Colchicine, Guaifenesin, and the Constitutionality of FDA Market Exclusivity for Approval Pioneers

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1. Introduction

Colchicine, an alkaloid isolated from the seeds of the meadow saffron crocus, *colchicum automnale*, has been used for treatment of gout since the 6th century A.D.\(^1\) While during the Renaissance it was regarded as dangerous and disappeared from medical practice for quite some time, it reappeared when a French military officer, Nicolas Husson, again started using it for the treatment of gout in 1808.\(^2\) This reintroduction was quickly followed by isolation of the active constituent of the plant in 1820\(^3\) and extensive scientific experimentation on its mechanism of action on acute gout in the mid-19th century.\(^4\) In 1883, researchers had worked out its empirical formula,\(^5\) and by 1955, scientists knew its structural formula.\(^6\) It has been used, sold, and researched for over 200 years, and there are some rumors that Benjamin Franklin himself, a known sufferer of gout, brought the treatment to the Americas.\(^7\)

In the 20th century, the drug was widely prescribed throughout the world. The research continued, and as of May 2010 there were over 16,000 articles on PubMed for colchicine, with 254 indexed as clinical trials.\(^8\) In 2007, state Medicaid filled 100,000 prescriptions of colchicine

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\(^{2}\)Id. at 196.


\(^{4}\)Hartung, *supra* note 1, at 196

\(^{5}\)Id.

\(^{6}\)Dowd, *supra* note 3.


and paid approximately $1 million in total for the drug. Researchers ended up knowing even more about the drug colchicine than the disease it was used to treat, as they used known mechanisms of colchicine to determine causes of gout.

With colchicine’s extensive history, widespread market availability, heavy prescription use, and large collection of documented research, it seems to hardly be a “new drug,” but the FDA disagrees. On July 30th, 2009, the FDA approved a new drug application (NDA) submitted by URL Pharma, Inc. (also known as Mutual Pharmaceuticals, Inc.), for the use of Colcrys-brand colchicine in acute gout. The FDA then forced all of URL Pharma’s competitors to stop manufacturing and shipping of the product. On top of this de facto market exclusivity that comes with the FDA removing all of one’s competitors from the market, the FDA went further and granted URL Pharma three years of de jure market exclusivity for using colchicine in the treatment of acute gout and seven years of market exclusivity for using colchicine in the treatment of familial Mediterranean fever (“FMF”). Beyond the market exclusivity, the FDA actually published essentially an eight-minute commercial for Colcrys, reminding everyone that “safety and effectiveness of drugs cannot be . . . established by anecdotal evidence” and that colchicine products other than Colcrys “may not be safe or effective, may have been manufactured under substandard conditions, may contain too much or too little, if any active

13 Ullman, supra note 8, at 27.
ingredients, and may not have the necessary label information or warnings.” \(^{14}\)

As a result of the monopoly, the price of colchicine has increased 20-fold. \(^{15}\) As stated by Dr. Stanley Cohen, president of the American College of Rheumatology, “It's not a new product. It's been out for hundreds of years. To all of a sudden have to pay $125 or $150 a month, after it only cost $5 or $10 a month, is a real problem.” \(^{16}\)

FDA market exclusivity was intended to complement the benefits granted by the U.S. Patent system; to give further reward for drug innovation to compensate for the long FDA approval process. \(^{17}\) The theory is that by encouraging through market exclusivity a drug company to get FDA-approved, Congress encourages the clinical trial data to be released into the public domain and inspire future scientific progress. \(^{18}\) Of course, this assumes that the clinical trials actually generate useful enough data to provide a rational basis for the length of market exclusivity granted.

So how did we get to this situation, where a company marketing a 1500 year-old drug that we know so much about is suddenly granted a monopoly for an unspectacular clinical trial - one single clinical trial, out of the 254 available on PubMed? Why do we choose to inflate the price twenty times for a product that is not novel? Why did we enrich a corporation so great for such a minor contribution to the field?

The answer deals with a combination of statutory changes, informal FDA arm-twisting,

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\(^{14}\) byronma2433, *colchicine.wmv*, YOUTUBE at 1:40 - 2:05 (Jul. 17, 2010), http://www.youtube.com/watch?v=TirONhYZTwY


\(^{16}\) Id.


and a curious result of Congressional delegation regarding unapproved drugs. But assuming that this FDA action is in line with Congressional delegation, this raises another question: can Congress constitutionally confer a monopoly to a company when that company does nothing to “promote . . . Progress?”\textsuperscript{19}

This paper will explore the history of this anomaly, starting with the foundations for the FDA approval process from the Food, Drug and Cosmetic Act of 1938 and continuing with all of the relevant statutory changes to the present. Then, the paper will look at the FDA Unapproved Drugs Initiative of 2006 and, through case studies, examine the process that the FDA followed in securing market exclusivity for these “new old drugs.” The paper will finally investigate whether such a practice is even constitutionally permissible under the Intellectual Property Clause.

2. The History of Approved Drugs

The scope of the FDA’s power has enlarged significantly over the past century through legislative changes by Congress. Many of these legislative changes were retroactive: drugs that were approved under previous iterations of the law were henceforth “unapproved” based on the new standards set forth by statute. Looking at one hundred years of changes to FDA’s approval scheme over the course of a few pages makes Congress look a little bit fickle, as they constantly shift standards across the decades. One has to be cognizant of the incredible length of time over which these standards changed and the specific reactionary incidents to which Congress responded, such as when a company decided to market diethylene glycol (antifreeze) to children in 1937 and when the drug thalidomide caused a wave of birth defects in 1962.\textsuperscript{20}

\textsuperscript{19}U.S. CONST. art.I, § 8, cl. 8.
At the beginning, Congress required only that products be accurately branded and unadulterated. Later, Congress required that the products also be tested for safety. After that, Congress required that the products be tested for both safety and efficacy. The various iterations of statutes at times had various exceptions for drugs that were grandfathered in under previous statutes, but then later iterations retroactively removed those exceptions. It is easy to understand why the approval status of some drugs is still uncertain.

a. The Federal Food and Drug Act of 1906 - No Authority for Drug Pre-Approval

Congress first brought drug regulation under federal law on June 30, 1906 as part of the Federal Food and Drug Act (“1906 Act”). While this statute prohibited adulterated and misbranded drugs, the Act did not implement any sort of approval process for new drugs.\(^\text{21}\) The 1906 Act did not grant the FDA authority to inquire into a drug’s safety, nor did it grant authority to inquire into a drug’s efficacy.\(^\text{22}\) Instead, the 1906 Act focused on whether a drug actually contained what was claimed, according to its strength and purity.\(^\text{23}\) Since there was no pre-marketing approval, drugs could be sold as long as the drug was indeed the drug advertised.\(^\text{24}\) Beyond this, the United States public operated on a principle of *caveat emptor.*


\(^{22}\) Id.

\(^{23}\) Id. Before this Act, the selling of misbranded products was a rampant problem in the United States. See Ilyse D. Barkan, *Industry Invited Regulation: The Passage of the Pure Food and Drug Act of 1906, 75 Am. J. Pub. Health* 18, 22 (Jan. 1985) available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1646146/pdf/amjph00277-0020.pdf (“Potted turkey had no turkey in it; potted chicken, no chicken. Cottonseed oil was sold as olive oil, in whole or in part. Rectified whiskey often contained little whiskey and much artificial coloring. Alcohol could be found in candy and in patent medicines. nostrums often contained narcotic or addictive drugs such as cocaine, opium, and morphine and were not labeled as such.”).

\(^{24}\) 21 U.S.C. §§ 1-15 (1934) available at http://www.fda.gov/regulatoryinformation/legislation/ucm148690.htm. See also Less than Effective (LTE) and Identical, Related and Similar (IRS) Drugs, Centers for Medicare and
b. The Federal Food and Cosmetic Act of 1938 - Authority for Pre-Market Approval
   Based on Safety

In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act (“1938 Act”),
granting to the FDA the authority to require pre-marketing approval for new drugs based on
safety, but not efficacy.\(^\text{25}\) This led to a flood of thousands of new drug applications (NDAs) from
various drug manufacturers around the country, as all drugs were now technically being
marketed illegally.\(^\text{26}\)

The FDA, however, could not handle this flood of NDAs, and in fact actually refused to
accept NDAs for what it considered to be “old drugs.”\(^\text{27}\) For the drugs that the FDA considered
to be either “generally recognized as safe” (“GRAS”) or “identical, related or similar” (“IRS”) to
an already-approved drug,\(^\text{28}\) pre-marketing approval was not required.\(^\text{29}\)

What Congress and the FDA actually considered “new drugs,” however, is in
question.\(^\text{30}\) It seems clear that Congress meant for “new drug” to mean more than “new active
ingredient;” a new dosage, or a new use also could have established a “new drug.”\(^\text{31}\) However,
for drugs that had the same active ingredient, dosage, and use, there were many FDA decisions
that permitted these drugs to be marketed without FDA approval because they were not

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\(^{25}\) COMPLIANCE POLICY GUIDE 2006, supra note 19 at 11 para. 2.
\(^{26}\) Peter Barton Hutt, The regulation of drug product by the US Food and Drug Administration,
THE TEXTBOOK OF PHARMACEUTICAL MEDICINE 534, 548 (John P. Griffin ed. 6\(^{\text{th}}\) ed. 2006).
\(^{27}\) Id.
\(^{28}\) COMPLIANCE POLICY GUIDE 2006, supra note 19 at 8.
\(^{29}\) Hutt, supra note 24 at 547-58.
\(^{30}\) Donald O. Beers, GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL
REQUIREMENTS 1-10 – 1-11 (6\(^{\text{th}}\) ed. 2004).
\(^{31}\) Id.
considered “new.” The FDA published opinions on which drugs were not considered “new,” but later revoked these opinions in 1968.

The 1938 Act also included a “grandfather clause,” which allowed a drug to escape the classification of a “new drug” as long as the exact same drug with the exact same labeling was previously sold in interstate commerce between 1907 and 1938.

c. The Federal Food and Cosmetic Act of 1962 - Authority for Pre-Market Approval Based on Safety and Efficacy

In 1962, Congress amended the Federal Food and Cosmetic Act of 1962 (“1962 Act”) to require pre-market approval based on both safety and efficacy. A quick acronym check reveals a problem. While under the 1938 Act a drug did not need approval if it was GRAS, under the 1962 Act the drug needed to be “generally recognized as safe and effective” (“GRASE”). This “effectiveness,” presumably, still had to be tested, which made many of the previously-approved drugs between 1938 and 1962 now “new drugs.”

To satisfy this “effectiveness” requirement, the FDA created the Drug Efficacy Study Implementation (“DESI”). This program enlisted the National Academy of Sciences (“NAS”) and the National Research Council (“NRC”) to act in an advisory role to the FDA on the efficacy

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32 There is also some suggestion that there was no rhyme or reason to these policy decisions, and that the FDA was simply making ad hoc decisions. Id.
33 21 C.F.R. § 310.100 (2011)
34 Beers, supra note 28 at 1-32 – 1-33.
35 COMPLIANCE POLICY GUIDE 2006, supra note 19 at 8. The enactment of this legislation was due in no small part to the thalidomide tragedy, in which thousands of newborn children suffered from birth defects after their mothers took thalidomide for morning sickness. See Michelle Meadows, Promoting Safe and Effective Drugs for 100 Years, FDA CONSUMER MAGAZINE (Jan-Feb 2006) available at http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm.
36 COMPLIANCE POLICY GUIDE 2006, supra note 19 at 8.
of over 3,400 products that were only GRAS, and not GRASE.\footnote{Compliance Policy Guide 2006, supra note 19 at 8.}

If a DESI study resulted in a finding of ineffectiveness for a certain drug, that drug and all of the products that were IRS to that drug would be classified as unapproved drugs that could not be marketed.\footnote{FDA Center for Drug Evaluation and Research, Bringing an Unapproved Drug into Compliance Course Script at 7, available at http://fdadrugcompliance.com/docs/Course.pdf. [hereinafter Compliance Course Script].} However, even if a DESI study resulted in a finding of effectiveness, the drug was still not off the hook: it was still qualified as a “new drug” by the FDA, and as a “new drug,” it was still unapproved.\footnote{Id.} As stated in an FDA-written course on how to manage unapproved drugs,

Marketing a drug in either group – ineffective or effective – without an approved application would subject the marketer to enforcement action. Too often, people mistakenly think that because a product is a DESI drug or an “old drug,” it does not need FDA’s prior approval prior to marketing. This is inaccurate.\footnote{Id.}

What, then, was the point of the DESI studies, if a drug would be seized regardless of the findings? Under 21 USC §355, the FDA allows submission of a 505(b)(2) NDA application.\footnote{21 U.S.C. § 355 (2008)} Instead of requiring all clinical trial evidence to originate from the applicant as in a 505(b)(1) NDA application, the FDA allows the applicant under 505(b)(2) to rely on FDA findings as evidence of a drug’s safety and effectiveness.\footnote{Regulatory Professionals, Inc., The 505(b)(2) New Drug Application – A Rapid Approval Route at 1 available at http://www.regprofessional.com/resources/505(b)(2).pdf.} This includes DESI studies.\footnote{Ken Phelps, What are DESI Drugs?, http://www.camargoblog.com/2009/06/01/what-are-desi-drugs/.} In addition, any generic manufacturer of a pioneer drug under DESI studies could file an abbreviated new drug
application ("ANDA") if it is exactly the same as a pre-1962 drug.\textsuperscript{45}

Although many drugs were retroactively unapproved as a result of this “efficacy” requirement, the 1962 Act did include a grandfather clause – one distinct from the grandfather clause of the 1938 Act.\textsuperscript{46} Under this grandfather clause, the 1962 Act exempts a drug from the efficacy requirement if a drug was used in U.S. commerce, was not considered a “new drug,” and was not covered by an application in the years before the 1962 Act was enacted.\textsuperscript{47}

d. \textbf{The Grandfather Clauses and “Old Drugs”}

According to the FDA, “the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a new drug.”\textsuperscript{48} Although the legislature twice made exceptions for drugs that were “grandfathered in” and the FDA itself made exceptions for “old drugs” that were GRASE, neither of these exceptions for marketing unapproved drugs have survived to this day.\textsuperscript{49} This is the result of a very narrow reading that the FDA and the courts have given to both grandfather clauses and old drugs.

e. \textbf{The Grandfather Clauses are Ineffective}

Theoretically, under the grandfather clauses, there was nothing stopping a drug

\textsuperscript{45} Hutt, \textit{supra} note 24 at 586.
\textsuperscript{46} Joseph D. Nally, \textit{FDA Pre-Approval Inspections/Investigations: The Road from Scale-Up and Post-Approval Changes to the Food and Drug Modernization Act}, \textit{GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS} 332 (Joseph D. Nally, ed. 6\textsuperscript{th} ed. 2006).
\textsuperscript{47} Id. For the 1962 grandfather clause, the test can be found in United States v. An Article of Drug . . . "BentexUlcerine", 469 F.2d 875, 878 (5th Cir. 1972) ("(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force (subsec. (p) of this section), and (C) was not covered by an effective application under section 505 of that Act (section 355 of this title), the amendments to section 201(p) (subsec. (p) of this section) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.")
\textsuperscript{48}\textit{COMPLIANCE POLICY GUIDE 2006, supra} note 19 at 11.
\textsuperscript{49} Karst, \textit{supra} note 35 at 39.
manufacturer from marketing the same drug that it marketed in the past. The main reason why the grandfather clauses met their demise, however, is because of the literal, narrow definition that the FDA and courts have given the labeling requirement.\textsuperscript{50} In \textit{United States v. Articles of Drug Consisting of Following: 5,906 Boxes}, 745 F.2d 105, 115 (1st Cir. 1984) the First Circuit Court of Appeals reversed a jury verdict and ruled in favor of the FDA because of differences in the labeling between the pre-1962 and post-1962 versions of the drug. While both the pre-1962 version and the post-1962 version of the labeling indicated that the drug could be used to allay nausea and vomiting, the pre-1962 version also included some example causes of the vomiting symptom. The court concluded that because the post-1962 version did not list any causes of vomiting, it implicitly encompassed more conditions of use, and therefore was different from the original labeling. Meanwhile, the pharmaceutical company was not allowed not use the old labeling because, “Nothing in the record indicates that these eleven causes are the only possible causes of nausea and vomiting . . . and trial testimony revealed that a number of other conditions can cause vomiting.”\textsuperscript{51} It would thus be “misbranded.”

The “same labeling” requirement is somewhat deceptive, because it is not as simple as just reproducing the exact same labeling from before 1962. Since the FDA also protects against the adulteration or misbranding of drugs, if there is new information known or new statutory changes that mandate a labeling change, the drug cannot possibly comply with its earlier labeling requirement.\textsuperscript{52} In 2000, two individuals tried to get marijuana covered under the grandfather clause because it was sold between 1906 and 1938.\textsuperscript{53} The FDA reminded them that the inclusion

\textsuperscript{50}Compliance Policy Guide 2006, \textit{supra} note 19 at 11.

\textsuperscript{51}Id. at 115.

\textsuperscript{52} Beers, \textit{supra} note 28 at 1-34.

\textsuperscript{53} Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, Dept. of Health and Human Services, FDA to Paul Klopper c/o Farmacy and Tod H. Mikuriya, M.D. 3 (Dec. 29,
of marijuana on Schedule I on the Controlled Substances Act, 21 U.S.C. 812(c), 21 CFR 1308.11(d)(19), mandated that marijuana products have a “C-1” on all labeling, thereby creating a change in labeling and excluding it from the clause.\textsuperscript{54}

In the decades that the grandfather clause has been present, only once has a court concluded that the drugs in question were “grandfathered” and these drugs were nevertheless condemned because they were misbranded.\textsuperscript{55}

\textbf{f. The “Old Drug,” GRASE Designation Is Very Difficult to Meet}

While it is still possible for a drug to be considered an “old drug” without the FDA saying so, the bar is very high.\textsuperscript{56} First, the drug must have general recognition by experts for its safety and effectiveness in the form of an “expert consensus,” where there is no “genuine dispute” amongst expert witnesses.\textsuperscript{57} Second, the drug must have sufficiently publicly available data to support that recognition, where in some cases the amount of data must be at least the amount of data required to receive FDA approval.\textsuperscript{58} Third, the drug must have been used for a “material time” and to a “material extent,” where 16.5 million tablets and 34.6 million tablets sold for a period of less than 2 years has been ruled not material enough.\textsuperscript{59} Moreover, the FDA’s judgment is entitled to great deference from the courts: as long as the FDA files an enforcement action with a declaration that the drug in question is “new,” the court will follow the FDA’s

\textsuperscript{54} Id. (“This would be true even if marihuana were rescheduled and placed in Schedules II through V: the inclusion of the ‘C’ symbol on the product would be viewed as a labeling change regarding the conditions of its use.”).

\textsuperscript{55} Beers, supra note 28 at 1-33 n. 147.

\textsuperscript{56} Id. at 1-25.

\textsuperscript{57} Id.

\textsuperscript{58} Id. at 1-28 citing Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 629-30, 632 (U.S. 1973); United States v. Articles of Drugs . . . 5,906 Boxes, 745 F. 2d 105, 116-117 (1st Cir. 1984).

\textsuperscript{59} Id. at 1-32, citing Premo v. United States, 629 F.2d 795, 804 (2nd Cir. 1980); United States v. Premo, 511 F. Supp. At 971 n.9 (D.N.J. 1981).
guidance unless it decides that the FDA is operating “arbitrarily and capriciously.”60

The reluctance to give a drug “old drug” classification has strong regulative support, as shown by the 2003 amendment to 21 CFR 310.3(h).61 This regulation states, in part, that the newness of a drug may arise because of:

(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.
(4) The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.
(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.

This definition of “newness” essentially declares that any drug that is not identical to a currently approved drug is considered “new,” especially due to factor number (5), in which any change to a drug’s labeling makes it a new drug. In addition, if these “newness” factors were not broad enough, 21 CFR 310.100(c) made it clear that even after a drug is considered an “old drug,” it may still, at a later point, be reclassified as a “new drug!”

(c) . . . Undisclosed or unreported side effects as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug may result in its becoming a "new drug" even though it was previously considered "not a new drug."62

In the decades that the “old drug” status was up for debate in front of courts, only one

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60 Id. at 1-47.
61 Id. at 1-14.
published decision reports a finding of old drug status against the FDA in a civil case.63

With the grandfather clauses from the 1938 Act and the 1962 Act gone and the “old drug” designation impossible to reach, the result is that effectively all drugs that have not gone through a formal approval process are being marketed illegally as unapproved drugs, even the ones used since the 6th century AD.64 One wonders, of course, why the legislature would bother putting in these grandfather clauses in express terms on two different occasions if they were never to be used, but this is the situation we are in today: that all drugs on the market must be approved, or else they are marketed illegally.

3. The Unapproved Drugs Initiative of 2006

Since for all practical purposes drugs now had to be approved in order to be marketed, FDA has the authority to seize any of these ancient-but-unapproved drugs at any time.65 However, the FDA declined to take action on most of these drugs until they declared their “Unapproved Drugs Initiative” in June 2006.66 As part of the Unapproved Drugs Initiative, the FDA released “Marketed Unapproved Drugs—Compliance Policy Guide (CPG),” which gave tremendous insight into a lot of the traditionally informal procedures that the FDA follows.67

64 Hartung, supra note 1.
67 Julia Kobick, Negotiated Rulemaking: The Next Step in Regulatory Innovation at the Food and Drug Administration?, 65 FOOD DRUG L.J. 425, 431 (2010) (“Since the 1970s, informal notice and comment rulemaking under section 553 of the APA, rather than formal rulemaking under sections 556 and 557 of the APA, has become the norm for agency rulemaking.”).
g. **Prioritization and De Facto, De Jure Market Exclusivity**

Due to the number of unapproved drugs in market circulation due in no small part due to their uncertain legal status, the FDA could not simply remove the thousands of unapproved drugs at once: the FDA thus needed to prioritize which drugs to remove.\(^68\) The FDA prioritizes target drugs by first identifying unapproved drugs according to their potential safety risk, the potential lack of effectiveness, and then health fraud drugs.\(^69\) After identifying a target unapproved drug, the FDA will request voluntary compliance with a market withdrawal, and subsequently issue a warning letter and later possibly initiate a seizure, injunction, or other proceeding.\(^70\)

Beyond the first three categories of prioritization, i.e. safety risk, lack of efficacy, and health fraud drugs, however, the FDA lists a fourth: “drugs that present direct challenges to the new drug approval and OTC drug monograph systems.”\(^71\) This category of drug is described by the FDA as “unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval.”\(^72\) Targeting these drugs, the FDA says, “makes it more likely that firms will comply with the new drug approval.”\(^73\)

In other words, it is official FDA policy that the FDA will wait until a manufacturer of an unapproved drug files an NDA and obtains FDA approval for that drug, after which time the

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\(^{68}\) **COMPLIANCE POLICY GUIDE 2006, supra** note 19 at 5 (“FDA Estimates that, in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval. . . Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts . . . ”).

\(^{69}\) FDA defines health fraud as “[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes.  Id. at 3.

\(^{70}\) Id. at 2.

\(^{71}\) Id. at 3.

\(^{72}\) Id.

\(^{73}\) Id.
FDA will remove all of its competitors from the market. This is not some sort of “reading between the lines” analysis – this is explicitly stated later in the document, which even provides for an informal grace period between when the “approval pioneer” obtains approval and when the FDA seizes the drugs of all of its competitors:

When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type.

The ramifications of this are that de facto market exclusivity for the “approval pioneer” as soon as the one-year grace period runs out, when all of its competitors are removed from the market by the FDA. This, too, is not simply the product of my own analysis, but is directly referred to by the FDA:

If FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer. FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.

Thus, FDA is using their authority to remove unapproved drugs from the market not only to make sure that there are no unapproved drugs on the mark, but also to provide an incentive in the form of market exclusivity for drug manufacturers to get FDA approval.

Meanwhile, this de facto market exclusivity does not bar a pharmaceutical company from also receiving de jure market exclusivity under the Orphan Drug Act, the Hatch-Waxman Act, or

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74 Id. at 5.
75 Id. at 6.
76 Id. at 7.
77 Id. (emphasis added)
the Pediatric Exclusivity Extension. With the Orphan Drug Act providing up to seven years of
market exclusivity, the Hatch-Waxman Act providing up to five years, and the Pediatric
Exclusivity Extension providing an additional six months, marketers of unapproved drugs have
a very strong incentive to procure FDA approval.

h. Case Studies of the “Approval Pioneers”

Many firms have taken advantage of the FDA’s tacit promise of market exclusivity by
becoming “approval pioneers,” and many firms have been removed from the market as a result.
The FDA publishes all enforcement actions as a result of the Unapproved Drug Initiative of 2006
on their website, including warning letters sent out to some of the unapproved firms and press
releases advising consumers to purchase the approved drugs. The drugs listed on the web site
are not esoteric, unheard of drugs, but rather commonly known drugs such as
epinephrine, ophthalmic salt solution, carbinoxamine, and morphine. Not all of these

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78See id. at 17 n. 12 (“The Agency understands that . . . newly approved drug products may, in
certain circumstances, be eligible for market exclusivity. . . [M]arketing exclusivity may delay
the approval of competitor products.”). See also Kesselheim, supra note 16 (giving a pessimistic
overview of the market exclusivity provisions).
79OFFICE OF THE INSPECTOR GENERAL: THE ORPHAN DRUG ACT IMPLEMENTATION AND IMPACT 1
(May 2001), http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf. See also Orphan Drug Act, 21
U.S.C. 360aa-360ee (1994); Hutt, supra note 24 at 559.
80Ashlee B. Mehl, The Hatch-Waxman Act and Market Exclusivity for Generic Drug
Manufacturers: an Entitlement or an Incentive?, 81 CHI.-KENT L. REV. 649, 653, available
Add-On?, PATENT BARISTAS: FRESHLY BREWED BIO/PHARMA CHAT (Mar. 22, 2007),
82Enforcement Activities by FDA: Enforcement Actions by Drug Class, U.S. FOOD AND DRUG
ADMINISTRATION (Jan. 12 2011),
83Warning Letter from Deborah M. Autor, Esq., Director, Office of Compliance, to Dennis J.
Carlo, PhD, President and CEO (Jun. 9 2010) available at
84Questions and Answers about FDA’s Enforcement Action Against Unapproved Ophthalmic
enforcement actions have resulted in market exclusivity for single firms, but many of them have.

Examples of approved old drugs that have resulted in market exclusivity for a single firm include colchicine,\textsuperscript{87} supra, guaifenesin,\textsuperscript{88} quinine,\textsuperscript{89} and codeine.\textsuperscript{90} I will describe the case studies of colchicine and guaifenesin below.

i. **Colchicine (Colcrys)**

Market exclusivity for Colcrys-brand Colchicine by the “approval pioneer” company URL Pharma\textsuperscript{91} is the most recent and most infamous product of the FDAs Unapproved Drug Initiative of 2006. While colchicine itself is an ancient drug used in the treatment of gout, as discussed supra, URL Pharma nevertheless was able to secure several months of de facto market

\begin{itemize}
  \item \textsuperscript{85}Balanced Salt Solution Products, U.S. FOOD AND DRUG ADMINISTRATION (Jun. 22 2009), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm119630.htm
  \item \textsuperscript{88}Questions and Answers for Patients and Healthcare Providers Regarding Single-ingredient Oral Colchicine Products, U.S. FOOD AND DRUG ADMINISTRATION (Sep. 30 2010), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm227961.htm. [hereinafter Colchicine FAQs]
  \item \textsuperscript{91}URL Pharma is also known as Mutual Pharmaceuticals, Inc.
\end{itemize}
exclusivity\textsuperscript{92} and three years of \textit{de jure} market exclusivity by doing one unspectacular week-long clinical trial in the treatment of gout.\textsuperscript{93} This trial, which related to the administration of low dosages of colchicine to elicit the same effects,\textsuperscript{94} has been openly criticized as ill-administered.\textsuperscript{95} Most of the NDA that elicited FDA approval was based on previously-collected data, and in fact the FDA told URL Pharma that they potentially only needed “one adequate and well-controlled study,” with the rest of the application “supplemented by publicly available information.”\textsuperscript{96}

Compare this single clinical trial to the efforts made by Takeda Pharmaceuticals, Inc., to approve their drug Uloric-brand febuxostat. Febuxostat, another gout medication, was approved by the FDA at the same time as Colcrys.\textsuperscript{97} While Colcrys manufacturer URL Pharma had to run a single nominal clinical trial on experimental uses of colchicine, Takeda had to pay for the entire development of the molecule, as well as phase 1, 2, and 3 clinical trials, with the phase 3 clinical trials including two three-year extensions.\textsuperscript{98} Yet, the price that Takeda charges for its

\textsuperscript{92} The FDA published a press release on September 30, 2010 ordering a stop to all manufacturing of colchicine 45 days afterward (November 14\textsuperscript{th}, 2010) giving Colcrys approximately two months of de facto market exclusivity so far. Bobo, \textit{supra} note 12. Meanwhile, for the treatment of acute gout, Colcrys received three years of \textit{de jure} market exclusivity. Kesselheim, \textit{supra} note 9 at 2045.

\textsuperscript{93} Id. For the FDA summary of the NDA, see CENTER FOR DRUG EVALUATION AND RESEARCH APPLICATION NUMBER: 22-351 SUMMARY REVIEW 10-15 (Jul. 30, 2009) \textit{available at} http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022351s000_SumR.pdf [hereinafter 22-351 APPLICATION].


\textsuperscript{95} The trial compared 1.8 mg colchicine over one hour compared to 4.8 mg colchicine over six hours, to which Dr. Edward Fudman, MD, stated “No one treats acute gout with that much colchicine anymore . . . [URL Pharma] set up a straw man to knock it down.” Ullman, \textit{supra} note 8, at 27. Dr. Chris Morris, MD, stated “These studies were not done with the current formulation of Colcrys.” Id.

\textsuperscript{96} 22-351 APPLICATION, \textit{supra} note 89 at 10 section 7.

\textsuperscript{97} Ullman, \textit{supra} note 8, at 27.

\textsuperscript{98} Id.
alternative gout medication is $120 a month, while Colcrys is now available at $300 a month.99

Meanwhile, the FDA granted seven years of exclusivity for Colcrys’s use in familial Mediterranean fever (“FMF”). One would expect, in exchange for this monopoly, URL Pharmawould give a significant scientific contribution to the field. In fact, URL Pharma contributed no new studies, instead relying on a 505(b)(2) application based on previous studies performed by others.100 According to URL Pharma, previous trials were the only available alternative for the FMF indication because it would be unethical to place patients needing colchicine on a placebo.101

As a result, URL Pharma was awarded this period of exclusivity for no contribution to the field except for filling out the forms of the FDA.102 Sufferers of FMF, such as Doris Webb of Morristown, TN, used to be able to spend $11 for a 90-day supply of pills that she would take two or three times a day. Now, Webb is faced with a cost of about $4.50 a pill, as the price has skyrocketed to fifty times what it used to be.103 While URL Pharma has established an assistance
program to help people that will inevitably be adversely affected by their monopoly, it doesn’t help everyone, and part of the program simply redistributes the cost onto the public.\textsuperscript{104} Colchicine prescriptions used to cost Medicare $1 million a year: that price has to risen to $50 million.\textsuperscript{105}

\textit{ii. \textsc{Extended-release Guaifenesin (Mucinex)}\textsuperscript{106}}

Market exclusivity for Mucinex-brand time-released guaifenesin by the “approval pioneer” company Adams Respiratory Therapeutics\textsuperscript{107} was granted by the FDA in 2002.\textsuperscript{108} Although the FDA granted its \textit{de facto} market exclusivity before the Unapproved Drugs Initiative of 2006, the Mucinex case serves as a precursor to the announced FDA policy in the CPG.\textsuperscript{109}

Like colchicine, guaifenesin has been used in various medical applications for hundreds of years, and has been marketed in the United States as an expectorant since at least the early 1950s.\textsuperscript{110}

\textsuperscript{104} Colchicine FAQs, \textit{supra} note 84 (“The [Patient Assistance Program] covers with annual incomes up to 6 times the Federal Poverty limit, patients without insurance, and certain Medicare beneficiaries enrolled in Part D. The [Co-Pay Assistance Program] applies to insured patients who do not qualify for the PAP, and permits eligible partners to reduce their co-payment to no more than $25.”)

\textsuperscript{105} Kesselheim, \textit{supra} note 9.

\textsuperscript{106} The exclusivity given to Mucinex occurred before the Unapproved Drugs Initiative of 2006. Still, the pattern that the FDA followed in waiting for a drug to be approved and subsequently removing all of its competitors from the market was the same as in 2006.

\textsuperscript{107} Tammy M. Muccio, \textit{Guaifenesin and FDA Approval of Marketed Unapproved Drugs: Protecting the Public or Protecting Profits?}, \textsc{Harvard Law School} 2 (May 3, 2007) \textit{available at} \url{http://leda.law.harvard.edu/leda/data/834/Muccio_07.pdf}. Adams Respiratory Therapeutics has since been acquired by Reckitt Benckiser. RB Press Release – Acquisition of Adams Respiratory Therapeutics By Reckitt Benckiser, \textsc{Reckitt Benckiser} (Oct. 12, 2007), \url{http://www.rb.com/site/RKBR/Templates/Media/InvestorsGeneral2.aspx?pageid=262&cc=GB}.

\textsuperscript{108} \textsc{Center for Drug Evaluation and Research Application Number: 21-282 Approval Letter 1 (Jul. 12, 2002) available at} \url{http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-282_Mucinex_Approv.pdf}.

\textsuperscript{109} \textit{Id. at} 22.

\textsuperscript{110} \textit{Id. at} 12, citing \textit{Coricidin Syrup}, 54 \textit{J. Nursing} 1259 (Oct. 1954) (referencing an advertisement
FDA to be GRASE since 1989, and did not require manufacturers of the drug to acquire FDA approval through additional NDAs as long as they complied with an over the counter (“OTC”) monograph.

While the FDA permitted the immediate release form to be marketed as according to the terms of the OTC monograph and recognized the drug to be safe and effective, the FDA was not convinced that the extended release form was similarly safe and effective. The FDA stated that since the extended release drugs contained significantly more active ingredient per dose, it could cause a “dose dump – releasing too much drug too quickly, potentially compromising patient safety and then failing to provide extended relief of symptoms.”

As a result, Adams Respiratory Therapeutics filed a 505(b)(2) NDA for extended release guaifenesin and received approval on July 12, 2002. As with any 505(b)(2) application, the study contains investigations of safety and effectiveness that were not conducted for or by the applicant. As the FDA stated in a mock-interview in a video released to the public,

Maria: Were non-clinical studies or clinical efficacy and safety trials required to support for a cough syrup containing glycercylguaiacolate).

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111 Id. at 14.
112 An OTC monograph is a set of guidelines for doses, labeling, indications, and warnings wherein if a manufacturer follows those guidelines, no additional NDA is required. Small Business Assistance: Frequently Asked Questions on the Regulatory Process of Over-the-Counter Drugs, U.S. FOOD AND DRUG ADMINISTRATION, (Jul. 12010), http://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm069917.htm (“These standards provide the marketing conditions for some OTC drug products including the active ingredients, labeling, and other general requirements . . . Marketing pre-clearance of OTC drug products by the FDA is not required if the standards of the applicable monograph are met.”).
113 Muccio, supra note 103 at 16.
114 Id.
[the Mucinex] NDA?

Dr. Lee: No. New non-clinical studies and new clinically efficacy and safety studies were not required to support the application.

Maria: So for these products, there was clear evidence of efficacy and safety based on the agencies prior findings . . . what was the main focus of this 505(b)(2) application, then?

Dr. Lee: This application focused on chemistry, manufacturing, and controls information and a comparison of the products’ pharmokinetic characteristics with those of the . . . referenced product.117

Yet, as with the colchicine application that would come later, Adams Respiratory Therapeutics was able to quickly achieve de facto market exclusivity for its extended release guaifenesin product. Within three months, the FDA had issued warning letters to approximately seventy companies notifying them of Adams successful submission of an NDA, and later sent correspondence requesting that the companies cease production of unapproved guaifenesin before May 21, 2003 and distribution before October 23, 2003.118 As a result, Mucinex became the only extended-release guaifenesin product on the market.119 While Adams Respiratory Therapeutics did not enjoy any de jure market exclusivity from its NDA,120 it has enjoyed de

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118 Muccio, supra note 103 at 19-20.
119 Muccio, supra note 103 at 20-21.
120 Adams Respiratory Therapeutics does have patent protection for some aspects of the extended release guaifenesin. See, e.g., U.S. PAT.6,372,252. Adams Respiratory Therapeutics has also been successful in using this patent to prohibit some competitors from entering the market. Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283 (Fed Cir 2010). However, what the patent covers is not as broad as the de facto market exclusivity that the FDA offered. URL Pharma, for example, filed an ANDA for extended release guaifenesin based on Adams’s NDA, and the CEO of Adams conceded that Adams’s patents could not cover Mutual’s proposed tablets. Letter from Wm Peter Rickman, Director, Division of Labeling and Program Support, to Robert Dettery, Mutual Pharmaceutical Company, Inc. (Aug. 9, 2006) available at http://web.archive.org/web/20061113174727/http://www.urlmutual.com/guaifenesin.pdf; URL Pharma, Inc., United Research Laboratories/Mutual Pharmaceutical Company Announce ANDA Filing for Guaifenesin Extended-Release Tablets, 600 Mg and 1200 Mg, MEDICAL NEWS TODAY
facto market exclusivity for the past seven years, ever since its competitors have been removed from the market.\footnote{25}

In the fiscal year ending in June 2004, Adams Respiratory Therapeutics posted 337\% more than revenues in the prior year as a result of the exclusivity.\footnote{26} In 2007, Bloomberg reported that the exclusivity should bring the company an additional $50 to $80 million in annual sales.\footnote{27} Meanwhile, sources reported a 700\%\footnote{28} increase in the cost of the product, and since Adams Respiratory Therapeutics’ application also qualified extended-release guaifenesin for

\footnote{25}{Not all firms complied with the FDA’s order to stop distribution, and the FDA decided to “take action” to stop marketing unapproved guaifenesin products on May 25, 2007. Kiberly Rawlings, \textit{FDA Takes Action to Stop Marketing of Unapproved Timed-Release Guaifenesin Drug Products}, U.S. FOOD AND DRUG ADMINISTRATION (May 25, 2007), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108921.htm; \textit{see also} Donna Young, \textit{Unapproved Guaifenesin Drugs Ordered Off the Market}, AMERICAN SOCIETY OF HEALTH SYSTEM PHARMACISTS (May 25, 2007) http://www.ashp.org/import/news/HealthSystemPharmacyNews/newsarticle.aspx?id=2579. So while the FDA seemed to have granted Adams Respiratory Therapeutics de facto market exclusivity, they did little to enforce it until 2007. Nevertheless, even though there was not pure market exclusivity, there was enough to lead to a substantial increase in Adams Respiratory Therapeutics’ profits, \textit{infra}.}
\footnote{26}{Muccio, \textit{supra} note 103 at 21.}
\footnote{28}{Muccio, \textit{supra} note 103 at 21.}
OTC use, consumers had to pay this cost without the benefit of insurance plans.\textsuperscript{125}

Using these case studies, and keeping in mind that many more cases exist, this paper will now focus on the constitutionality of the FDA’s grants of market exclusivity in the context of the Intellectual Property Clause.\textsuperscript{126}

4. The Intellectual Property Clause Is Both a Grant and Limitation on Congress

The Intellectual Property Clause of the Constitution states,

\begin{quote}
“The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.”\textsuperscript{127}
\end{quote}

As one of the enumerated powers of Congress, this clause is in its nature a grant of authority, but carries with it an explicit limitation that reflected the Framers’ hostility towards monopolies.\textsuperscript{128} In both the “for limited Times” language and the preamble, “To promote . . . Progress,” this clause has explicit textual restrictions that seem to restrain Congress from wantonly issuing monopolies left and right. As stated by James Madison,

\begin{quote}
Monopolies . . . ought to be granted with caution, and guarded with strictness against abuse. The Constitution of the U.S. has limited them to two cases, the authors of Books, and of useful inventions, in both which they are considered as a compensation for a benefit actually gained to the community as a purchase of property which the owner otherwise might withhold from public use.\textsuperscript{129}
\end{quote}

While some courts have concluded that these words provide no restriction at all,\textsuperscript{130} most

\begin{flushright}
\textsuperscript{125} Id. \\
\textsuperscript{126}U.S. CONST. art.I, § 8, cl. 8. \\
\textsuperscript{127} Id. \\
\textsuperscript{128} Tyler T. Ochoa and Mark Rose, The Anti-Monopoly Origins of the Patent and Copyright Clause, 84 J. OF THE PAT. AND TRADEMARK OFFICE SOC., 909, 925, 928 (Dec. 2002) (“It is clear that many of the Framers were concerned with restraining monopolies of all kinds. . . the Clause appears to have been designed not so much to limit the means by which Congress could promote the progress of science and useful arts, but rather to limit the duration and purposes for which exclusive rights could be granted.”). \\
\textsuperscript{129}Id. at 928. \\
\end{flushright}
courts have recognized these words to present a significant limitation.\(^{131}\)

In part, this limitation is in place because from a theoretical standpoint, the monopolies that Congress is allowed to give under the Intellectual Property Clause are not true monopolies at all.\(^{132}\) True monopolies deal with a government misappropriation of a public good to a single private party. Inventions and creative writings, meanwhile, could not possibly be in that category because the work never existed as a public good before the creation. As stated in *U.S. v. Dubilier Condenser Corp.*, 289 U.S. 178, 187 (1933),

Though often so characterized a patent is not, accurately speaking, a monopoly, for it is not created by the executive authority at the expense and to the prejudice of all the community except the grantee of the patent. . . . . The term 'monopoly' connotes the giving of an exclusive privilege for buying, selling, working, or using a thing which the public freely enjoyed prior to the grant. Thus a monopoly takes something from the people. **An inventor deprives the public of nothing which it enjoyed before his discovery, but gives something of value to the community by adding to the sum of human knowledge.**

Thus, while an inventor may restrict for some limited time the use of his own contribution to society, it is not a true monopoly because society never had the invention to begin with. In *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the Supreme Court of the United States

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\(^{132}\)Seymour v. Osborne, 78 U.S. 516, 534 (1871) ("Letters patent are not to be regarded as monopolies, created by the executive authority at the expense and to the prejudice of all the community except the persons therein named as patentees, but as public franchises granted to the inventors of new and useful improvements for the purpose of . . . reducing the same to practice for the public benefit, as contemplated by the Constitution and sanctioned by the laws of Congress.").
was called upon to determine the validity of patents in light of a new statutory criteria for patent eligibility: the test for “obviousness.”

In the decision, the court considered the Intellectual Property Clause, and wrote,

The clause is both a grant of power and a limitation. This qualified authority . . . is limited to the promotion of advances in the ‘useful arts.’ The Congress in the exercise of the patent power may not overreach the restraints imposed by the stated constitutional purpose. Nor may it enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby. Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must "promote the Progress of . . . useful Arts." This is the standard expressed in the Constitution and it may not be ignored.

Thus, while it grants an authority for Congress to grant a monopoly, it only grants authority under certain given conditions. This language has been echoed in subsequent, more modern cases, such as Bonito Boats, Inc., 489 U.S. at 146 (“[T]he Clause contains both a grant of power and certain limitations upon the exercise of that power. Congress may not . . . ‘authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available.’”), and most recently in the Stevens dissent of Bilski v. Kappos.

i. The Source of FDA Authority is Intertwined With the IP Clause Limitations

In Hipolite Egg Co. v. United States, the Supreme Court analyzed FDA authority under the 1906 Act as stemming from the Commerce Clause of the U.S. Constitution. When discussing the requirement that an adulterated or misbranded product be in interstate commerce

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133 Id. at 3.
134 Id. at 5-6 (emphasis added).
135 130 S. Ct. 3218, 3252 (2010) (“This clause ‘is both a grant of power and a limitation . . . This is the standard expressed in the Constitution and it may not be ignored.’”).
136 Hipolite Egg Co. v. United States, 220 U.S. 45, 57 (1911)
in order for the FDA to use its power of seizure, the court stated,

The [1906 Act] rests, of course, upon the power of Congress to regulate interstate commerce; and, defining that power, we have said that no trade can be carried on between the states to which it does not extend, and have further said that it is complete in itself, subject to no limitations except those found in the Constitution.\(^{137}\)

The scope of the Commerce Clause has been broadened to an incredible extent since the 1906 Act, and as a result has allowed Congress to regulate everything from racial discrimination in country motels\(^ {138}\) to a farmer’s small crop of wheat for his personal use.\(^ {139}\) However, while the Commerce Clause itself has considerable breadth, the limitations presented by other clauses Constitution still present an obstacle to Congressional power under the Commerce Clause. Congress may not, for example, compel state legislatures to adopt Congressional regulations on toxic waste disposal because it would violate the 10\(^{th}\) Amendment;\(^ {140}\) nor may Congress pass a statute abrogating state sovereign immunity guaranteed under the 11\(^{th}\) Amendment;\(^ {141}\) nor may Congress exclude hippies from its food stamp program because it would violate the Due Process Clause of the Fifth Amendment, the guarantee of equal protection.\(^ {142}\) Rather, the presence of limitations in separate clauses can very well limit the Commerce Clause itself, because why would the Framers expressly include a limitation if such a limitation would be rendered ineffective by another clause of the Constitution?\(^ {143}\)

5. A Framework Supplied by Professors Heald and Sherry

In the article “Implied Limits on the Legislative Power: The Intellectual Property Clause

\(^{137}\) Id. (emphasis added).
\(^{139}\) Wickard v. Filburn, 317 U.S. 111, 128-29 (1942).
\(^{143}\) I would like to note that I came to this conclusion myself before reading Heald and Sherry, infra, and thus do not cite the article for this section, even though some of the case studies and conclusions and example cases are the same.
as an Absolute Constraint on Congress,” Professors Heald and Sherry argue that the Intellectual Property Clause imposes a strict, absolute limitation on the Commerce Clause.\textsuperscript{144} In this article, Heald and Sherry write about the implicit limitations that must be read into the Commerce Clause when it begins to expand so far that it conflicts with other clauses.\textsuperscript{145} Heald and Sherry include an extensive history and account of example cases when the Commerce Clause is limited by other clauses in the Constitution. Heald and Sherry include, for example, situations where the Commerce Clause is restricted by the limitations of the Tenth Amendment,\textsuperscript{146} the Eleventh Amendment,\textsuperscript{147}Article III,\textsuperscript{148} and most importantly, even Article I powers. In \textit{Railway Labor Executives Ass'n v. Gibbons},\textsuperscript{149} for example, the Supreme Court struck down a Congressional law that required a railroad to pay large sums of money to laid off employees because it was not a uniform law and the Bankruptcy Clause only gives Congress power “To establish \ldots uniform Laws on the subject of Bankruptcies throughout the United States.”\textsuperscript{150} Even though this law may have been within the grasp of the Commerce Clause, the conflict with the Bankruptcy Clause restricted Congress’s authority.

After an extensive analysis of the anti-monopoly historical underpinnings of the

\textsuperscript{144} Paul J. Heald and Suzanna Sherry, \textit{Implied Limits on the Legislative Power: The Intellectual Property Clause as an Absolute Constraint on Congress}, 2000 U. ILL. L. REV. 1119, 1156 (2000). \textsuperscript{145} Heald and Sherry distinguish these “inter-clause conflicts” from situations where the Commerce Clause simply does not extend. For example, the Supreme Court decision in United States v. Lopez, 514 U.S. 549, 602 (1995) is a situation in which the regulation of guns in school zones was simply not “substantially related” to interstate commerce; where the Congress’s power falters not because of a separate clause in the Constitution, but because of a lack of Congressional authority. See Heald and Sherry, \textit{supra} note 137 at 1123.

\textsuperscript{146} Id. at 1127 citing Printz v. United States, 521 U.S. 898 (1997); New York v. United States \textit{supra} note 133 at 168.

\textsuperscript{147}Id. at 1126-27 citing Alden v. Maine, 527 U.S. 706, 714-28 (1999); Seminole Tribe, \textit{supra} at 59-73; Monaco v. Mississippi, 292 U.S. 313, 322-328 (1934); Ex parte New York, 256 U.S. 490 (1921); Hans v. Louisiana, 134 U.S. 1 (1890).

\textsuperscript{148}Id. at 1127 citing Plaut v. Spendthrift Farm, Inc., 513 U.S. 211 (1995).

\textsuperscript{149} 448 U.S. 1301 (1980).

\textsuperscript{150} Id.
Intellectual Property Clause, Heald and Sherry examine the structure of the Intellectual Property Clause. Heald and Sherry note that “no other grant of power to Congress begins with a prescription of proper legislative purpose,” and that the words “limited terms” and “exclusive rights” manifest implicit limitations within the Intellectual Property Clause. Finally, after reviewing the common law surrounding the Intellectual Property Clause, Heald and Sherry deduce “four principles of constitutional weight” that may run afoul to the Intellectual Property Clause:

1. The Suspect Grant Principle: Scrutiny under the Intellectual Property Clause is only triggered when Congress effects a grant of exclusive rights that imposes monopoly-like costs on the public;

2. The Quid Pro Quo Principle: A suspect grant may only be made as part of a bargained-for exchange with potential authors or inventors;

3. The Authorship Principle: A suspect grant must initially be made to either the true author of a writing or to the party responsible for a new advance in the useful arts;

4. The Public Domain Principle: A suspect grant may not significantly diminish access to the public domain.

Heald and Sherry go on to apply these principles to many of the questionable congressional grants of monopoly, such as copyright term extensions, database protections as a result of the Supreme Court’s decision in *Feist Publications, Inc. v. Rural Telephone Service Co.*, and most relevant to our case, the special protections afforded to orphan drugs. For the purposes of this paper, I will apply this framework to the current FDA practices of granting market exclusivity to the “approval pioneers.”

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151 Id. at 1142-1154.
152 Id. at 1154-55.
153 Id. at 1167
154 Id. at 1168-76
155 Id. at 1176-79
156 Id. at 1187-89.
6. Granting Market Exclusivity to the “Approval Pioneers” is Unconstitutional

Using Heald and Sherry’s framework, I conclude that the FDA practice of following a course of conduct to grant market exclusivity to approval pioneers is an unconstitutional use of Congressional authority. While the FDA does have the power to remove unapproved drugs from the market, I conclude that they may not do so when the reason for removal is to grant a monopoly to an approval pioneer.

a. Scrutiny Under the IP Clause is Triggered by the Suspect Grant Principle

Heald and Sherry define the Suspect Grant Principle as a triggering condition, where scrutiny under the Intellectual Property Clause is triggered “when Congress effects a grant of exclusive rights that imposes monopoly-like costs on the public.”

Under this principle, there is no question that the FDA’s grants of *de jure* and *de facto* market exclusivity need to be scrutinized under the Intellectual Property Clause. In the case of colchicine, the price of a commonly-used drug increased somewhere between twenty and fifty times, depending on the source.\(^\text{157}\) In the case of sustained-reliefguaifenesin, prices increased 700%.\(^\text{158}\) While that reflects the monopoly-like effect on consumers who can afford the product, one must also remember that there are many consumers who will be unable to afford the product, for example those who do not qualify for Colcrys’s PAP or CAP, or those who must purchase Mucinex over the counter without the benefit of insurance. These populations inevitably form a loss of consumer surplus, resulting in deadweight loss, market inefficiency, and similarity to a monopoly.\(^\text{159}\)

In fact, the “monopoly-like” characteristic of these deals between the FDA and the

\(^{158}\)Muccio, *supra* note 103 at 21.
\(^{159}\)Mark Hirschey, *FUNDAMENTALS OF MANAGERIAL ECONOMICS* 462 (9th Ed. 2008).
“approval pioneers” is more similar to a true monopoly even than an issued patent. As stated in U.S. v. Dubilier Condenser Corp., supra, “The term ‘monopoly’ connotes the giving of an exclusive privilege of . . . selling . . . a thing which the public freely enjoyed prior to the grant,” while “an inventor deprives the public of nothing which it enjoyed before his discovery.” In the case of market exclusivity for approval pioneers, we are dealing with the former, where the FDA unilaterally gives to the approval pioneer market exclusivity over drugs that the public just previously “freely enjoyed.”

For these reasons, the FDA’s actions resulting in de jure and de facto market exclusivity should be considered a suspect grant and must be scrutinized under the Intellectual Property Clause.

b. The Suspect Grant Does Not Fulfill the Quid Pro Quo Principle

Heald and Sherry define the Quid Pro Quo Principle as a condition, where once a suspect grant is scrutinized under the Intellectual Property Clause, a suspect grant may only be made as a part of a “bargained-for exchange with potential authors or inventors.”

Under this principle, I argue that the FDA’s grants of de jure and de facto market exclusivity were not bargained-for because the FDA received only nominal consideration in exchange for multi-million dollar grants of market exclusivity. The very premise of a 505(b)(2) application, as mentioned above, is to provide a shortcut for companies to get FDA approval with no new clinical trial data. Instead, the FDA accepts applications that are nothing more than compilations of data made publicly available by others – and in the case of DESI studies,

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161 Regulatory Professionals, Inc., supra note 41.
these data are from the FDA itself!\textsuperscript{162} Even if the FDA were to claim that they received something in return, i.e., the centralization of data in a formal filing system, it is simply not adequate consideration to support a “bargained-for” theory. As stated in the classic contracts case \textit{In re Greene},\textsuperscript{163} “The parties may shout consideration to the housetops,” and yet still there is no \textit{quid pro quo}.

Further evidence that this exchange was not “bargained-for” can be found in the case of Takeda Pharmaceuticals and their gout treatment, Uloric-brand febuxostat. Recall that Takeda Pharmaceuticals developed a new molecule and underwent years of clinical trials and before they were afforded a grant of market exclusivity comparable to URL Pharma’s grant.\textsuperscript{164} The proposition that both of these products were in a similar “bargained-for” context is ludicrous: in one situation, a company gave to society an entire molecule, and in the other, a company put already-known data into an application, and yet they both received comparable market exclusivity.\textsuperscript{165}

Perhaps, \textit{en masse}, the many unapproved drugs that could be forced through the approval process could one day “promote . . . Progress” by instilling more confidence in the available drugs on the market or by making the system more robust.\textsuperscript{166} That, however, is not the question we are asking under this principle: we are asking if the individual approval pioneer is actually giving something to suffice for a \textit{quid pro quo} in exchange for years of market exclusivity.

For these reasons, the FDA’s actions resulting in \textit{de jure} and \textit{de facto} market exclusivity does not fulfill the Quid Pro Quo Principle.

\textsuperscript{162} Phelps, \textit{supra} note 42.
\textsuperscript{163} 45 F.2d 428, 430 (S.D.N.Y. 1930)
\textsuperscript{164} Ullman, \textit{supra} note 8, at 27.
\textsuperscript{165} I believe that the situation is much more similar to a conditional gift than a \textit{quid pro quo} scenario, i.e., if you go through the motions and fill out the forms, we will kick your competitors off the market.
\textsuperscript{166} U.S. CONST. art.I, § 8, cl. 8.
c. The Suspect Grant Does Not Fulfill The Authorship Principle

Heald and Sherry define the Authorship Principle as a condition, where once a suspect grant is scrutinized under the Intellectual Property Clause, a suspect grant must initially be made to either “the true author of a writing or to the party responsible for a new advance in the useful arts.”

The FDA’s suspect grant cannot fulfill this condition because there is no “author” or “inventor” with which the FDA has bargained. The approval pioneers who filed the NDA under 505(b)(2) did not make anything useful, novel, or non-obvious; they simply followed the application and collected other potential inventors’ publicly available data. As conceded by the FDA in a mock interview regarding the NDA of extended-release guaifenesin, “New non-clinical studies and new clinically efficacy and safety studies were not required to support the application.”

In the case of the Colcrys application for use in FMF, there was literally no additional data in the application because they said that it would be unethical to complete a placebo trial with the current knowledge of the efficacy of FMF. In this case, perhaps the inventor who discovered that colchicine was so effective for FMF should be getting market exclusivity, but certainly not the approval pioneer who merely reproduces the data.

Would this mean that no pure 505(b)(2) application could receive market exclusivity because it was not based on studies made by the approval pioneers? This is possible, regardless of the intent of Congress, as Congress only has as much authority as the Constitution grants it.

\[\text{Mucinex Video, supra note 112.}\]
\[\text{Ullman, supra note 8, at 27.}\]
\[\text{The FDA itself has come to a similar conclusion regarding “DESI Upgrades.” A DESI upgrade is when the FDA, after reviewing new data, changed its initial conclusion that there}\]
For these reasons, the FDA’s resulting in *de jure* and *de facto* market exclusivity does not fulfill the Authorship Principle.

d. **The Suspect Grant Violates the Public Domain Principle**

Heald and Sherry define the Public Domain Principle as where once a suspect grant is scrutinized under the Intellectual Property Clause, a suspect grant may not significantly diminish access to the public domain.

The FDA’s suspect grant significantly diminishes access to drug products currently in the public domain in three ways. First, the suspect grant in both the cases of colchicine and guaifenesin raised the price of the drug considerably, restricting public access to the drug itself.

Second, when the FDA enforced the market exclusivity, the FDA ordered all competing firms to stop “manufacturing” the product, which is more than just “marketing.” By stopping manufacture of the product, the FDA stopped any non-sale use of the drugs by any competitor of the approval pioneer, such as scientific research. This, in effect, is even more powerful than the rights afforded to patent holders, because the FDA becomes the “enforcer” of the market exclusivity. Under patent protection, meanwhile, parties must assert their own rights, and may not assert them in certain, negligible situations.

Finally, it is important to remember that these unapproved drugs could have been under patent protection in the past, in one form or another. If this is the case, if there is even one

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expired patent that covered one of the unapproved drugs in the past, subjecting the public to market exclusivity would be upsetting the careful balance that underlies the patent system. Under Madison’s theory, in which he considered patents “as a compensation for a benefit actually gained to the community as a purchase of property,” the community has already paid their purchase price for the property.\textsuperscript{173} Forcing the public to “pay” for the technology again is outside of the limits of the Constitution. As stated in \textit{John Deere v. Graham}, “Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available.”\textsuperscript{174}

For these reasons, the FDA’s actions resulting in \textit{de jure} and \textit{de facto} market exclusivity does not fulfill the Public Domain Principle, and therefore, this is an impermissible granting of a monopoly-like power due to the limitations imposed by the Intellectual Property Clause. As stated in \textit{Hipolite Egg Co. v. U.S.}, FDA authority within the commerce clause is “subject to no limitations except those found in the Constitution,” and the Intellectual Property Clause is one such limitation.

\textbf{7. Ramifications of Unconstitutionality}

While according to the analysis above it appears that the FDA may not have the power to grant market exclusivity to approval pioneers, this puts us in a very uncomfortable doctrinal situation: what is the FDA to do, if they are unable to remove unapproved drugs from the market? Surely companies cannot market unapproved drugs against the FDA’s regulations. The answer is that while the FDA does not have approval to grant market exclusivity to certain firms, they \textit{do} have the authority to stop other firms from marketing unapproved drugs. But they are not merely two sides of the same coin: the difference is the motivation behind the FDA

\textsuperscript{173}Ochoa and Rose, \textit{supra} note 122 at 928.
\textsuperscript{174} 383 U.S. at 5-6.
When the FDA decided to take action against the unapproved drugs, it decided to take action not only because there were unapproved drugs being sold illegally, but also because they were making good on their deal to offer an approval pioneer a period of market exclusivity.\(^{175}\) The FDA was remarkably candid with this information, even explicitly detailing the plan of “de facto” market exclusivity when an approval pioneer first enters the market with an approved version of the drug: “FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.”\(^{176}\)

But the truth is, this isn’t de facto market exclusivity at all: this is de jure market exclusivity! It is a government organization making a conscious decision to give a carrot to the approval pioneer and a stick to those who remain unapproved. It may not be statutory de jure market exclusivity as in the Orphan Drug Act,\(^{177}\) but it is still market exclusivity given through some government actor. What the FDA is doing now is awarding market exclusivity based on a course of planned, announced conduct. Especially considering that the FDA uses mostly informal rulemaking procedures, anyway,\(^{178}\) this de facto market exclusivity is, in fact, de jure.

True de facto market exclusivity would result from no government planning at all. It would arise from the spontaneous use of FDA power to remove a number of competitors that

\(^{175}\) See, for example, the case studies of colchine and guaifenesin, supra, as well as the case study for codeine and quinine.

\(^{176}\) COMPLIANCE POLICY GUIDE 2006, supra note 19 at 6-7.


results in a single supplier remaining. It would occur when a single manufacturer, through his own good efforts to comply with federal regulations, finds himself in a very advantageous market position. This *de facto* market exclusivity would be entirely permissible, if only because it is not a “suspect *grant* of authority.”\(^{179}\) This market exclusivity, rather, would be the result of Congress naturally carrying out its duties, and could easily be covered by the Necessary and Proper Clause.\(^{180}\) However, the informal guarantee of market exclusivity to approval pioneers is indeed a *de jure* grant of authority and subject to conflict with the Intellectual Property Clause.

The FDA, thus, can have a plan of action to remove unapproved drugs from the market, but not a plan of action to enrich the approval pioneers. If the approval pioneers happen to be enriched in the process, that is a case of true *de facto* market exclusivity, and would be permissible. But if the FDA, through its own informal promises, attempts to use market exclusivity as an incentive to entice approval pioneers to obtain FDA approval, that is constitutionally impermissible.

### 8. Conclusion

Over the course of a hundred years of immense changes in drug regulation law, the FDA finds itself with thousands of unapproved drugs on its hands. Some of them are known to be safe and effective, some of them are only known to be safe, and some are known to be neither safe nor effective, instead finding their place in the marketplace simply because they have always been in the marketplace.

The FDA has an interest – a very valid interest – in making sure that all of these drugs are approved and verifiably safe and effective. To accommodate this interest, Congress has given to

\(^{179}\) Heald and Sherry, *supra* note 137 at 1167.  
\(^{180}\) U.S. CONST. art.I, § 8, cl. 18.
the FDA powers that allow it to keep unapproved drugs off the market. Under the Commerce Clause, these powers are well within Congressional authority.

However, the power to keep unapproved drugs off the market does not include a power to grant monopolies to drug manufacturers. While the Commerce Clause alone may have provided this power if it were read in a vacuum, the Intellectual Property Clause imposes a limitation on Congressional authority by imposing specific conditions under which monopolies may be given.

Thus, while the FDA may exercise its power of keeping unapproved drugs off the market, and while some companies who follow the rules may find themselves in a favorable market position, the FDA may not pursue a planned course of conduct to enrich a single company with a monopoly without regard to the limitations of the Intellectual Property Clause of the Constitution.