additives, which is similar to how a drug that is deemed GRASE is not subject to the NDA process.<sup>80</sup> To be GRAS, and thus not a food additive subject to premarket review, a product must be:

[G]enerally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.<sup>81</sup>

Despite their similar beginnings, GRAS and GRASE have diverged in importance.<sup>82</sup> The GRAS designation is still used by manufacturers to avoid the pre-review and pre-approval for food additives.<sup>83</sup> In defining what is required to establish a GRAS designation, FDA has promulgated regulations to implement GRAS in 21 C.F.R. § 170.3 and 21 C.F.R. § 170.30.<sup>84</sup>

78. See, e.g., *Generally Recognized as Safe (GRAS)*, FDA.GOV, <http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm> (last visited Oct. 22, 2011) [hereinafter *Generally Recognized*]. There is no effectiveness requirement for food additives, which is why the food additive standard is GRAS and not GRASE.

79. See Degnan, *supra* note 29, at 556 (“Borrowing from the ‘new drug’ definition enacted in 1938, most of the bills submitted during the eighty-fourth and eighty-fifth Congresses used a formulation of the ‘generally recognized as safe’ standard for defining a food additive.”).

80. *Guidance for Industry Frequently Asked Questions About GRAS*, FDA.GOV, <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm061846.htm#Q2> (last visited Oct. 22, 2011) [hereinafter *Guidance*].

81. 21 U.S.C. § 321(s) (2006).

82. One major factor supporting the relevance of GRAS designations today is the fact that companies still file notices with FDA of food additives they have determined as GRAS, while GRASE designations are assessed so deferentially to FDA that drug manufacturers do not use the classification. *GRAS Notice Inventory*, FDA.GOV, <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing> (last visited Sept. 30, 2011) [hereinafter *GRAS Notice Inventory*] (listing of the GRAS notices sent to the FDA since 1998).

83. See, e.g., *id.* (listing all of the GRAS notices sent to FDA since 1998).

84. See, e.g., *Generally Recognized*, *supra* note 78 (outlining various Code of Federal Regulation provisions that have been implemented for dealing with

Together, the CFR provisions provide for general recognition to be established through either scientific evidence, or if a drug was in use before 1958, then general recognition can be established through its common usage in food.<sup>85</sup> Notably, there are differences based on whether the product is claiming to be GRAS based on scientific procedures or through experience.<sup>86</sup>

Also, there is more FDA infrastructure for dealing with GRAS products.<sup>87</sup> For example, in the 1970s FDA established the GRAS affirmation process in which individuals could ask FDA to review a substance to determine if it qualified as GRAS.<sup>88</sup> Although the affirmation procedure is no longer in use, a replacement notification procedure was proposed in which one seeking to obtain GRAS status makes its own decision that its substance is GRAS and then informs the FDA of its determination instead of having to apply to the FDA to affirm that the substance was GRAS.<sup>89</sup>

Overall, this notification procedure has resulted in a GRAS designation that is still in use today.<sup>90</sup> To make the requisite GRAS showing:

A company develops a chemical or other ingredient for food use. The company finds published articles about safety and/or has expert statements about safety of the food, and prepares a package of support. The company mails a "notification" letter to FDA with these attachments. [Then,] [f]or about 93% of these letters, FDA responds that it has 'no questions.' In these responses to notifications, FDA specifically expresses that it is not making a GRAS decision and the company can proceed at its own risk.<sup>91</sup>

#### D. THE DRUG DEVELOPMENT PROBLEM

The incredibly high costs associated with drug development negatively impact both consumers, who are subjected to high drug prices, and manufacturers who have to make eco-

---

GRAS classifications for food additives).

85. *Id.*

86. *See, e.g., Guidance, supra* note 80.

87. *See generally id.* (noting all of the processes and procedures in FDA in relation to getting a GRAS designation).

88. *Id.*

89. *Id.* There is no formal rule on the notification procedure yet.

90. *See, e.g., GRAS Notice Inventory, supra* note 82 (listing notices submitted to FDA for GRAS food additives with the most recent listed being Sept. 28, 2011 when accessed on Nov. 15, 2011).

91. O'Reilly, *supra* note 10, at 12 (bullets omitted).

conomic decisions as to which type of drug would produce the most revenue for the input costs.<sup>92</sup> Thus, many potential solutions have been proposed for lowering drug development costs.

### 1. Problems with the Current NDA-Required System

A large problem with the NDA system exists in the high costs and time-intensive nature of the process.<sup>93</sup> Although the FDA approval process is important for assuring the safety and efficacy of drugs on the market, certain drugs may not need the NDA process to establish safety and efficacy; however, in the current system these drugs are still subjected to the NDA process. An example of one such situation is provided by levothyroxine products.<sup>94</sup> Levothyroxine products were sold lawfully on the market without FDA approval for over forty years; however, questions as to bioequivalence and bioavailability led to FDA requiring that the products be approved via an NDA.<sup>95</sup> Abbott, a manufacturer of a levothyroxine product named Synthroid, tried to persuade FDA to allow a GRASE designation for its product that had been used for so many years, thus, establishing its safety and efficacy.<sup>96</sup> FDA was not persuaded and required Abbott to seek approval via the NDA process.<sup>97</sup>

Thus, drugs that have certain indicia of safety and efficacy are required to go through the costly NDA process even if manufacturers can arguably meet the requirements to obtaining GRASE status.<sup>98</sup> This system is depriving consumers of safe and effective drugs and driving up drug costs.<sup>99</sup>

### 2. Proposed Solutions

The proposed solutions run the gamut from micro-level proposals relating to assistance with prescription pill payment, to macro-level proposals for changes for drug manufacturers, FDA, or both. This Note focuses exclusively on solutions proposed at the FDA-level.

---

92. *See infra* note 161 and accompanying text.

93. *See supra* notes 1–15 and accompanying text.

94. ABOOD, *supra* note 14, at 73.

95. *Id.*

96. *Id.*

97. *Id.*

98. *See id.*

99. *See infra* note 162 and accompanying text (explaining that drug manufacturers pass off expenses associated with getting their drug to market to the consumers who purchase the drug).



a. Fast-tracking

FDA began instituting programs in 1987 for fast-track approval of certain drugs for life-threatening and other serious illnesses.<sup>100</sup> AIDS advocates, and later cancer advocates, provided the impetus for the programs.<sup>101</sup> Similar programs were implemented in the early 1990's, and eventually the programs were formally adopted in the 1997 FDA Modernization Act.<sup>102</sup> Fast-tracking encompasses different programs and initiatives that seek to speed up drug research and development while also facilitating increased dialogue between the drug companies and FDA.<sup>103</sup> Overall, fast-tracking provisions were proposed as a means to fill existing gaps in medical treatment where there was no treatment currently available or the treatment available did not adequately serve all patients.<sup>104</sup>

Fast-tracking programs offer several advantages to manufacturers.<sup>105</sup> For example, fast-tracking provides more communication with FDA during the research and development stages, which correlates with being able to better predict FDA's ultimate decision.<sup>106</sup> In addition, with a fast-track designation, a drug application has a greater chance of qualifying for a special priority review, a process which shortens the period for FDA's review by four months.<sup>107</sup>

The accelerated-approval system uses surrogate end points as an attempt to predict the effects of a drug for a certain usage at an earlier stage than would be possible otherwise.<sup>108</sup> This system has allowed many to get access to new drugs sooner.<sup>109</sup>

b. Off-label Prescription

Another method implemented to avoid the high cost of get-

---

100. Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503, 503 (1995).

101. Thomas G. Roberts & Bruce A. Chabner, *Beyond Fast Track for Drug Approvals*, 351 NEW ENG. J. MED. 501, 501 (2004).

102. *Id.*

103. *Id.*

104. Shulman & Brown, *supra* note 100, at 503.

105. Roberts & Chabner, *supra* note 101, at 501-02.

106. *Id.*

107. *Id.* at 502.

108. *Id.*

109. *Id.*

ting drugs approved by FDA is off-label prescribing of medications.<sup>110</sup> Off-label prescription occurs when a drug is prescribed for a use that is not approved by FDA.<sup>111</sup> Prescribing of drugs off label is commonplace and legal, but it is often done without studies supporting the use.<sup>112</sup> By prescribing a drug off label, doctors are prescribing drugs for uses that have not been studied.<sup>113</sup> Employing this system, drugs approved by FDA for one purpose can avoid the cost of both research and development and FDA approval for a different use of the drug.

The balance of the Note explains why FDA should regulate GRASE drugs similarly to how the Agency regulates GRAS food additives.

## II. ANALYSIS

The tremendous implications of FDA's drug-approval process affect American society at all levels. FDA's ability to ensure that commercially available drugs are safe supports the requirement that manufacturers engage in costly research and development.<sup>114</sup> However, the assurance of safety and efficacy must be balanced against concerns for access to potentially life-saving therapies.<sup>115</sup> In addition, economic concerns weigh on this balancing act. This Note recognizes that countless other concerns, outside of those enumerated above, affect any proposed solution for achieving a balance. Accordingly, all solu-

---

110. See Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008) (discussing how FDA approves a drug for a use, not the drug generally, and FDA plays a “limited role” once a drug is on the market which has led to off-label prescribing of drugs to avoid getting the drug approved for many different uses and dosages which would generally require a NDA).

111. *Id.*

112. *Id.*

113. See, e.g., *id.* (“Evaluations have shown that off-label use is common . . . but often not supported by strong evidence.”) (footnotes omitted).

114. See Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y, L. & ETHICS 717, 730 (2005) (discussing how FDA's role as gatekeeper ensures that manufacturers conduct studies showing drug safety before the drug is introduced to the market).

115. See generally Clayton R. Portell, Note, *Live or Let Die: Will the Courts Recognize in Terminally Ill Patients a Fundamental Right to Choose Non-FDA Approved Drugs or Does the FDA's Stringent Approval Process Carry Sufficient Merit?*, 5 IND. HEALTH L. REV. 123 (2008) (discussing how FDA's regulations for getting drugs to market have prevented some with access to treatments that could potentially have saved their lives, and ultimately, calling for reform).

tions will likely fall short in some way. However, this Note's goal is to propose one particular solution to the complex problem that brings the countless conflicting interests close to equilibrium. This Section first explains why the previously proposed solutions are insufficient for getting drugs to market more quickly and for less money without compromising safety and/or efficacy. Next, revival of the GRASE concept is proposed as a potential solution.

#### A. PROBLEMS WITH PREVIOUS PROPOSED SOLUTIONS

##### 1. Fast-Tracking

Despite the promise of fast-tracking and other related processes, there are also problems with these methods. One problem relates to the ability of surrogate endpoints to predict the success of a treatment.<sup>116</sup> Surrogate endpoints are often used in studies supporting approvals based on speeding up the review process.<sup>117</sup> Surrogate endpoints facilitate shorter study times because they provide an indication earlier in time than is thought to be predicative of the ultimate endpoint.<sup>118</sup> For example, a surrogate endpoint in a cancer study could be tumor reduction.<sup>119</sup> Tumor reduction is not the ultimate endpoint in cancer studies, but measuring tumor reduction offers a way to study the effects of anti-cancer drugs earlier.<sup>120</sup> The use of sur-

---

116. See, e.g., Arthur Schatzkin & Mitchell Gail, *The Promise and Peril of Surrogate End Points in Cancer Research*, 2 NATURE REV. CANCER 19, 19 (2002) (discussing the ability of surrogate endpoints, used in cancer studies, to accurately predict the actual effectiveness of the drug being studied at producing prolonged cancer remission, compared to an actual endpoint of cancer drugs).

117. See, e.g., *id.* (discussing the use of surrogate endpoints in cancer drugs, which are often subjected to an expedited approval process).

118. See *id.* ("Both experimental and observational studies of cancer need to have an end point. Traditionally, in aetiological and prevention studies, that end point has been the incidence of cancer itself, whereas in therapeutic trials, the end point is usually time to cancer recurrence or death. But cancer takes a long time to develop in an individual and is rare in the population. Therefore, aetiological studies and prevention trials must be large and lengthy to be meaningful. Similarly, many therapeutic trials require a long follow-up of large numbers of patients. Surrogate end points—markers of preclinical cancer or of imminent recurrence—are therefore an attractive alternative.")

119. Thomas R. Fleming & David L. DeMets, *Surrogate End Points in Clinical Trials: Are We Being Misled?*, 125 ANNALS INTERNAL MED. 605, 605 (1996).

120. See *id.* ("In theory, for a surrogate end point to be an effective substitute for the clinical outcome, effects of the intervention on the surrogate must

rogate endpoints, in cancer and other disease studies, “might not be acceptable because the quality of evidence they provide on treatment effects or exposure associations is lower than that obtained by studying the effects of treatment or exposure on a true cancer [or other disease] end point.”<sup>121</sup>

Another problem with the various expedited processes is policy-related. By moving one drug to the front of the approval line another drug is being pushed back. Thus, these processes effectively lower the cost for one drug while increasing the cost for another.<sup>122</sup> In addition, deciding which drugs qualify for expedited processes involves policy-related considerations, i.e., determining what it means to be “serious or life-threatening.”<sup>123</sup>

## 2. Off-Label Prescribing by Doctors

Despite the huge savings for manufacturers resulting from off-label prescribing of drugs, there are risks associated with this method. Most notably, off-label use could have harmful impacts on health because drugs are being prescribed without being fully studied and established as safe and effective for the off-label use.<sup>124</sup> A drug that has not been shown to be safe and effective before getting to market could cause health consequences reminiscent of the Elixir Sulfanamide or may not work at all, and thus waste patient’s time that could be spent pursuing other treatment options. While FDA does have the ability to regulate off-label promotion,<sup>125</sup> prescription of drugs for off-

---

reliably predict the overall effect on the clinical outcome.”).

121. Schatzkin & Gail, *supra* note 116, at 19.

122. This assumes that the longer a drug sits at FDA waiting for approval the company cannot sell the drug and thus cannot make money, which just costs the manufacturer more to keep things running during the waiting period. For example, “[p]harmaceutical companies . . . [hate] these delays [in FDA approval] because for each extra month FDA took to approve an NDA, a pharmaceutical company lost a month in marketing a drug with patent protection.” James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD & DRUG L.J. 261, 261 (2005). However, the patent term extension granted for the time FDA takes in drug approval may ameliorate at least some of these losses.

123. See, e.g., Roberts & Chabner, *supra* note 101, at 502 (describing the requirement that a drug seeking fast track approval must be designated for treating a “serious or life-threatening illness.”).

124. See Stafford, *supra* note 110, at 1427.

125. See *Position Statement: Off-Label Use of Medical Products*, AM. ACAD. ORTHOPEDIC SURGEONS (June 2009), <http://www.aaos.org/about/papers/position/1177.asp> (“The FDA regulates the marketing approval or clearance,

label uses is common and FDA does not have the authority to regulate the actions of doctors,<sup>126</sup> raising questions about how much FDA can actually regulate off-label use by mechanisms it currently employs like monitoring corporate marketing of drugs to ensure drugs are not promoted for off-label use.<sup>127</sup>

## B. REVIVING GRASE DRUGS

As illustrated by the brief discussion of other macro-level solutions, each involves undesirable side effects that could ultimately affect the safety and/or efficacy of drugs reaching the market. Employing the GRASE concept would reduce the cost of getting certain drugs to market, by avoiding the NDA process, without ultimately compromising the resultant drug's safety and efficacy.

### 1. Description of the proposal for reviving GRASE

To achieve GRASE status, a drug must be "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed."<sup>128</sup> In addition, interpretation of this provision has further required that the evidence produced be publically available and known to the scientific community as published peer-reviewed articles.<sup>129</sup> Thus, any drug achieving GRASE status would have demonstrated its safety and efficacy, while avoiding the costly FDA approval processes.

To revive GRASE, FDA could issue a guidance document

---

labeling, and promotion of pharmaceutical, medical device, and biologic products in the United States. These products may only be labeled, promoted, and advertised for the uses that the FDA has approved or cleared.").

126. *Id.* ("The government has long recognized that physicians may prescribe or administer any legally marketed product for an off-label use within the practice of medicine. . . . The practice of medicine is regulated by state laws, and surgeons should adhere to all applicable state and federal laws and regulations.").

127. *See, e.g.,* Stafford, *supra* note 110, at 1427 ("Off-label uses have not been formally evaluated, and evidence provided for one clinical situation may not apply to others. As an area of controversy, off-label use is subject to the contradictory expectations of various stakeholders, including health care payers, the pharmaceutical industry, physicians, and consumers. The FDA has a role in balancing these expectations, but it currently does so primarily through regulating corporate marketing.").

128. 21 U.S.C. § 321(p)(1) (2006).

129. *See* discussion *supra* note 63.

indicating its change of heart in regards to GRASE drugs.<sup>130</sup> Initially implementing the GRASE provision would not take much more than this because the provision is already in the Act and has been mooted by FDA's own actions in setting the bar for achieving GRASE status impossibly high.<sup>131</sup> Notably, some courts have affirmed FDA's stringent and limited applicability of GRASE for drugs, virtually equating the standard of proof required to that required by an NDA also exist.<sup>132</sup> However, these decisions could also likely be overcome by an FDA-issued guidance because of the very deferential approach that courts take towards FDA decisions in most cases, especially for GRASE, as evidenced by court adoption of FDA's stringent approach.<sup>133</sup> If FDA did not itself revive GRASE, a court hypothetically could reinvigorate the concept by overruling precedent limiting the doctrine's applicability.<sup>134</sup> However, because courts are bound by precedent and are largely deferential to FDA,<sup>135</sup> this seems a less likely route to revival.

---

130. See *Guidances*, FDA.GOV, <http://www.fda.gov/regulatoryinformation/guidances/default.htm> (last visited Jan. 14, 2012) ("Guidance documents represent FDA's current thinking on a topic. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations."). Even taking the relatively conservative approach the FDA officially states in regards to guidance documents, the weight of the documents is evident because they give insight to companies on how FDA feels about issues. A company, thus, that follows FDA's approach in guidance documents is much more likely to have a positive experience with the agency than a company that disregards the guidance documents.

131. JAMES T. O'REILLY, *supra* note 13, § 13:44.

132. *Id.*

133. See discussion, *supra* note 13 and accompanying text.

134. See generally O'REILLY, *supra* note 13 (discussing the role of courts in adopting FDA's limited view of the applicability of GRASE for drugs). Thus, the same courts could overrule their precedent. This seems less likely, however, because of judicial deference to FDA, courts' reluctance to overrule precedent, and the fact that GRASE cases will most likely not even be brought because of the established precedent which limits the courts ability to make such a decision.

135. See, e.g., Timothy K. Armstrong, *Chevron Deference and Agency Self-Interest*, 13 CORNELL J.L. & PUB. POL'Y 203, 204 (2004) ("When a party aggrieved by a federal government agency's interpretation of a statute or regulation seeks judicial review, the reviewing court typically applies the *Chevron* doctrine and defers to the agency's interpretation so long as it is reasonable and not contrary to the statutory or regulatory text.") (footnotes omitted). *Contra* James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939 (2008) [hereinafter *Losing Deference*] (proposing generally that judicial

If GRASE were revived, FDA would need to implement an infrastructure to deal with GRASE applications. FDA would not have to look far for an example of how to deal with GRASE applications because it has a well-functioning system already for GRAS food additives.<sup>136</sup> In addition, because the GRAS designation was initially based on GRASE drug concepts,<sup>137</sup> applying the concept back to GRASE is consistent. Using the GRAS notification system, a manufacturer who believes its product to be GRAS may submit notification of this designation to FDA.<sup>138</sup> FDA then responds to the notification.<sup>139</sup>

In a GRASE Notification System, a drug manufacturer seeking GRASE status for its drug would submit a notification of this designation to FDA. Along with this notification the manufacturer would be required to submit its data, either scientific or through experience through usage as provided in the Act, showing that its drug meets the requisite general recognition of safety and efficacy. The standard for general recognition would be the same as outlined *supra*. However, if FDA wanted to expand the applicability of GRASE even further, it could relax its requirements of having peer-reviewed studies as evidence of a proposed GRASE drug's safety and effectiveness. Perhaps, a standard could be put in place where at least some evidence must be found in a published peer-reviewed journal; however, other unpublished studies could be used as supplementary evidence. Employing this system of evidence, FDA would still protect consumers while being able to get safe and effective drugs to market quickly and at lower costs than currently possible. Finally, FDA would issue a response within 180 days and either grant GRASE status or require safety and efficacy to be shown through an NDA.

For a GRASE Notification System to work, courts would have to give less deference to FDA's safety views when those views are contrary to a majority of doctors and scientists.<sup>140</sup> An

---

deference towards FDA may be waning with the popularity of the agency).

136. See *generally Guidance, supra* note 80 (discussing in detail the GRAS notification process and describing how one seeking GRAS status can apply for it).

137. See Degnan, *supra* note 29, at 556.

138. *Guidance, supra* note 80.

139. *Id.*

140. See *Losing Deference, supra* note 135, at 940 ("The judicial deference given to the Agency is usually attributed to the FDA's century-long legacy of

outlier's opinion should not be considered sufficient for establishing that there is no consensus among the scientific community in GRASE designations.<sup>141</sup> Accordingly, an FDA scientist that expresses doubts about the safety of a drug applying for GRASE designations should not prevent the finding of scientific consensus. Allowing an FDA scientist's concerns that have minimal, if any, support outside the agency is too deferential to the agency. In addition, this level of deference to the view of FDA scientists, at the exclusion of the opinions of countless other outside and disinterested scientists, affords an opportunity for corruption.

To remedy this deference problem courts should be presented with the views regarding a drug's general recognition of safety and efficacy of both FDA scientists and outside scientists.<sup>142</sup> After hearing from experts with differing views regarding general recognition of safety and efficacy the court could be well-informed to weigh the evidence presented and make a ruling as to general recognition. This method, although imperfect because many judges are not scientific experts, provides for a more neutral and balanced decision regarding general recognition to be made.

The GRASE Notification System would allow drug manufacturers with drugs that can be shown through either scientific evidence or evidence of common usage to be generally rec-

---

scientific expertise. However, in recent years, the news media has disdained the Bush Administration's political manipulation of the FDA and has questioned the Agency's scientific integrity. This criticism of the Administration's political manipulations of the FDA (for the benefit of conservative political constituencies) may diminish the willingness of federal judges to defer to our nation's most distinguished regulatory Agency. And if the FDA loses its legacy of deference, its ability to regulate efficiently will diminish significantly.") (footnotes omitted). Thus, FDA may be afforded less deference by courts, which would diminish FDA's ability to effectively veto all drugs for which GRASE status is being sought.

141. See generally O'REILLY, *supra* note 13, § 13.34 ("[G]uided by the Supreme Court's attitude of deferential acceptance, federal judges declined to overturn FDA decisions about 'general recognition' despite some sophisticated arguments of well-prepared challengers."). The FDA determination of general recognition to which courts have generally deferred may, at least in theory, be based on as little as one FDA scientist's decision that the drug in question does not meet the requirements for 'general recognition.'

142. In fact, GRAS status can be shown independently of government by outside experts. See *How U.S. FDA's GRAS Notification Program Works*, FDA.GOV (Jan. 2006), <http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/ucm083022.htm>. Thus, if independent experts are used for GRAS designations, so too, should they be used for GRASE.



ognized as safe and effective to get to market without having to go through the NDA process. Because of the time and cost associated with the NDA process, drugs qualifying for the GRASE notification system would get to market more quickly and at a lesser expense.<sup>143</sup> In addition, the drug getting to market would still be safe and effective for its proposed use because it would have to satisfy the stringent requirements of general recognition of safety and efficacy.<sup>144</sup> The general recognition showings have actually been equated to the safety and efficacy proof needed for an NDA application.<sup>145</sup>

If the aforementioned changes were implemented, the GRASE Notification System could afford a useful alternative for getting a drug to market. A similar standard is used in the GRAS system and has not rendered the GRAS concept ineffective for food additives.<sup>146</sup>

## 2. Support for revival of GRASE

Revival of the GRASE concept for drugs finds support in the concept's presence in the Act. Various canons of statutory interpretation echo the importance of the inclusion of the GRASE concept in the statute. For example, when engaging in statutory interpretation, courts aim to make the entire statute effective.<sup>147</sup> In addition, the canon against surplusage provides that a part of the statute should not be made ineffectual by the statutory reading.<sup>148</sup> To comply with these canons of interpretation, a court should give renewed effect to the GRASE provi-

---

143. See *supra* Part I.D for a discussion of the costs associated with drug development and the NDA process for an illustration of the great potential savings of a GRASE designation.

144. This would be very similar to the existing GRAS system which ensures safety. The GRASE system would not only ensure safety, but would also ensure drug efficacy for the proposed usage.

145. See *supra* note 134 and accompanying text.

146. See, e.g., O'Reilly, *supra* note 10, at 7 (describing the requirement of 'general recognition' for both GRAS and GRASE together); see also *GRAS Notice Inventory*, *supra* note 82 (a listing of GRAS foods, which is still currently being added to, which shows how the GRAS designation is still applicable today).

147. Catherine E. Vance, *Some Canons of Statutory Construction*, WHEELING JESUIT U. (2005), <http://procom.wju.edu/347/347unit1/canonsStatConst/CLLA-canons-of-statutory-construction.pdf> (citing *Negonsott v. Samuels*, 507 U.S. 99 (1993)).

148. *Id.* (quoting *Mountain States Tel. & Tel. Co. v. Pueblo of Santa Ana*, 472 U.S. 237 (1985)).

sion of the Act, because the current interpretation of GRASE, which has basically rendered it inoperative, violates the canons. Thus, FDA could rely on these canons of interpretation in changing its interpretation of GRASE.

Using the GRAS system to inform the GRASE Notification System also finds support in the canons of statutory construction. The internal consistency canon supports the proposal that:

Every part of a statute must be viewed in connection with the whole so as to harmonize all parts, if practicable, and give sensible and intelligent effect to each, for it is not to be presumed that the legislature intended any part of a statute to be without a meaning.<sup>149</sup>

Thus, the fact that FDA has implemented a GRAS notification system supports the employment of a similar system for GRASE drugs because both concepts fall within the Act. In addition, the GRAS provision was based on the GRASE provision,<sup>150</sup> which further supports the applicability of FDA's interpretation of GRAS to GRASE.

Although foods are arguably less dangerous, overall, than drugs are, the GRAS system is still a good model for a potential GRASE system. FDA could employ the same standards for "general recognition" for both GRAS and GRASE. However, in implementing a GRASE system, FDA would require applicant drugs to establish both general recognition of safety and efficacy.<sup>151</sup> Thus, by the very nature of the different requirements that food additives and drugs must meet to attain GRAS or GRASE status, respectively, the higher potential risk associated with drugs is addressed.

Further support comes from the fact that GRASE is still used in certain cases for OTC drugs.<sup>152</sup> If a showing of general recognition of safety and efficacy is sufficient to get some OTC drugs recognized as GRASE,<sup>153</sup> then it follows that the same should be allowable for prescription drugs. In addition, the inherent risks of danger between OTC drugs and prescription drugs are closer than the risk between drugs and food; thus, those not persuaded by the use of GRAS in food additives could

149. *Id.* (quoting *General Motors Acceptance Corp. v. Whisnant*, 387 F.2d 774 (5th Cir. 1968)).

150. See *supra* notes 79–83 and accompanying text.

151. By adding the requirement of efficacy, GRASE drugs would be subject to a high standard for qualification. See Rajesh Yelugoila, *GRASE Grandfathered and DESI Drugs*, REG.ONE (Mar. 23 2012), <http://www.regulatoryone.com/2012/03/grase-grandfathered-and-desi-drugs.html>.

152. See *supra* Part I.B. (discussing the use of OTC Drug Monographs).

153. ABOOD, *supra* note 14, at 73.

be satisfied with this argument.

### 3. How Application of the GRASE Concept Could Lower Drug Development Costs

A GRASE Notification System could help decrease the high cost of getting certain drugs to market in the United States. First, for drugs that meet the requirements of “general recognition of safety and efficacy,” the costs associated with research and development as well as FDA approval would be drastically decreased.<sup>154</sup> This voluntary system would cost much less than the filing of an NDA.<sup>155</sup> In addition, the time to get the drug on the market would be much shorter, because manufacturers of GRASE drugs would not be subject to the lengthy and costly NDA process.<sup>156</sup>

With a GRASE Notification System, FDA would still be getting information from the drug manufacturers on the safety and efficacy of drugs. FDA could also exercise its input via the notification response or seizure actions if the agency believes that the drug is misbranded as GRASE.<sup>157</sup> Thus, unlike other proposals for decreasing the time and cost associated with getting a drug to market, notably off-label prescribing, the safety and efficacy of the GRASE drug for the particular use would be shown.

However, if FDA wanted to expand the applicability of GRASE even further, it could relax its requirements of having peer-reviewed studies as evidence of a proposed GRASE drug’s safety and effectiveness.<sup>158</sup> Perhaps a standard could be put in place where at least some evidence must be found in a published peer-reviewed journal; however, other unpublished stud-

---

154. See, e.g., O’Reilly, *supra* note 10, at 1 (describing GRASE as “an alternative to the expense of [a] new drug application.”).

155. See *id.* (“This status [GRAS or GRASE] can save its holders millions in approval costs, not to mention the time that those processes take.”).

156. See *id.* (highlighting both the financial and time saving benefits of GRAS and GRASE status).

157. See 21 U.S.C. § 334(a)(1) (2006) (providing for the ability to seize adulterated and misbranded drugs in interstate commerce).

158. See O’REILLY *supra* note 13, §13.33 (“Drug GRASE claims are very difficult to win over FDA’s objections. An absence of published peer journal articles about a compound is proof that the requisite general recognition does not exist.”). Thus, if FDA changed its position and no longer required peer-reviewed journal articles, at least theoretically, more drugs could qualify for GRASE status.

ies could be used as supplementary evidence. Employing this system of evidence, FDA would still protect consumers while being able to get safe and effective drugs to market quickly and at lower costs than currently possible.

Another benefit stemming from a GRASE revival could be getting more drugs to market that manufacturers do not want to spend the money getting approved through the NDA process.<sup>159</sup> By having a cheaper alternative to the NDA processes, drug manufacturers would have more impetus to produce drugs that do not have as much economic promise, like drugs for rare diseases.<sup>160</sup> Despite the small profit margin for drugs for rare diseases, getting these drugs on the market as GRASE would be profitable to manufacturers because they would have less research and development and approval costs to redeem.<sup>161</sup>

Accordingly, a GRASE drug manufacturer may be able to offer the drug at a lower cost to patients.<sup>162</sup> Overall, the revival of the GRASE concept would help alleviate the high cost associated with getting a drug to market for certain drugs, while still affording the safety and effectiveness information needed by FDA to ensure that the drug is acceptable for use by American consumers.

### III. CONCLUSION

Getting a drug to market is a lengthy and expensive process in the United States. This problem has a wide range of im-

---

159. See generally discussion *supra* Part I.D (fast-tracking FDA programs). These programs were instituted to provide economic incentives for the development of drugs that would not otherwise be profitable for companies to produce. Thus, because GRASE would provide a less expensive alternative to the NDA process, it could stimulate drug companies to produce drugs that would not have been financially rewarding if the NDA process had to be followed.

160. See, e.g., discussion *supra* Part I.D (discussing fast-tracking and other economic incentives given to drug companies that develop drugs for uncommon diseases or for diseases predominantly affecting the poor). Because GRASE offers economic benefits, it could operate as a similar process to incentivize drug development that might not otherwise occur.

161. See, e.g., O'Reilly, *supra* note 10, at 1 (describing GRASE as a cost effective alternative to the NDA process); see also Eric Kimbuende et al., *Prescription Drug Costs*, KAISEREDU.ORG (Feb. 2010), <http://www.kaiseredu.org/Issue-Modules/Prescription-Drug-Costs/Background-Brief.aspx> (“Manufacturers try to recoup the research and development, costs for drugs that make it to the market as well as those that do not enter the marketplace.”).

162. Kimbuende et al., *supra* note 161 (describing how drug manufacturers try to recover the money spent on drug development and illuminating how one consequence has been increased cost of pharmaceuticals for consumers).

plications for America's public health and its economy. Public health implications include a low incentive for manufacturers to develop drugs for the treatment of diseases affecting the poor and for rare diseases. On the economic front, a manufacturer that goes through the FDA drug approval process may end up charging consumers more for its product in an attempt to pass on its costs.

The current solutions for this problem, both those proposed and those implemented, fail to adequately assure either the safety and/or effectiveness of the drugs that would avoid the NDA process. However, reviving the GRASE concept, enumerated in 21 U.S.C. § 321(p)(1), would lower the cost of getting certain drugs to market without compromising the safety and effectiveness data provided about the drug. The proposed revival of the GRASE concept would employ a system similar to the notification system for GRAS food additives, with less deference to FDA and a relaxation on the requirement for exclusively published, peer-reviewed supporting articles. Through this system, GRASE drugs would be able to avoid both a large portion of the expensive research and development process as well as the user fee associated with filing an NDA with FDA. Attaining a GRASE designation would save drug manufacturers both time and money. The savings could be passed on to consumers, increasing access to the medication. In addition, the availability of this lower-cost alternative to the NDA process could create greater incentive for the development of drugs that commonly have a small grossing market. Thus, reviving the GRASE concept could also help to reduce current disparities in healthcare.