WRITTEN TESTIMONY OF

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BEFORE THE

UNITED STATES SENATE

COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON INTELLECTUAL PROPERTY

ON

"THE STATE OF PATENT ELIGIBILITY IN AMERICA, PART I"

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Executive Summary

What is at stake in this focus on patent eligibility in the United States is not just righting the ship on patent eligible subject matter, it is sending a clear message to the Supreme Court that it must not, and can never, alter the sense and meaning of federal legislation through judicial exceptions to federal statutes and/or conscious disregard for their literal wording and meaning. Congress has the sole right to create federal legislation under the U.S. Constitution, and the American people have the right to demand that it be applied as written.

The legislative history of 35 U.S.C. § 101 confirms that Congress codified and repeatedly amended the Patent Act from its time of enactment in 1790 to the most recent codification in 2011, using its exclusive power under Art. 1, §8, cl. 8 of the Constitution to promote the progress of science and the useful arts to motivate both inventions and applied discoveries. In contrast, the history of applying Section 101 by the Supreme Court in its opinions goes from little or no statutory construction or discussion of legislative intent to the creation of "judicial exceptions" to the federal statute to full boar direct contradiction of it. The derogation of patent eligibility from what Congress enacted to what the Supreme Court created has resulted in the loss of protection for certain key innovations and following that, the loss of motivation to develop them at all. It has also made the United States less competitive on a global basis and a less attractive country in which to carry out fundamental research.

What is also at stake is human lives. The highest public interest is life itself. Nature is often the best source to find solutions for diseases. Nonlimiting examples of life-saving or disease curative drugs that are naturally occurring and would not be patentable, and thus would likely not have been developed under the Supreme Court case of *AMP v. Myriad Genetics*[1] include penicillin, amoxil, tetracycline, cyclosporin, cephalosporin, streptomycin, chloramphenicol, insulin, Taxol, doxorubicin, vincristine, vinblastine, and many others. A further selected list is provided in Attachment 4. No one would doubt that these drugs have saved lives, have improved the quality of life and have been transformative to our health care. It is essential that researchers be given a wide berth to discover new drugs with the confidence that they, or their companies, can recoup their investment of time and

[1] 569 U.S. 576 (2013).

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cost. If not, the next generation of these drugs will never be found, much less developed. The Supreme Court's *Myriad* case stands in the way of future life-saving drugs. For the sake of lives and health, it must be abrogated.

The price of future essential drugs from natural sources will be irrelevant if there are no new drugs developed in these categories. Opponents confuse drug discovery with drug pricing. Typical drug research and discovery occurs ten years or more before any pricing decisions are even considered. Drug prices are dependent on the labyrinth and length of the extraordinarily expensive and complex clinical trials, excessive administrative responsibilities, insurance and provider complexities and other aspects of drug development, not just, and often not primarily, data exclusivity and patent protection. Opponents should not comingle drug pricing for distracting effect with the issue of motivating basic drug discovery.

Opponents argue that if isolated natural products are patent eligible subject matter (as required by statute), then other companies or universities cannot enter that market until the patent expires. This is absolutely true. And the Constitution itself, going back to 1787, embeds this principle as the core means to motivate inventions and discoveries. Our founding fathers knew that our country's success depends on the ability to promote the progress of science and the useful arts by securing for limited time the exclusive right to discoveries. If opponents disagree with this, they will have to amend the constitution. Absent that, this framework stays as the highest law of our land.

The Subcommittee on Intellectual Property of the Senate Judiciary Committee should be commended for its dedicated attention to this problem. The draft amendment to 35 U.S.C. § 101 proposed by the Subcommittee embodies a well-written consensus driven solution that will fix the patent eligibility problem.

The addition of Section 100(k) affirms the longstanding Congressional intent that patent eligibility requires human intervention, i.e., is limited to inventions and applied discoveries. Such confirmation should not be necessary, given the Committee Reports accompanying the 1952 Act which indicate that Congress intended statutory subject matter to "include anything under the sun that is made by man."[2] But apparently it is necessary, as the Supreme Court has repeatedly asserted justification for its judicial exceptions as required to remove the law of gravity and the conversion of mass into energy.

[2] S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952)#

The removal of "new" from Section 101(a) affirms Congress' intent that patent eligibility and patentability must be considered separately, which is consistent with the term "subject to the conditions and requirements of this title", that has been in the Patent Act since 1952.[3]

The proposed changes to Section 112(f) creates new patent law, which is not directly related to patent eligibility, but instead relates to patentability requirements for the adequate enablement and written description requirements in the specification. It has not been the law to date that functional claims are limited to the structures, materials and acts in the specification, and certainly not in the area of chemistry, pharmaceuticals and biotechnology. Sec. 112(f) may or may not be a good compromise addition to the statutory revisions. I suggest that Section 112(f) be subject to further discussion, so that the full ramifications of such are fully run to ground, as there has not been sufficient consideration of all potential downstream effects.

The Additional Legislative Provisions are well-written and excellent additions to Section 101. The direct rejection of judicial exceptions to patentability and the abrogation of all cases establishing or interpreting these exceptions is the hallmark of this patent legislations. I am especially grateful, and the people of the United States should be grateful, that the Subcommittee shows the strength of the full power granted to it under the Constitution to demand compliance from the Supreme Court for its legislation as written and enacted.

At the end of this written testimony, I also take the opportunity to discuss the effect of the Myriad decision on us personally. I also provide my personal remarks on patent eligibility as a breast cancer survivor whose life was saved (along with thousands of other women afflicted with breast cancer) by medicines that would not be motivated, protected or developed under the Supreme Court case of *AMP v. Myriad Genetics*.[4]

[3] Pub. L. No. 82-593, 66 Stat. 792 (1952).
[4] 569 U.S. 576 (2013).#

Written Statement

I. Introduction

By way of introduction, I am a registered patent attorney with over 30 years of experience in private and corporate practice. From 2006-2010, I was the Senior Vice President and Chief Patent Counsel at GlaxoSmithKline, where I served as the worldwide head of patents for all litigation and transactional matters. I do not speak for GlaxoSmithKline nor any other company or entity, including my current clients, and my views are strictly independent of their positions on policy. My views may disagree with theirs in key respects. I have not discussed my Testimony with any companies before submission.

Prior to my position at GSK, I was an equity partner at the global law firm of King & Spalding, where I founded the Pharmaceutical and Biotechnology Patent Practice.

Since 2010, I have been the Principal of Knowles Intellectual Property Strategies, LLC which specializes in the area of pharmaceuticals and biotechnology, providing guidance on complex IP matters, patent litigation strategy and assistance, licensing, patent prosecution, opinions, obtaining and protecting the full value of innovation, investor support, and monetization of assets. We represent clients ranging from emerging companies to mid-cap companies, large public companies, universities and investors.

I am also a frequent speaker and author on U.S. patent law and policy issues. Further details about my background are provided in my C.V., which is provided as Attachment 1.

II. Unconstitutional Application of Section 101 by the Supreme Court

I am the co-author with Anthony Prosser of a law review article titled "Unconstitutional Application of 35 U.S.C. 101 by the U.S. Supreme Court", published in January 2019, which is the culmination of several years of deep legal research on the application of patent eligibility in the U.S.[5] We reviewed every Patent Act and amendment from 1790 through 2011, and compared it with Supreme Court case law on patent eligibility during the same period. I provide a copy of our

[5] Sherry Knowles & Anthony Prosser, Unconstitutional Application of 35 U.S.C. §101 by the U.S. Supreme Court, 18 J. Marshall Rev. Intell. Prop. L. 144 (2018).

article as Attachment 2 to this Testimony, and ask that it be fully incorporated by reference into my Testimony.

The unambiguous conclusion of this extensive research is that the Supreme Court has shown extraordinary judicial activism, has penciled two words out of the federal patent eligibility statute, and has without any legal authorization created its own judicial exceptions to the statutory law, which has changed the meaning of the statute. It has created a new patent eligibility rubric that does not align with the statutory language. It has crossed the line from interpretation to creation of patent law, which violates the Constitutional separation of powers.

Congress was given the sole power to create patent law under the Constitution. The Supreme Court is limited to strict statutory construction guided by legislative intent, regardless of whether it agrees with the underlying policy of the law.

Despite extensive legal research, we have not identified any legal power granted to the Supreme Court to pencil words out of a statute. Despite extensive legal research, we have also not identified any legal power granted to the Supreme Court to create judicial exceptions to federal statutes. See *Henry Schein v. Archer*[6] where Justice Kavanaugh rejected the application of a judicial exception to the federal statute at issue.

Between 1790 and 2011, Congress defined the scope of patent eligibility in the broad disjunctive "invents **OR** discovers" through 30 recodifications or amendments of The Patent Act. It removed the word "discovers" in 1793 and then purposefully restored the disjunctive "invents or discovers" eligibility scope in 1836 which it has maintained through today. *See* Knowles and Prosser, Attachment 2, pg. 149.

The 1952 Patent Act was passed only four years after the controversial Supreme Court Decision of *Funk Bros. Seed Co. vs. Kalo Inoculant Co.* [7]*(see section 3 below)* and amid increasing criticism that the courts had introduced subjectivity into its determination of what is an invention, without a proper statutory test.[8]

Congress's response to these criticisms was to do the following:

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[6] 139 S. Ct. 524 (2019).
[7] 333 U.S. 127 (1948).#
[8] *See The Vague Concept of "Invention" as Replaced by Sec 103 of the 1952 Patent Act,"* Giles s. Rich, J. of Patent Office Society, Dec, 1964, XLVI No. 12. (Attachment 3).#

(i) Add three new definitions to Section 100, each of which refers to both an invention and a discovery, loudly confirming the patent eligibility of each.
   a. Section 100(a) The term "invention" means invention or discovery.
   b. Section 100(f) The term "inventor" means the individual, or if a joint invention, the individuals collectively who invented or discovered the subject matter of the invention.
   c. Section 100(g) The term "joint inventor" and "coinventor" mean any 1 of the individuals who invented or discovered the subject matter of a joint invention.

(ii) Create Section 103 to provide an objective test for definition obviousness to abrogate the Supreme Court's insistence on subjectivity.

With regard to (i), Congress would not have repeatedly used two separate words if it thought they meant the same thing.

The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man."[9] It is worth noting this quote was made by the Examiner in Chief of the Patent Office when summarizing the Patent Office's understanding of the bill. This quote was then used in the report to the Senate presented by Congressman Wiley, essentially adopting the Patent Office's interpretation as correct.[10]

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Thus, Congress' intention was clear that any manmade invention or applied discovery falls within the scope of patent eligibility.

During the Hearings leading to the 1952 Patent Act, the Department of Justice requested that the word "discovery" be removed from the statute.

> Section 100 of the bill, "definitions," defines "invention" to include discoveries. While the term "discovery" is used in the patent law as synonymous with invention and it has been recognized that the act of discovery is an essential part of the invention, under existing law discoveries, as such are not patentable. . . The section might have the effect of creating doubt as to existing law on the subject of discovery and might result in opening the door to a huge new area of patents, and permit the creation of monopolies in some of the fundamental and far-reaching discoveries in the fields of chemistry, physics, medicine, mathematics, et cetera. . . The Department would be opposed to the

[9] H.R. Rep. No. 82-3760, 1st Sess., 37 (1951).
[10] S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952).

> creation of any new area of monopoly which would be exempt from the operation of the anti-trust laws in the absence of clear evidence that such extension is necessary to provide adequate incentive for scientific effort. There would appear to be no such necessity with respect to the broad field of "discoveries."[11]

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The sole response to the DOJ comments was a short "Thank you, Mr. Brown" and a request to call the next speaker.[12] Congress clearly disagreed with the Department of Justice because it did the exact opposite—it added three definitions to Section 100 definitions that specifically refer to inventions and discoveries in the disjunctive. It also provided legislative intent to include anything under the sun made by man.

With regard to (ii), Judge Rich described the state of the threshold for patenting after the doorknob case of *Hotchkiss v. Greenwood*,[13] where the Supreme Court held that the work was no more than that of a skilled mechanic and not an inventor.[14]

> This requirement finally evolved into a "standard of invention" which the courts pretended as being raised and lowered like an elevator as though it were something tangible. They also proclaimed in all seriousness—and are doing so this very moment—that this "standard" was to be found in the Constitution, where there are only two words on which it could possibly be predicated, the word "inventors" and the word "discoveries". You really have to be on the Supreme Court to find a "standard" there because the only way it can work is this: if you think the lower court was wrong in sustaining the patent, you proclaim it applied too low a standard and reverse its decision, saying, "*That was not an invention*."

The *Hotchkiss* case and resulting subjective test for patenting forced Congress to substantially amend the Patent Act to create a new requirement for patentability—Section 103 non-obviousness—to remove subjectivity from the patent analysis and replace it with objectivity, being measured against the work of a person of ordinary skill in the art.

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[11] H.R. Rep. No. 82-3760, 1st Sess., 94 (1951); H.R. Rep. No. 3760 at 94.
[12] *Id.* at 98.
[13] 52 U.S. 248 (1850).#
[14] *See The Vague Concept of "Invention" as Replaced by Sec 103 of the 1952 Patent Act,"* Giles s. Rich, J. of Patent Office Society, Dec, 1964, XLVI No. 12. (Attachment 3).

Judge Rich concluded his talk (which was memorialized in his article) with the following reasons to require that patenting be assessed objectively, not subjectively:

> Because looking for the presence of "invention" in addition to compliance with 103 defeats the legislative purpose.
>
> Because talking about unobviousness and "invention" as different things leads to weird and confused thinking.
>
> Because testing patentability by the presence of "invention" gives judges and the Patent Office too much freedom to decide patentability of new and useful inventions on the basis of a personal view as to what should be patentable, instead of accepting the view of the legislature on that question of national policy.
>
> Because it will do more than anything else I can think of to bring about that long-sought-for greater uniformity of opinion on patentability.
>
> Because it makes the prerequisites to patentability intelligible.
>
> To quote Learned Hand—the well named judge—once more, maybe I am only "shoveling smoke." Time alone will tell.[15]

Whereas *Hotchkiss*' subjective test of "invention" resulted in Congress's action to create an objective obviousness standard, it is equally true that the subjective "invention" test at the time went to patent eligibility itself, as it was used as a subjective threshold test. Clearly, Judge Rich, as a highly respected jurist who was a co-author of the 1952 Patent Act, disagreed that a subjective threshold test was good for the country. The Supreme Court has now migrated back to its subjective standard for patent eligibility by failure to carry out strict statutory construction of, and actually ignoring, the words of Sections 100 and 101 guided by the 1952 legislative intent and instead has now again created a subjective common law test for patent eligibility. So Judge Rich was right --time did tell--, and the Supreme Court mucked it up all over again, to the point that it has passed over the line of constitutionality. This compels Congress to have to act again, just as it did in 1952.

[15] *See The Vague Concept of "Invention" as Replaced by Sec 103 of the 1952 Patent Act,"* Giles s. Rich, J. of Patent Office Society, Dec, 1964, XLVI No. 12. (Attachment 3).

III. Supreme Court Opinions on Patent Eligibility

The hallmark of the Supreme Court's opinions on patent eligibility has been an almost total absence of strict statutory construction and a total disregard for Congressional intent. The Supreme Court cites back to itself as the primary authority on patent eligibility. It has converted a topic of constitutionally mandated statutory law into a topic of unauthorized common law. The Supreme Court has run roughshod over the Constitution and shown a lack of interest in the limitations on its power. A full discussion is provided in Knowles and Prosser, Attachment 2.

Funk Brothers v. Kalo

In the controversial *Funk*[16] case the Court stated:

> He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.[17]

While the Court gave lip service in the last sentence to patent eligibility of products that are applications of laws of nature, it rejected the *Funk* invention which was exactly that. The Supreme Court's *Funk* opinion did not even mention the governing statute, much less look at legislative intent. It solely referred to its own prior cases as authority for its opinion.

Gottschalk v. Benson

The first major patent eligibility case after the passage of the 1952 Patent Act was *Gottschalk v. Benson*.[18] Justice Douglas writing for the Supreme Court held that programming a computer with a mathematical formula that converts binary coded decimal numbers into pure binary numerals is not patent eligible, because it is the use of an idea:

> The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself. It may be that the patent laws should be extended to cover these programs, a policy matter to which we are not competent to speak.

[16] *Funk Bros.*, 333 U.S.127.
[17] *Id*. at 129.
[18] 409 U.S. 63 (1972).#

The Supreme Court was concerned with affirming such a broad scope of monopoly, but that was not its decision to make, which should be limited to strict statutory construction. The *Gottschalk* opinion also commented from the "Report of the President's Commission on the Patent System," referring to problems involved in examining computer software programs and recommending that they not be patent eligible.[19] The Court relied on its own earlier *Funk* case law (which also did not carry out a statutory analysis or look at legislative intent), and an un-adopted recommendation from a Committee to the President in the Executive Branch, instead of carrying out strict statutory construction or reviewing legislative intent of the only branch of government delegated the responsibility to create the law.

The Court stated that "If these programs are to be patentable, considerable problems are raised which only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain." However, the word "process" was in the governing patent eligibility statute, Section 101, and so the Court, faithfully applying the statute without injecting its own views, should have passed the claim through the eligibility statute and then required consideration under Sections 102, 103, and 112, whether it liked the answer or not. It did the opposite of what was constitutionally required. It ignored the words of the statute, rejected the claims, and said Congress should look at this, instead of passing the invention under the clear wording of the statute and writing an opinion that the Court doesn't know if this is a wise result and Congress should look at it.

Parker v. Flook

In the Court's opinion in *Parker v. Flook,*[20] it admitted that the decision in *Gottschalk* could not have been decided based on a literal reading of 35 U.S.C. § 101. The Court focused its treatment of what is patent eligible on what constitutes a process:

> The plain language of § 101 does not answer the question. It is true, as respondent argues, that his method is a "process" in the ordinary sense of the word. But that was also true of the algorithm, which described a method for converting binary-coded decimal numerals into pure binary numerals, that was involved in *Gottschalk v. Benson*. *The holding that the discovery of that method could not be patented as a "process" forecloses a purely literal reading of § 101.* Reasoning that an

[19] *Gottschalk*, 409 U.S. at 72.
[20] *Parker v. Flook*, 437 U.S. 584, 587 (1978).

> algorithm, or mathematical formula, is like a law of nature, *Benson* applied the established rule that a law of nature cannot be the subject of a patent.[21]

The Supreme Court used the term "law of nature" to override the literal wording of Section 101 and Congressional intent, that states that applied processes are patent eligible.

The Supreme Court stated that a claim to an improved method of calculation, even when tied to a specific chemical manufacturing process, is unpatentable subject matter. In this case, the claim was to a catalytic chemical conversion of hydrocarbons using an alarm schedule based on how the operator wanted the reaction to go. Thus it was a manufacturing process claim, which at a minimum is an application of a discovery, with industrial utility.

Even though the *Parker* Court admitted that the *Gottschalk* opinion did not literally follow Section 101 statute, it then rationalized doing this again and bootstrapped itself into inconsistent common law by stating:

> It is our duty to construe the patent statutes as they now read, in light of our prior precedents, and we must proceed cautiously when we are asked to extend patent rights in areas wholly foreseen by Congress.

The upshot of this is the Supreme Court's admission that it isn't following the statute, followed by an insistence that from then on, it would follow its own precedent until corrected by Congress. This will be discussed further below in the section on statutory stare decisis.

Diamond v. Chakrabarty

The Court in *Diamond v. Chakrabarty*[22] addressed the meaning of manufacture under Section 101 and whether genetically engineered bacteria are patent eligible. Justice Burger, for a 5-4 Court (dissenting: Brennan, White, Marshall and Powell), confirmed that the term manufacture is intentionally broad.

The Supreme Court in this case names and institutionalizes the Supreme Court's parallel interpretation of what should be patent eligible, based on its own prior case law.

> This is not to suggest that § 101 has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable. See *Parker v. Flook*, 437 U.S. 584, 98

[21] *Id*. at 586 (emphasis added).#
[22] 447 U.S. 303.

> S.Ct. 2522, 57 L.Ed.2d 451 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67, 93 S.Ct. 253, 255, 34 L.Ed.2d 273 (1972); *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130, 68 S.Ct. 440, 441, 92 L.Ed. 588 (1948); *O'Reilly v. Morse*, 15 How. 62, 112–121, 14 L.Ed. 601 (1854); *Le Roy v. Tatham*, 14 How. 156, 175, 14 L.Ed. 367 (1853). Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Funk, supra*, 333 U.S., at 130, 68 S.Ct., at 441.[23]

None of these exceptions are listed in Section 101. Instead, the Committee Reports accompanying the 1952 Act indicates that Congress intended statutory subject matter to "include anything under the sun that is made by man."[24] Laws of nature, physical phenomenon and abstract ideas do not fall within Section 101 because they are not applied discoveries. There was no need to create judicial exceptions that are extra-statutory to reach the correct conclusion.

Bilski v. Kappos

In *Bilski v. Kappos*,[25] the Supreme Court finally admitted that its judicial exceptions to the federal statute are not required by the statutory text, although it asserted that the exceptions are "consistent with" it.[26] The Court also, for the first time, rationalized its judicial exceptions to the federal statute as "statutory stare decisis."[27] The Court thus acknowledged that it was acting outside of the bounds of the statutory language, and suggests its position that if the Court has created and used its own patent law for a long enough time, it should be able to continue. However, as discussed above, Congress has also repeatedly reaffirmed the "invention or discovery" standard from 1790 through 2011. And, since Congress is solely authorized to create patent law, these repeated recodifications prevail.

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[23] *Chakrabaty*, 447 U.S. at 303-04.
[24] *Id*. at 309-10 (citing S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952)); H.R. Rep. No.1923, 82d Cong., 2d Sess., 6 (1952).
[25] 561 U.S. 593 (2010). The Bilski patent application concerned methods to hedge (de-risk) investments in energy. *Id*. The method provided a technique by which an energy company can sell energy at one price to consumers based on historical averages and to another set of consumers with a different price calculation that will decrease its losses if the underlying energy cost changes unexpectedly. *Id*. The Primary Patent Examiner, Board of Patent Appeals and Interferences, Federal Circuit Court, and finally U.S. Supreme Court all rejected the claims based on patent eligibility. *Id*. The Courts could also have easily rejected the claims based on 35 U.S.C. § 102 or 35 § U.S.C. 103, as basic hedging strategies have been known for centuries.
[26] *Id*. at 593-94.
[27] *Id*. Of course, even statutory stare decisis, to the extent it is consistent with the Constitution, does not allow the removal of words from a federal statute.

> The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: "laws of nature, physical phenomena, and abstract ideas." *Chakrabarty, supra,* at 309, 100 S.Ct. 2204. While these exceptions are not required by the statutory text, they are consistent with the notion that a patentable process must be "new and useful." *And, in any case, these exceptions have defined the reach of the statute as a matter of statutory stare decisis going back 150 years.* See *Le Roy v. Tatham,* 14 How. 156, 174–175, 14 L.Ed. 367 (1853). The concepts covered by these exceptions are "part of the storehouse of knowledge of all men ... free to all men and reserved exclusively to none." *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130, 68 S.Ct. 440, 92 L.Ed. 588 (1948).[28]

The Court continued with its acknowledgement that it is acting outside of the bounds of the statute, and it can only go so far:

> Any suggestion in this Court's case law that the Patent Act's terms deviate from their ordinary meaning has only been an explanation for the exceptions for laws of nature, physical phenomena, and abstract ideas. See *Parker v. Flook,* 437 U.S. 584, 588–589, 98 S.Ct. 2522, 57 L.Ed.2d 451 (1978). This Court has not indicated that the existence of these well-established exceptions gives the Judiciary *carte blanche* to impose other limitations that are inconsistent with the text and the statute's purpose and design. Concerns about attempts to call any form of human activity a "process" can be met by making sure the claim meets the requirements of § 101.[29]

This quote again reflects the Court's pattern to cite to its own earlier cases instead of the wording of the statute in what should be a strict statutory construction case.

Mayo Collaborative Servs. v. Prometheus Labs., Inc.

In *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*,[30] the Court addressed whether a claim to optimizing the therapeutic efficacy of a treatment using 6-thiopurine for a gastrointestinal disorder with a discovered metabolic algorithm is patent eligible under Section 101. Justice Breyer, writing for the Court, mentions Section 101 at the beginning of the opinion, solely to introduce the Supreme Court's judicially created exceptions to it.[31] There is no further discussion of the statute or

[28] *Bilski*, 561 U.S. at 602
[29] *Id.* at 603.
[30] 566 U.S. 66 (2012).
[31] *Id*. at 70-71.#

legislative history or intent. The whole of the opinion refers back to earlier Supreme Court precedent and the evolution of the Court's evolving common law on the subject, based on its own view of what should be patent eligible.

> Section 101 of the Patent Act defines patentable subject matter. It says: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. *The Court has long held that this provision contains an important implicit exception.* "[L]aws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond v. Diehr,* 450 U.S. 175, 185, 101 S.Ct. 1048, 67 L.Ed.2d 155 (1981); see also *Bilski v. Kappos,* 561 U.S. 593, 130 S.Ct. 3218, 3233–3234, 177 L.Ed.2d 792 (2010); *Diamond v. Chakrabarty,* 447 U.S. 303, 309, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980); *Le Roy v. Tatham,* 14 How. 156, 175, 14 L.Ed. 367 (1853); *O'Reilly v. Morse,* 15 How. 62, 112–120, 14 L.Ed. 601 (1854); cf. *Neilson v. Harford,* Webster's Patent Cases 295, 371 (1841) (English case discussing same).[32]

The Court then admits that it cannot take its own judicially created exceptions too far or else they will destroy Congress' patent law *in toto*:

> *The Court has recognized, however, that too broad an interpretation of this exclusionary principle could eviscerate patent law.* For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas. . . Still, as the Court has also made clear, to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words "apply it." See, *e.g., Benson, supra,* at 71–72, 93 S.Ct. 253.[33]

From here, the Court digresses into economic analysis and the balance between patent protection and third party freedom to operate.

> These statements reflect the fact that, even though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery, those laws and principles, considered generally, are "the basic tools of scientific and technological work." *Benson, supra,* at 67, 93 S.Ct. 253. *And so there is a danger that*

[32] *Mayo*, 566 U.S. at 70-71 (emphasis added).
[33] *Id.* at 71 (emphasis added).#

> *the grant of patents that tie up their use will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to "apply the natural law," or otherwise forecloses more future invention than the underlying discovery could reasonably justify.*[34]

The Constitution has not granted any authority to the Supreme Court to carry out economic analysis of what should be patent eligible, nor is it equipped to do so. The Supreme Court does not have the power to commission white papers, take testimony, review independent evidence, have one-on-one meetings with stakeholders or to take depositions, which are necessary to create public policy. Amicus briefs, while useful, do not take the place of these tools. The Supreme Court is arguably the worst equipped of the three branches of the government to evaluate patent policy. For this reason, our founding fathers did not give the Supreme Court the authority to set policy, although, as illustrated by the *Mayo* case, the Court has crossed that line. Creating a careful balance between the scope of incentive to promote the progress of science and impeding ancillary research is the sole domain of Congress.

Further, the Court makes the surprising admission that since it is not equipped to determine which applied laws of nature should be patent eligible, it will simply reject all of them:

> Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying "building-block" concern.[35]

Alice v. CLS Bank

In *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*[36], the Supreme Court further described its' common law test for patent eligibility described in *Mayo*. It held that only those claims that pass a subjective "inventive" test are patent eligible[37]

The new Supreme Court two-step inquiry for determining patent eligibility asks:

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[34] *Mayo*, 566 U.S. at 86 (emphasis added).
[35] *Id*. at 89.
[36] 573 U.S. 208 (2014)
[37] *Mayo*, 566 U.S. at 72-73; *Alice*, 573 U.S. at 221.

1) Are the claims at issue directed to judicially excepted subject matter, in the form of an "abstract idea," law of nature," or "natural phenomenon?[38]

2) If so, do the claims contain an "inventive concept" sufficient to "transform" the claimed ineligible concept into a patent eligible application.[39]

The Supreme Court's subjective test for an inventive concept requires that the claim include "significantly more" than the judicially excepted subject matter to ensure that "the [claim] is more than a drafting effort designed to monopolize the [abstract idea]."[40] It is not enough under this two-part test, that there be an application of a discovery, which is the only requirement under Section 101. The Supreme Court instead crafted its own test that now requires that the practical implementation or practice of a new and useful discovery be "inventively" applied, that is include elements or additional features that are not "well known" or "conventional."[41]

Thus, under this two-part test, determinations of patentable eligible subject matter under Section 101 requires the non-statutory consideration of aspects such as the prior art and claim scope that are simply not included in the statutory language of Section 101.[42] This results in a patent eligibility analysis that subjectively changes over time with the advancement of technology, for what is "new" or "non-conventional" today, may very well be "well known" and "conventional" tomorrow.

This two-part test also results in a patent eligibility analysis that ignores the plain language of Section 101 which provides protection for applied "inventions or discoveries," not the "inventive" applicability of new discoveries. The Alice rubric is <u>not</u> an interpretation of Section 101, it is an unconstitutional judicial construction of the law. The Supreme Court's eschewing of patent protection for the practical application of new discoveries has no basis whatsoever in the text of Section 101, and errs by failing to capture the plain and unambiguous scope of Section 101 and patent-eligible subject matter, subjecting many fundamental applications of scientific advances outside the scope of available patent protection.

The implementation of such a subjective, sliding scale test as to what constitutes patent eligible subject matter is not what Congress intended with the

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[38] *Alice*, 573 U.S. at 218.

[39] *Id.* at 221.#

[73]#Lg1#

[74]#Lg1#dw#5540551#

[75]#Dvshfwv#ri#sulru#duw#duh#dgguhvvhg#lq#wkh#vwdwxwru|#uhtxluhp hqw#ri#.#135#qryhow|,#dqg#.#136#qrq0reylxvqhvv,1#

passage of Section 101. This subjective, sliding scale test creates absurd results, wherein an easily and/or inexpensively applied new discovery of significant importance which fundamentally alters a field of endeavor may not be patent eligible simply because it is applied using conventional or well-known means.[43] Such a perverse outcome does little to advance the useful arts in this country, and hinders the United States' ability to continue to lead the progression of innovation in the world.

AMP v. Myriad Genetics

In *AMP v. Myriad*,[44] the Supreme Court considered the patent eligibility of certain isolated gene sequences which encode the BRACA1 and BRACA2 genes, the presence of which are highly predictive of the potential to get breast cancer. The Court held the claims patent ineligible under 35 U.S.C. § 101.[45]

Writing for a unanimous Court, Justice Thomas again failed to carry out any statutory construction or discuss legislative intent. The case was decided based on the judicially created exceptions to the statute and the Court's view of economic policy, neither of which are empowered to the Court by the Constitution.

> We have "long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo,* 566 U.S., at ——, 132 S.Ct., at 1293 (internal quotation marks and brackets omitted). Rather, " 'they are the basic tools of scientific and technological work' " that lie beyond the domain of patent protection. *Id.,* at ——, 132 S.Ct., at 1293. As the Court has explained, without this exception, there would be considerable danger that the grant of patents would "tie up" the use of such tools and thereby "inhibit future innovation premised upon them." *Id.,* at ——, 132 S.Ct., at 1301. This would be at odds with the very point of patents, which exist to promote creation. *Diamond v. Chakrabarty,* 447 U.S. 303, 309, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980) (Products of nature are not created, and " 'manifestations ... of nature [are] free to all men and reserved exclusively to none' ")…..As we have recognized before, patent protection strikes a delicate balance between creating "incentives that lead to creation, invention, and discovery" and "imped[ing] the flow of information that might permit, indeed spur, invention." *Id.*, 132

[43] *See, e.g., Ariosa Diagnostics Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1380-81 (Fed. Cir. 2015) (Linn, J., concurring) (noting that "[t]he Supreme Court's blanket dismissal of conventional post-solution steps" bars patent eligibility to a "truly meritorious" invention).
[44] 569 U.S. 576 (2013).
[45] *Id*. at 594.

> S.Ct., at 1305. We must apply this well-established standard to determine whether Myriad's patents claim any "new and useful ... composition of matter," § 101, or instead claim naturally occurring phenomena.[46]

In a stroke of extraordinary judicial activism, the Supreme Court stated:

> [G]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry. See *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 68 S.Ct. 440, 92 L.Ed. 588.[47]

It is hard to imagine a more unconstitutional statement than the Supreme Court ruling that discoveries cannot be patented when the statute it is applying states that any invention or discovery can be patented. In other words, the Court says "A not B" while the statute says "A or B."

And, while the *Myriad* statement that an applied discovery is not an invention is inconsistent with Section 101, it is all the more inconsistent with the definition of three inventions added in 1952 in section 100 (a, f and g) that patent eligible subject matter can be an invention or a discovery.

The Supreme Court, citing to its own judicially created exceptions to the statute and its associated common law precedent back to *Funk*, now refuses to grant a patent on the commercial application of a manmade discovery, even if it meets all of the requirements of Section 101. In addition, it requires all lower courts to obey the Supreme Court instead of Congress.

IV. The Use of Statutory Stare Decisis in the Application of Section 101

In Bilski v. Kappos, the Supreme Court said:

> The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: "laws of nature, physical phenomena, and abstract ideas." *Chakrabarty, supra,* at 309, 100 S.Ct. 2204. While these exceptions are not required by the statutory text, they are consistent with the notion that a patentable process must be "new and useful." *And, in any case, these exceptions have defined the reach of the statute as a matter of statutory stare decisis going back 150 years.* See *Le Roy v. Tatham,* 14 How. 156, 174–175, 14 L.Ed. 367

[46] *Id*. at 589.#
[47] *Myriad*, 569 U.S. at 576.

> (1853). The concepts covered by these exceptions are "part of the storehouse of knowledge of all men ... free to all men and reserved exclusively to none." *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130, 68 S.Ct. 440, 92 L.Ed. 588 (1948).[48]

Opponents of patent eligibility Congressional reform argue that Congress can't change the Supreme Court law due to "statutory stare decisis" going back 150 years.

This position was soundly rejected by the Supreme Court when it addressed statutory stare decisis at length in the case of *Kimble v. Marvel Entertainment*.[49] The case involved the question whether patent royalties end on the date of expiration of a patent, as held in the prior Supreme Court case of *Brulotte v. Thys Co*.[50] The Supreme Court held that where precedent interprets a statute, stare decisis carries enhanced force, since critics are free to take their objections to Congress. The Supreme Court made the following observations, which are central to the patent eligibility matter at hand:

> An argument that we got something wrong—even a good argument to that effect—cannot by itself justify scrapping settled precedent…..All of our interpretive decisions, in whatever way reasoned, effectively become part of the statutory scheme, subject (just like the rest) to congressional change. Absent special justification, they are balls tossed to Congress's court, for acceptance or not as that branch elects.
>
> Indeed, we apply statutory stare decisis even when a decision has announced a "judicially created doctrine" designed to implement a federal statute. *Halliburton C. v. Erica P. John Fund, Inc.*, 573 U.S. __(2014).
>
> [E]ven assuming that Brulotte relied on an economic misjudgement, Congress is the right entity to fix it….Accordingly, statutory stare decisis—in which this Court interprets and Congress decides whether to amend—retains its usual strong force….And as we have shown, that doctrine does not ordinarily bend to "wrong on the merits"-type arguments; it instead assumes Congress will correct

[48] *Bilski*, 561 U.S. 593 (2010) (emphasis added).
[49] 135 S. Ct., 2410 (2015).
[50] 379 U.S. 29 (1964).#

whatever mistakes we make…..For the choice of what patent policy should be lies first and foremost with Congress.

Therefore, Kimble stands for two important points:

1. Statutory stare decisis ONLY pertains to litigation between parties in court.

   It has no effect at all on policy discussions in Congress.

   a. Any entity arguing to Congress that it must maintain the Supreme Court's judicially created exceptions and the Alice rubric because of the Court's 150 years of statutory stare decisis is flat wrong. Even the Supreme Court does not believe that. Congress is free to legislate any patent policy it decides is in the country's best interest regardless of prior Supreme Court law.

2. The Supreme Court is telling Congress that it will not fix the patent eligibility problem. It will have to be fixed by Congress.

V. Comments on Draft Legislation

I have reviewed the proposed legislation issued on May 22, 2019, from Senators Coons and Tillis and Representatives Collins, Johnson, and Stivers which addresses patent eligible subject matter. I am in favor of the current draft text. It is simple and reaffirms the statutory language that goes back to the first codification of the Patent Act in 1790, and which has been repeatedly recodified by Congress through the 1952 Patent Act. It is the law that motivated the great inventions of brilliant scientists.

As proposed, Section 101 would provide:

(a) Whoever invents or discovers any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
(b) Eligibility under this section shall be determined only while considering the claimed invention as a whole, without discounting or disregarding any claim limitation.

As an initial matter, proposed Section 101 maintains the availability of patent protection for both technical innovations and the practical application of scientific discoveries by retaining "inventions or discoveries" within the text. As every patent act since 1790 has done. The proposed statute reiterates the clear intent of Congress to provide patent protection for practically applied scientific discoveries. Additional proposed legislative provisions include:

> The provisions of section 101 shall be construed in favor of eligibility.
>
> No implicit or other judicially created exceptions to subject matter eligibility, including "abstract ideas," "laws of nature," or "natural phenomena," shall be used to determine patent eligibility under section 101, and all cases establishing or interpreting those exceptions to eligibility are hereby abrogated.
>
> The eligibility of a claimed invention under section 101 shall be determined without regard to: the manner in which the claimed invention was made; whether individual limitations of a claim are well-known, conventional or routine; the state of the art at the time of the invention; or any other considerations relating to sections 102, 103, or 112 of this title.

By mandating that the eligibility of a claimed invention be determined without regard to a) the manner in which the claimed invention was made, b) whether individual limitations of a claim are well-known, conventional or routine, the state of the art at the time of the invention, or any other considerations relating to Sections 102, 103, or 112, it is clear that proposed Section 101 seeks to avoid a repeat of the current Supreme Court two-step inquiry for determining patent eligibility, recognizing the harm the current "inventive" application standard has caused to, for example, the patent protection eligibility of the practical application of scientific discoveries. Barring the import of the state of the art into the determination of patent subject matter eligibility, as well as the consideration of whether claim elements are well-known or conventional, preserves the desired objective standard of patent subject eligibility, and avoids the needless and wholly subjective determination of whether claim elements are or are not routine. In doing so, the proposed statute avoids a sliding scale of patent eligibility which changes based on the current state of the art, and installs a legal framework for patent eligibility that can be consistently applied throughout time, regardless of the particular state of the art.

The proposed statute also takes a strong stand in demanding that no implicit or other judicially created exceptions to subject matter eligibility, including "abstract ideas," "laws of nature," or "natural phenomena," may be used to determine patent eligibility under Section 101, and that all cases establishing or interpreting those exceptions to eligibility are hereby abrogated. Unfortunately, this explicit language is necessary to prevent the Supreme Court from invoking statutory stare decisis in any future construction of Section 101, and clearly re-establishes Congress's desire that patent eligibility for claimed inventions be broad and permissive.

With this said, of course, the statute does not provide for the patentability of "abstract ideas," laws of nature," or "natural phenomena" *per se*. Rather, proposed Section 100 (k) defines the term "useful" in Section 101 as "any invention or discovery that provides specific and practical utility in any field of technology through human intervention. Thus, the proposed statute through its definition of "useful" requires that any scientific discovery be claimed in such a way that the claim is directed to the practical application of such discovery. Natural laws, abstract ideas, and natural phenomena in and of themselves and without practical application can never qualify for patent protection because the definition of "useful" requires a "practical utility" before it qualifies for protection. Accordingly, proposed Section 101 balances the desire for broad, permissible patent eligibility without encompassing subject matter such as abstract ideas that are not tied to a practical application through human intervention. For example, under proposed Section 101, a natural phenomena—such as the relationship between a genetic mutation and the development of a disease or disorder—remains ineligible for patent protection, while the process of applying that relationship to achieve a useful, tangible, and concrete result—such as diagnosis of the disease or disorder in a patient—is eligible for patent protection, as testing a patient for a disease or disorder is not a natural phenomenon, but rather the practical application of the phenomena through human invention.

Finally, it is important to recognize that the final clause of Section 101(a)--"subject to the conditions and requirements of this title"--ensures that a claimed invention must still satisfy the "conditions and requirements" set forth in the remainder title 35. These statutory conditions and requirements better serve the function of screening out unpatentable inventions than the overly-restrictive application of Section 101 as currently applied by the Supreme Court. If a claim is unduly broad, or if it fails to include sufficient specificity, the appropriate ground of rejection is Section 112, for claims must "particularly point out and distinctly claim"

the invention, or Sections 102 or 103, for too broad a claim may invariably read on the prior art.

VI. Irreconcilable Outcomes based on Supreme Court's 101 Subjective Test and Application of Literal Wording of Congress' 101 Statute

The ultimate proof that the Supreme Court's Section 101 analysis is irreconcilable with the literal wording of Congress's statute, and thus unconstitutional, is established by comparing the outcome of cases using the two disparate tests for patent eligibility.

a. *Ariosa v. Sequenom:*[51]

Method for performing a prenatal diagnosis for genetic disorders of a fetus, by obtaining a blood sample from the mother, isolating and amplifying a paternally inherited nucleic acid from the mother's blood, and analyzing the paternally inherited nucleic acid for defects.

Federal Circuit/Supreme Court (cert. denied): **Not patent eligible** subject matter because the claim simply refers to a law of nature and an instruction to "apply it"

Literal Wording of Sec. 101: **Patent eligible** subject matter because the claim covers the application of a discovery that a mother's blood carries a very small amount of cell free-fetal DNA that can be isolated and tested for abnormalities. Represents a huge advance in healthcare because it can substitute a finger prick for amniocentesis.

b. Ass'n for Molecular Pathology v. Myriad Genetics, Inc.[52]

Claims directed to isolated DNA of the BRCA1 and BRCA2 gene sequences, mutations of which are implicated in the development of hereditary breast and ovarian cancer.

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[51] 788 F.3d 1371 (Fed. Cir. 2015) rehearing, en banc, denied by *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282, 2015 U.S. App. LEXIS 20842 (Fed. Cir., 2015), US Supreme Court certiorari denied by *Sequenom, Inc. v. Ariosa Diagnostics, Inc.*, 2016 U.S. LEXIS 4087 (U.S., June 27, 2016).

[52] 569 U.S. 576 (2013)

Federal Circuit/Supreme Court: **Not patent eligible** subject matter because separated gene segments are a product of nature and not made patent eligible by isolation.

Literal Wording of Sec. 101: **Patent eligible** subject matter because isolated gene segments do not exist in nature and exist in an isolated form only through human intervention. The identification and isolation of BRCA1 and BRCA2 lead to the development of critical medical tests for detecting genetic mutations and assessing a patient's cancer risk.

c. BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp[53]

Method to test blood samples for BRACA1 and BRACA2 genetic mutations to determine if the patient has an elevated risk of developing cancer.

Federal Circuit/Supreme Court: **Not patent eligible** subject matter because the method claims recite an "abstract idea," and under the two-part test put forth in *Alice*, the additional elements of the claim "do not add "enough" to make the claims as a whole patent-eligible," as they "set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications."[54]

Literal Wording of Sec. 101: **Patent eligible** subject matter because the claim is to an process of applying the relationship between having a genetic mutation and developing cancer to determine the risk of developing cancer in a patient - a useful, tangible, and concrete result—as testing a patient for this risk is not an abstract idea, but the practical application of the discovered relationship through human intervention. Provides a major advancement in identifying those most at risk for developing hereditary based breast and ovarian cancer.

d. Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC[55]

Method for diagnosing neurotransmission or developmental disorders such as Myasthenia gravis by detecting autoantibodies in a patient to a protein called muscle-specific tyrosine kinase ("MuSK").

Federal Circuit/Supreme Court (cert. denied): **Not patent eligible** subject matter because the claims are directed to a natural law, and the additional steps lack

[53] 774 F.3d 755 (Fed. Cir. 2014).
[54] *Id*. at 764.
[55] 915 F.3d 743 (2019)

an "inventive concept" under *Alice*, as the steps use conventional techniques, the claims failed to provide an inventive concept

Literal Wording of Sec. 101: **Patent eligible subject matter** because the claim is to an applied process of applying the relationship between the presence of an autoantibody in bodily fluid and neurological diseases to determine whether a patient has a neurological disease- a useful, tangible, and concrete result-as testing a patient for this disease is not a natural law, but the practical application of the discovered relationship through human intervention.

e. Mayo Collaborative Servs. v. Prometheus Labs., Inc.[56]

Method of optimizing the proper dosage of thiopurine drugs to treat immune-mediated gastrointestinal disorders, wherein thiopurine drugs are metabolized differently by different patients with autoimmune diseases, in order to avoid harmful side effects or ineffectiveness of the administered drugs.

Federal Circuit/Supreme Court: **Not patent eligible** subject matter because the relationships between concentrations of metabolites in the blood and the likelihood that a thiopurine drug dosage would prove ineffective or cause harm were known laws of nature, and there was no inventive concept in the claimed application of the natural laws.

Literal Wording of Sec. 101: **Patent eligible** subject matter because the claim is to a process of applying the relationship between the concentration of metabolites in the blood and the likelihood that a thiopurine drug dosage would prove ineffective or cause harm in order to optimize drug administration- a useful, tangible, and concrete result-as analyzing the metabolite and adjusting the dosage of the drug administered is not a law of nature, but the practical application of the discovered relationship through human intervention. Provides a major advancement in treating patients with thiopurine drugs by identifying those at risk for being harmed by a potential dose of the drug that is too high.

VII. Effect of Supreme Court's Development of Unconstitutional Case Law on Us Personally

The assumption that companies and investors make rational decisions leads to a conclusion that the research and investment on isolated natural products as new

[56] 566 U.S. 66 (2012)#

medicines precipitously declined after *Myriad* and will continue to stall until *Myriad* is abrogated. As a patent attorney representing life sciences companies, I have first-hand knowledge that this is true. Companies adamantly will not pursue a lengthy and costly product development program without any assurance of a repayment and return on the investment. Nor should they. Capital is like water. It flows toward the area of least pressure. The Supreme Court's unconstitutional decisions have forced research funding away from isolated natural products and personal diagnostics.

To understand the profound effect that isolated natural products have had on us personally, in terms of treatment of disorders and diseases, including life threatening diseases, I provide Attachment 4 and Attachment 5. Attachment 4 is a list of selected isolated natural product drugs that have been commonly used. Many are on the World Health Organization's List of Essential Medicines. Unless you are a trained scientist, you likely can't look at a drug's name and determine if it would fall under the Myriad test as a patent ineligible drug. This list is a stark recognition of the effect. Now consider a world in which none of these drugs had been ever been discovered, developed, or marketed. There is no need to consider drug pricing or availability because they would not exist from the beginning. How many millions of people would have faced an early death or had crippling diseases? How many family members would have been affected? What loses to our society would we have had without these people? If all of these drugs had been subtracted from our health care system, we would live in a very different and more difficult world. This would have been the effect of the *Myriad* decision if that decision had been the law in the United States historically, and not just as of 2013.

Attachment 5 is a 2014 article in the Journal of Natural Products that reports on Natural Products as a source of new drugs from 1981-2014. It provides a wealth of information about the historic use of natural products and their derivatives.

In 2014, I worked on a project with Georgia Tech Economics Assistant Professor Matthew J. Higgins through the IMS Heath and Pharmaprojects program to determine the number of natural product dosages that were sold in the United States between 2001 and 2011 for a range of drugs. We selected ten top-selling natural product therapeutics. The surprising result was that United States patients had benefited by taking almost 13 billion doses of just these ten drugs during this ten-year period. These drugs would not have been patent eligible under *Myriad*, and thus not commercialized, using the assumption that corporations act rationally and would not develop drugs without market protection. Please consider whether you, your friends or family members have been treated with any of these drugs. Of course,

this leads to the question of what drugs we will not get the benefit of in the future if commercialization continues to be stalled by Supreme Court's interpretation of Section 101 and its Myriad decision.

Natural Products sold in the United States From 2001-2011 (in Sales Units)	
▪ Clavulanic acid	5,338,207,765
▪ Penicillin	3,483,851,173
▪ Tetracycline	1,922,758,255
▪ Taxol	1,554,822,780
▪ Epogen	384,546,232
▪ Adriamycin	10,433,433
▪ Insulin	8,035,843
▪ Vincristine	4,994,779
▪ Vinblastine	1,230,034
▪ Streptomycin	447,367
TOTAL = 12,709,327,661	

Breast Cancer

Invasive breast cancer will affect about 1 in 8 women in the course of their lifetime. As of January 2019, more than 3.1 million women have had a history of breast cancer. In 2019, an estimated 268,600 new cases of invasive breast cancer will be diagnosed. About 41,760 women in the U.S. are expected to die in 2019 from breast cancer.[57]

I am one of these 3.1 million women and now a breast cancer survivor. I was diagnosed with HER2-positive, infiltrating ductile carcinoma, which is a fast-growing invasive breast cancer.

If *Mayo/Myriad* had been the law years ago, I would not be giving Testimony to the Subcommittee because I almost certainly would have died. My life was saved by Doxorubicin (Adriamycin), an antibiotic fermentation product of bacteria and paclitaxel, a natural product found in tree bark. Neither of these products are patent eligible under *Myriad*. They would not have existed when I needed them.

According to the Susan G. Komen Foundation, there are nine commonly used chemotherapies for early stage and locally advanced breast cancer.

[8]: #Vwdwlvwlfv#urp #euhdvwfdqfhuruj1#

Doxorubicin is a required component of four of the most common combinations.

Taxol, or its derivative doxetaxel, is a required component in seven of the combinations.

If doxorubicin and Taxol had not been discovered, developed and marketed, how many more of the hundreds of thousands of women with breast cancer would have faced an early death?

I took the time to locate the two patents she had identified which were related to the natural product drugs administered to me: U.S. Patent Nos. 3,590,028 and 5,641,803. Without corporate support for these drugs based on an expectation of patent protection, I, along with hundreds of thousands of other women, might not have become a breast cancer *survivor*.

And of course, the anti-cancer drugs listed in Attachment 3 are also used to treat cancers other than breast cancer. This greatly expands the number of people in the United States who would have faced an early death if *Myriad* had been the law a long time ago.

I have been motivated to make this unusual personal statement to support all of the brave friends I met in infusion wards fighting for their lives with the only hope coming from news that their doctors will tell them there is a new clinical trial they can try or a new diagnostic that can tell them more about the monster growing inside them. Because of the *Myriad* and *Mayo* decisions, pharmaceutical and biotech companies are almost certainly no longer doing fundamental research to identify natural product-based drugs that can be used to save lives in the future. This may be one of the worst legacies of *Myriad*.

VIII. Conclusion

For all of the reasons set out above, I strongly endorse the proposed amendments to Secs. 100 and 101 proposed by the Subcommittee on Intellectual Property of the Committee on the Judiciary of the U.S. Senate and support their expeditious enactment.

ATTACHMENT 1

TO WRITTEN TESTIMONY OF

SHERRY M. KNOWLES

PRINCIPAL, KNOWLES INTELLECTUAL PROPERTY STRATEGIES, LLC

BEFORE THE

UNITED STATES SENATE

COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON INTELLECTUAL PROPERTY

ON

"THE STATE OF PATENT ELIGIBILITY IN AMERICA, PART I"

JUNE 4, 2019

2:30 PM

Sherry M. Knowles, M.S., Esq.
KNOWLES IP STRATEGIES, LLC

400 Perimeter Center Terrace • Suite 200 • Atlanta, Georgia 30346

KEY QUALIFICATIONS

Sherry M. Knowles is an intellectual property attorney with over 30 years of experience in global corporate and private practice. From 2006-2010, she was the Senior Vice President and Chief Patent Counsel at GlaxoSmithKline, where she served as the worldwide head of patents for all litigation and transactional matters. Since 2010, she has been the Principal of a law firm that specializes in the area of pharmaceuticals and biotechnology, providing guidance on complex IP matters, patent litigation strategy and assistance, licensing, patent prosecution, opinions, obtaining and protecting the full value of innovation, investor support, and monetization of assets, for clients ranging from large pharmaceutical companies to mid-cap companies, emerging companies, universities, and investors. Prior to her position at GSK, Ms. Knowles was an equity partner at the firm of King & Spalding, where she founded the Pharmaceutical and Biotechnology Patent Practice.

PROFESSIONAL EXPERIENCE

Knowles IP Strategies, LLC, Principal **2010 – present**
Atlanta, Georgia

GlaxoSmithKline, Senior Vice President and Chief Patent Counsel **2006 – 2010**
Atlanta, Georgia

- Led all patent-related litigation and transactional legal matters
- Led Global Patents Executive Team
- Member of Scientific Advisory Board, Technology Investment Board, Product Management Board, and Legal Management Team
- Oversaw over 1900 pending U.S. patent applications, 2200 granted U.S. patents, 14,000 pending foreign applications, and over 15,000 granted foreign patents

King & Spalding LLP, Equity Partner **1997 - 2006**
Atlanta, Georgia

- Founded Biotechnology and Pharmaceutical Patent Practice
- Represented companies, foundations, and universities in connection with patent prosecution, strategy, litigation, contracts, licensing, financing and other corporate intellectual property issues relating to pharmaceutical, biotechnology and chemical inventions
- Created and defended patent rights in HIV drug Emtricitabine, the most widely prescribed medicine for HIV and the cornerstone of the Gilead HIV portfolio

EDUCATION

J.D., University of Georgia
Magna cum laude
Order of the Coif
Benjamin Z. Phillips Scholar

M.S., Clemson University
Cum laude in Organic Chemistry

B.S., **Duke University**
Cum laude, Chemistry
With distinction in Chemistry

SELECTED PUBLICATIONS

Knowles, S.M. and Prosser, A.R. (2018). "Unconstitutional application of 35 U.S.C. § 101 by the Supreme Court," *John Marshall Review of Intellectual Property Law*. 18:999 (2018).

Knowles, S.M. and Bellows, B.R., (2016) "Twenty Years after TRIPS Agreement-Are We Closer to Global Substantive Patent Harmonization?", *Intellectual Asset Management Magazine*, Issue 75, December 2015/January 2016.

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Knowles, S.M. (2010). "Fixing the legal framework for pharmaceutical research," *Science* 327:1083-1084

Knowles, S.M. (2010). Response to Letter to the Editor*, Science* 328:1354.

SELECTED PRESENTATIONS

Patent Masters Symposiums (March 25-26 and June 24-25, 2019), Washington, D.C., *Faculty*

Patents and Data Sharing Workshop (Dec. 6, 2018), Center for Law, Science, and Innovation, Sandra Day O'Connor College of Law, Arizona State University, *Speaker*

World IP Forum, New Delhi, India (Nov. 14-16, 2018), *Plenary Speaker*

"Section 101 Considerations in Biopharmaceutical Adversarial PTAB Proceedings," PLI PTAB Conference, New York, NY (Sept. 21, 2018)

2017 Global Series of Federal Circuit Bar Association with European Patent Lawyers Association (September 25 and 26, 2017, London, U.K.), *Invited Speaker*

"The Economic Contribution of Technology Licensing," USPTO-CPIP Tech Licensing

Conference (June 8, 2016), *Invited Speaker (Licensing and Commercialization in the Life Sciences)*

WIPO Conference on IP and Development, World Intellectual Property Organization (WIPO), Geneva, Switzerland (Apr. 7-8, 2016), *Invited Speaker*

"International Forum on Intellectual Property and Trade 2015: Adjudication, Administration, and Innovation," Federal Circuit Bar Association Global Series, Shanghai, China (Oct. 19-20, 2015), *Invested Speaker (Intellectual Property and Trade Challenges)*

"Reconsidering the Incentives for Innovation in the Biotech Industry," World IP Forum, Bangkok, Thailand (Sept. 15-27, 2015), *Invited Speaker*

WIPO Expert Forum on International Technology Transfer, World Intellectual Property Forum (WIPO), Geneva, Switzerland (Feb. 16-28, 2015), *Keynote Speaker and Panelist*

"Creating the Optimal Legal Framework to Motivate Innovation in Developing Countries," International Intellectual Property Law Association Annual Congress 2015, Dubai, United Arab Emirates (Jan. 5-6, 2015), *Panelist*

Co-chair of conference on "Creating and Leveraging IP in Developing Countries" ("CLIPDC 2013") with Co-chairs Ms. Astrid Ludin (Commissioner of the South African Patent Office) and Ms. Mavis Nyalto (Acting Head, National IP Management Office of South Africa) (Nov. 2013)

"Piecing Together the IP Puzzle of Business Transactions," Corporate IP Institute, Georgia State University College of Law and J. Mack Robinson College of Business, Atlanta, Georgia (Oct. 24-25, 2012), *Panelist*

"Updates on Biotech Patent Law," New York University School of Law, New York, NY (Apr. 30, 2012), *Panelist*

Accelerating Innovation and Intellectual Property in South Africa, Cape Town, South Africa (Sept. 19-21, 2011), *Co-Organizing Chair*

"The Role of Intellectual Property in Development," World Bank, Washington, D.C. (Dec. 16, 2010), *Moderator*

"Proposed USPTO Rule Changes: The GSK/Tafas Suit in Opposition & Predictions," Patent Litigation IX, Sedona Conference, Sedona, Arizona (Oct. 15-16, 2008), *Panelist*

PROFESSIONAL ORGANIZATIONS

Member, AIPLA, IPO, Federal Circuit Bar Association

Chair, IP Subcommittee, PhRMA, 2008

Chair Emeritus, IP Subcommittee, PhRMA, 2009, 2010

Member, InterPat (Association of the Chief Patent Counsels of the major pharmaceutical companies), 2006-2010; InterPat Executive Committee, 2008-2010

PROFESSIONAL RECOGNITIONS

Top ten key individuals, companies or institutions that have shaped the IP marketplace in the last eight years, recognized by Intellectual Asset Management Magazine (2011)

Jefferson Medal for exceptional contribution to Intellectual Property awarded by New Jersey Intellectual Property Lawyers Association to GSK, with Ms. Knowles as the representative

(2010)

Key role in the case of *GlaxoSmithKline and Tafas v. Dudas*, 541 F. Supp. 2d 805 (E.D. Va. 2008). On October 9, 2007, GSK became the first and only company in the U.S. to file a lawsuit to challenge the Final Rules published by the US Patent and Trademark Office on August 7, 2007. During the course of litigation, 20 amicus briefs were filed by parties in support of GSK and Dr. Tafas, including from the AIPLA, PhRMA, BIO, IPO, Washington Legal Foundation and CropLife America. The litigation concluded in October 2009, when Commissioner Kappos made the decision to withdraw all contested regulations and GSK agreed to join with the PTO in a motion to dismiss all litigation.

GSK recognized as "In-House IP Team of the Year" for 2009 selected from all corporations globally, during Ms. Knowles' tenure, by Managing IP Magazine

Top 10 Most Influential People Intellectual Property, *Managing IP Magazine*, 2008

World's 250 Leading IP Strategists, *IAM*, 2011

World's 300 Leading IP Strategists, *IAM*, 2012, 2013, 2014, 2015, 2015, 2016, 2017, 2018, 2019

World's 1000 Leading Patent Professionals, *IAM*, 2015, 2016, 2017, 2018, 2019

Top 250 Women in IP*, Managing IP Magazine*, 2014, 2016-2019

IP Stars, *Managing IP's Magazine*, 2016, 2017, 2018, 2019

NON-PROFIT ACTIVITIES

Founder and Executive Director, The Malmar Knowles Family Foundation and its flagship initiative, The Kectil Program, providing leadership, ethics, and innovation training for talented youth in developing countries. Since 2017, The Kectil Program has mentored over 1500 youth in 63 developing or least developed countries, and has hosted youth leadership meetings in Kenya, Nigeria, Ghana, India and Vietnam and has upcoming 2019 meetings in St. Lucia and Taiwan (for youth in Southeast Asia). Also provided fully funded scholarships to over 50 highly talented youth from 16 developing countries for travel and accommodations to Atlanta, GA for intensive leadership and innovation courses in 2017 and 2019.

Headed organization of GSK's Knowledge Pool for the treatment of neglected tropical diseases in least developed countries. This is the first industry initiative to donate intellectual property, know-how and experience to qualified projects via a pool to accelerate capacity building and the development of drugs for commercially neglected diseases. Ms. Knowles led the selection of BIO Ventures for Global Health to be the administrator of the Pool. She also played a leading role in bringing key participants to the Pool, including the Technology Innovation Agency of South Africa. Ms. Knowles executed the Memorandum of Understanding on behalf of GSK with South Africa. She was also instrumental in obtaining the participation of iThemba Pharmaceuticals (a South African emerging company partially funded by the South African government to identify new drugs to treat tuberculosis), and Emory University Institute for Drug Discovery, which focuses on treating the most neglected diseases.

ATTACHMENT 2

TO WRITTEN TESTIMONY OF

SHERRY M. KNOWLES

PRINCIPAL, KNOWLES INTELLECTUAL PROPERTY STRATEGIES, LLC

BEFORE THE

UNITED STATES SENATE

COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON INTELLECTUAL PROPERTY

ON

"THE STATE OF PATENT ELIGIBILITY IN AMERICA, PART I"

JUNE 4, 2019

2:30 PM

THE JOHN MARSHALL
REVIEW OF INTELLECTUAL PROPERTY LAW

UNCONSTITUTIONAL APPLICATION OF 35 U.S.C. § 101 BY THE U.S. SUPREME COURT

SHERRY KNOWLES AND DR. ANTHONY PROSSER

ABSTRACT

"A or B" is inconsistent with "A not B." This describes why the application of 35 U.S.C. § 101 by the U.S. Supreme Court is inconsistent with the U.S. Constitution, and thus unconstitutional. This article tracks the legislative history of patent eligibility from 1790 to 2011, and the parallel but inconsistent U.S. Supreme Court case law during this period. In following its own case law, the Court has shown extraordinary judicial activism, has penciled out two words of the federal statute ("or discovers"), and has penciled a word out of the U.S. Constitution ("discoveries").

Cite as Sherry Knowles and Anthony Prosser, *Unconstitutional Application of 35 U.S.C. § 101 by the U.S. Supreme Court*, 18 J. MARSHALL REV. INTELL. PROP. L. 144 (2018).

UNCONSTITUTIONAL APPLICATION OF 35 U.S.C. § 101 BY THE U.S. SUPREME COURT

SHERRY KNOWLES AND DR. ANTHONY PROSSER

UNCONSTITUTIONAL APPLICATION OF 35 U.S.C. § 101 BY THE U.S. SUPREME COURT

SHERRY KNOWLES AND DR. ANTHONY PROSSER *

I. INTRODUCTION

"A or B" is inconsistent with "A not B." This describes why the application of 35 U.S.C. § 101 by the U.S. Supreme Court is inconsistent with the U.S. Constitution, and thus unconstitutional.

The U.S. Constitution is among the most brilliant documents ever crafted. It is the supreme law of our land and alone creates the carefully balanced tripartite framework for the federal government. As well said by James Madison, "In framing a government which is to be administered by men over men you must first enable the government to control the governed, and in the next place oblige it to control itself."[1]

Article I, Section 8, Clause 8 of the U.S. Constitution gives Congress the sole power to "promote the Progress of Science and the Useful Arts, by securing for limited times to Authors and *Inventors* the exclusive Right to their respective Writings and *Discoveries*."[2] Thus, the U.S. Constitution does two things: it grants the power to create the laws that promote the progress of science solely to Congress, and it associates inventors with discoveries. The U.S. Constitution does not use the word "patent," and it does not tell Congress what kind of advances should be promoted to progress science.

Congress has used its exclusive power under Art. I, Sec. 8, Clause 8 to declare how the country will promote the progress of science, by defining the scope of subject matter that the country will motivate through the use of a temporary government-granted monopoly. This is often referred to as the patent eligibility statute. The current version of the statute is 35 U.S.C. § 101, which states:

> Whoever *invents or discovers* any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[3]

And here we come to "A or B," which is "invents or discovers." Section § 101 unambiguously refers to "invents" and "discovers" in the disjunctive. Thus, according to its plain meaning, Congress has used its exclusive grant of power from the U.S. Constitution in Art. I, § 8, cl. 8 to promote the progress of science by a grant securing for a limited time the exclusive right to either an invention or a discovery. Both

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[1] THE FEDERALIST NO. 51, at 322 (James Madison) (Clinton Rossiter ed., 1999).

[2] U.S. CONST. art. I, § 8, cl. 8 (emphasis added).

[3] 35 U.S.C. § 101 (2012) (emphasis added).

words "inventors" and "discoveries" are used in the U.S. Constitution.[4] And, both inventions and discoveries have resulted in important fundamental advancements of society.[5] It is not out of the pale to conclude that it is in the country's best interest to promote the progress of science by motivating and temporarily rewarding both of them.

Where the U.S. Constitution grants sole authority to Congress to create law in an area, the U.S. Supreme Court is limited to statutory construction.[6] The Supreme Court as recently as 2000 has stated that "when the statute's language is plain, the sole function of the courts—at least where the disposition required by the text is not absurd—is to enforce it according to its terms."[7] The court has stated "time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there."[8] This assumption is "elementary" to judicial analysis of statutes.[9] The Supreme Court even respects the grammatical structure of sentences.[10] Thus, sometimes statutory interpretation can turn on the very punctuation used by Congress.[11]

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[4] U.S. CONST. art. I, § 8, cl. 8.

[5] *Invention*, WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY (3d ed. 1961). The term "invention" is commonly defined in dictionaries either in circular fashion as the act of inventing or alternatively, according to the patentability requirements of novelty, non-obviousness, adequate description, and enablement. It has also been referred to as an act of ingenuity or genius and not of ordinary skill. In contrast, discovery has been used to refer to learning how something works. Congress has clarified its intent that these terms are limited to things made by man, which is not necessary for definition of invention but affirms Congress' intent that its use of the term discovery in the statute refers to *applied* discoveries, in other words, an application made by man of what something is or does; *see* H.R. REP. NO. 82-1923, 2d Sess., 6 (1952). Examples of marketed pharmaceutical drugs (or drug combinations) that are synthetic and fall into the category of invention include Crestor, Lipitor, Advair, Symbicort, Januvia, Atripla, Viagra, Cialis, Ritalin, and Revlimid. Examples of marketed drugs that have been discovered in nature and then isolated and used in a non-naturally occurring form with important therapeutic uses include penicillin, tetracycline, epogen, adriamycin, insulin, vincristine, vinblastine, streptomycin, and Vitamin B_{12}. Clearly, both categories have improved health, promoted the progress of science, improved our standard of living, and saved countless lives.

[6] *See* Hartford Underwriters Ins. Co. v. Union Planters Bank, N.A., 530 U.S. 1, 6 (2000); Connecticut Nat'l Bank v. Germain, 503 U.S. 249, 253-254 (1992); Caminetti v. United States, 242 U.S. 470, 485 (1917).

[7] *Hartford*, 530 U.S. at 6.

[8] *Connecticut*, 530 U.S. at 253-254 (citing several cases in support and going further to state that "When the words of a statute are unambiguous, then, this first canon is also the last" and the "judicial inquiry is complete").

[9] *Caminetti*, 242 U.S. at 485 ("It is elementary that the meaning of a statute must, in the first instance, be sought in the language in which the Act is framed, and if that is plain, and if the law is within the constitutional authority of the lawmaking body which passed it, the sole function of the courts is to enforce it according to its terms.").

[10] *See* D.C. v. Heller, 554 U.S. 570, 598 (2008) (affirming the Court of Appeals' opinion that in part relied on the placement of a comma in the Second Amendment); *see also* Lockhart v. U.S., 136 S. Ct. 958, 962 (2016) (quoting a book on statutory construction by Scalia regarding the interpretation of limiting clauses and phrases which "should ordinarily be read as modifying only the noun or phrase that it immediately follows").

[11] *See* Ali v. Fed. Bureau of Prisons, 552 U.S. 214, 229 (2008) (where in the opinion of the four-judge dissent, the majorities holding improperly placed "implicit reliance upon a comma at the beginning of a clause").

Supreme Court Justice Ruth Bader Ginsburg was recently asked on The Colbert Report TV show whether a hot dog is a sandwich. She replied, "You tell me what a sandwich is and then I'll tell you if a hot dog is a sandwich."[12] This is an example of strict statutory construction—the Court must read the literal words of the statute and apply them to the facts. Under the Constitution, as illustrated by Justice Ginsburg, it is the requirement and limitation of the Supreme Court to construe the literal meaning of every word of 35 U.S.C. § 101 and apply it to the facts at hand. This is the case whether the court agrees with the wording of the statute or not.[13]

Notwithstanding its legal prohibition, the U.S. Supreme Court has created its own parallel law in the area of patent eligibility. The Supreme Court case law on this subject, which has taken on the nature of common law, is directly inconsistent with the wording of 35 U.S.C. § 101. It runs roughshod over the U.S. Constitution. In following its own case law, it has penciled out two words of the federal statute ("or discovers") and penciled a word out of the U.S. Constitution ("Discoveries").

The pinnacle of the U.S. Supreme Court's unconstitutional treatment of patent eligibility is found in the *Ass'n for Molecular Pathology v. Myriad*[14] decision, where Justice Thomas, writing for a unanimous Court, stated that: "Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry."[15] In this passage, Justice Thomas reaffirmed the Supreme Court's view that a "discovery" is not patent eligible under § 101. In other words, according to the Supreme Court, "A not B" (an invention but not a discovery is patent eligible). This is despite the clear disjunctive wording of the statute that states that "whoever invents or discovers . . . may obtain a patent therefor" under Congress' sole authority to promote the progress of science.[16] *Myriad* is exemplary of the Supreme Court line of cases holding "A not B," and thus B is not patent eligible.

The legislative history of 35 U.S.C. § 101 below confirms that Congress repeatedly amended the patent eligibility statute from its time of enactment in 1790 to the most recent codification in 2011, and has maintained and reaffirmed its delegation of exclusive power to reward both inventions and discoveries. In contrast, the history of applying § 101 by the Supreme Court in its opinions goes from little or no statutory construction or discussion of legislative intent to the creation of "judicial exceptions" to the federal statute to full boar direct contradiction of it.

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[12] Sophi Tatum, *Ruth Bader Ginsburg Settles it for Stephen Colbert: Hot Dogs are Sandwiches*, CNN POLITICS (Mar. 22, 2018), https://www.cnn.com/2018/03/22/politics/ruth-bader-ginsburg-stephen-colbert-workout/index.html.

[13] *See* Pennsylvania v. Union Gas Co., 491 U.S. 1, 30 (1989) (Scalia, J., concurring in part and dissenting in part) ("It is our task, as I see it, not to enter the minds of the Members of Congress—who need have nothing in mind in order for their votes to be both lawful and effective—but rather to give fair and reasonable meaning to the text of the United States Code, adopted by various Congresses at various times.").

[14] 569 U.S. 579 (2013).

[15] *Id*. at 577.

[16] 35 U.S.C. § 101.

II. CONGRESS' LEGISLATIVE HISTORY ON PATENT ELIGIBILITY

Congress has historically shown a keen interest in the wording of the codified patent law, including on patent eligible subject matter. On numerous occasions prior to the Patent Act of 1952 Congress passed amendments and entirely new Patent Acts that contained small changes in word choice regarding patent eligibility.[17] Despite these various amendments and acts, detailed further below, Congress has consistently included both inventions and discoveries as patent eligible subject matter. The language on patent eligibility and the definition of invention in the Patent Act of 1952 remains intact today and was not amended by the recent America Invents Act.[18]

The Patent Act of 1790[19] is the first time Congress used its constitutional power to codify what can be patented. The Act stated that "he, she, or they, hath or have *invented or discovered* any useful art, manufacture, engine, machine, or device, or any improvement thereon not before known or used" is entitled to a patent.[20] The first Patent Act, like the Patent Act we practice under today, goes further to define rules for patentability of patent eligible subject matter. The Act required that inventions had to be useful and could only be enforced if they were novel.[21] The Act also required a majority vote between the Secretary of State, Secretary for the Department of War, and the Attorney General to conclude that the "invention or discovery" was "sufficiently useful and important."[22]

The Patent Act of 1793[23] repealed the prior Patent Act and made small changes to the definition of patent eligible subject matter. The Act states that if "they have invented any new and useful art, machine, manufacture or composition of matter, or any new and useful improvement on any art, machine manufacture or composition of matter" then they are entitled to patent protection.[24] While the word "discovered" was removed from the patent eligibility paragraph, it appears that this may have just been an oversight, as "discovery," "discovered," and "discoverer," are used throughout the remainder of the statute.[25] The addition of "new" as a limitation to patent eligible subject matter can be traced to our modern day novelty requirement under 35 U.S.C. 102.[26] The Patent Act of 1793 also removed the requirement for a vote that the invention is "sufficiently useful and important."[27] These changes, made

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[17] *See* Patent Act of 1793, Pub. L. No. 2-53, 2 Stat. 318 (1793); Patent Act of 1836, Pub. L. No. 24-357, 5 Stat. 117 (1836); Patent Act of 1842, Pub. L. No. 27-288, 5 Stat. 543 (1842); Patent Act of 1870, Pub. L. No. 41-230, 15 Stat. 198 (1870); Patent Act of 1897, Pub. L. No. 55-391, 29 Stat. 692 (1897); Plant Patent Act of 1930, Pub. L. No.71-312, 46 Stat. 376 (1930); Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. 792 (1952).

[18] 35 U.S.C. § 100 (2012) (Leahy-Smith America Invents Act (AIA) of 2011).

[19] Pub. L. No. 1-34, 1 Stat. 109 (1790) (current enacted version at 35 U.S.C. § 100 (2012)).

[20] *Id*. at 110 (emphasis added).

[21] *Id*. at 111. Section 5 of the Patent Act provided instruction for when a court could repeal a patent, including if "the patentee was not the first and true inventor or discoverer."

[22] *Id*. at 110.

[23] Pub. L. No. 2-53, 2 Stat. 318 (1793).

[24] *Id*. at 310.

[25] *Id*. at 321-323.

[26] 35 U.S.C. § 102 (2012).

[27] Pub. L. No. 2-53, 2 Stat. 318 (1793).

so quickly after the first Patent Act, clearly show that Congress was active and thoughtful in defining what could be patented.

The Patent Act of 1794[28] was passed to amend the prior Patent Act to reinstate court proceedings that had been dismissed as a consequence of repealing the Patent Act of 1790. The Act did not amend patent eligibility. The Patent Act of 1800[29] similarly left patent eligibility untouched but handled several technical matters including: (1) modifying the oath requirement;[30] (2) providing that resident aliens can apply for patents subject to some restrictions;[31] and (3) changing the infringement damage calculation from *at least* three times license fee to three times the actual damages.[32] The first Patent Act of 1832[33] provided that any patents that had been invalidated as a result of an inventor's unintentional failure to comply with the best mode or oath requirement could have their patent reinstated by the Secretary of State.[34] The second Patent Act of 1832[35] expanded patent rights to aliens who intended to become U.S. citizens (effectively removing the two-year residency requirement). While these acts do not change any patentability definitions, they do, again, refer to "discovery" or "discoveries" in their text, and demonstrate the keen interest Congress had in the details of patent law.

The Patent Act of 1836,[36] repealed all prior Patent Acts and reintroduced the disjunctive discovered or invented language at the beginning of the statute, reaffirming that both are patent eligible. In fact, Congress placed the word discovered before invented.[37] In relevant part, the Act said "That any person or persons having discovered or invented any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvement on any art, machine, manufacture, or composition of matter" is entitled to a patent.[38] Restoring the "discoveries" language in the patent eligibility section purposefully clarified that discoveries are eligible for patent protection. The Act also established the Patent Office and the Commissioner of Patents position.[39]

Within four months of the Patent Office fire of 1836, Congress passed the Patent Act of 1837[40] to address the problems arising from the destruction of most of the Patent Office's records and models. The Act maintained the disjunctive "discovered or invented" patent eligibility scope. The Act also allowed recording of

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[28] Pub. L. No. 3-58, 2 Stat. 393 (1794).

[29] Pub. L. No. 6-25, 3 Stat. 37 (1800).

[30] *Id*. at 38 ("*Provided always*, [t]hat every person petitioning for a patent for any invention, art or *discovery*, pursuant to this act, shall make oath or affirmation . . . that such invention, art or *discovery* hath not to the best of his or her knowledge or belief, been known or used either in this or any foreign country.") (emphasis added).

[31] *Id.* "[T]he rights and privileges given, intended or provided to citizens of the United States, respecting patents for new inventions, *discoveries*, and improvements, . . . are extended and given to all aliens who at the time of the petitioning . . . shall have resided for two years within the United States." *(emphasis added).*

[32] *Id*. "[A] sum equal to three times the actual damage sustained by such patentee."

[33] Pub. L. No. 22-162, 4 Stat. 559 (1832).

[34] *Id*. at 559.

[35] Pub. L. No. 22-203, 4 Stat. 577 (1832).

[36] Pub. L. No. 24-357, 5 Stat. 117 (1836).

[37] *Id*. at 119.

[38] *Id*.

[39] *Id*. at 118-119.

[40] Pub. L. No. 24-409, 5 Stat. 191 (1837).

previously destroyed Patent Office records and raised the number of Examining Clerks from one to two.[41]

The Patent Act of 1839 also maintained the "discovered or invented" eligibility language.[42] In addition, it provided for more Examiners and codified that inventors who had first filed their patent applications overseas could also apply for a U.S. patent.[43] The speed at which Congress reacted to the Patent Office's needs in this time period is notable.

The Patent Act of 1842[44] increased the scope of patent eligible subject matter. The Act again maintained the "discovered or invented" disjunctive patent eligibility scope and added subject matter that can now be traced to modern day design patents.[45]

There were over a dozen[46] Patent Acts passed between 1842 and 1870. These Acts all maintained the broad scope of the disjunctive invention or discovery patent eligibility threshold. In 1870 Congress consolidated the patents, copyrights, and trademark laws into one lengthy law of 111 sections.[47] During this massive effort, Congress still maintained almost the exact same wording regarding patent eligibility, notably including the disjunctive invented and discovered language.[48] The Patent Act of 1897 also maintained this standard.[49]

The next major expansion to patent eligibility came in 1930 when Congress passed the Plant Patent Act of 1930.[50] The Act says in relevant part:

> Any person who has invented or discovered any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvements thereof, or who has invented or discovered and asexually

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[41] *Id*. at 191-192.

[42] Pub. L. No. 25-292, 5 Stat. 353 (1839).

[43] *Id*. at 353.

[44] Pub. L. No. 27-288, 5 Stat. 543 (1842).

[45] *Id*. at 543-544.

[46] The Patent Act of 1870 references a number of prior patents acts that were consolidated including: The Act of August 6, 1846, chapter 90, volume 9, page 59; May 27, 1848, chapter 47, volume 9, page 231; March 8, 1849, chapter 108, volume 9, page 895; March 8, 1851, chapter. 82, volume 9, page 617; August 8, 1852, chapter 107, volume 10, page 75; August 8, 1852, chapter 108, volume 10, page 76; March 8, 1858, chapter 97, volume 10, page 209; April 22, 1854, chapter 52, volume 10, page 276; March 8, 1855, chapter 175, volume 10, page 648; August 18, 1856, chapter 129, volume Il, page 81; March 8, 1859, chapter 80, volume 11, page 410; February 18,1861, chapter 87, volume 12, page 180; March 2, 1861, chapter 88, volume 12, page 246; March 8,1863, chapter 102, volume 12, page 796; June 25, 1864, chapter 159, volume 18, page 194; March 8, 1865, chapter 112, volume 18, page 588; June 27, 1866, chapter 148, volume 14, page 76; March 29, 1867, chapter 17, volume 15, page 10; July 20, 1868, chapter 177, volume 15, page 119; July 28, 1868, chapter 227, volume 15, page 168; and March 8, 1869, chapter 121, volume 15, page 298.

[47] Pub. L. No. 41-230, 15 Stat. 198 (1870).

[48] *Id.* ("That any person who has invented or discovered any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvement thereof.").

[49] Pub. L. No. 55-391, 29 Stat. 692 (1897) ("Any person who has invented or discovered any new and useful art, machine, manufacture, or composition of matter, or any new and useful improvements thereof.").

[50] Pub. L. No.71-312, 46 Stat. 376 (1930).

> reproduced any distinct and new variety of plant, other than tuber-propagated plant.[51]

Finally, after the rich history of expanding and refining (but not limiting) patent eligibility described above, Congress passed the modern day eligibility criteria in The Patent Act of 1952.[52]

> Whoever *invents or discovers* any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[53]

The 1952 Act also added a definition for the term "invention." The Act states that: "The term 'invention' means invention or discovery."[54] While this circular definition of invention is not helpful in defining what an invention is or is not, it does emphasize Congress' insistence that discoveries are patent eligible.

The Hearings before the Subcommittee of the Committee on the Judiciary of the House of Representatives pertaining to the 1952 Act are enlightening. The congressional record shows the intent to maintain "discoveries" was purposeful. For example, The Department of Justice ("DOJ") gave testimony to Congress (Mr. Bryson presiding), with a range of comments on various proposed sections of the Act.[55] With respect to patent eligibility, the DOJ requested removal of "discoveries" from the definition of invention with the assertion that it was inconsistent with the decisions of the Supreme Court.[56] Specifically, Mr. Brown for the DOJ said that:

> Section 100 of the bill, "definitions," defines "invention" to include discoveries. While the term "discovery" is used in the patent law as synonymous with invention and it has been recognized that the act of discovery is an essential part of the invention, under existing law discoveries, as such are not patentable. . . The section might have the effect of creating doubt as to existing law on the subject of discovery and might result in opening the door to a huge new area of patents, and permit the creation of monopolies in some of the fundamental and far-reaching discoveries in the fields of chemistry, physics, medicine, mathematics, et cetera. . . The Department would be opposed to the creation of any new area of monopoly which would be exempt from the operation of the anti-trust

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[51] *Id*. at 376.

[52] Pub. L. No. 82-593, 66 Stat. 792 (1952).

[53] *Id*. at 797 (emphasis added); *see also* Pub. L. No. 112-29, 125 Stat. 284 (2011) (Leahy-Smith America Invents Act (AIA)). The America Invents Act maintains the same language for patent eligibility.

[54] 35 U.S.C. § 100 (2012); *see also* Pub. L. No. 112-29, 125 Stat. 284 (2011) (Leahy-Smith America Invents Act (AIA)). The America Invents Act keeps the same definition of "invention."

[55] H.R. Rep. No. 82-3760, 1st Sess., 93 (1951).

[56] H.R. Rep. No. 82-3760, 1st Sess., 94 (1951); *see also* H.R. Rep. No. 80-4061, 2d Sess., 82 (1951). The Justice Department objected to the addition of discoveries to the definition of invention on at least two occasions. First, they stated that they "recommend that no hasty action be taken toward the enactment of a statutory definition of "invention." And then they went as far as to say, "under existing law discoveries, as such, are not patentable."

> laws in the absence of clear evidence that such extension is necessary to provide adequate incentive for scientific effort. There would appear to be no such necessity with respect to the broad field of "discoveries."[57]

After Mr. Brown's testimony was read into the record, the sole response to the DOJ comments was a short "Thank you, Mr. Brown" from Mr. Bryson for Congress without comment, and a request to call the next speaker.[58] And as clear from the codified law, the DOJ's suggestion was not accepted, even after the testimony that it would be inconsistent with Supreme Court cases.

Congress also heard from Mr. Fellner, the manager of the patent department of the Salsbury's Laboratories in Iowa.[59] Mr. Fellner made comments without a prepared statement on proposed sections 101 and 103.[60] Mr. Fellner wanted to include language that had been omitted from the old bill H.R. 9133 in the new version H.R. 3760. H.R. 9133 stated, "An invention in the nature of a discovery as embodied in a new and useful art, machine, manufacture or composition of matter, or new and useful improvement thereof may be patented."[61] Mr. Fellner raised the issue of the highly controversial 1948 Supreme Court, *Funk Bros.*[62] decision, holding that the discovery of a new mixture of bacteria that had commercial application to the inoculation of various agricultural species was not patent eligible. Fellner testified that the *Funk Bros.* product solved a great problem by providing a new compatible mixture of bacteria for crop development, and he implied that the decision to reject the patent was very problematic to industry.

Congressman Willis asked, "As I understand it, from the point of view of the industry you represent, their requirements would have been met by the adoption of section 101 of the old bill, H.R. 9133, particularly using the second paragraph beginning with "an invention in the nature of a discovery?"[63] Mr. Fellner agreed. To that, Congressman Willis made the important observation:

> You do not consider that the new bill, section 101 of H.R. 3760 with the definition, accomplishes what you have in mind? In other words, is it not simply a question of some condition? Does not the definition preceding section 101, embodied in section 100, carry all the implications you used in the second paragraph of section 101 of H.R. 9133? You see, in H.R. 9133, you did not have the definition contained in section 100 of the new bill. Now with these definitions, would not they supply the purpose of the second paragraph in the old bill? What it was intended to cover?[64]

This Congressional statement urges the conclusion that the subcommittee thought that taking the extra step to add "discoveries" into the definition of invention in

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[57] H.R. Rep. No. 82-3760, 1st Sess., 94 (1951); H.R. Rep. No. 3760 at 94.

[58] *Id*. at 98.

[59] *Id*. at 116-124.

[60] *Id*.

[61] *Id*. at 117.

[62] Funk Bros. Seed Co. vs. Kalo Inoculant Co. 333 U.S. 127 (1948). This case is discussed in detail in Section II. below.

[63] H.R. Rep. No. 82-3760 at 120.

[64] *Id*.

section 100 reaffirmed its intent that discoveries are considered part of the subject matter Congress wants to motivate via the patent system.

Later on in Mr. Fellner's testimony, he was questioned by Congressman Crumpacker.

> Mr. CRUMPACKER. Does not the language of the pending bill say "whoever discovers any new and useful process, machine, manufacture, or composition of matter" may obtain a patent covering it? I would think that would specifically cover the case you referred to. And, if the Supreme Court has interpreted the words as you indicate, I do not see how including that language in the paragraph would cause them to make a different interpretation.
>
> Mr. FELLNER. I believe that the Supreme Court in that particular case did not interpret it in the way the bill here originally contemplated.[65]

After finishing his comments on *Funk,* Mr. Fellner was asked to go on to the next paragraph.[66] The overall Congressional discussion at the Hearing indicates Congress considered that by taking the step to add the discoveries to the new definition of invention in section 100 before section 101, it was affirming its intent that promoting discoveries will progress science, which should be enough. It was not.

In summary, between 1790 and 2011, Congress defined the scope of patent eligibility in the broad disjunctive "invention or discovery." It did remove the word "discovered" for a short period of time (1793-1836 (and even then referred to discoveries, multiple times, later in the text of the code)), and then purposefully restored the disjunctive "invention or discovery" eligibility scope which it maintained through at least two dozen Patent Act amendments and is maintained today. The early enactments of Congress solidified and confirmed the statutory scope of patent eligibility.[67] The Supreme Court acknowledges that:

> Early congressional enactments "provid[e] 'contemporaneous and weighty evidence' of the Constitution's meaning," Bowsher v. Synar, 478 U.S. 714, 723–724, 106 S.Ct. 3181, 3186, 92 L.Ed.2d 583 (1986) (quoting Marsh v. Chambers, 463 U.S. 783, 790, 103 S.Ct. 3330, 3335, 77 L.Ed.2d 1019 (1983)). Indeed, such "contemporaneous legislative exposition of the Constitution ..., acquiesced in for a long term of years, fixes the construction to be given its provisions." Myers v. United States, 272 U.S. 52, 175, 47 S.Ct. 21, 45, 71 L.Ed. 160 (1926) (citing numerous cases).[68]

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[65] *Id*. at 122.
[66] *Id*. at 123.
[67] Printz v. United States, 521 U.S. 898 (1997).
[68] *Id*. at 905.

III. HISTORY OF U.S. SUPREME COURT TREATMENT OF PATENT ELIGIBILITY

The earliest U.S. Supreme Court opinion sometimes referred to by the Court in the march of patent eligibility cases is the 1852 case of *Le Roy v. Tatham*.[69] A patent was issued to John and Charles Hanson on August 31st, 1837, on a combination of machine parts to make wrought lead pipes,[70] which was later assigned to Tatham. The Patent Act of 1836, which codified the requirement for patent claims[71] to be presented in a patent specification, had just been enacted and, thus, there was very little experience by patentees or the judiciary with patent claims at the time.[72] The patentee stated that while the individual pieces of the equipment were known, their new combination allowed them to succeed in making perfect strong lead pipes.[73] The Circuit Court for the Southern District of New York had charged the jury that the originality of the machinery did not consist in its novelty, but instead, in bringing a newly discovered principle into practical application, by which a useful article of manufacture is produced and wrought pipe made as distinguished from cast pipe.[74] The Supreme Court determined that "The question whether the newly developed property of lead, used in the formation of pipes, might have been patented, if claimed as developed, without the invention of machinery, was not in the case."[75] It held that there was error in the Circuit Court's instruction, "that the novelty of the combination of the machinery, specifically claimed by the patentees as their invention, was not a material fact for the jury, and that on that ground, the judgment must be reversed."[76]

The Court said in dicta, referring to the decision of the Circuit Court:

> The word principle is used by elementary writers on patent subjects, and sometimes in adjudications of courts, with such a want of precision in its application, as to mislead. It is admitted, that a principle is not patentable. A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right. Nor can an exclusive right exist to a new power, should one be discovered in addition to those already known. Through the agency of machinery a new steam power may be said to have been generated. But no one can appropriate this power exclusively to himself, under the patent laws. The same may be said of electricity, and of any other power in nature,

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[69] Le Roy v. Tatham, 55 U.S. 156 (1853).

[70] *Id*. at 171. The claim was "the combination of the following parts, above described, to wit, the core and bridge, or guide-piece, the chamber, and the die, when used to for pipes of metal, under heat and pressure, in the manner set forth, or in any other manner substantially the same."

[71] Pub. L. No. 24-357, 5 Stat. 117 (1836) (Patent Act 1836.).

[72] Le Roy v. Tatham, 55 U.S. 156 (1853); EDMUND BURKE, LIST OF PATENTS FOR INVENTIONS AND DESIGNS ISSUED BY THE UNITED STATES FROM 1790 TO 1847 WITH THE PATENT LAWS AND DECISIONS OF THE COURTS OF THE UNITED STATES FOR THE SAME PERIOD (J. & G.S. Gideon, 1st ed. 1847). To the best of the authors' knowledge, the Tatham patent was never given a patent number and was only cataloged in the previously-cited book issued by Edmund Burke, the Commissioner of Patents, and is not readily available for review.

[73] 55 U.S. 156 at 171.

[74] *Id*.

[75] *Le Roy*, 55 U.S. at 177.

[76] *Id*.

> which is alike open to all, and may be applied to useful purposes by the use of machinery . . . A new property discovered in matter, when practically applied, in the construction of a useful article of commerce or manufacture, is patentable; but the process through which the new property is developed and applied, must be stated, with such precision as to enable an ordinary mechanic to construct and apply the necessary process. [77]

Thus, the *Le Roy* case was remanded on novelty grounds, not patent eligibility, and even the early *Le Roy* Court affirmed that the practical application of a property discovered in nature is patent eligible. The later case of *O'Reilly v. Morse*,[78] faithfully quoted *Le Roy* for support that while Tatham was not entitled to a patent on what happens when hot lead cools, it was entitled to a process for making lead pipe using that principle.[79]

The first Supreme Court case on the course of deviating law from the wording of the federal statute on patent eligibility was the controversial 1948 case of *Funk Bros. Seed Co. vs. Kalo Inoculant Co*.[80] The case involved a product that included several strains of root-nodule bacteria that can be used as a mixed culture to inoculate a range of plants.[81] The previously sold products included only single strains, on the belief that the strains inhibit each other so they could not be mixed.[82] Bond discovered that there are strains of root-nodule bacteria that do not inhibit each other, and so multi-strain bacterial products are possible.[83] The Court held:

> The application of this newly-discovered natural principle to the problem of packaging of inoculants *may well have been an important commercial advance*. But once nature's secret of the non-inhibitive quality of certain strains of the species of Rhizobium was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it certainly was not the product of invention. *There is no way in which we could call it such unless we borrowed invention from the discovery of the natural principle itself. That is to say, there is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention*. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed. All that remains, therefore, are advantages of the mixed inoculants themselves. They are not enough. Since we conclude that the product claims do not disclose an invention or

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[77] *Le Roy*, 55 U.S. at 174-75.

[78] O'Reilly v. Morse, 56 U.S. 62 (1854).

[79] *O'Reilly*, 56 U.S. at 117 (stating that in this case, "the patentee had discovered that lead, recently set, would under heat and pressure in a close vessel reunite perfectly after a separation of its parts so as to make a wrought instead of cast pipe. And the court held that he was not entitled to a patent for this newly discovered principle or quality in lead, and that such a discovery was not patentable. But that he was entitled to a patent for the new process or method in the art of making lead pipe, which this discovery enabled him to invent and employ.").

[80] Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948).

[81] *Id*. at 129-131.

[82] *Id*. at 130.

[83] *Id*.

> discovery within the meaning of the patent statutes, we do not consider whether the other statutory requirements contained in 35 U.S.C. § 31, 35 U.S.C.A. § 31, R.S. § 4886 are satisfied.[84]

In the italicized language, Justice Douglas stated that a commercial product based on the application of a discovery about how nature works to produce a new and useful scientific advance cannot form the basis for a patent unless it is also an invention.[85] This statement not only directly contradicts the earlier *Le Roy* opinion, it also directly contradicts the statutory determination by Congress that any composition of matter "invention or discovery" is patent eligible. This faulty analysis formed the initial threads for the Supreme Court's parallel case law on patent eligibility, and is repeatedly cited by the Court as its authority.

Under *Le Roy*, the *Funk* multi-strain product would have been patent eligible, as it stated "A new property discovered in matter, when practically applied, in the construction of a useful article of commerce or manufacture, is patentable."[86]

The *Funk* case is also one of the first in the line of Supreme Court cases on patent eligibility that uses false examples to support its opinion. The Court stated:

> The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.[87]

Here, even though the Court gave lip service in the last sentence to applications of laws of nature, it rejected the Funk invention which was exactly that. Patents are used to protect commercial endeavors that have an element made by man, and thus they attempt to cover products, processes, and manufactures with commercial uses, which are almost always based on how nature works because that is the world we live in. Even if one creates a new scientific pathway, it is fundamentally based on a discovery of how nature works.

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[84] *Id*. at 132 (emphasis added).

[85] *Id*. There was, in fact, a fatal flaw in the patent claims selected for litigation of U.S. Patent No. 2,200,532 to Kalo, however, it was not patent eligibility. The claims failed the written description and enablement requirements contained in the Patent Act of 1870 – 15 Stat. at 201, because they did not name the mutually non-inhibiting bacteria to be used in the product. The Patent also included claims that were limited to the identified useful strains of bacteria, but those were not litigated. Immeasurable damage and confusion was caused by using patent eligibility as the rationale for invalidating the patent instead of patentability.

[86] Le Roy v. Tatham, 55 U.S. 156, 174-175 (1853); *see* Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 129 (1948) (emphasizing that "We do not have presented the question whether the methods of selecting and testing the non-inhibitive strains are patentable. We have here only product claims. Bond does not create state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable. For patents cannot issue for the discovery of the phenomena of nature.").

[87] *Funk Brothers*, 333 U.S. at 129.

Was it outside the pale that Congress would authorize the protection of a new product that is a combination of several strains of root-nodule bacteria that can be used as a mixed culture to inoculate a range of plants and advance agriculture? Of course not. Even the Supreme Court admitted this was a useful new commercial product. Would it help farmers? Yes. Did it promote the progress of science? Yes. Was it a useful application of a discovery? Yes.[88] Was the *Funk* decision inconsistent with *Le Roy?* Yes.

The 1948 *Funk* decision was issued a few years before the codification of the 1952 Act. As indicated in the above legislative history leading to the 1952 Act, the addition of the definition of invention (to include discoveries) in section 100 and inclusion of "invents or discovers" in section 101 confirm Congress' intent on the issue.

The next case in this series and the first after the passage of the 1952 Act was *Gottschalk v. Benson*.[89] In *Gottschalk*, Justice Douglas writing for the Supreme Court held that programming a computer with a mathematical formula that converts binary coded decimal numbers into pure binary numerals is not patent eligible, because it is the use of an idea:

> The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself. It may be that the patent laws should be extended to cover these programs, a policy matter to which we are not competent to speak.

The Court was concerned with affirming such a broad scope of monopoly, but that was not their decision to make, which should be limited to strict statutory construction. The decision was heavily dependent on its own prior holding in *Funk Brothers*,[90] also written by Justice Douglas without any statutory construction or legislative intent analysis, as well as *Le Roy v. Thathan*[91] and *O'Reilly v. Morse*[92]. In

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[88] *Id*. at 135-138. The dissent of Justice Burton and Justice Jackson desired affirming the appellate court decision and upholding the patent, because in their opinion the claims satisfied the patent eligibility requirements. *See also id*. at 443-444. Justice Frankfurter in his concurring opinion opined that the invention was patent eligible but failed other patentability requirements. Frankfurter states:

> Multi-purpose tools, multivalent vaccines, vitamin complex composites, are examples of complexes whose sole new property is the conjunction of the properties of their components. Surely the Court does not mean unwittingly to pass on the patentability of such products by formulating criteria by which future issues of patentability may be prejudged. In finding Bond's patent invalid I have tried to avoid a formulation which . . . would lay the basis for denying patentability to a large area within existing legislation.

[89] Gottschalk v. Benson, 409 U.S. 63 (1972).

[90] Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948).

[91] Le Roy v. Tatham, 55 U.S. 156 (1853) (holding that a claim to "the use of motive power of the electric or galvanic current, which I call electro-magnetism, however developed for marking or printing intelligible characters, signs, or letters, at any distances, being a new application of that power of which I claim to be the first inventor or discoverer" was not patent eligible as an abstract idea). However, the patent claim could have been stricken with more fidelity to the statute with a

fact, the only reference to the wording of 35 USC § 101 in *Gottschalk* is in a footnote.[93] The *Gottschalk* opinion also commented from the "Report of the President's Commission on the Patent System," referring to problems involved in examining computer software programs and recommending that they not be patent eligible.[94] Thus the Court relied on its own earlier case law, and an un-adopted recommendation from a Committee to the President in the Executive Branch, instead of carrying out strict statutory construction or reviewing legislative intent of the only branch of government delegated the responsibility to create the law. Regardless whether one is of the belief the right decision was made in this case, the Supreme Court did not carry out the required disciplined legal process of statutory construction, and it laid the groundwork for the further deviation from the required statutory interpretation.

In the Court's opinion in *Parker v. Flook,*[95] it admitted that the decision in *Gottshalk* could not have been decided based on a literal reading of 35 U.S.C. § 101.[96] The Court focused its treatment of what is patent eligible on what constitutes a process:

> This case turns entirely on the proper construction of § 101 of the Patent Act, which describes the subject matter that is eligible for patent protection. It does not involve the familiar issues of novelty and obviousness that routinely arise under §§ 102 and 103 when the validity of a patent is challenged. For the purpose of our analysis, we assume that respondent's formula is novel and useful and that he discovered it. We also assume, since respondent does not challenge the examiner's finding, that the formula is the only novel feature of respondent's method. The question is whether the discovery of this feature makes an otherwise conventional method eligible for patent protection.
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> The plain language of § 101 does not answer the question. It is true, as respondent argues, that his method is a "process" in the ordinary sense of the word.[9] But that was also true of the algorithm, which described a method for converting binary-coded decimal numerals into pure binary numerals, that was involved in Gottschalk v. Benson. *The holding that the discovery of that method could not be patented as a "process" forecloses a purely literal reading of § 101.* Reasoning that an algorithm, or

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holding that the claims failed the written description or enablement requirement, contained in the Patent Act of 1836.

[92] O'Reilly v. Morse, 56 U.S. 62, 136 (1853).

[93] *Gottschalk*, 409 U.S. at 64-65 (reciting 35 U.S.C. § 101).

[94] *Id.* at 70-71.

[95] Parker v. Flook, 437 U.S. 584, 587 (1978).

[96] *Id.* at 585. In *Parker*, Justice Stevens, writing for the Court, addressed the patent eligibility of patent application that described a method of updating alarm limits that included three steps: an initial step measuring the present value of the process variable (*e. g.*, the temperature); an intermediate step which uses an algorithm to calculate an updated alarm-limit value; and a final step in which the actual alarm limit is adjusted to the updated value. The only difference between the conventional methods of changing alarm limits and that described in patent application was in step two.

> mathematical formula, is like a law of nature, *Benson* applied the established rule that a law of nature cannot be the subject of a patent.[97]

There was a sharp dissent from Justices Stewart, Rehnquist, and Burger:

> The Court today says it does not turn its back on these well-settled precedents, *ante*, at 2527–2528, but it strikes what seems to me an equally damaging blow at basic principles of patent law by importing into its inquiry under 35 U.S.C. § 101 the criteria of novelty and inventiveness. Section 101 is concerned only with subject-matter patentability. Whether a patent will actually *issue* depends upon the criteria of §§ 102 and 103, which include novelty and inventiveness, among many others. It may well be that under the criteria of §§ 102 and 103 no patent should issue on the process claimed in this case, because of anticipation, abandonment, obviousness, or for some other reason. But in my view the claimed process clearly meets the standards of subject-matter patentability of § 101.[98]

The next in the series of U.S. Supreme Court decisions on patent eligibility was *Diamond v. Chakrabarty*[99] in 1980, where the Court addressed the meaning of manufacture under § 101 and whether genetically engineered bacteria are patent eligible. Justice Burger, for a 5-4 Court (dissenting: Brennan, White, Marshall and Powell), confirmed that the term manufacture is intentionally broad.[100] Importantly, *Chakrabarty* is one of the few[101] of this line of cases in which the Supreme Court actually uses the words "statutory interpretation" and refers to legislative history; however it construes the terms "manufacture" and "composition of matter" not "discovers."

> The question before us in this case is a narrow one of statutory interpretation requiring us to construe 35 U.S.C. § 101, which provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."
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> Specifically, we must determine whether respondent's micro-organism constitutes a "manufacture" or "composition of matter" within the meaning of the statute.[5]
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> The relevant legislative history also supports a broad construction. The Patent Act of 1793, authored by Thomas Jefferson, defined statutory subject matter as "any new and useful art, machine, manufacture, or composition of

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[97] *Parker*, 437 U.S. at 586.

[98] *Parker*, 437 U.S. at 598-599.

[99] Diamond v. Chakrabarty, 447 U.S. 303 (1980).

[100] *Chakrabaty*, 447 U.S. at 317.

[101] J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 127 (2001). The case of *J.E.M. v. Pioneer* likewise held that plant varieties are manufactures under 101, with similar reasoning.

> matter, or any new or useful improvement [thereof]." Act of Feb. 21, 1793, § 1, 1 Stat. 319. The Act embodied Jefferson's philosophy that "ingenuity should receive a liberal encouragement." Writings of Thomas Jefferson 75–76 (Washington ed. 1871). See *Graham v. John Deere Co.*, 383 U.S. 1, 7–10, 86 S.Ct. 684, 688–690, 15 L.Ed.2d 545 (1966). Subsequent patent statutes in 1836, 1870, and 1874 employed this same broad language. In 1952, when the patent laws were recodified, Congress replaced the word "art" with "process," but otherwise left Jefferson's language intact. The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man." S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952).[102]

However, the Supreme Court goes further and starts to name and institutionalize the Supreme Court's parallel interpretation of what should be patent eligible, and then rules in the positive.

> This is not to suggest that § 101 has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable. See *Parker v. Flook*, 437 U.S. 584, 98 S.Ct. 2522, 57 L.Ed.2d 451 (1978); *Gottschalk v. Benson*, 409 U.S. 63, 67, 93 S.Ct. 253, 255, 34 L.Ed.2d 273 (1972); *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130, 68 S.Ct. 440, 441, 92 L.Ed. 588 (1948); *O'Reilly v. Morse*, 15 How. 62, 112–121, 14 L.Ed. 601 (1854); *Le Roy v. Tatham*, 14 How. 156, 175, 14 L.Ed. 367 (1853). Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Funk, supra*, 333 U.S., at 130, 68 S.Ct., at 441.[103]

Here we see the Court defining judicial exceptions to a federal statute. The Court states that "laws of nature, physical phenomena and abstract ideas" are not patent eligible. None of these exceptions are listed in 35 U.S.C. § 101. Instead, the Committee Reports accompanying the 1952 Act indicates that Congress intended statutory subject matter to "include anything under the sun that is made by man."[104] The Court itself, in later cases, repeatedly refers to these "carve-outs" of the statute as judicial exceptions not examples.

We also again see exaggerated and false examples of "discovery" to discredit the term. Pure unapplied mathematical relationships, such as $E=mc^2$ and the law of

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[102] *Chakrabaty*, 447 U.S. at 307-310.

[103] *Chakrabaty*, 447 U.S. at 303-304.

[104] 447 U.S. at 309-310 (citing S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952)); H.R. Rep. No.1923, 82d Cong., 2d Sess., 6 (1952). It is worth noting that the inventions "include anything under the sun that is made by man" quote was made by the Commissioner of Patents when summarizing the Patent Office's understanding of the bill. This quote was then used in the report to the Senate presented by Congressman Wiley, essentially adopting the Patent Office's interpretation as correct.

gravity $F=G(m_1m_2/r^2)$ are not made by man.[105] Congress has already given clear legislative intent that such are not patent eligible. The Court needed to go no further than statutory construction and legislative intent to reach a patent eligibility decision. It did not need to create exceptions to what Congress codified. Even if one were to go to the absurd to say these mathematical principals were intended by Congress to be patent eligible as discoveries of processes of nature falling under 35 U.S.C. § 101, they would certainly be caught by the novelty standard (35 U.S.C. 102), as these laws have been in existence since the big bang, around 13.7 billion years ago. The Court should stop using senseless examples of unapplied mathematics.

In *Diamond v. Diehr*,[106] Justice Rehnquist for the Court affirmed the patent eligibility of a process for making rubber, focusing on the subject of what is the scope of "process" added to 101 in the 1952 Act.[107]

> As in *Chakrabarty*, we must here construe 35 U.S.C. § 101 which provides: "Whoever, invents or discovers any new and useful process, machine manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." In cases of statutory construction, we begin with the language of the statute. *Unless otherwise defined, "words will be interpreted as taking their ordinary, contemporary, common meaning," Perrin v. United States, 444 U.S. 37, 42, 100 S.Ct. 311, 314, 62 L.Ed.2d 199 (1979), and, in dealing with the patent laws, we have more than once cautioned that "courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.' " Diamond v. Chakrabarty, supra, at 308, 100 S.Ct., at 2207 quoting United States v. Dubilier Condenser Corp., 289 U.S. 178, 199, 53 S.Ct. 554, 561, 77 L.Ed. 1114 (1933).*
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> The Patent Act of 1793 defined statutory subject matter as "any new and useful art, machine, manufacture or composition of matter, or any new or useful improvement [thereof]." Act of Feb. 21, 1793, ch. 11, § 1, 1 Stat.

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[105] *Id*. Albert Einstein was a highly skilled Patent Examiner at the Swiss Patent Office in 1905 when he published four groundbreaking articles in Annalen der Physik (the photoelectric effect, special relativity, Brownian motion and mass/energy interconversion). It is the last that propounded the formula $E=mc^2$. If Einstein had thought he was working on patent eligible subject matter, he was in the perfect position at the Swiss Patent Office, and with his superior intellect and not much money in his pocket, the incentive, to file a patent application on it. He did not. The reference to $E=mc^2$ is an example used in a number of S. Ct. decisions relating to § 101 for distracting dramatic effect.

[106] Diamond v. Diehr, 450 U.S. 175 (1981).

[107] *Id*. at 177-181. The claimed process used a mold for precisely shaping uncured rubber under heat and pressure and then curing it in the mold so that the product would retain its shape and be functionally operative after the molding is completed, ensuring the production of molded articles which are properly cured. *Id*. The patentee asserted the industry has not been able to obtain uniformly accurate cures because the temperature of the molding press could not be precisely measured, thus making it difficult to do the necessary computations to determine cure time and said their contribution to the art to resided in the process of constantly measuring the actual temperature inside the mold. *Id*. at 190-193. The continuous measuring of the temperatures inside the mold cavity, the feeding of this information to a digital computer which constantly recalculates the cure time, and the signaling by the computer to open the press, created a new process.

> 318. Not until the patent laws were recodified in 1952 did Congress replace the word "art" with the word "process." It is that latter word which we confront today, and in order to determine its meaning we may not be unmindful of the Committee Reports accompanying the 1952 Act which inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man." S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952), U.S.Code Cong. & Admin.News 1952, pp. 2394, 2399. Although the term "process" was not added to 35 U.S.C. § 101 until 1952 a process has historically enjoyed patent protection because it was considered a form of "art" as that term was used in the 1793 Act.[108]

In *Bilski v. Kappos*,[109] the Supreme Court finally admitted that its judicial exceptions to the federal statute are not required by the statutory text, although it asserted that the exceptions are "consistent with" it.[110] The Court also, for the first time, rationalized its judicial exceptions to the federal statute as "*statutory stare decisis*."[111] The Court thus acknowledged that it was acting outside of the bounds of the statutory language, and suggests its position that if the Court has created and used its own patent law for a long enough time, it should be able to continue. However, as discussed above, Congress has also repeatedly reaffirmed the "invention or discovery" standard from 1790 through 2011. And, since Congress is solely authorized to create patent law, these repeated recodifications prevail. The Court's quote below also conflates the consideration of the general categories of patent eligibility (inventions or discoveries) with the separate patentable subject matter requirements of novelty and obviousness. Later court cases took this conflation in a more draconian direction.[112]

> The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: "laws of nature, physical phenomena, and abstract ideas." *Chakrabarty, supra,* at 309, 100 S.Ct. 2204. While these exceptions are not required by the statutory text, they are consistent with the notion that a patentable process must be "new and useful." *And, in any case, these exceptions have defined the reach of the statute as a matter of*

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[108] *Diehr*, 450 U.S. at 180-182 (emphasis added).

[109] Bilski v. Kappos, 561 U.S. 593 (2010). The Bilski patent application concerned methods to hedge (de-risk) investments in energy. *Id*. The method provided a technique by which an energy company can sell energy at one price to consumers based on historical averages and to another set of consumers with a different price calculation that will decrease its losses if the underlying energy cost changes unexpectedly. *Id*. The Primary Patent Examiner, Board of Patent Appeals and Interferences, Federal Circuit Court, and finally U.S. Supreme Court all rejected the claims based on patent eligibility. *Id*. The Courts could also have easily rejected the claims based on 35 U.S.C. § 102 or 35 § U.S.C. 103, as basic hedging strategies has been known for centuries.

[110] *Id*. at 593-94.

[111] *Id*. Of course, even statutory stare decisis, to the extent it is consistent with the Constitution, does not allow the removal of words from a federal statute.

[112] *See e.g.* Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015) (holding that method to measure fetal DNA in the blood of a pregnant woman which avoided the previous need to invasively harvest blood from the fetus was not patent eligible); *cert. denied*, Sequenom, Inc. v. Ariosa Diagnostics, Inc., 136 S. Ct. 2511 (2016).

> *statutory stare decisis going back 150 years.* See *Le Roy v. Tatham,* 14 How. 156, 174–175, 14 L.Ed. 367 (1853). The concepts covered by these exceptions are "part of the storehouse of knowledge of all men ... free to all men and reserved exclusively to none." *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130, 68 S.Ct. 440, 92 L.Ed. 588 (1948).[113]

The Court continued with its acknowledgement that it is acting outside of the bounds of the statute, and it can only go so far:

> Any suggestion in this Court's case law that the Patent Act's terms deviate from their ordinary meaning has only been an explanation for the exceptions for laws of nature, physical phenomena, and abstract ideas. See *Parker v. Flook,* 437 U.S. 584, 588–589, 98 S.Ct. 2522, 57 L.Ed.2d 451 (1978). This Court has not indicated that the existence of these well-established exceptions gives the Judiciary *carte blanche* to impose other limitations that are inconsistent with the text and the statute's purpose and design. Concerns about attempts to call any form of human activity a "process" can be met by making sure the claim meets the requirements of § 101.[114]

This quote also reflects the Court's predilection to cite to its own earlier cases instead of the wording of the statute in what should be a strict statutory construction case. This is a theme running throughout these cases and the basis for the deviation from the required application of the literal terms of the law as passed by Congress.

In *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*,[115] the Court addressed whether a claim to optimizing the therapeutic efficacy of a treatment using 6-thiopurine for a gastrointestinal disorder with a discovered metabolic algorithm is patent eligible under § 101. Justice Breyer, writing for the Court, mentions § 101 at the beginning of the opinion, solely to introduce the Supreme Court's judicially created exceptions to it.[116] There is no further discussion of the statute or legislative history or intent. The whole of the opinion refers back to earlier Supreme Court precedent and the evolution of the Court's evolving common law on the subject, based on its own view of what should be patent eligible.

> Section 101 of the Patent Act defines patentable subject matter. It says: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. *The Court has long held that this provision contains an important implicit exception.* "[L]aws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond v. Diehr,* 450 U.S. 175, 185, 101 S.Ct. 1048, 67 L.Ed.2d 155 (1981); see also *Bilski v. Kappos,* 561 U.S. 593, ——, 130 S.Ct. 3218, 3233–3234, 177

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[113] *Ariosa Diagnostics*, 788 F.3d at 3225 (emphasis added).
[114] *Ariosa Diagnostics*, 788 F.3d at 3225.
[115] Mayo Collaborative Servs. v. Prometheus Labs, Inc., 566 U.S. 66 (2012).
[116] *Id*. at 70-71.

> L.Ed.2d 792 (2010); *Diamond v. Chakrabarty,* 447 U.S. 303, 309, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980); *Le Roy v. Tatham,* 14 How. 156, 175, 14 L.Ed. 367 (1853); *O'Reilly v. Morse,* 15 How. 62, 112–120, 14 L.Ed. 601 (1854); cf. *Neilson v. Harford,* Webster's Patent Cases 295, 371 (1841) (English case discussing same).[117]

The Court then admits that it cannot take its own judicially created exceptions too far or else they will destroy Congress' patent law *in toto*:

> *The Court has recognized, however, that too broad an interpretation of this exclusionary principle could eviscerate patent law.* For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas. . . Still, as the Court has also made clear, to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words "apply it." See, *e.g., Benson, supra,* at 71–72, 93 S.Ct. 253.*[118]*

From here, the Court digresses into economic analysis and the balance between patent protection and third party freedom to operate.

> These statements reflect the fact that, even though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery, those laws and principles, considered generally, are "the basic tools of scientific and technological work." *Benson, supra,* at 67, 93 S.Ct. 253. *And so there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to "apply the natural law," or otherwise forecloses more future invention than the underlying discovery could reasonably justify.*[119]

The Constitution has not granted any authority to the Supreme Court to carry out economic analysis of what should be patent eligible, nor is it equipped to do so. The Supreme Court does not have the power to commission white papers, take testimony, review independent evidence, have one-on-one meetings with stakeholders or to take depositions, which are necessary to create public policy. Amicus briefs, while useful, do not take the place of these tools. The Supreme Court is arguably the worst equipped of the three branches of the government to evaluate patent policy. For this reason, our founding fathers did not give the Supreme Court the authority to set policy, although, as illustrated by the *Mayo* case, the Court has crossed that line. Creating a careful balance between the scope of incentive to promote the progress of science and impeding ancillary research is the sole domain of Congress.

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[117] *Id*.
[118] *Mayo*, 566 U.S. at 71 (emphasis added).
[119] *Id*. at 86 (emphasis added).

Further, the Court makes the surprising admission that since it is not equipped to determine which applied laws of nature should be patent eligible, it will simply reject all of them:

> Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying "building-block" concern.[120]

The Executive Branch of the United States filed an *Amicus Curiae* in this case, urging that the Supreme Court more closely align its decision with the wording of the statute, which throws a wide net for patent eligibility and then a finer net using the requirements for patentability using § 102 for novelty and § 103 for obviousness.[121] The Court responded:

> The Government argues that virtually any step beyond a statement of a law of nature itself should transform an unpatentable law of nature into a potentially patentable application sufficient to satisfy § 101's demands. Brief for United States as *Amicus Curiae*. The Government does not necessarily believe that claims that (like the claims before us) extend just minimally beyond a law of nature should receive patents. But in its view, other statutory provisions—those that insist that a claimed process be novel, 35 U.S.C. § 102, that it not be "obvious in light of prior art," § 103, and that it be "full[y], clear[ly], concise[ly], and exact[ly]" described, § 112—can perform this screening function. In particular, it argues that these claims likely fail for lack of novelty under § 102.[122]

And, after admitting it cannot take its own judicially created exceptions too far or it will destroy patent law, the court defends the scope of its exceptions on the basis that if the court applies the words of § 101 literally, it will destroy its own parallel judicial exceptions to the code which would be inconsistent with the Court's case law.

> This approach, however, would make the "law of nature" exception to § 101 patentability a dead letter. The approach is therefore not consistent with prior law. The relevant cases rest their holdings upon section 101, not later sections. *Bilski,* 561 130 S. Ct. 3218, 177 L.Ed.2d 792; *Diehr, supra* ; *Flook, supra* ; *Benson,* 409 U.S. 63, 93 S. Ct. 253, 34 L.Ed.2d 273.[123,124]

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[120] *Id*. at 89.

[121] Mayo Collaborative Servs. v. Prometheus Labs., *Inc*., 2011 WL 4040414 (U.S.), 11 (2011).

[122] Mayo Collaborative Servs. v. Prometheus Labs, Inc., 566 U.S. 66, 89 (2012).

[123] *Id*.

[124] *Id*. at 89-90 (emphasis added). The Court also quoted to H.R. Rep. No.1923, 82d Cong., 2d Sess., 6 (1952) ("A person may have 'invented' a machine or a manufacture, which may include anything under the sun that is made by man, *but it is not necessarily patentable under section 101*

The Supreme Court ultimately refused to apply the literal terms of § 101 in light of its "better established" deviating common law analysis.[125] It stated that "These considerations lead us to decline the Government's invitation to substitute §§ 102, 103, and 112 inquiries for the "better established" inquiry under § 101."[126] The Court's "better established" inquiry is its own case law. Compliance with the Constitution and the associated federal statute, however, is not an invitation.

The unconstitutional application of § 101 by the Supreme Court reached it apex in the 2013 case of *AMP v. Myriad Genetics*,[127] where it eliminated any shadows of "consistency" with the statutory language and instead head-on disobeyed it.

In *Myriad*, the Supreme Court considered the patent eligibility of certain isolated gene sequences which encode the BRACA1 and BRACA2 genes, the presence of which are highly predictive of the potential to get breast cancer.[128] The Court held the claims patent ineligible under 35 U.S.C. § 101.[129]

Writing for a unanimous Court, Justice Thomas focused not on the statutory language of 101 or legislative intent, but again instead, the judicially created exceptions to the statute and the economic policy reason for them, neither of which are empowered to the Court by the Constitution.

> We have "long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo,* 566 U.S., at ——, 132 S.Ct., at 1293 (internal quotation marks and brackets omitted). Rather, " 'they are the basic tools of scientific and technological work' " that lie beyond the domain of patent protection. *Id.,* at ——, 132 S.Ct., at 1293. As the Court has explained, without this exception, there would be considerable danger that the grant of patents would "tie up" the use of such tools and thereby "inhibit future innovation premised upon them." *Id.,* at ——, 132 S.Ct., at 1301. This would be at odds with the very point of patents, which exist to promote creation. *Diamond v. Chakrabarty,* 447 U.S. 303, 309, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980) (Products of nature are not created, and " 'manifestations ... of nature [are] free to all men and reserved exclusively to none' ")…..As we have recognized before, patent protection strikes a delicate balance between creating "incentives that lead to creation, invention, and discovery" and "imped[ing] the flow of information that might permit, indeed spur, invention." *Id.,* at ——, 132 S.Ct., at 1305. We must apply this well-established standard to determine whether Myriad's patents claim any "new and useful ... composition of matter," § 101, or instead claim naturally occurring phenomena.[130]

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unless the conditions of the title are fulfilled"). However, this Congressional statement actually supports the United States Amicus brief that the other sections of 35 U.S.C. (102, 103, and 112) should be determinative as long as the patent claims refers to something made by man.

[125] *Id.* at 90.

[126] *Id.* at 91-92.

[127] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).

[128] *Ass'n for Molecular Pathology*, 569 U.S. at 576.

[129] *Id.* at 594.

[130] *Id.* at 589.

In a stroke of extraordinary judicial activism, the Supreme Court stated:

> groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry. See *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 68 S.Ct. 440, 92 L.Ed. 588.[131]

It is hard to imagine a more unconstitutional statement than the Supreme Court ruling that discoveries cannot be patented when the statute it is applying states that any invention or discovery can be patented. In other words, the Court says "A not B" while the statute says "A or B." And, while the *Myriad* statement that a discovery is not an invention is inconsistent with 101, it is all the more inconsistent with the definition of invention added in 1952 in section 100 that an invention is a discovery. The Supreme Court, citing to its own judicially created exceptions to the statute and its associated common law precedent back to *Funk*, now refuses to grant a patent on the commercial application of a manmade discovery, even if it meets all of the requirements of § 101. In addition, it requires all lower courts to obey the Supreme Court instead of Congress.[132]

IV. CONCLUSION

How should the Supreme Court handle patent eligibility issues? Literally apply the statute and legislative history! It works quite well. Review the proposed claimed patent subject matter on the basis of whether it describes anything made by man and whether it is an invention or applied discovery. If so, proceed to the analysis of whether it is new and useful, and described in a manner that allows one of ordinary skill in that field to carry it out. Do not stray into economic analysis or the virtues of, or exceptions to, statutory patent eligibility or how Congress decided to exercise its discretion to promote the progress of science through a limited term monopoly versus third party freedom to operate, or the size of the created monopoly—the Court was not given that authority nor is it equipped to address it. If the decision, faithfully applying the statute, causes damage to an industry or subgroup, it is up to Congress to decide whether to fix it.

In law school, we learn that there is no right without a remedy. In the case of *Marbury v. Madison*, the U.S. Supreme Court held that it can review the

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[131] *Id*. at 576.

[132] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013). It is interesting to note that the Supreme Court was way out of its technical depth in addressing the Myriad genetic technology and made statements that sound odd to those in the field of genetics. For example, the Court held that cDNA is patent eligible because it is not naturally occurring, but isolated mRNA is not patent eligible because it is naturally occurring. However, cDNA is the simple hybrid of mRNA and is generated by using mRNA as the template, similar to a mold. Viruses, in fact, make cDNA through the use of reverse transcriptase of mRNA. The Government's Amicus Brief, which disagreed with 15 years of the well-established issuance of patents on isolated gene products by the U.S. Patent Office – yes, pitting two federal agencies of the Executive Branch (Center for Disease Control and National Institutes of Health) against the federal agency authorized to grant patents, the U.S. Patent Office – on useful isolated genes for diagnostics and therapeutics proposed this non-scientific distinction to give the Court an illusion of splitting the baby.

constitutionality of federal statutes.[133] However, who oversees the constitutionality of U.S. Supreme Court decisions? There is no private right of action in the U.S. for this. The sole remedy is to urge Congress to pass a law reversing the Supreme Court position. However, why should Congress have to pass a new law when the current law is clear on its face, just to say, we meant what we said the first time?

And when we say that there is no right without a remedy, does the term remedy mean any remedy or an effective, timely remedy? It took Congress 5-10 years to pass the America Invents Act. Does this mean the United States might have to wait another 5-10 years to force the Supreme Court to limit its patent opinions to strict statutory construction and legislative intent? And what if the law takes longer due to the preoccupation of Congress with other issues of national urgency? How many industries will be destroyed and applied discoveries not advanced for the promotion of science in the meantime? This takes us to a dark conclusion that there may be no short-term action available to force the Supreme Court to faithfully obey the Constitution.

The IPO,[134] AIPLA,[135] and ABA[136] have all proposed changes to the § 101 statute to address the issues described in this article. The IPO and AIPLA approaches are similar, which is not surprising given that many of the same people belong to both organizations. The ABA position is substantially different. The authors are strongly against the ABA position, which would codify, and thus retroactively justify, the Supreme Court's judicially created exceptions to § 101. Not only are these exceptions not necessary, but it would give the Court the impression that it can ignore the wording of a statute, create parallel and contradicting common law which is then retroactively accepted. How far would this go and into which unrelated areas?

We end where we start, with the quote from James Madison "In framing a government which is to be administered by men over men you must first enable the government to control the governed, and in the next place oblige it to control itself."[137]

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[133] Marbury v. Madison, 5 U.S. 137 (1803).

[134] *Proposed Amendments to Patent Eligible Subject Matter Under 35 U.S.C. § 101*, IPO (Feb. 7, 2017), https://www.ipo.org//wp-content/uploads/2017/02/20170207_IPO-101-TF-Proposed-Amendments-and-Report.pdf. The proposed 101 section by IPO adds a sole exception to patent eligibility. That "a claimed invention is ineligible . . . only if the claimed invention as a whole . . . exists in nature independently of and prior to any human activity."

[135] *AIPLA Legislative Proposal and Report on Patent Eligible Subject Matter*, AIPLA (May 12, 2017), https://www.aipla.org/detail/news/2018/08/27/AIPLA-Announces-Legislative-Proposal-on-Patent-Eligibility. The proposed 101 section by AIPLA also adds the sole exception to patent eligibility.

[136] *Re: Request for Comments Related to Patent Subject Matter Eligibility*, ABA (Mar. 28, 2017), https://www.americanbar.org/content/dam/aba/administrative/intellectual_property_law/advocacy/advocacy-20170328-comments.authcheckdam.pdf. The proposed 101 section by the ABA provides that subject matter is not patent eligible if the "scope of the exclusive rights under such a claim would preempt the use by others of all practical applications of a law of nature, natural phenomenon, or abstract idea."

[137] THE FEDERALIST NO. 51, at 322 (James Madison) (Clinton Rossiter ed., 1999).

ATTACHMENT 3

TO WRITTEN TESTIMONY OF

SHERRY M. KNOWLES

PRINCIPAL, KNOWLES INTELLECTUAL PROPERTY STRATEGIES, LLC

BEFORE THE

UNITED STATES SENATE

COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON INTELLECTUAL PROPERTY

ON

"THE STATE OF PATENT ELIGIBILITY IN AMERICA, PART I"

JUNE 4, 2019

2:30 PM

The Vague Concept of "Invention" as Replaced by Sec. 103 of the 1952 Patent Act

By Giles S. Rich *

I believe in incentive systems. Over 20 years ago a prize competition lured me into some intense study and writing [1] which, through a traceable chain of events, has led to my being here tonight.

I did not win the prize. Neither did the other contestants, save one.[2] But they all contributed something. That is the way incentive systems work. They bring out all kinds of efforts, excellent, good, mediocre, indifferent, and bad. But the *system* brings forth the effort. Society benefits from the good and mediocre, as well as the excellent, efforts. The bad efforts don't hurt it any. They may even prevent others from making mistakes if they are made known.

The patent and copyright laws create such incentive systems. The copyright laws provide an incentive which brings out the greatest works of literature and art as well as a lot of trash. The patent system works in a similar way. But you can't get cream without producing milk and, anyway, it is the milk that society lives on.

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* Associate Judge, United States Court of Customs and Patent Appeals.

This article is the speech delivered by the author on June 18, 1964 in accepting the Kettering Award for 1963 from The Patent, Trademark, and Copyright Research Institute of The George Washington University. It was previously published in the Institute's publication "IDEA" Conference Number 1964, page 136.

In the present version the author has made a few minor corrections and revisions.

[1] The Linthicum Foundation Competition, 1941, Dean John H. Wigmore, Northwestern University Law School, Chairman. The writer's contribution was published in five installments in the Journal of the Patent Office Society, Vol. 24, pp. 85, 159, 241, 328, and 422, commencing Feb. 1942.

[2] The winner was Laurence I. Wood whose paper was published in book form, 1942, by Commerce Clearing House, Inc., under the title *Patents and Antitrust Law*. He is presently a vice president and general counsel of General Electric Company.

I don't suppose you will be surprised if I talk about the patent system. The aspect of it I will talk about is the one I think causes the most trouble, the clarification of which I therefore believe would do the most good.

As groundwork I will first state an axiomatic but too-little-thought-of principle. A monopoly merely gives rise to *power* which can be put to either good or bad uses. Hence, in the case of monopolies created by government grant, which is all patents are so far as the rights they create are concerned,[3] we have to distinguish between good and bad monopolies.

I will take two well-known examples from history. First, the bad monopoly. Queen Elizabeth granted to one Darcy, a member of her court, a monopoly of playing-cards for 21 years so that he could make some money. But playing-cards were old and well-known and others were making a living from making and selling them in England. This monopoly, which was by Royal Letters Patent, therefore took from the public a freedom in business which it had long enjoyed before the patent; and it was bad.[4]

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[3] Dean Wigmore, n. l, in his foreword to the Wood book, n. e, said:

> * * * I take the opportunity to intrude my personal opinion, that neither Courts nor treatise-writers have been radical enough in defending the legitimacy of the "monopoly" in a patent, as distinguished from the ordinary trade-monopoly. Is it not a fact that every property-right we have is a "monopoly"? The right to our house or our automobile is simply a right to keep anyone else from entering or using it without our consent; and is that not a monopoly?
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> * * * *
>
> Of course patent-rights can be so *used* as to merit the distrust attaching to a monopoly, - by contracts fixing prices, by tying agreements, by pools and the like. But so can gold-mines and all the necessities of life by bargains be used monopolistically; yet no one blames the mine-owning right itself or the food-ownership right itself; the blame is directed to the use of it.
>
> And so I for one regard it as unfortunate that courts and treatise-writers have not stood up more boldly for the fundamental rightness of the patent right itself. I say "for one", because I do not recall reading anywhere an adequate defence of the theory of the patent-right.

[4] *Darcy* v. *Allin*, 11 Co. Rep. 846; 1 W. P. C. 1. See *Monopolies and Patents* by Harold G. Fox, U. of Toronto Press, 1947, p. 318. The case also has the popular title "The Case of Monopolies."

In Venice in 1594 the Doge, on behalf of the government, granted to the great Galileo a "privilege," which was the Venetian name for a patent, on a machine which he had *invented* "for raising water and irrigating land with small expense and great convenience," on the condition that it had never before been thought of or made by others. Galileo made a couple of significant remarks in his petition for the privilege. He said, "it not being fit that this invention, which is my own, discovered by me with great labor and expense, be made the common property of everyone;" and also, that if he were granted the privilege, "I shall the more attentively apply myself to new inventions for universal benefit." In short, he was not inclined to divulge his invention only to have it copied; but if the government would give him some reasonable protection he would not only divulge it and build it but might even apply himself to making some more inventions. Deeming this to be a *good* use to which to put a limited monopoly, the Council voted to grant him a "privilege" or patent of monopoly for 21 years.[5]

The Venetians were accustomed to doing this, having granted about 1600 "privileges" in the 15th and 16th centuries.[6]

In the 17th century the English, in 1624, enacted a statute [7] abolishing and prohibiting future monopolies of the bad Darcy sort and authorizing the continuing grant of Letters Patent for new inventions within the realm, a practice which has continued to this day.

The founding fathers came to America from the mother country, bringing with them knowledge of this practice of granting monopolies. In the nearly 150 years of the colonial period preceding the Federal Constitution, the colonies and then the States granted numerous patents for new inventions as well as monopolies to

[5] Journal of the Patent Office Society, Centennial Number, "History of the Patent Office," July 1936, Vol. 18, p. 23.

[6] Id. Most of the privileges were for copyrights but a small percentage were for inventions.

[7] The Statute of Monopolies, May 25, 1624, 21 Jac. I, c. 3. For its history see Fox, supra, n. 4, Chap. IX, pp. 113-126.

encourage the founding of new industries, including, as the English did, encouragement of setting up in America industries already practiced abroad.[8]

It is not surprising that, when it came to the writing of a Constitution, provision should be incorporated, with no controversy at all, for Congress to make laws for the granting of patents to inventors, or that George Washington should urge its speedy enactment, or that the very first Congress should enact our first Patent Act of 1790.[9]

Then began our patent system. One might describe it as a great experiment which goes on continuously, getting more complex all the time, in which this Institute is playing, for the first time, a vital role in finding out how the system as a whole actually works, as an aid to preserving its basic principles and saving the obvious good that is in it.

In this experiment, which involves a mixture of economics, law, technology, and psychology, we still have the centuries-old problem of monopoly power being utilized for socially good and socially bad ends and of deciding which is which.

The greedy nature of some men is such that there are always pressures toward the creation of bad monopolies. Undue preoccupation with countering this pressure, however, has quite blurred the vision of many well-intentioned but not too well-informed people to the good uses monopoly can be put to and to the good that monopoly power can do, properly channeled and not so proscribed as to lose its effective power.

Paradoxically, in the working of the patent system, monopoly often promotes competition. Numerous instances are all around us, wherever two products serving the same general purpose have achieved, with the aid of patent protection, commercial production. And only after such production is there any possibility of market competition.

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[8] See JPOS, supra, n. 5, pp. 35-58.
[9] Id. pp. 55-62.

To this point I have taken note that the *primary* distinction between good and bad patent monopolies is that the good patent does not monopolize something the public *already has,* so as to take something away from the public. The invention covered by the good patent must be *new;* and so our statutes have always provided, though the provision was not always enforced.[10]

But beyond bare novelty one must go one further and troublesome step to have a sound system and keep the monopoly on the good side.

As we refrain from granting patents on inventions that are not new, we must also refrain from granting patents on those inventions which would arise *spontaneously,* given the need or the desire for them, as the yelp of the dog surely follows from stepping on his tail, or with *only a nominal expenditure of time, effort, money or wit*—especially if the invention is one of real utility likely to meet with substantial or popular demand.

It was not long after the Patent Act of 1836—in 1850 in fact—that the United States Supreme Court made this clear in the "doorknob case," *Hotchkiss* v. *Greenwood.*[11] What was involved was the trial judge's charge to a jury that if *no more ingenuity or skill was required* to construct the patented doorknob *than was possessed by an ordinary mechanic acquainted with the business,* then the patent was invalid.

The Supreme Court approved the charge. The opinion said: "In other words, the improvement is *the work of the skilled mechanic, not that of the inventor.*" (My emphasis.) The decision made clear that patents are not to be granted on inventions which are no more than what the ordinary mechanic acquainted with the business would produce as a matter of course in the pursuit of his calling. Such mechanics are *expected* to produce *new* things, such as were involved in that case, which was

[10] Id. pp. 77-82, 230. Under the 1793 Act, for example, there was no examination for novelty over a period of 43 years. About 10,000 patents issued under that act for terms of 14 years, less than the number issued today in 3 months.

[11] 52 U. S. 248.

the attaching of an old clay doorknob to an old metal shank in precisely the same manner that metal doorknobs had been attached to such shanks before. Technically the assembly was *new*, but the court found novelty was not enough.

In referring to "mechanics" in this matter we can take them to be representative of a class—all those with *ordinary* skill in the various callings, ordinary shoemakers, ordinary chemists, electronic technicians of ordinary skill, etc.

Due to the reasoning of the case, that the new doorknob "was the work of the skillful mechanic, not that of the inventor," what came out of it after 1850, and is still with us, was an injection into the law of what has ever since been called the "requirement for invention."

As is usual with a "doctrine" derived from a court opinion, the doctrine persists while the facts out of which it arose are forgotten. The opinion in the first case is quoted to the judge in a second and he does an opinion embroidering on it, his words being quoted in turn and reembroidered and so on.

I think the resulting situation with respect to the law on the "requirement for invention" was well summed up by Judge Learned Hand, who knew as much patent law as any judge ever has, at a Senate hearing in which your then Dean Colclough and I both participated in 1955, as follows:

> You could find nearly anything you liked if you went to the opinions. It was a subject on which judges loved to be rhetorical. * * * patent lawyers * * * like to quote all those things. There are lots of them.[12]

This proliferation of views on what did and did not amount to "invention" went on for 100 years. We were enlightened with the view that "invention" resulted from the exercise of the "inventive faculties" and other circular reasoning. Our standard text, Walker on Patents in its seventh or first Deller edition, said "An

[12] Hearings pursuant to S. Res. 92, 84th Cong., 1st Sess., on the American Patent System, Oct. 10-12, 1955, p. 113.

invention is the result of an inventive act."[13] Whole books on the patent law were written around such concepts. People collected the statements pro and con in volumes equally divided about in the middle—"invention" on one side, lack of it on the other.[13a] Negative and positive tests for detecting its presence evolved. So did exceptions to each test. And patent lawyers selectively quoted all of this mass of material as though it proved something. Judges like Learned Hand found, in his words, that "They never seemed to tend toward enlightenment."[14]

This requirement finally evolved into a "*standard* of invention" which the courts pretended was being raised and lowered like an elevator as though it were something tangible. They also proclaimed in all seriousness—and are doing so this very moment—that this "standard" was to be found in the Constitution, where there are only two words on which it could possibly be predicated, the word "inventors" and the word "discoveries."[14a] You really have to be on the Supreme Court to find a "standard" there because the only way it can work is this: if you think the lower court was wrong in sustaining the patent, you proclaim that it applied too low a standard and reverse its decision,[15] saying, "*That* was not an '*invention.*' "

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[13] Walker on Patents, First Deller Ed., Vol. 1, p. 110. The second Deller Ed. says the same thing in Vol. 2, § 103, as would be expected of any text undertaking to reflect what the courts have said.

[13a] For example, "Invention and the Law," by H. A. Toulmin Jr., Prentice-Hall, Inc. 1936; Deller's Walker on Patents, 2d ed., § 126 "Cases involving Patentable Invention" and § 127 "Cases Not involving Patentable Invention," pp. 328-402 consisting of citations only.

[14] Hearings, n. 12 supra, p. 113.

[14a] I am not unaware of the statement of the *objective* in Art. 1, sec. 8, clause 8, "To promote the progress of * * * useful arts." See my "Principles of Patentability," 28 Geo. Wash. L. Rev. 393, 42 JPOS 75. When Congress exercised its power under that clause and set up a patent system, so long as the *system as a whole* functions to further the Constitutional objective, it would not seem that the statement of the objective could set any "standard" for the patentability of any single invention.

[15] See *Great Atlantic & Pacific Tea Co.* v. *Supermarket Equipment Corp.*, 340 U. S. 147, 87 USPQ 303 (1950), where the two concurring opinions below were held to have applied a "standard of invention * * * that is less exacting than that required * * *."

Some judges got it fixed in their minds that if a thing is an "invention" then it is patentable and if it is not patentable then it is not an "invention," not realizing that the same things are invented over and over—by the use of the inventive faculties or by inventive acts or what have you—and although clearly "inventions," their originators being as firmly convinced of it as was Galileo, they are not patentable for want of novelty. So it is customary for judges to approach all inventions gingerly in their opinions by referring to them as "alleged" or "supposed" inventions.

All an invention is, however, is something which has been found out, or devised, or discovered. The question today is not what to call it but whether, under the statute, it is patentable. Hundreds of "real" or "true" inventions, all resulting from "inventive acts" and the exercise of the "inventive faculties," are held unpatentable every day for lack of novelty.

The Patent Office, of course, proceeded on the same basis, and still does so to a dwindling extent, rejecting applications for want of "invention" and granting them when it could be persuaded that "invention" was present. And through it all the patent lawyers and the judges persisted in telling all concerned that "invention" was something which could not be defined, like God! Patent validity came as a matter of grace, from on high. This was a messy state of affairs. The surprising thing is it worked so well. But not well enough.

In 1941 a Commission, appointed by President Roosevelt, and headed by Charles F. Kettering,[16] came out with a report which said:

> One of the greatest technical weaknesses of the patent system is the lack of a definitive yardstick as to *what is invention.* To provide such a yardstick and to assure that the various courts of law and the Patent Office *shall use the same standards,* several changes are suggested. It is proposed that Congress shall

[16] For a note on who Kettering was and his prolific accomplishments in the fields of business, research and inventing, see "The Kettering Archives" by Eugene B. Jackson, 44 Jour. Pat. Office Soc. 331, May 1964.

declare a national standard whereby [mark these words] *patentability* of *an* invention shall be determined by the objective test as to its advancement of the arts and sciences. [My emphasis.][17]

One apparent thought there was to stop talking about whether a thing is or is not an "invention," to take anything presented as *an* invention, and then to determine its *patentability* according to a standard which Congress was to declare, Congress never having said anything about it up to that time.

For some years nothing came of the Kettering Commission proposal but in the 79th, 80th, and 81st Congresses, from 1945 through 1949, identical bills were pending entitled, unfortunately but almost inevitably, "A bill to declare a national policy for determining invention." Now I have just said that the problem was not really to determine "invention," but to determine the *patentability of* inventions and this matter of language is one of major concern. Kettering got a hold on the distinction, but it keeps fading away like Alice's cat.

People don't think so much as they talk; and when they do think, they tend to think in words, at least about legal abstractions. Words are used to describe things, concepts, and experiences we have in common so that we can communicate. This thing, this concept, this experience every patent examiner, lawyer, and judge had come up against in practice was called the "requirement of invention," or just "invention"—the undefinable something or other that has to be there. This proves to be a cliché, meaningless though it is, that is hard to break away from. I taught for many years, and presumably my students learned, that the prerequisites to patentability were novelty, utility, and invention, and, of course the absence of a one-year statutory bar. There was nothing else *to* teach. Thinking and its concomitant words had not progressed beyond that point in the '30s and '40s. But today they have. Any current textbook and most cases, you will find, use the old terminology. But it isn't true any more and hasn't been for eleven and a half years—in my opinion, that is.

[17] Report of National Patent Planning Comm., June 18, 1943, H. Doc. 239, 78th Cong., pp. 6, 10.

My not believing in ghosts or angels doesn't mean, *in law,* that there are no ghosts or angels, because if you think there are, and are frightened or informed by them, then they exist. As long as judges say there is a requirement for "invention," and many still do, then there is one. If you take a patent into court and the judge invalidates it for want of "invention" you *know* there is one. But why am I saying there is none? Am I talking theory or law; if law, then what kind of law? Or am I talking nonsense?

The outcome of those bills to determine invention, and one or two other bills, was that Congress got interested in revising and codifying the patent law and did so.[17a] In the new law (Title 35 U. S. C.) is a section, 103, described at the time by those who wrote it, at least in one place, as "incorporating a requirement for invention."[18] It was also described more carefully and accurately elsewhere[19] as providing a "*condition* which exists in our law and has existed for more than 100 years . . . by reason of decisions of the courts." (My emphasis.) And that "condition" is described in the title of this new section 103 as one for the existence of "non-obvious subject matter." The addition of section 103 was stated in the House Report on the bill[20] to be *one of the two major changes or innovations in the statute.*

What section 103 itself says is that what is patented must *not* have been *obvious* to one of *ordinary* skill *in the art involved,* at the *time* the invention was made. The parallel with what would be expected of the "ordinary mechanic acquainted with the business" in the "doorknob case" should be clear.

This is not a "standard of invention" and it is not called a "requirement of invention." The presence or

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[17a] See Giles S. Rich, "Congressional Intent — Or, Who Wrote the Patent Act of 1952?", in *Patent Procurement and Exploitation,* BNA 1963, pp. 61-78.

[18] House Report No. 1923, 82nd Cong., 2nd Sess., to accompany H. R. 7794, p. 5.

[19] Id. p. 7.

[20] Id. p. 5.

absence of "invention" is not mentioned. The use of the term "invention" was, in fact, carefully avoided with a view to making a fresh start, free of all the divergent court opinions and rhetorical pronouncements about "invention."[21] And in doing that it was contemplated, as the House Report states,[22] that "This section should have a stabilizing effect and minimize great departures which have appeared in some cases."

As has been pointed out by P. J. Federico, one of the drafters of that section, in his Commentary,[23] what section 103 was gunning for was

> * * * some modification * * * in the direction of moderating the extreme degrees of strictness exhibited in a number of judicial opinions over the past dozen or so years; that is, that some change of attitude more favorable to patents is hoped for. This is indicated by the language used in section 103 as well as by the general tenor of remarks of the Committees in the reports and particular comments.

The real vice or inadequacy of the judge-made requirement for "invention" was in the truism Mr. Federico also restated, "the so-called standard of invention * * * is an unmeasurable quantity having different meanings for different persons." It left every judge practically scott-free to decide this often controlling factor according to his personal philosophy of what inventions *should* be patented, whether or not he had any competence to do so or any knowledge of the patent system as an operative socioeconomic force. This was too great a freedom because it involves national policy which should be declared by Congress, not by individual judges or even groups of judges on multiple-judge courts. In section 103 Congress made such a policy declaration. It did not there declare what should constitute "invention." It was a statement of something *to take the place of* this vague concept. And it was made in the face of judicial declara-

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[21] The writer speaks from personal knowledge as one of the drafters.
[22] Note 18, at p. 7.
[23] "Commentary on the New Patent Act," by P. J. Federico, 1954, published in Vol. 1 of 35 U.S.C.A.

tions, promulgated in the *absence* of a statute, which Congress expressly desired to modify.

I would like to inject a new term into the language so we can discuss the matter rationally. I would like to call it the THIRD REQUIREMENT of patentability. The statute sets out all the requirements in as clear a form as is possible in a general statute—albeit that is a skeletonized form to which the courts must add the substance. Section 101 says inventions must be *new* and *useful,* requirement one and two; section 102 defines novelty; and section 103 lays down the *third requirement.* I repeat its clear-cut title:

"Conditions for patentability; non-obvious subject matter."

Upon examination in the Patent Office or upon adjudication in court, under the statute, when novelty, utility, and unobviousness as defined in section 103 are found to exist, and provided there is no one-year statutory bar, then there is *paientability* and *that is the end of the matter.* An examination for the presence or absence of "invention," or adherence to precedents on that muddy issue, is not called for and is not proper. It is a work of supererogation. It illustrates, furthermore, a failure to grasp the meaning of the statutory provisions. There is no such prerequisite in the statutory law.

When, as is the case with the "requirement for invention," the century's accumulation of judicial precedents range from A to Z and Congress, looking at the situation under the guiding light of Kettering's statement that *this is no yardstick and the greatest technical weakness of the patent system,* determines to make a yardstick and says the measure shall be "M", right in the middle of the alphabet, it behooves everyone concerned with administering that law to follow the measure "M" and to stop flitting about arbitrarily from A to Z lighting upon that letter which seems most appealing.

But what do we have today? A host of lawyers, examiners and judges all doing their level best to follow

the law as Congress wrote it? Anything but that! What we have today is a mish-mash, and that is a nice old English term—older than the 1624 Statute of Monopolies. Why do we have a mish-mash?

First, a century of thinking and writing about a phenomenon in one set of nomenclature is a hard thing to overcome. Also a lot of people go on administering the patent laws and practicing under them without bothering to read the revision of them, so they are not aware that there has been a change.

Second, by hindsight it is apparent that those most intimately concerned with the writing and expounding of the new patent act in 1952, themselves brought up in the "requirement for invention" tradition (and I speak as one of them), did a very poor job of informing the public what it was they had done. One reason for that was that, on the average, their own comprehension of what they had done was not too clear. Remember, they were all of the school that "invention" *could not* be defined and there they were, trying to put a provision on that very subject into the statute. In going as far as seemed to be possible in that direction, they knew they were not making a *definition* but rather a *statement of policy, a specific required approach* to a difficult problem, which approach they thought would stop some of the nonsense derogatory of the patent system that had been going on. In pursuit of that objective, the drafters and Congress did at least one thing, by way of a statement of policy to counteract a judicial trend, which has had a clear-cut effect. Following a phrase casually dropped by the Supreme Court in *Cuno* v. *Automatic*,[24] in 1941, that "the new device, however useful it may be, must reveal the flash of creative genius," some courts took off on a quest for such a flash and, not finding it, invalidated patents. The last sentence of section 103 stopped this abruptly with the legislative command: "Patentability shall not be negatived by the manner in which the inven-

[24] *The Cuno Engineering Corp.* v. *The Automatic Devices Corp.*, 314 U. S. 84, 51 USPQ 272 (1941).

tion was made." But the judicial reaction to the first sentence,[25] in contrast, got to be all fouled up.

Third, the members of the bar have a lot to answer for in creating and perpetuating the mish-mash because it is they who, desiring to make use of some of the extreme cases antedating the patent act to invalidate patents in litigation, played down section 103 and early in its life persuaded a number of courts that it made no change whatever but was "mere codification."[25a] They are now paying more attention to section 103 as they learn that it can help them when they are on the other side, but they are learning slowly and my generation of lawyers, at least, is still talking, out of habit, in terms of "invention." Just listen to them!

Find me a trial lawyer for an infringer who will not urge on the court, as the existing test for "invention," the views expressed by the Justices of the Supreme Court in *A & P* v. *Supermarket,* in 1950,[26] two years before the effective date of section 103, and I will joyfully transfer my Kettering Award to him. He would deserve it more than I do. I have no clients. Herein lies a grave defect in the development of sound law through adversary proceedings.

Fourth, in the legislature the mish-mash has been described in detail, up to 1957 (the first 5 years of the act), in Senate Committee Study No. 7. What is its

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[25] § 103. *Conditions for patentability; non-obvious subject matter*

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[25a] A little reflection should show that when judicial precedents constituting the "law" range from the very liberal to the most strict, it is a patent absurdity to speak of a statute taking a middle ground as a "codification" of existing law. See note 17a, supra.

[26] Supra, n. 15, 340 U. S. 147. This was a case preeminently in the minds of the drafters of the 1952 Patent Act, having been decided during the writing of the first drafts. See note 17a.

title? "Efforts to Establish a Statutory Standard of Invention."[27] The Senate Patent Subcommittee is still striving to bring about a higher degree of uniformity in the courts, in the various groups of the Patent Office, and between the two organizations, but in what terms does it do its own thinking? The subcommittee's annual Report (No. 107), April 3, 1963, is concerned about the "Patent Office 'standard of invention '" and refers to the development by that office of a "policy statement pertaining to standards of invention." The report for the next year (No. 1018), May 1, 1964, again refers to the need to eliminate differences within the Patent Office and between it and the courts "concerning the standard of invention." Meanwhile, apparently without the committee's knowledge, the Patent Office Academy has been teaching that there is no "standard of invention," that "invention" is meaningless, and that the prerequisite is as stated in section 103. Might it not do some good and help to achieve the uniformity the subcommittee so much desires if its own members, and staff, could convince themselves, in spite of what uninformed or misinformed judges have said, that the 1952 Patent Act was intended by their fellow legislators to *replace* the "standard of invention," which never was a standard, with a requirement of unobviousness to a particular kind of person at a particular time?

Amid the confusion, there are some encouraging signs in the courts. During the first few years after the 1952 act, many courts took the position that Congress really had done *nothing* in enacting section 103 and went about their old business of looking for "invention." Then in 1955 came Judge Learned Hand's *Lyon* v. *Bausch & Lomb*[28] opinion and in 1960 his *Reiner* v. *I. Leon*[29] opinion, both of which realistically appraised and appreciated

[27] Study of the Subcommittee on Patents, Trademarks and Copyrights of the Committee on the Judiciary, U. S. Senate, 85th Cong., 1st Sess., pursuant to S. Res. 95, Study No. 7 (1958).

[28] *Lyon* v. *Bausch & Lomb Optical Co.*, 224 F. 2d 530, 106 USPQ 1 (2d Cir. 1955).

[29] *Reiner et al.* v. *I. Leon Co.*, 285 F. 2d 501, 128 USPQ 25 (2d Cir. 1960).

what section 103 had done, namely, to restore the law to what it had been 20 or 30 years earlier and, as he said, "to change the slow but steady drift of judicial decision that had been hostile to patents * * *." In the former opinion he remarked that " 'invention' became perhaps the most baffling concept in the whole catalogue of judicial efforts to provide postulates for indefinitely varying occasions." In the latter he said "It is not for us [the judiciary] to decide what 'discoveries' shall 'promote the progress of science and the useful arts' sufficiently to grant any 'exclusive right' of [to?] inventors. Nor may we approach the interpretation of § 103 * * * with a predetermined bias." While saying "The test laid down [103] is indeed misty enough," he was able, with the evidence provided, to follow it. Certiorari was denied in both of these cases. In both cases the patents were sustained. The Supreme Court could easily have upset him had it wanted to. In fact, Judge Hand remarked to me and others at that Senate hearing in 1955[30] "Oh, they must take it," referring to *Bausch & Lomb*. Later during the hearing he testified,[31] "whether we were right in construing it [§ 103] as meaning that the old rules were to apply, remains to be seen. I hope the case will go up." From the viewpoint of the writers of the law, his *Bausch & Lomb* opinion was the first to comprehend their true intent. It has been allowed to stand.

Last April (1964) the Fourth Circuit Court of Appeals, which in 1954 said 103 merely codified the law, came to the conclusion in *Marvel* v. *Bell*,[32] after reading a number of cases which "have undertaken to comprehensively set forth the standard of invention to be used as a test," that

> When the mass of verbiage has been distilled, however, we have little more to guide us than the test which is incorporated in section 103 * * *.

and went in search of the "objective criteria of [un]obviousness." Perhaps, next time, that court will take

[30] Supra, n. 12.
[31] Id. p. 120.
[32] 330 F. 2d 164, 141 USPQ 269.

the final step and *start* with the statute, ignoring the "mass of verbiage" it replaces. It seems a logical place to start, especially since it was intended to displace some of those cases in which the verbiage appears.

Last May (1964) the Sixth Circuit Court of Appeals, in *Monroe Auto Equipment Co.* v. *Heckethorn Mfg. Co.*,[33] said, "It is virtually a practical impossibility to define adequately that abstraction which we call invention,"[34] and then, in spite of that difficulty, said "we must have objective references and a place from which to start. For this we turn to the statute * * * § 103." A very good place to start! But then the court came to a very unnecessary conclusion "that invention is synonymous with unobviousness. Thus to say that a device lacks invention and that it is obvious is to state the same legal proposition in two ways."[35] It concluded that while obviousness "does not begin to solve the problem," it

[33] 332 F. 2d 406, USPQ 553.

[34] The full quotation is (141 USPQ at 553):

> It is virtually a practical impossibility to define adequately that abstraction which we call invention. Long ago the Supreme Court said: "The truth is the word cannot be defined in such a manner as to afford any substantial aid in determining whether a particular device involves an exercise of the inventive faculty or not. In a given case we may be able to say that there is invention of a very high order. In another we can see that there is lacking that impalpable something which distinguishes invention from simple mechanical skill." McClain v. Ortmayer, 141 U. S. 419, 427 [Nov. 2, 1891]. This court consistently has echoed this view. [Cases cited.]

[35] A case was cited for this proposition, *In re Jacoby, Jr.*, 309 F. 2d 513, 135 USPQ 317, 50 CCPA 734, in which the opinion was written by the present author. The Patent Office Board of Appeals had said the claimed invention "must be unobvious and involve invention." In a footnote to a reluctant but needed quotation of that statement the writer said:

> To add to the statement that it must be unobvious, as required by 35 U. S. C., 103, the further statement that it must "involve invention" is merely to state the same legal proposition in two different ways. It would seem to suffice to state it once, and that, preferably, in the words of the statute.

It should be clear that this was intended to put the proposition, developed more forcefully in the present paper, as gently as possible and that it was *not* intended to suggest that "invention" and "unobviousness" as provided in section 103 are alternative *equivalents* for determining patentability, which they are not.

"gives us a touchstone for the contextual meaning of invention." It also concluded that in a patent case decision is arrived at by three steps: a determination of what the prior art was, what the patentee has made, and whether it would have been obvious, viewing the prior art from the time just prior to when the patented device was made. That is just what section 103 says! It is beginning to take hold and the next step will be to realize, what should be so clear, that when the unobviousness question has been determined, there is nothing more to do and the question of "invention" can be forgotten.[36]

I cite these as straws in the wind. A study in the Columbia Law Review in 1963[37] concludes that "nothing

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[36] Along with it can be forgotten the "complexities" of another issue wrestled with by the court in deciding whether "unobviousness" is a question of law or fact. Compare *Armour & Co.* v. *Wilson & Co.*, 274 F. 2d 143, 124 USPQ 115 (7th Cir. 1960). The presence or absence of "invention" before 1953 was always, in my judgment, the determination of an issue of public policy — what inventions *should* be patented. As such it is a "question of law." This policy has now been legislatively expressed in section 103. In that section (note 25, supra) the following potential issues of fact appear: (1) What are the *differences* between "the invention" and "the prior art"? (2) What is disclosed by the prior art presumed to have been available to the inventor? (3) What was the level of ordinary skill in the art at the time the invention was made? (4) Other fact issues relating to *circumstances* indicative of the presence or absence of obviousness, traditionally taken into account in determining "invention," such as long-felt need, immediate copying, sudden displacement of existing practices or devices, difficulty of achievement, failure of others, etc. Once these *facts* have been assembled, there remains the ultimate statutory requirement of unobviousness, the third requirement for patentability, which becomes a matter of statutory *application* and as such must be a question of law. As the court concluded in the *Armour & Co.* case, supra, "The development of the factual content necessary to statutory construction is a question of fact." It may be *several* such questions, however. As the court did *not* conclude in *Armour & Co.*, after the fact issues are settled, the determination of unobviousness is necessarily a legal conclusion arising out of the facts, pursuant to the statute — a question of law.

The *Armour* case concluded (1960), in the separate opinion devoted to the fact or law question, that after the facts were settled, "We examine the *standard of invention* applied to these facts as a question of law." (My emphasis.) But under section 103 there is no "standard of invention." The directive of the statute is to determine whether the invention "would have been obvious" on the basis of the *differences*, the *ordinary* skill, and as of the *time* of invention. *These* are the factors, and these alone, by which courts are to determine the existence of the third requirement. Leastwise, that is what the statute provides.

[37] "The Standard of Patentability — Judicial Interpretation of Section 103 of the Patent Act," 63 Col. L. Rev. 306-325 (Feb. 1963).

indicates that the courts are moving toward a common interpretation of the statute." I am not so sure. I say give them time. They are stirring like live cocoons. We have only had this statute for a dozen years and the judges who have been there that long, as many of them have, are still indoctrinated with the old "standard of invention" terminology they learned from the old patent lawyers and the old textbooks. There will be new editions of all three in due course.

I might mention the Court of Customs and Patent Appeals which has been turning out a consistent stream of opinions, for at least the eight consecutive years of which I have personal knowledge, strictly applying the obviousness formula of section 103 to determine *patentability,* not the presence of invention, and slowly but surely warping the Patent Office into basing its actions on the statute. The results are beginning to show in the actions and board opinions we review. I believe our view has invaded the Patent Office Academy. The Patent Office Solicitor's office writes its briefs in the language of the statute.

Assistant Secretary of Commerce Hollomon made a speech in New York in March, 1964, in which he is reported to have said that he "believes that the courts and the Patent Office should both follow the same standard *of patentability.*" This would be nice but is obviously impossible until one or the other of them decides to standardize. A good place to begin would be the Patent Office, a lot easier than in the courts. Dr. Hollomon further said "that a standard of *patentability* should be more definitely set forth." He is to be complimented on his terminology, in not talking about a "standard of invention," but I think we should experiment with *using* the section 103 standard before we try to create another one. I find it very workable. It was a harder job to get it than he may imagine and in twelve years no better one has been proposed. The "criteria which may be worked out," referred to in the Revision Note to

section 103, have never materialized. I doubt they ever will.

I have had two practical suggestions in the back of my mind for some time. One is to have a sort of wall-paper border printed up to run around all the patent examiner's rooms on which the words NEW - USEFUL - UNOBVIOUS - PATENTABLE IF NO BAR are repeated endlessly. This could be designed into the proposed new Patent Office building. Most inscriptions on the present Patent Office are not very useful. They might also inscribe the Constitutional clause so people could see that it contains no *standard* for determining patentability.

The other suggestion—and this one is more serious—is based on the discovery that lecture courses are given for new and other Federal judges from time to time on how to be a judge, printed in books and given to the judges, compliments of the West Publishing Company. This Institute or some other disinterested party or organization should prepare a lecture on the basic elements of patent law in up-to-date terminology as used in Title 35 U. S. C. and see to it that the Federal judges get it. Even a glossary would help, in which it would appear that the "requirement for invention" became obsolete in 1953 by an act of Congress, along with many prior court opinions discussing it, being replaced by unobviousness as defined in 103 as the THIRD REQUIREMENT for patentability. By limiting the lecture to the terms of the statute and their clear meanings I do not see how the bar could object and many judges would be grateful.

I was recently discussing this subject with a young patent lawyer, urging that we should all stop talking about the "standard of invention." She said, "What difference does it make?" That is a fair question which has to be answered, and with my present answers I will end:

The differences it will make—the reasons why we *must* learn to make this change—are these, among others:

- Until we stop talking about a "requirement for invention." it will never be clear that THE THIRD

REQUIREMENT is that stated in section 103 *and no other*; that when 103 has been complied with, there is no further and different requirement called "invention"; that compliance with 103 is the policy judgment of Congress on how to bring the invention within the Constitutional purpose.

- Because looking for the presence of "invention" in addition to compliance with 103 defeats the legislative purpose.
- Because talking about both unobviousness and "invention" as different things leads to weird and confused thinking.
- Because testing patentability by the presence of "invention" gives judges and the Patent Office too much freedom to decide patentability of new and useful inventions on the basis of a personal view as to what *should* be patentable, instead of accepting the view of the legislature on that question of national policy.
- Because it will get all those concerned with the administration of the patent system—Patent Office, Courts, and the bar—speaking the same language, a sine qua non to the communication of intelligence.
- Because you cannot use "invention" as both an abstract noun and a concrete noun in the same statute or opinion without confusion. The invention is the thing that has been produced by the "inventor." There will be muddy thought as long as one has to say: this invention (in the concrete sense) is unpatentable because it is not an invention (in the abstract sense).
- Because it will do more than anything else I can think of to bring about that long-sought-for greater uniformity of opinion on patentability.

- Because it makes the prerequisites to patentability intelligible.

As I hope I have been.

To quote Learned Hand—that well-named judge—once more, maybe I am only "shovelling smoke." Time alone will tell.

Progress of Patent Examining Program

By H. B. Whitmore *

In order to keep the readers of the Journal of the Patent Office Society informed on the progress the Office is making in reducing its backlog of pending patent applications and the period of pendency of patent applications, it is planned to periodically report the results of such progress in the JPOS. The graph on the opposite page indicates the progress to date.

The Office goal, of course, is to attain a rate of 100,000 disposals per year (8,333 per month) for the next five year period. Studies to date indicate that the Office has a reasonably good chance of accomplishing this goal as a result of the benefits being realized from compact prosecution and the new examining program initiated July 1, 1964, and particularly as a result of the increasing degree of cooperation now being evidenced by the examiners and the applicants and their attorneys and agents. It is anticipated that the Office will be in a position to make a firm evaluation of the possibility of meeting this long range goal about six months hence, after the initial phases of the new examining program are completed.

* Superintendent of the Examining Corps. U. S. Patent Office.

ATTACHMENT 4

TO WRITTEN TESTIMONY OF

SHERRY M. KNOWLES

PRINCIPAL, KNOWLES INTELLECTUAL PROPERTY STRATEGIES, LLC

BEFORE THE

UNITED STATES SENATE

COMMITTEE ON THE JUDICIARY

SUBCOMMITTEE ON INTELLECTUAL PROPERTY

ON

"THE STATE OF PATENT ELIGIBILITY IN AMERICA, PART I"

JUNE 4, 2019

2:30 PM

MARKETED NATURAL PRODUCTS

Below is a non-limiting list of marketed natural products which would not have been patent eligible if they were developed today. Products whose names are followed with ** are on the WHO list of essential medicines.

Absent the prior statutory eligibility jurisprudence that allowed these drugs to be patented, several of them may have never been developed at all. Many of these drugs have saved thousands of lives and are affordable enough for widespread use in even developing countries.

Natural Product Antibiotic Drugs		
Generic Name	**Trade Name**	**Year introduced**
Aztreonam**	Azactam	
Carumonam	Amasulin	1988
Cephalosporin**		
Cyclosporin**		
Chloramphenicol**		
Clavulanic acid**	Augmentin, Timentin, et. al.	
Daptomycin**	Cubicin	2003
Erythromycin**		
Fidaxomicin	Dificid	2011
Fosfomycin trometamol**	Monuril	1988
Gentamicin**	Cidomycin, genticyn, et. al.	1964
Imipenem**		
Isepamicin	Isepacin	1988
Micronomicin sulfate	Sagamicin	1982
Miokamycin	Miocamycin	1985
Mupirocin**	Bactroban	1985
Netilmicin sulfate	Netromicine	1981
Norcardicin		
Penicillin G		
Penicillin V		
RV-11	Zalig	1989
Spectinomycin**	Trobicin	
Teicoplanin**	Targocid	1988
Tetracycline**	Sumycin, et. al.	1978
Vancomycin**		

Natural Product Anticancer Drugs		
Generic Name	**Trade Name**	**Year introduced**
Aclarubicin	Aclacin	1981
Actinomycin D		1964
Aminolevulinic acid HCl	Levulan	2000
Angiotensin II	Delivert	1994
Arglabin	Arglabin	1999
Asparaginase**		1969
Bleomycin**		1966
Carzinophilin		1954
Chromomycin A3		1961
Daunomycin		1967
Doxorubicin**	Adriamycin	1966
Docetaxel**	Taxotere	1995
Homoharringtonine	Ceflatonin	2012
Ingenol mebutate	Picato	2012
Leucovorin		1950
Masoprocol	Actinex	1992
Mithramycin		1961
Mitomycin C		1956
Neocarzinostatin		1976
Paclitaxel**	Taxol	1993
Paclitaxel nanoparticles	Abraxane	2005
Paclitaxel nanoparticles	Nanoxel	2007
Paclitaxel nanoparticles	Genoxol-PM	2007
Paclitaxel nanoparticles	PICN	2014
Pentostatin	Nipent	1992
Peplomycin	Pepleo	1981
Romidepsin	Istodax	2010
Sarkomycin		1954
Solamargines	Curaderm	1989
Streptozocin		Pre-1977
Testosterone**		Pre-1970
Trabectedin	Yondelis	2007
Vinblastine**		1965
Vincristine**		1963

Natural Products for Pain Management and Anesthesia		
Generic Name	**Trade Name**	**Year introduced**
Acetylsalicyclic acid**	Asprin	
Atropine**	Atropen	
Codeine**		
Ephedrine**	Ephedrine	1926
Hycosine**	Kwellis, Transdermscop, et. al.	approximately 1900
Morphine**	Statex, Oramoph, et. al.	1827

Natural Products for use as Antidotes		
Generic Name	**Trade Name**	**Year introduced**
Acetylcysteine**	Acetadote, Fluimucil, et. al.	1968
Calcium Gluconate**	Calcium Gluconate	1920s
Deferoxamine**	Desferal	1968
Penicillamine**	Cuprimine	1970

Additional Natural Products		
Generic Name	**Trade Name**	**Year introduced**
Artemisinin	Artemisin	1987
Colchicine	Colcrys and Mitigare	1961
Ephedrine**	Adrenaline	
Hydrocortisone**	A-hydrocort, Corlef, et. al.	1941
Voglibose	Basen	1994

ATTACHMENT 5

TO WRITTEN TESTIMONY OF

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JUNE 4, 2019

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JOURNAL OF NATURAL PRODUCTS

Review

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Natural Products as Sources of New Drugs from 1981 to 2014

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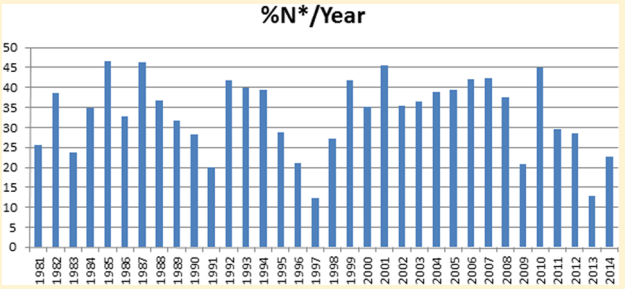
Supporting Information

ABSTRACT: This contribution is a completely updated and expanded version of the four prior analogous reviews that were published in this journal in 1997, 2003, 2007, and 2012. In the case of all approved therapeutic agents, the time frame has been extended to cover the 34 years from January 1, 1981, to December 31, 2014, for all diseases worldwide, and from 1950 (earliest so far identified) to December 2014 for all approved antitumor drugs worldwide. As mentioned in the 2012 review, we have continued to utilize our secondary subdivision of a "natural product mimic", or "NM", to join the original primary divisions and the designation "natural product botanical", or "NB", to cover those botanical "defined mixtures" now recognized as drug entities by the U.S. FDA (and similar organizations). From the data presented in this review, the utilization of natural products and/or their novel structures, in order to discover and develop the final drug entity, is still alive and well. For example, in the area of cancer, over the time frame from around the 1940s to the end of 2014, of the 175 small molecules approved, 131, or 75%, are other than "S" (synthetic), with 85, or 49%, actually being either natural products or directly derived therefrom. In other areas, the influence of natural product structures is quite marked, with, as expected from prior information, the anti-infective area being dependent on natural products and their structures. We wish to draw the attention of readers to the rapidly evolving recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from whence it was isolated", and therefore it is considered that this area of natural product research should be expanded significantly.



INTRODUCTION

It is now 18 years since the publication of our first review covering drugs from 1984 to 1995;[1] 12 years since the second, which covered the period from 1981 to 2002;[2] eight years since our third, covering the period 1981 to the middle of 2006;[3] and four years[4] since our last full analysis (covering the period 1981 to 2010), of the sources of new and approved drugs for the treatment of human diseases. In the present review we have also covered the four years from the beginning of 2011 to the end of 2014. In the last four years we have also published intermediate reports on natural products as leads to potential drugs,[5] the sources of antitumor compounds,[6] a general discussion on bioactive macrocycles from Nature,[7] an e-book series on natural products from microbial sources,[8−10] and a very recent book chapter on natural products in medicinal chemistry.[11] All of these articles have emphasized that natural product and/or natural product structures continue to play a highly significant role in the drug discovery and development process.

In Table 1, we have shown the genesis of our category codes and the years that we started with them. This is for the benefit of readers who are not familiar with these definitions and their derivation. The detailed reasoning behind the subgroup definition is given later under results.

That Nature in one guise or another has continued to influence the design of small molecules is shown by inspection of the information given below, where with the advantage of now 34 years of data from 1981 to 2014 the system has been able to be refined. We have eliminated some duplicated entries that crept into the original data sets and have continued to revise some source designations, as newer information has been obtained from diverse sources. In particular, as behooves authors originally from the National Cancer Institute (NCI), in the specific case of cancer treatments, we have continued to consult the records of the U.S. FDA and have added comments from investigators who

Table 1. Codes Used in Analyses

code	brief definition/year
B	Biological macromolecule, 1997
N	Unaltered natural product, 1997
NB	Botanical drug (defined mixture), 2012
ND	Natural product derivative, 1997
S	Synthetic drug, 1997
S*	Synthetic drug (NP pharmacophore), 1997
V	Vaccine, 2003
/NM	Mimic of natural product, 2003

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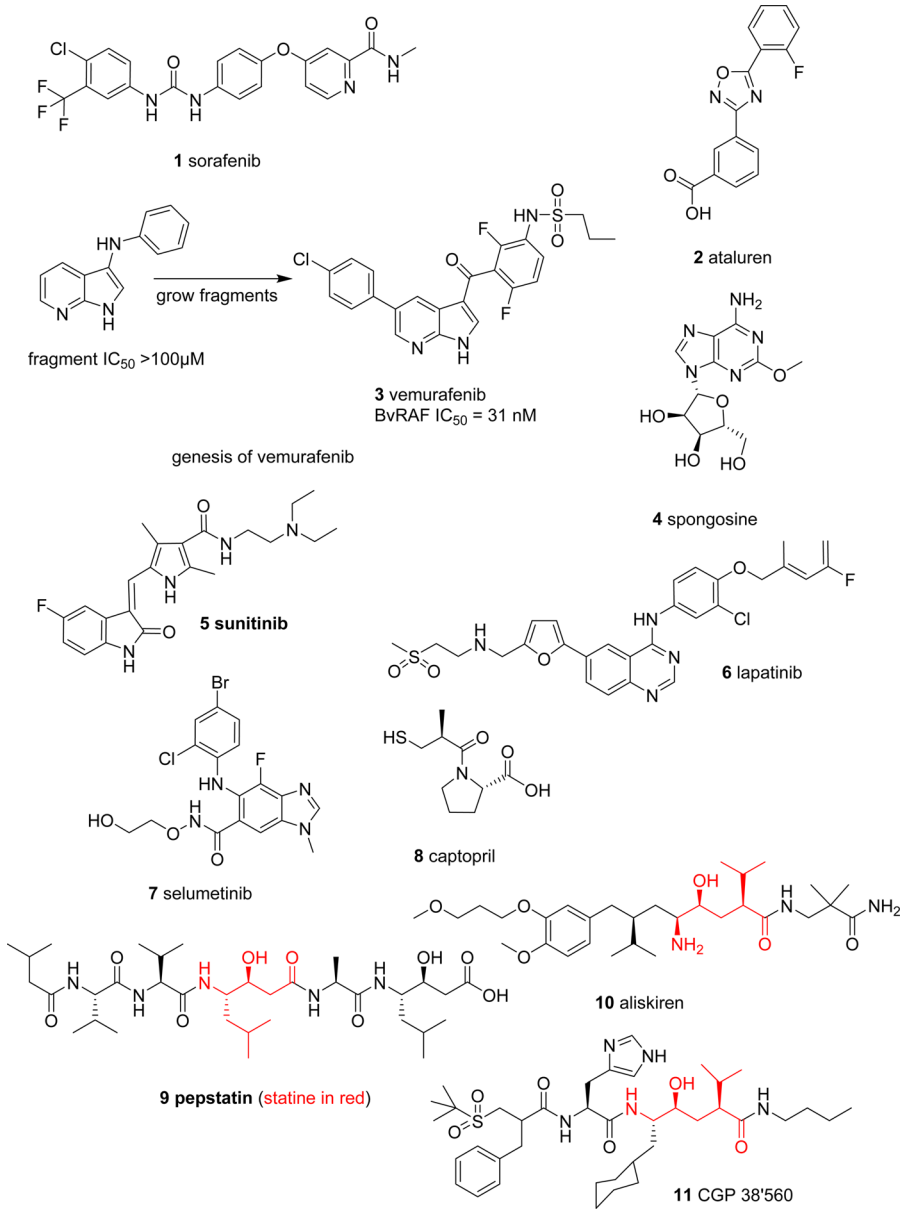
Chart 1



have informed us of compounds that may have been approved in other countries and that were not included in our earlier searches. As was done previously, the cancer data will be presented as a stand-alone section from the beginning of formal chemotherapy in the very late 1930s or early 1940s to the present, but information from the last 34 years will be included in the data sets used in the overall discussion.

A trend mentioned in our 2003 review,[2] namely, the development of high-throughput screens based on molecular targets, had led to a demand for the generation of large libraries of compounds; however, the shift away from large combinatorial libraries that was becoming obvious at that time has continued even today, with the emphasis continuing to be on small focused (100−3000 plus) collections that contain much of the "structural aspects" of natural products. As mentioned in our 2012 review,[4] various names have been given to this process, including "diversity oriented syntheses",[12−16] but we prefer to refer simply to "more natural-product-like", in terms of their combinations of heteroatoms and significant numbers of chiral centers within a single molecule,[17] or even "natural product mimics" if they happen to be direct competitive inhibitors of the natural substrate (the origin of our subset listed as "?/NM"). It should also be pointed out, yet again, that Lipinski's fifth rule effectively states that the first four rules do not apply to natural products nor to any molecule that is recognized by an active transport system when considering "druggable chemical entities".[18−20] An excellent paper by Koehn in 2012 gives a listing in Table 1 in that article of the 26 drugs approved between 1981 and 2011 based on 18 natural product structures that do not obey the "rule of 5" and its strictures.[21] This paper together with one from Sweden by Doak et al.[22] and a very recent contribution by Camp et al.[23] should be part of any discussion on this aspect of natural product drugs.

Commentaries on the "industrial" perspective in regard to drug sources and high-throughput screening were published by the GSK group[24] in 2011, and very recently an intriguing article on what has been called "high throughput screening-dark chemical matter" (HTS-DCM) has opened the discussion on

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molecules, some of which are based on natural products, that show no activities in in vitro assays but a number of which have very close structural analogues that are active.[25,26] These papers, the first of which is a perspective on the second much larger paper, should also be read in conjunction with a recent paper showing the natural product compound equivalents (invalid metabolic panaceas (IMPS))[27] to the pan-assay interference compounds (PAINS) that cause major problems in HTS programs.[28,29]

Although combinatorial chemistry in one or more of its manifestations has now been present as a discovery source for approximately 80% of the time covered by this review, to date, we still can only find one formal *de novo* new chemical entity reported in the public domain, with a second possibility discovered in a similar manner, with both approved for drug use. The first was the antitumor compound known as sorafenib (Nexavar, **1**) from Bayer, approved by the FDA in 2005 for treatment of renal cell carcinoma, and then in 2007, another approval was given for treatment of hepatocellular carcinoma. It has been approved in more than 100 countries as of the middle of 2014 for these two indications, and in late 2013, the U.S. FDA approved it for treatment of thyroid cancer with further approval for the same indication following in 2014 in the European Union and Japan. As is customary, it is still in multiple clinical trials in both combination and single-agent therapies. The second drug that probably came about from a *de novo* sourcing is ataluren (Translarna; **2**),[30] which was approved in the EU in 2014 and launched in Germany the same year for the treatment of patients with genetic disorders due to a "nonsense" mutation. The mechanism of this small molecule can be seen in a diagrammatic mode at the following URL: http://www.ptcbio.com/en/pipeline/ataluren-translarna/. However, the first anticancer drug constructed by use of fragment screening and model fitting, vemurafenib (**3**), was approved by the FDA in 2011, and the story behind this and other small-molecule antitumor agents was well described in a review in 2012 by Hoelder et al., which should be consulted for more information on this style of approach to drug discovery.[31]

As mentioned by the present authors and a significant number of other authors in prior reviews on this topic, the developmental capability of combinatorial chemistry as a means for structural optimization, once an active skeleton has been identified, is without par. An expected surge in productivity, however, did not appear to materialize in the years from 2004 to 2014. Thus, the number of new active substances (NASs) from our data set, also known as new chemical entities (NCEs), which we consider to encompass all molecules, including biologics and vaccines, hit a 24-year low of 24 in 2004 (although 7, or 29%, of these were assigned to the "ND" category), leading to a rebound to 52 in 2005, with 25% being "N" or "ND" and 37% being biologics ("B") or vaccines ("V"). The next four years from 2006 to 2009 averaged 40, with 35−45% being vaccines or biologics, although in these four years, four "botanicals" were approved. In 2010 and 2011, the figures again dropped to 33 and 34, respectively, but then in 2012 to 2014, the figures rebounded to 60, 47, and 65, respectively, but biologics and vaccines were significant proportions of these totals.

These figures are further developed covering the full details by year in Figures 2 and 4 (see the Discussion section below), together with other graphs such as Figure 5, showing total small molecules/year, Figure 6, showing the percentage of natural-product-based compounds and their derivatives. Plus in this review, we have also added the S* series of compounds to these.

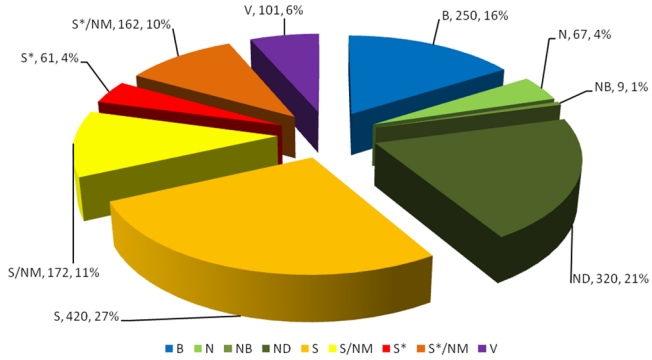

Figure 1. All new approved drugs 1981−2014; n = 1562.

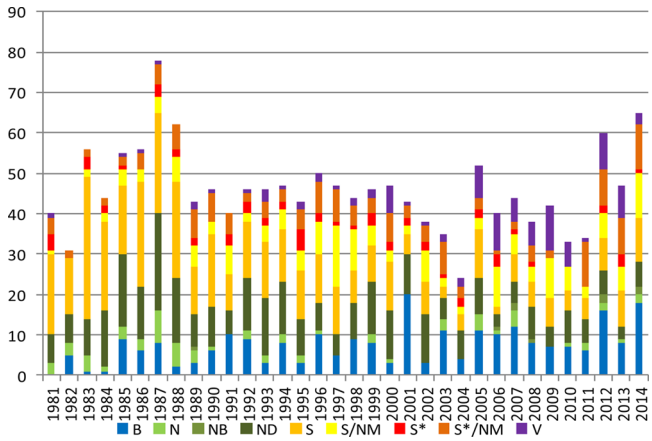

Figure 2. All new approved drugs by source/year.

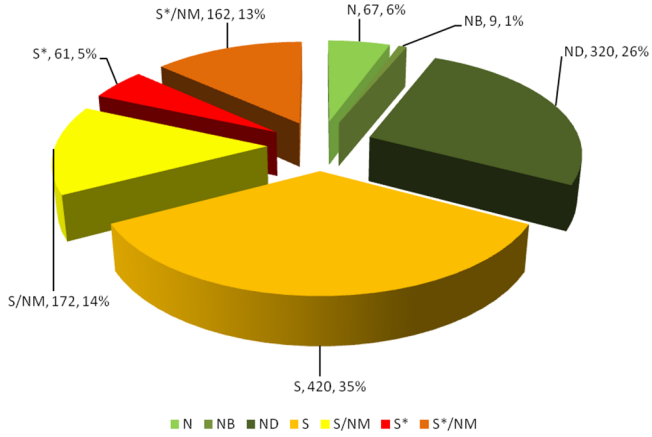

Figure 3. All small-molecule approved drugs 1981−2014s; n = 1211.

The use of the S* classification originally arose as a result of doubts expressed by some colleagues working in the chemical synthesis area who questioned the claim that nucleoside analogues synthesized in the laboratory actually evolved from the discoveries by the Bergmann group in the 1950s of the arabinose-containing natural products from marine sponges.[32−34]

The justification for the addition of the "S*" category to natural-product-based compounds and their derivatives in this review is that a large number of the "S*" structures are based on naturally derived nucleosides or very closely related scaffolds, and their relevance to drug discovery will be published in a review in the first half of 2016. Figure 7 then shows the percentage of just

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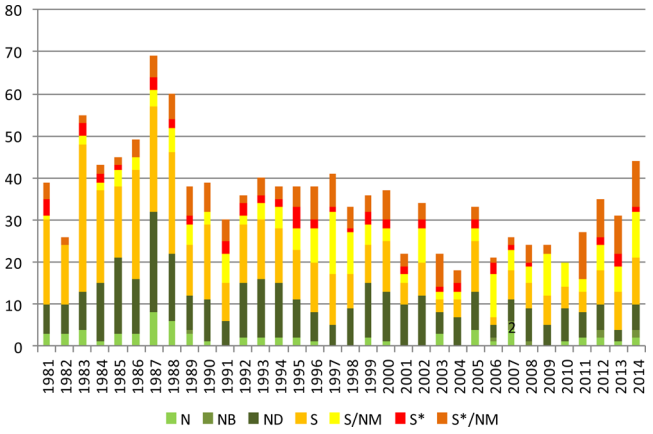

Figure 4. All small-molecule approved drugs by source/year.

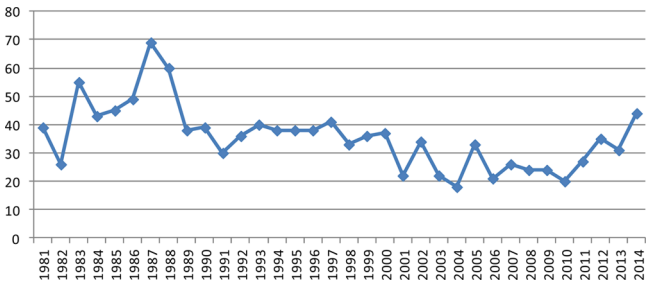

Figure 5. Total small molecules/year.

the "N*" categories over the 34 years. What is of significant importance in this area is the very recent paper from the Gerwick group demonstrating the isolation of spongosine (**4**) from a *Vibrio harveyi* strain isolated from the same sponge species (*Tectitethya crypta*) as used by Bergmann 60+ years earlier.[35] However, to allow for comparisons with earlier reviews, we have not altered the categories in the analyses. Fortunately, however, research is still being conducted by (bio)synthetic groups on the modification of active natural product skeletons as leads to novel agents. This was exemplified recently by publications in 2014–2015 from the groups of Szychowski et al.,[36] Bathula,[37] Thaker,[38] Williams,[39] Miller,[40] and Novaes et al.[41] and an excellent perspective by Nicolaou in 2014.[42]

Against this backdrop, we now present an updated analysis of the role of natural products in the drug discovery and development process, dating from January 1981 through December 2014. As in our earlier analyses,[1−4] we have consulted the *Annual Reports of Medicinal Chemistry*, in this case from 1984 to 2014,[43−74] and to obtain more comprehensive coverage of the 1981−2014 time frame we have added data from the publication *Drug News and Perspective*,[75−95] the successor listings in *Drugs of Today*,[96−101] and searches of the Prous (now Thomson-Reuter's *Integrity*) database, as well as by including information from individual investigators. As in the last review, the biologics data prior to 2005 were updated using information culled from disparate sources that culminated in a 2005 review on biopharmaceutical drugs.[102] We have continued our attempts to capture vaccine data for the past few years, but this area of the database is still not as complete as we would hope.

As in previous reviews in this series, we have continued to include relevant references in a condensed form in Tables 3−6 and 9−11. If we had attempted to provide full citations, the numbers of references cited in the present review would become overwhelming. In these tables, "ARMC ##" refers to the volume of *Annual Reports in Medicinal Chemistry* together with the page on which the structure(s) and commentary can be found. We should point out that due to a change effective in 2015, the ARMC is now known as *Medicinal Chemistry Reviews*. Similarly, "DNP ##" refers to the volume of *Drug News and Perspective* and the corresponding page(s), although this journal has now ceased publication as of the 2010 volume. Similarly "DT ##" refers to the relevant volume of *Drugs of Today* and the corresponding page(s), and an "I ######" is the accession number in the Prous (now Thomson-Reuters, *Integrity*) database. Finally, in the overall listing of antitumor agents from the middle 1930s to 2014 (Table 9) we have used "Boyd" to refer to a review article[103] on clinical antitumor agents, an earlier book on the same subject,[104] and "M'dale" to refer to *Martindale*[105] with the relevant page noted.

It must be noted that the "year" header in all tables is formally equivalent to the "year of introduction" of the drug in the first country in which it was approved. We only count a drug once,

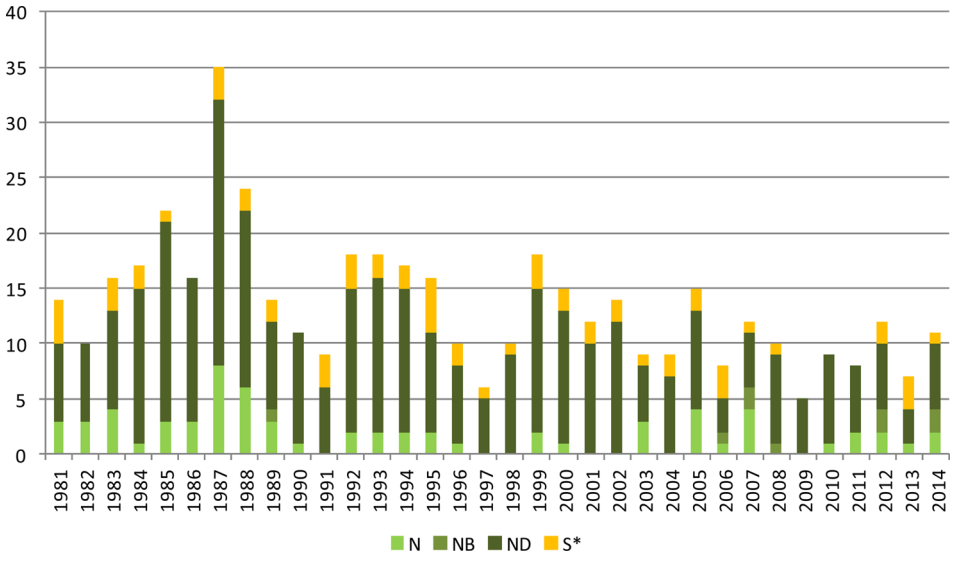

Figure 6. N, NB, ND, and S* categories by year, 1981−2014.

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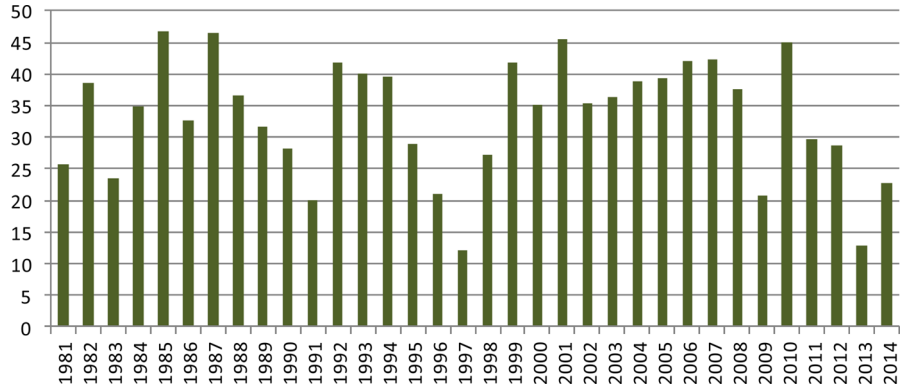

Figure 7. Percentage of N* by year, 1981−2014.

even if subsequently it is approved in other countries or for other indications. Over the years, we have realized that there are discrepancies between sources as to the actual year, often due to differences in definitions between sources. Some reports will use the year of approval (registration by non-USA FDA equivalent organizations), while others will use the first recorded sales. We have generally taken the earliest year in the absence of further information.

RESULTS

As in previous reviews, we have, except in a case that will be noted later in this review where a therapy used NCEs (two unapproved agents) in the approved combination, only covered NCEs in the present analysis. As mentioned in earlier reviews, if one reads the U.S. FDA and PhRMA Web sites, the numbers of New Drug Application (NDA) approvals are in the high tens in some of the past few years. The FDA Drugs Database needs to be assessed by anyone using it for drugs previously approved in other countries versus new drugs only approved in the USA to obtain more accurate figures, and there will be differences due to our noting drugs approved the first time anywhere and then not counting the same compound the first time it was approved by the FDA. Using our data (see Figures 2, 4, and 5) the number of NCEs has ranged from the 20's to just over 50 per year from 1989 to 2011 and in 2013 for approved NCEs (note that Figures 4 and 5 count only small molecules), although in 2012 and 2014 the figures reached 60 and 65, respectively. The reader needs to bear in mind that our vaccine numbers are not complete, so the overall numbers could increase. If one now removes biologicals and vaccines, thus noting only "small molecules" (including peptides such as Byetta), then the figures show that over the same time frame the numbers have ranged from close to 40 for most of the 1989 to 2000 time frame (except for 2002) to close to 20 from 2001 to 2010, with the exception of 2002 and 2004, when the figures climbed above 30. In the last four years (2011 to 2014), the numbers have now climbed from 28 in 2011 to 44 (cf., Figures 2 and 4).

Now with 34 years of data to analyze, it was decided to add another graph to the listings, together with one of significant interest to the natural products community. In Figure 6 we have plotted a bar graph from 1981 to 2014 showing the results in numbers/year when the designations used are an "N" or a subdivision ("NB" or "ND"). This time, we have deliberately included the "S*" designation (for the reasons elaborated earlier), which could be considered as "inspired by a natural product structure". This figure demonstrates that even in 2014 10 of the 44 approved small-molecule drugs are "N", "NB", and "ND" with one "S*", which account for 25% of the 44 approved NCEs that year. If we just use the "N", "NB", and "ND" designations over the complete 34 years, then the mean and standard deviation figures in percentages are 33 ± 9, and in Figure 7 we have shown the percentage for "N*" values by year. Readers can determine their own ratios for their "year of interest", as desired.

As in our earlier reviews,[1−4] the data have been analyzed in terms of numbers and classified according to their origin using the previous major categories and their subdivisions.

Major Categories of Sources. The major categories used are as follows:

"B": Biological, usually a large (>50 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host

"N": Natural product, unmodifed in structure, though might be semi- or totally synthetic

"NB": Natural product "botanical drug" (in general these have been recently approved)

"ND": Derived from a natural product and is usually a semisynthetic modification

"S": Totally synthetic drug, often found by random screening/modification of an existing agent

"S*": Made by total synthesis, but the pharmacophore is/was from a natural product

"V": Vaccine

Subcategory. "NM": Natural product mimic (see rationale and examples below, as they give the reasoning for the extension of the "S" and "S*" categories from 2003 onward)

In the field of anticancer therapy, the advent in 2001 of Gleevec, a protein tyrosine kinase inhibitor, was justly heralded as a breakthrough in the treatment of leukemia. This compound was classified as an "/NM" on the basis of its competitive displacement of the natural substrate, ATP, in which the intracellular concentrations can approach 5 mM. We have continued to classify most PTK inhibitors that are approved as drugs under the "/NM" category for exactly the same reasons as elaborated in the 2003 review,[2] although nowadays, some later kinase inhibitors are not competitive inhibitors of ATP and thus would not be classified this way. The latest discussion on this aspect of PTKs can be read in the 2015 paper by Fabbro et al.[106] (Fabbro can be considered the "developmental father of Gleevec"), which should be read in conjunction with his 2002 paper on PTKs as targets.[107] In addition, the very interesting recent review by Vijayan et al.[108] should be consulted, as it demonstrates, together with the 2015 paper from Fabbro et

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Table 2. New Chemical Entities and Medical Indications by Source of Compound 1/1/1981−12/31/2014[a]

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
COPD	8						3		5	
analgesic	17		1			11	3	2		
anesthetic	5					5				
anti-Alzheimer	6	1	1		1		3			
anti-Gaucher's disease	5	3			1				1	
anti-Parkinsonian	12				1	1	5	1	4	
antiallergic	18		1	1	4	12				
antianginal	5					5				
antiarrhythmic	17		1			14			2	
antiarthritic	22	6	1	1	3	4	6		1	
antiasthmatic	14	1			3	2	6		2	
antibacterial	140	1	11		71	29			1	27
anticancer	174	33	17	1	38	23	20	13	24	5
anticoagulant	22	5			13			1	3	
antidepressant	27					8	17		2	
antidiabetic, types 1 and 2	52	23	1		6	4	11	1	6	
antiemetic	11					1	2		8	
antiepileptic	17				2	11		2	2	
antifungal	32	1			3	25	3			
antiglaucoma	14				5		5	1	3	
antihistamine	14					14				
antihyperprolactinemia	4				4					
antihypertensive	80				2	28	15	2	33	
anti-inflammatory	51	1			13	37				
antimigraine	10					2	1		7	
antiobesity	6				1	1	4			
antiparasitic	16		2		5	5		3		1
antipsoriatic	11	4		1	3		1	1	1	
antipsychotic	11					3	6		2	
antithrombotic	30	13	1		5	2	6		3	
antiulcer	34	1	1		12	20				
antiviral	139	14			4	14	5	24	17	61
anxiolytic	10					8	2			
benign prostatic hypertrophy	4		1		1	1	1			
bronchodilator	8				2				6	
calcium metabolism	20				8	9	3			
cardiotonic	13				3	2	3		5	
chelator	4					4				
contraception	9				8		1			
cystic fibrosis	4	1				3				
diuretic	6					4	2			
erythropoiesis	5	5								
gastroprokinetic	4					1	2		1	
hematopoiesis	7	7								
hemophilia	19	19								
hemostatic	4	4								
hormone	22	12			10					
hormone replacement therapy	8				8					
hyperphosphatemia	5					5				
hypnotic	12					12				
hypocholesterolemic	13		4		1	2	1		5	
hypolipidemic	8		1			7				
immunomodulator	4	2	1		1					
immunostimulant	12	6	3		2	1				
immunosuppressant	14	6	5		3					
irritable bowel syndrome	5				1	1			3	
macular degeneration	6	4			1	1				
male sexual dysfunction	5								5	
multiple sclerosis	10	4			2	2		1	1	
muscle relaxant	10				4	2	1	3		
neuroleptic	9					1	6		2	

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Table 2. continued

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
nootropic	8				3	5				
osteoporosis	6	3			2	1				
platelet aggregation inhibitor	4				3		1			
respiratory distress syndrome	7	4	1			1	1			
urinary incontinence	6					2	3		1	
vasodilation	5				3	2				
vulnerary	8	5			2	1				
grand total	1328	189	54	4	268	359	149	55	156	94

[a]Diseases where ≤3 drugs approved 1981−2014: 234 drugs fall into this category and are subdivided as follows: B, 81; N, 15; ND, 46; S, 47, S/NM. 15; S*, 4; S*/NM, 18. The diseases covered the following; 5α-reductase inhibitor, ADHD, CAPS, CHF, CNS stimulant, Castleman's disease, Crohn's disease, Cushing's syndrome, Fabry's disease, Hunter syndrome, inborn errors of bile synthesis, inflammatory bowel disease, Japanese encephalitis, Lambert-Eaton myasthenic syndrome, Lyme disease, acute MI, MMRC, Morquio A syndrome, PAH, PCP/toxoplasmosis, PNH, Pompe's disease, Turner syndrome, abortifacient, acromelagy, alcohol deterrent, allergic rhinitis, anabolic metabolism, analeptic, anemia, antisickle cell anemia, antismoking, antiacne, antiatherosclerotic, anticonvulsant, antidiarrheal, antidote, antiemphysemic, antihyperuricemia, antihypotensive, antinarcolepsy, antinarcotic, antinauseant, antiperistaltic, antiprogestogenic, antirheumatic, antisecretory, antisepsis, antiseptic, antispasmodic, antispastic, antitussive, antityrosinaemia, antixerostomia, atrial fibrillation, benzodiazepine antagonist, β-lactamase inhibitor, blepharospasm, bone disorders, bone morphogenesis, bowel evacuant, cancer adjuvant, cardioprotective, cardiovascular disease, cartilage disorders, cervical dystonia, choleretic, chronic idiopathic constipation, cognition enhancer, congestive heart failure, constipation, coronary artery disease, cystinosis, cytoprotective, diabetic foot ulcers, diabetic neuropathies, digoxin toxicity, dispareunia, dry eye syndrome, dyslipidemia, dysuria, endometriosis, enzyme, expectorant, eye disorders, fertility inducer, free-running circadian disorder, gastroprotectant, genital warts, hematological, hemorrhage, hepatoprotectant, hereditary angioedema, homocystinuria, hyperammonemia, hypercholesterolemia (and familial), hyperparathyroidism, hyperphenylalaninemia, hypertriglyceridemia, hyperuricemia, hypoammonuric, hypocalciuric, hypogonadism, hyponatremia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, immediate allergy, infertility (female), inflammatory bowel disease, insecticide, insomnia, joint lubricant, lipodystrophy (and in HIV), lipoprotein disorders, lipoprotein lipase deficiency, lupus erythematosus, mucolytic, mucopolysaccharidosis, mucositis, myleodysplasia, narcolepsy, nasal decongestant, neuropathic pain, neuroprotective, neutropenia, ocular inflammation, opiate detoxification, opiod-induced constipation, osteoarthritis, overactive bladder, ovulation, pancreatic disorders, pancreatitis, pertussis, photosensitizer, phytotoxicity in adults, pituitary disorders, porphyria, premature birth, premature ejaculation, progestogen, psychostimulant, pulmonary arterial hypertension, purpura fulminans, rattlesnake antivenom, reproduction, restenosis, schizophrenia, sclerosant, secondary hyperthryoidism, sedative, short bowel syndrome, skin photodamage, smoking cessation, strabismus, subarachnoid hemorrhage, thrombocytopenia, treatment of GH deficiency, ulcerative colitis, urea cycle disorders, uremic pruritis, urolithiasis, vaccinia complications, varicella (chicken pox), vasoprotective, venous thromboembolism.

al.,[106] that kinase modulation occurs in a large number of other diseases, and not just in cancer.

Thus, PTK inhibitors have a wide range of possible targets and, in the cases of some specific approved antitumor-directed kinase inhibitors, have a very large number of "targets" in the human kinome. Thus, sunitinib (**5**) affects a very considerable number of different kinase "families", whereas lapatinib (**6**) is restricted to one class, and the as yet unapproved PTKi selumetinib (AZD6244; **7**) appears to be quite specific. These effects can be seen in the figures in the 2015 paper by Fabbro et al.[106] and are further elaborated on by Tilgada et al.,[109] demonstrating that the targets of PTKi's are not just in cancer and related diseases. As previously, we have continued to extend the "/SM" category to cover other direct inhibitors/antagonists of the natural substrate/receptor interaction whether obtained by direct experiment or by *in silico* studies followed by direct assay in the relevant system.

Similarly, a number of new peptidic drug entities, although formally synthetic in nature, are simply produced by chemical synthetic methods rather than by the use of fermentation or extraction. In some cases, an end group might have been changed for ease of recovery. However, a number of compounds produced totally by synthesis are in fact isosteres of the peptidic substrate and are thus "natural product mimics" in the truest sense of the term. We gave some examples of this type of interplay in our 2012 review, in which we mentioned the path to the "sartans".[4]

Derivation of Oral Renin Inhibitors. Expanding upon this aspect of chemistry and pharmacology, we now will show how the first orally active renin inhibitor was derived starting from pepstatin. In Scheme 1 we show an idealized representation of the angiotensin system pathway, showing the physiological route from renin (an aspartic proteinase) through to the angiotensin-converting enzyme (ACE), to yield the hexapeptide angiotensin II. It was knowledge that this enzyme is a zinc-containing carboxy-peptidase that enabled the Squibb group back in the 1970s to synthesize the pseudodipeptide captopril (**8**) as the first ACE inhibitor to be approved by the FDA.

However, the "prime target" in the system is inhibition of renin since that is the enzyme that starts the cascade, and, unlike ACE, it does not hydrolyze the "kinin" peptides (bradykinin, etc.). Renin was known to be an aspartic proteinase, and it could be inhibited by the bacterial peptide pepstatin (**9**). This compound contains the unusual amino acid statine, which contains as a dipeptide mimic a hydroxyethylene isostere, and it was the basis of a long-term project at Merck to synthesize renin inhibitors, and later HIV-protease inhibitors, based on this substituent mimicking the transition state of the aspartic proteinase/substrate pair.[110,111] Although none of their peptide structures provided a renin inhibitor that was approved as a drug, their work demonstrated the potential for such substitutions to be effective drug leads, albeit from Ciba-Geigy (now Novartis), en route to an orally active renin inhibitor. The first of what were known as type-I inhibitors[112] contained the dipeptide isostere (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-6-cyclohexylhexanoic acid at the P1−P1′ position and also mimicked angiotensinogen from residue P3 to P1′ using the nomenclature from Schetchter and Berger.[113]

The story of the search for orally active renin inhibitors, although formally nonpeptidic but still containing the hydroxyethylene transition state dipeptide isostere, was given in detail by Novartis scientists in two papers, demonstrating that the search

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Table 3. Antibacterial Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
raxibacumab	ABthrax	2012	I 336061		B
carumonam	Amasulin	1988	ARMC 24	298	N
daptomycin	Cubicin	2003	ARMC 39	347	N
fidaxomicin	Dificid	2011	DT 48(1)	40	N
fosfomycin trometamol	Monuril	1988	I 112334		N
isepamicin	Isepacin	1988	ARMC 24	305	N
micronomicin sulfate	Sagamicin	1982	P091082		N
miokamycin	Miocamycin	1985	ARMC 21	329	N
mupirocin	Bactroban	1985	ARMC 21	330	N
netilimicin sulfate	Netromicine	1981	I 070366		N
RV-11	Zalig	1989	ARMC 25	318	N
teicoplanin	Targocid	1988	ARMC 24	311	N
apalcillin sodium	Lumota	1982	I 091130		ND
arbekacin	Habekacin	1990	ARMC 26	298	ND
aspoxicillin	Doyle	1987	ARMC 23	328	ND
astromycin sulfate	Fortimicin	1985	ARMC 21	324	ND
azithromycin	Sunamed	1988	ARMC 24	298	ND
aztreonam	Azactam	1984	ARMC 20	315	ND
biapenem	Omegacin	2002	ARMC 38	351	ND
cefbuperazone sodium	Tomiporan	1985	ARMC 21	325	ND
cefcapene pivoxil	Flomox	1997	ARMC 33	330	ND
cefdinir	Cefzon	1991	ARMC 27	323	ND
cefditoren pivoxil	Meiact	1994	ARMC 30	297	ND
cefepime	Maxipime	1993	ARMC 29	334	ND
cefetamet pivoxil HCl	Globocef	1992	ARMC 28	327	ND
cefixime	Cefspan	1987	ARMC 23	329	ND
cefmenoxime HCl	Tacef	1983	ARMC 19	316	ND
cefminox sodium	Meicelin	1987	ARMC 23	330	ND
cefodizime sodium	Neucef	1990	ARMC 26	300	ND
cefonicid sodium	Monocid	1984	ARMC 20	316	ND
cefoperazone sodium	Cefobis	1981	I 127130		ND
ceforanide	Precef	1984	ARMC 20	317	ND
cefoselis	Wincef	1998	ARMC 34	319	ND
cefotetan disodium	Yamatetan	1984	ARMC 20	317	ND
cefotiam HCl	Pansporin	1981	I 091106		ND
cefozopran HCl	Firstcin	1995	ARMC 31	339	ND
cefpimizole	Ajicef	1987	ARMC 23	330	ND
cefpiramide sodium	Sepatren	1985	ARMC 21	325	ND
cefpirome sulfate	Cefrom	1992	ARMC 28	328	ND
cefpodoxime proxetil	Banan	1989	ARMC 25	310	ND
cefprozil	Cefzil	1992	ARMC 28	328	ND
cefsoludin sodium	Takesulin	1981	I 091108		ND
ceftaroline fosamil acetate	Teflaro	2011	DT 48(1)	40	ND
ceftazidime	Fortam	1983	ARMC 19	316	ND
cefteram pivoxil	Tomiron	1987	ARMC 23	330	ND
Ceftibuten	Seftem	1992	ARMC 28	329	ND
ceftizoxime sodium	Epocelin	1982	I 070260		ND
ceftobiprole medocaril	Zeftera	2008	ARMC 44	589	ND
ceftriaxone sodium	Rocephin	1982	I 091136		ND
cefuroxime axetil	Zinnat	1987	ARMC 23	331	ND
cefuzonam sodium	Cosmosin	1987	ARMC 23	331	ND
cetolozane/tazobactam	Zerbaxa	2014	DT 51(1)	47	ND
clarithromycin	Klaricid	1990	ARMC 26	302	ND
dalbavancin	Dalavance	2014	DT 51(!)	47	ND
dalfopristin	Synercid	1999	ARMC 35	338	ND
dirithromycin	Nortron	1993	ARMC 29	336	ND
doripenem	Finibax	2005	DNP 19	42	ND
ertapenem sodium	Invanz	2002	ARMC 38	353	ND
erythromycin acistrate	Erasis	1988	ARMC 24	301	ND
flomoxef sodium	Flumarin	1988	ARMC 24	302	ND
flurithromycin ethylsuccinate	Ritro	1997	ARMC 33	333	ND

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Table 3. continued

generic name	trade name	year introduced	volume	page	source
fropenam	Farom	1997	ARMC 33	334	ND
imipenem/cilastatin	Zienam	1985	ARMC 21	328	ND
lenampicillin HCI	Varacillin	1987	ARMC 23	336	ND
loracarbef	Lorabid	1992	ARMC 28	333	ND
meropenem	Merrem	1994	ARMC 30	303	ND
moxalactam disodium	Shiomarin	1982	I 070301		ND
oritavancin	Orbactiv	2014	DT 51(1)	47	ND
panipenem/betamipron	Carbenin	1994	ARMC 30	305	ND
quinupristin	Synercid	1999	ARMC 35	338	ND
retapamulin	Altabax	2007	ARMC 43	486	ND
rifabutin	Mycobutin	1992	ARMC 28	335	ND
rifamixin	Normix	1987	ARMC 23	341	ND
rifapentine	Rifampin	1988	ARMC 24	310	ND
rifaximin	Rifacol	1985	ARMC 21	332	ND
rokitamycin	Ricamycin	1986	ARMC 22	325	ND
roxithromycin	Rulid	1987	ARMC 23	342	ND
sultamycillin tosylate	Unasyn	1987	ARMC 23	343	ND
tazobactam sodium	Tazocillin	1992	ARMC 28	336	ND
telavancin HCl	Vibativ	2009	DNP 23	15	ND
telithromycin	Ketek	2001	DNP 15	35	ND
temocillin disodium	Temopen	1984	ARMC 20	323	ND
tigecycline	Tygacil	2005	DNP 19	42	ND
balafloxacin	Q-Roxin	2002	ARMC 38	351	S
bedaquiline	Sirturo	2012	1 386239		S
besifloxacin	Besivance	2009	DNP 23	20	S
ciprofloxacin	Ciprobay	1986	ARMC 22	318	S
enoxacin	Flumark	1986	ARMC 22	320	S
finafloxacin hydrochloride	Xtoro	2014	DT 51(1)	48	S
fleroxacin	Quinodis	1992	ARMC 28	331	S
garenoxacin	Geninax	2007	ARMC 43	471	S
gatilfloxacin	Tequin	1999	ARMC 35	340	S
gemifloxacin mesilate	Factive	2003	ARMC 40	458	S
grepafloxacin	Vaxor	1997	DNP 11	23	S
levofloxacin	Floxacin	1993	ARMC 29	340	S
linezolid	Zyvox	2000	DNP 14	21	S
lomefloxacin	Uniquin	1989	ARMC 25	315	S
moxifloxacin HCl	Avelox	1999	ARMC 35	343	S
nadifloxacin	Acuatim	1993	ARMC 29	340	S
nemonoxacin	Taigexyn	2014	DT 51(1)	48	S
norfloxacin	Noroxin	1983	ARMC 19	322	S
ofloxacin	Tarivid	1985	ARMC 21	331	S
pazufloxacin	Pasil	2002	ARMC 38	364	S
pefloxacin mesylate	Perflacine	1985	ARMC 21	331	S
prulifloxacin	Sword	2002	ARMC 38	366	S
rufloxacin hydrochloride	Qari	1992	ARMC 28	335	S
sitafloxacin hydrate	Gracevit	2008	DNP 22	15	S
sparfloxacin	Spara	1993	ARMC 29	345	S
taurolidine	Taurolin	1988	I 107771		S
tedizolid phosphate sodium	Sivextro	2014	DT 51(1)	47	S
temafloxacin hydrochloride	Temac	1991	ARMC 27	334	S
tosufloxacin	Ozex	1990	ARMC 26	310	S
trovafloxacin mesylate	Trovan	1998	ARMC 34	332	S
brodimoprin	Hyprim	1993	ARMC 29	333	S*/NM
	Bexsero	2013	DT 50(1)	69	V
	Prevenar 13	2009	DNP 23	17	V
	Quattrovac	2012	I 770186		V
	Synflorix	2009	DNP 23	17	V
	Typbar	2013	DT 50(1)	68	V
ACWY meningoccal PS vaccine	Mencevax	1981	I 420128		V
BK-4SP	Tetrabik	2012	I 697562		V
botulism antitoxin	Bat	2013	DT 50(1)	77	V

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Table 3. continued

generic name	trade name	year introduced	volume	page	source
DTPw-HepB-Hib	Quinvaxem	2006	DNP 20	26	V
DTP vaccines	Daptacel	2002	I 319668		V
H. influenzae b vaccine	Hibtitek	1989	DNP 03	24	V
H. influenzae b vaccine	Prohibit	1989	DNP 03	24	V
hexavalent vaccine	Hexavac	2000	DNP 14	22	V
hexavalent vaccine	Infantrix HeXa	2000	DNP 14	22	V
Hib-MenCY-TT	Menhibrix	2012	I 421742		V
MCV-4	Menactra	2005	DNP 19	43	V
MenACWY-CRM	Menveo	2010	I 341212		V
MenACWY-TT	Nimenrix	2012	I 421745		V
meningitis b vaccine	MeNZB	2004	DNP 18	29	V
meningococcal vaccine	Menigetec	1999	DNP 14	22	V
meningococcal vaccine	NeisVac-C	2000	DNP 14	22	V
meningococcal vaccine	Menjugate	2000	DNP 14	22	V
MnB rLP2086	Trumenba	2014	DT 51(1)	51	V
oral cholera vaccine	Orochol	1994	DNP 08	30	V
pneumococcal vaccine	Prevnar	2000	DNP 14	22	V
PsA-TT	MenAfriVac	2010	I 437718		V
Vi polysaccharide typhoid vaccine	Typherix	1998	DNP 12	35	V

involved significant computerized structure−activity relationships using the crystal structure of human renin to optimize the chemistry, before finally leading to the drug candidate, SPP-100, which became the drug aliskiren (**10**) and gained FDA approval in March 2007 and EMA approval in August 2007. The first paper, in 2000,[114] gave the chemical basis for the initial discoveries of pseudopeptidic agents and the use of structure-based drug design with modifications around the initial type-I inhibitor (CGP 38′560; **11**). The second paper, published in 2003,[115] gave the next chapter in the story, the work leading up to aliskiren. Finally, a thorough analysis of the various molecules and routes leading to aliskiren was published by Novartis scientists in 2010, and this should be consulted for the full story.[116]

Also of interest are some recent publications that under certain conditions could almost be considered as potential for "repurposing" of this drug and perhaps others with the same target. Following a study on the conformation of aliskiren in solution and when bound to its receptor, by Politi et al., in 2011[117] the data were used to calculate binding of aliskiren to a model of the HIV protease (an aspartic proteinase). This study also demonstrated that the FDA-approved (2013) SGLT-2 inhibitor canagliflozin (**12**) and the approved HIV protease inhibitor darunavir (**13**) may have cross-activities in renin inhibition as well as their regular approved pharmacological targets, thus potentially repurposing these compounds.[118]

Biologically Active Peptides. A review covering the preparation of biologically active peptides was published in 2014 and makes interesting reading when the methodologies are compared with those covering the synthesis of pseudopeptides that inhibit aspartic proteinases.[119]

Modifications of Natural Products by Combinatorial Methods. These techniques often produce entirely different compounds that may bear little if any resemblance to the original lead, but are legitimately assignable to the "/NM" category. In addition to the citations given in our previous reviews covering these methodologies, there have been some recent publications that can be consulted in order to demonstrate how "privileged structures from Nature" are demonstrated sources of molecular skeletons around which one may build libraries.[120−123]

Overview of Results. The data that have been analyzed in a variety of ways are presented as a series of bar graphs and pie charts and two major tables in order to establish the overall picture and then are further subdivided into some major therapeutic areas using a tabular format. The time frame covered is the 34 years from January 1, 1981, to December 31, 2014.

- New Approved Drugs: From all source categories; pie chart (Figure 1)
- New Approved Drugs: By source/year; bar graph (Figure 2)
- Sources of All NCEs: Where four or more drugs were approved per medical indication, their sources are shown, and listings of diseases with ≤3 approved drugs (Table 2)
- Sources of Small-Molecule NCEs: All subdivisions; pie chart (Figure 3)
- Sources of Small-Molecule NCEs: By source/year; bar graph (Figure 4)
- Total Small Molecules: By year; point chart (Figure 5)
- N/NB/ND and S* Categories: By year; bar graph (Figure 6)
- Percentage of N* Sources: By year; bar graph (Figure 7)
- Antibacterial Drugs: Generic and trade names, year, reference, and source (Table 3)
- Antifungal Drugs: Generic and trade names, year, reference, and source (Table 4)
- Antiviral Drugs: Generic and trade names, year, reference, and source (Table 5)
- Antiparasitic Drugs: Generic and trade names, year, reference, and source (Table 6)
- Anti-infective Drugs: All molecules, source, and numbers (Table 7)
- Anti-infective Drugs: Small molecules, source, and numbers (Table 8)
- Anticancer Drugs: Generic and trade names, year, reference by source (Table 9; Figure 8 all drugs pie chart; Figure 9, small molecules pie chart)
- All Anticancer Drugs (very late 1930s−12/2014): Generic and trade names, year, and reference by source (Table 10; Figure 10 pie chart; Figure 11, bar graph)

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Table 4. Antifungal Drugs from 1/1/1981 to 12/31/2010 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
interferon gamma-n1	OGamma100	1996	DNP 10	13	B
anidulafungin	Eraxis	2006	DNP 20	24	ND
caspofungin acetate	Cancidas	2001	DNP 15	36	ND
micafungin sodium	Fungard	2002	ARMC 38	360	ND
amorolfine hydrochloride	Loceryl	1991	ARMC 27	322	S
butoconazole	Femstat	1986	ARMC 22	318	S
ciclopirox olamine	Loprox	1982	I 070449		S
cloconazole HCl	Pilzcin	1986	ARMC 22	318	S
eberconazole	Ebernet	2005	DNP 19	42	S
efinaconazole	Jublia	2013	DT 50(1)	66	S
fenticonazole nitrate	Lomexin	1987	ARMC 23	334	S
fluconazole	Diflucan	1988	ARMC 24	303	S
flutrimazole	Micetal	1995	ARMC 31	343	S
fosfluconazole	Prodif	2003	DNP 17	49	S
itraconazole	Sporanox	1988	ARMC 24	305	S
ketoconazole	Nizoral	1981	I 116505		S
lanoconazole	Astat	1994	ARMC 30	302	S
luliconazole	Lulicon	2005	DNP 19	42	S
naftifine HCl	Exoderil	1984	ARMC 20	321	S
neticonazole HCl	Atolant	1993	ARMC 29	341	S
oxiconazole nitrate	Oceral	1983	ARMC 19	322	S
posaconazole	Noxafil	2005	DNP 19	42	S
sertaconazole nitrate	Dermofix	1992	ARMC 28	336	S
sitafloxacin hydrate	Gracevit	2008	DNP 22	15	S
sulconazole nitrate	Exelderm	1985	ARMC 21	332	S
tavaborole	Kerydin	2014	DT 51(1)	51	S
terconazole	GynoTerazol	1983	ARMC 19	324	S
tioconazole	Trosyl	1983	ARMC 19	324	S
voriconazole	Vfend	2002	ARMC 38	370	S
butenafine hydrochloride	Mentax	1992	ARMC 28	327	S/NM
liranaftate	Zefnart	2000	DNP 14	21	S/NM
terbinafine hydrochloride	Lamisil	1991	ARMC 27	334	S/NM

- Antidiabetic Drugs: Generic and trade names, year, reference, and source (Table 11)

The extensive data sets shown in the figures and tables referred to above continue to highlight the continuing role that natural products and structures derived from or related to natural products from all sources have played, and continue to play, in the development of the current therapeutic armamentarium of the physician. Inspection of the data shows the continued important role for natural products in spite of the greatly reduced level of natural-products-based drug discovery programs in major pharmaceutical houses.

Inspection of the rate of NCE approvals as shown in Figures 2 and 4−7 demonstrate that even in 2014 the natural products field is still producing, or is involved in, ∼40% of all small molecules in the years 2000−2008, with a drop to ∼20% in 2009, followed by a rebound to 45% in 2010, and then fluctuation between a low of ∼13% in 2013 to between 25% and 30% in the other years of the second decade of the 21st century. The mean and standard deviation for these 15 years are 34 ± 9%, without including any of the natural-product-inspired classifications ("S*", "S*/NM", and "S/NM").

As was shown in the 2012 review, a significant number of all NCEs still fall into the categories of biological ("B") or vaccines ("V"), with 351 of 1562, or 23% (differs slightly from Figure 1 due to rounding), over the full 34-year period, and it is admitted that not all of the vaccines approved in these 34 years have been identified. We hope that in the last 14 or 15 years a majority have been captured, although some of the more obscure anti-influenza variants may not have been. Thus, the proportion of approved vaccines may well be higher over the longer time frame. Inspection of Figure 2 shows the significant proportion that these two categories hold in the number of approved drugs from 2000, where, in some years, these categories accounted for ca. 50% of all approvals. If the three "N" categories are included, then the proportions of formally nonsynthetics are even higher for these years, although this figure would increase if the "S*" variants are included.

***De Novo* Combinatorial Drugs.** As mentioned earlier, in spite of many years of work by the pharmaceutical industry devoted to high-throughput screening of very significant numbers of combinatorial chemistry products (cf. Macarron's[20,24,25] and Wassermann's[26] papers on the industrial perspectives), during this time period, only two approved drugs could be found that fall under the *de novo* combinatorial category, sorafenib (**1**) and ataluren (**2**), with vemurafenib (**3**) potentially falling into this category due to the use of fragment-based methods.

Natural Product Mimics. Overall, of the 1562 NCEs covering all diseases/countries/sources in the years 01/1981−12/2014, and using the "NM" classifications introduced in our 2003 review,[2] the 334 compounds falling into these categories accounted for 21%, or if using just the small molecules where the divisor drops to 1211, the figure becomes 28%. This demonstrates the influence of "other than formal synthetics" on drug discovery and approval (Figures 1 and 3). In the 2012 review, the corresponding figures were ∼20% for all drugs and 25% for small molecules.[4]

Disease Area Breakdowns. It should be noted before proceeding with this and subsequent sections that we altered some of the "disease nomenclature terminology", for example, rolling in all antidiabetic treatments under one category rather than subdividing into types 1 and 2. Thus, a direct comparison of Table 2 in this review with its predecessor tables needs to take such modifications into account. Inspection of Table 2 demonstrates that, overall, the major disease areas that have been investigated (in terms of numbers of drugs approved) in the pharmaceutical industry continue to be infectious diseases (microbial, parasitic, and viral), cancer, hypertension, antidiabetic, and inflammation, all with over 50 approved drug

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Table 5. Antiviral Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
	Oralgen	2007	I 415378		B
IGIV-HB	Niuliva	2009	DNP 23	16	B
immunoglobulin intravenous	Gammagard Liquid	2005	I 231564		B
interferon alfa	Alfaferone	1987	I 215443		B
interferon alfa-2b	Viraferon	1985	I 165805		B
interferon alfacon-1	Infergen	1997	ARMC 33	336	B
interferon alfa-n1	Wellferon	1986	I 125561		B
interferon alfa-n3	Alferon N	1990	DNP 04	104	B
interferon beta	Frone	1985	I115091		B
palivizumab	Synagis	1998	DNP 12	33	B
peginterferon alfa-2a	Pegasys	2001	DNP 15	34	B
peginterferon alfa-2b	Pegintron	2000	DNP 14	18	B
resp syncytial virus IG	RespiGam	1996	DNP 10	11	B
thymalfasin	Zadaxin	1996	DNP 10	11	B
enfuvirtide	Fuzeon	2003	ARMC 39	350	ND
laninamivir octanoate	Inavir	2010	I 340894		ND
oseltamivir	Tamiflu	1999	ARMC 35	346	ND
zanamivir	Relenza	1999	ARMC 35	352	ND
daclatasvir dihydrochloride	Daklinza	2014	DT 51(1)	48	S
dasabuvir	Exviera	2014	DT 51(1)	50	S
delavirdine mesylate	Rescriptor	1997	ARMC 33	331	S
dolutegravir	Tivicay	2013	DT 50(1)	63	S
efavirenz	Sustiva	1998	ARMC 34	321	S
elvitegravir	Viteka	2013	DT 50(1)	63	S
foscarnet sodium	Foscavir	1989	ARMC 25	313	S
imiquimod	Aldara	1997	ARMC 33	335	S
maraviroc	Celsentri	2007	ARMC 43	478	S
nevirapine	Viramune	1996	ARMC 32	313	S
propagermanium	Serosion	1994	ARMC 30	308	S
raltegravir potassium	Isentress	2007	ARMC 43	484	S
rilpivirine hydrochloride	Edurant	2011	DT 48(1)	41	S
rimantadine HCI	Roflual	1987	ARMC 23	342	S
asunaprevir	Sunvepra	2014	DT 51(1)	48	S/NM
cobicistat	Tybost	2013	DT 50(1)	63	S/NM
darunavir	Prezista	2006	DNP 20	25	S/NM
ledipasvir	Harvoni	2014	DT 51(1)	48	S/NM
peramivir	PeramiFlu	2010	I 273549		S/NM
abacavir sulfate	Ziagen	1999	ARMC 35	333	S*
acyclovir	Zovirax	1981	I 091119		S*
adefovir dipivoxil	Hepsera	2002	ARMC 38	348	S*
cidofovir	Vistide	1996	ARMC 32	306	S*
clevudine	Levovir	2007	ARMC 43	466	S*
didanosine	Videx	1991	ARMC 27	326	S*
emtricitabine	Emtriva	2003	ARMC 39	350	S*
entecavir	Baraclude	2005	DNP 19	39	S*
epervudine	Hevizos	1988	I 157373		S*
etravirine	Intelence	2008	DNP 22	15	S*
famciclovir	Famvir	1994	ARMC 30	300	S*
ganciclovir	Cymevene	1988	ARMC 24	303	S*
inosine pranobex	Imunovir	1981	I 277341		S*
lamivudine	Epivir	1995	ARMC 31	345	S*
penciclovir	Vectavir	1996	ARMC 32	314	S*
sofosbuvir	Solvadi	2013	DT 50(1)	64	S*
sorivudine	Usevir	1993	ARMC 29	345	S*
stavudine	Zerit	1994	ARMC 30	311	S*
telbividine	Sebivo	2006	DNP 20	22	S*
tenofovir disoproxil fumarate	Viread	2001	DNP 15	37	S*
valaciclovir HCl	Valtrex	1995	ARMC 31	352	S*
valganciclovir	Valcyte	2001	DNP 15	36	S*
zalcitabine	Hivid	1992	ARMC 28	338	S*
zidovudine	Retrovir	1987	ARMC 23	345	S*

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Table 5. continued

generic name	trade name	year introduced	volume	page	source
amprenavir	Agenerase	1999	ARMC 35	334	S*/NM
atazanavir	Reyataz	2003	ARMC 39	342	S*/NM
boceprevir	Victrelis	2011	DT 48(1)	41	S*/NM
favipiravir	Avigan	2014	DT 51(1)	50	S*/NM
fomivirsen sodium	Vitravene	1998	ARMC 34	323	S*/NM
fosamprenevir	Lexiva	2003	ARMC 39	353	S*/NM
indinavir sulfate	Crixivan	1996	ARMC 32	310	S*/NM
lopinavir	Kaletra	2000	ARMC 36	310	S*/NM
neflinavir mesylate	Viracept	1997	ARMC 33	340	S*/NM
ombitasvir	Viekira Pak	2014	DT 51(1)	50	S*/NM
paritaprevir	Viekira Pak	2014	DT 51(1)	50	S*/NM
ritonavir	Norvir	1996	ARMC 32	317	S*/NM
saquinavir mesylate	Invirase	1995	ARMC 31	349	S*/NM
simeprevir	Sovirad	2013	DT 50(1)	63	S*/NM
telaprevir	Incivek	2011	DT 48(1)	41	S*/NM
tipranavir	Aptivus	2005	DNP 19	42	S*/NM
vaniprevir	Vanihep	2014	DT 51(1)	49	S*/NM
	ACAM-2000	2007	I 328985		V
	Bilive	2005	DNP 19	43	V
	Celtura	2009	DNP 23	17	V
	Celvapan	2009	DNP 23	17	V
	Daronix	2007	I 427024		V
	Fluval P	2009	DNP 23	17	V
	Fluzone Quadrivalent	2013	DT 50(1)	68	V
	Focetria	2009	DNP 23	17	V
	Grippol Neo	2009	DNP 23	16	V
	Hexyon	2013	DT 50(1)	69	V
	Imvanex	2013	DT 50(1)	69	V
	Optaflu	2007	I 410266		V
	Pandremix	2009	DNP 23	17	V
	Panenza	2009	DNP 23	17	V
	Panflu	2008	DNP 22	16	V
	Vaxiflu-S	2010	I 698015		V
	VariZIG	2005	I 230590		V
	Vepacel	2012	I 768351		V
9vHPV	Gardasil 9	2014	DT 51(1)	52	V
HPV vaccine	Gardasil	2006	DNP 20	26	V
anti-Hep B immunoglobulin	HepaGam B	2006	DNP 20	27	V
antirabies vaccine	Rabirix	2006	DNP 20	27	V
attenuated chicken pox vaccine	Merieux Varicella	1993	DNP 07	31	V
BBIL/JEV	Jenvac	2013	DT 50(1)	68	V
chimerivax-JE	Imojev	2012	I 292954		V
CSL-401	Panvax	2008	DNP 22	16	V
FLU-Q-QIV	Fluarix Quadrivalent	2012	DT 50(1)	68	V
GSK-1562902A	Prepandrix	2008	DNP 22	16	V
GSK-2282512A	Fluarix Quadrivalent	2012	I 709665		V
H5N1 avian flu vaccine		2007	I 440743		V
hepatitis a vaccine	Aimmugen	1995	DNP 09	23	V
hepatitis a vaccine	Havrix	1992	DNP 06	99	V
hepatitis a vaccine	Vaqta	1996	DNP 10	11	V
hepatitis b vaccine	Biken-HB	1993	DNP 07	31	V
hepatitis b vaccine	Bio-Hep B	2000	DNP 14	22	V
hepatitis b vaccine	Engerix B	1987	I 137797		V
hepatitis b vaccine	Fendrix	2005	DNP 19	43	V
hepatitis b vaccine	Hepacure	2000	DNP 14	22	V
hepatitis b vaccine	Meinyu	1997	DNP 11	24	V
hepatitis a and b vaccine	Ambirix	2003	I 334416		V
HN-VAC	HNVAC	2010	I 684608		V
inact hepatitis a vaccine	Avaxim	1996	DNP 10	12	V
influ A (H1N1) monovalent		2010	I 678265		V
influenza vaccine	Invivac	2004	I 391186		V

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Table 5. continued

generic name	trade name	year introduced	volume	page	source
influenza vaccine	Optaflu	2008	DNP 22	16	V
influenza virus (live)	FluMist	2003	ARMC 39	353	V
influenza virus vaccine	Afluria	2007	I 449226		V
KD-295		2014	DT 51(1)	52	V
measles/rubella vaccine		2011	DT 48(1)	44	V
Medi-3250	FluMist Quadrivalent	2012	I 669909		V
MR vaccine	Mearubik	2005	DNP 19	44	V
rec hepatitis B vaccine	Supervax	2006	DNP 20	27	V
rotavirus vaccine	Rotarix	2005	DNP 18	29	V
rotavirus vaccine	Rota-Shield	1998	DNP 12	35	V
rotavirus vaccine	Rotateq	2006	DNP 20	26	V
rubella vaccine	Ervevax	1985	I 115078		V
varicella virus vaccine	Varivax	1995	DNP 09	25	V
VCIV	PreFluCel	2010	I 444826		V
zoster vaccine live	Zostavax	2006	DNP 20	26	V

Table 6. Antiparasitic Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
artemisinin	Artemisin	1987	ARMC 23	327	N
ivermectin	Mectizan	1987	ARMC 23	336	N
arteether	Artemotil	2000	DNP 14	22	ND
artemether	Artemetheri	1987	I 90712		ND
artesunate	Arinate	1987	I 91299		ND
eflornithine HCl	Ornidyl	1990	DNP 04	104	ND
mefloquine HCI	Fansimef	1985	ARMC 21	329	ND
albendazole	Eskazole	1982	I 129625		S
delamanid	Deltyba	2014	DF 51(1)	48	S
halofantrine	Halfan	1988	ARMC 24	304	S
lumefantrine	?	1987	I 269095		S
quinfamide	Amenox	1984	ARMC 20	322	S
atovaquone	Mepron	1992	ARMC 28	326	S*
bulaquine/ chloroquine	Aablaquin	2000	DNP 14	22	S*
trichomonas vaccine	Gynatren	1986	I 125543		V

therapies. It should be noted, however, that the numbers of approved drugs/disease do not correlate with the "value" as measured by sales. For example, the best-selling drug of all at the moment is atorvastatin (Lipitor), a hypocholesterolemic descended directly from a microbial natural product, which sold over (U.S.) $11 billion in 2004, and, if one includes sales by Pfizer and Astellas Pharma over the 2004 to 2014 time frames, sales have hovered in the range (U.S.) $12−14 billion depending upon the year. However, this figure is almost sure to be eclipsed in short order by the new drugs approved for hepatitis C treatments such as sofosbuvir (**14**), which is a masked nucleotide, but is currently classified by us as an "S*", although it is obviously based upon an NP scaffold.

Table 8. Small-Molecule Anti-infective (Antibacterial, Fungal, Parasitic, and Viral) Drugs (n = 221)

indication	total	N	ND	S	S/NM	S*	S*/NM
antibacterial	112	11	71	29			1
antifungal	31		3	25	3		
antiparasitic	14	2	5	5		2	
antiviral	64		4	14	5	24	17
total	221	13	83	73	8	26	18
percentage	100	5.9	37.6	33.0	3.6	11.8	8.1

Anti-infectives in General. This is the major category by far including antiviral vaccines, with 326 (25%) of the total drug entities (1328 for indications ≥4; Table 2) falling into this one major human disease area. On further analysis (Tables 7 and 8), the influence of biologicals and vaccines in this disease complex is such that only 22% are synthetic in origin (Table 7). If one considers only small molecules (reducing the total by 105 to 221; Table 8), then the synthetic figure goes up to 33%, marginally greater than in our 2012 report.[4] As reported previously,[1−4] these synthetic drugs tend to be of two basic chemotypes, the azole-based antifungals and the quinolone-based antibacterials.

Anitbacterial Agents. Nine small-molecule drugs were approved in the antibacterial area from January 2011 to December 2014. One, fidaxomycin (**15**), was classified as an "N"; four were classified as "ND", with the first, ceftaroline (**16**), being a semisynthetic cephalosporin, the second being another cephalosporin derivative, cetolozane (**17a**) in combination with

Table 7. All Anti-infective (Antibacterial, Fungal, Parasitic, and Viral) Drugs (n = 326)

indication	total	B	N	ND	S	S/NM	S*	S*/NM	V
antibacterial	141	1	11	71	29			1	28
antifungal	32	1		3	25	3			
antiparasitic	15		2	5	5		2		1
antiviral	138	14		4	14	5	24	17	60
total	326	16	13	83	73	8	26	18	89
percentage	100	4.9	4.0	25.5	22.4	2.4	8.0	5.5	27.3

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Table 9. Anticancer Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
	Rexin-G	2007	I 346431		B
131I-chTNT		2007	I 393351		B
alemtuzumab	Campath	2001	DNP 15	38	B
bevacizumab	Avastin	2004	ARMC 40	450	B
blinatumomab	Blincyto	2014	DT 51(1)	55	B
catumaxomab	Removab	2009	DNP 23	18	B
celmoleukin	Celeuk	1992	DNP 06	102	B
cetuximab	Erbitux	2003	ARMC 39	346	B
denileukin diftitox	Ontak	1999	ARMC 35	338	B
H-101		2005	DNP 19	46	B
ibritumomab	Zevalin	2002	ARMC 38	359	B
interferon alfa2a	Roferon-A	1986	I 204503		B
interferon, gamma-1a	Biogamma	1992	ARMC 28	332	B
interleukin-2	Proleukin	1989	ARMC 25	314	B
ipilimumab	Yervoy	2011	DT 48(1)	45	B
mobenakin	Octin	1999	ARMC 35	345	B
mogamulizumab	Poteligeo	2012	I 433141		B
nimotuzumab	BIOMAb EFGR	2006	DNP 20	29	B
nivolumab	Optivo	2014	DT 51(1)	56	B
obinutuzumab	Gazyva	2013	DT 50(1)	70	B
ofatumumab	Arzerra	2009	DNP 23	18	B
panitumumab	Vectibix	2006	DNP 20	28	B
pegaspargase	Oncaspar	1994	ARMC 30	306	B
pembrolizumab	Keytruda	2014	DT 51(1)	56	B
pertuzumab	Omnitarg	2012	I 300439		B
racotumomab	Vaxira	2013	DT 50(1)	72	B
ramucirumab	Cyramza	2014	DT 51(1)	55	B
rituximab	Rituxan	1997	DNP 11	25	B
sipuleucel-T	Provenge	2010	I 259673		B
tasonermin	Beromun	1999	ARMC 35	349	B
teceleukin	Imumace	1992	DNP 06	102	B
tositumomab	Bexxar	2003	ARMC 39	364	B
trastuzumab	Herceptin	1998	DNP 12	35	B
aclarubicin	Aclacin	1981	P090013		N
aminolevulinic acid HCl	Levulan	2000	DNP 14	20	N
angiotensin II	Delivert	1994	ARMC 30	296	N
arglabin	?	1999	ARMC 35	335	N
homoharringtonine	Ceflatonin	2012	I 090682		N
ingenol mebutate	Picato	2012	I 328987		N
masoprocol	Actinex	1992	ARMC 28	333	N
paclitaxel	Taxol	1993	ARMC 29	342	N
paclitaxel nanoparticles	Abraxane	2005	DNP 19	45	N
paclitaxel nanoparticles	Nanoxel	2007	I 422122		N
paclitaxel nanoparticles	Genexol-PM	2007	I 811264		N
paclitaxel nanoparticles	PICN	2014	DT 51(1)	58	N
pentostatin	Nipent	1992	ARMC 28	334	N
peplomycin	Pepleo	1981	I090889		N
romidepsin	Istodax	2010	DNP 23	18	N
trabectedin	Yondelis	2007	ARMC 43	492	N
solamargines	Curaderm	1989	DNP 03	25	NB
abiratenone acetate	Zytiga	2011	DT 48(1)	44	ND
alitretinoin	Panretin	1999	ARMC 35	333	ND
aminolevulinic-CO_2CH_3	Metvix	2001	DNP 15	34	ND
amrubicin HCl	Calsed	2002	ARMC 38	349	ND
belotecan hydrochloride	Camtobell	2004	ARMC 40	449	ND
bf-200 ala	Ameluz	2012	I 431098		ND
brentuximab vedotin	Adcetris	2011	DT 48(1)	45	ND
cabazitaxel	Jevtana	2010	I 287186		ND
carfilzomib	Kyprolis	2012	I 413092		ND
cladribine	Leustatin	1993	ARMC 29	335	ND
cytarabine ocfosfate	Starsaid	1993	ARMC 29	335	ND

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Table 9. continued

generic name	trade name	year introduced	volume	page	source
docetaxel	Taxotere	1995	ARMC 31	341	ND
elliptinium acetate	Celiptium	1983	I091123		ND
epirubicin HCl	Farmorubicin	1984	ARMC 20	318	ND
eribulin	Halaven	2010	I 287199		ND
etoposide phosphate	Etopophos	1996	DNP 10	13	ND
exemestane	Aromasin	1999	DNP 13	46	ND
formestane	Lentaron	1993	ARMC 29	337	ND
fulvestrant	Faslodex	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	Mylotarg	2000	DNP 14	23	ND
hexyl aminolevulinate	Hexvix	2004	I 300211		ND
idarubicin hydrochloride	Zavedos	1990	ARMC 26	303	ND
irinotecan hydrochloride	Campto	1994	ARMC 30	301	ND
ixabepilone	Ixempra	2007	ARMC 43	473	ND
mifamurtide	Junovan	2010	DNP 23	18	ND
miltefosine	Miltex	1993	ARMC 29	340	ND
pirarubicin	Pinorubicin	1988	ARMC 24	309	ND
pralatrexate	Folotyn	2009	DNP 23	18	ND
talaporfin sodium	Laserphyrin	2004	ARMC 40	469	ND
temsirolimus	Toricel	2007	ARMC 43	490	ND
topotecan HCl	Hycamptin	1996	ARMC 32	320	ND
trastuzumab emtansine	Kadcyla	2013	DT 50(1)	69	ND
triptorelin	Decapeptyl	1986	I 090485		ND
valrubicin	Valstar	1999	ARMC 35	350	ND
vapreotide acetate	Docrised	2004	I 135014		ND
vinflunine	Javlor	2010	I 219585		ND
vinorelbine	Navelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	Smancs	1994	ARMC 30	313	ND
aminoglutethimide	Cytadren	1981	I 070408		S
amsacrine	Amsakrin	1987	ARMC 23	327	S
arsenic trioxide	Trisenox	2000	DNP 14	23	S
bisantrene hydrochloride	Zantrene	1990	ARMC 26	300	S
carboplatin	Paraplatin	1986	ARMC 22	318	S
flutamide	Drogenil	1983	ARMC 19	318	S
fotemustine	Muphoran	1989	ARMC 25	313	S
heptaplatin/SK-2053R	Sunpla	1999	ARMC 35	348	S
lobaplatin	Lobaplatin	1998	DNP 12	35	S
lonidamine	Doridamina	1987	ARMC 23	337	S
miriplatin hydrate	Miripla	2010	DNP 23	17	S
nedaplatin	Aqupla	1995	ARMC 31	347	S
nilutamide	Anadron	1987	ARMC 23	338	S
olaparib	Lynparza	2014	DT 51(1)	56	S
oxaliplatin	Eloxatin	1996	ARMC 32	313	S
plerixafor hydrochloride	Mozobil	2009	DNP 22	17	S
pomalidomide	Pomalyst	2013	DT 50(1)	70	S
porfimer sodium	Photofrin	1993	ARMC 29	343	S
ranimustine	Cymerine	1987	ARMC 23	341	S
sobuzoxane	Parazolin	1994	ARMC 30	310	S
sorafenib	Nexavar	2005	DNP 19	45	S
vismodegib	Erivedge	2012	I 473491		S
zoledronic acid	Zometa	2000	DNP 14	24	S
alectinib hydrochloride	Alecensa	2014	DT 51(1)	56	S/NM
anastrozole	Arimidex	1995	ARMC 31	338	S/NM
apatinib mesylate	Aitan	2014	DT 51(1)	56	S/NM
bicalutamide	Casodex	1995	ARMC 31	338	S/NM
bortezomib	Velcade	2003	ARMC 39	345	S/NM
camostat mesylate	Foipan	1985	ARMC 21	325	S/NM
ceritinib	Zykadia	2014	DT 51(1)	55	S/NM
dasatinib	Sprycel	2006	DNP 20	27	S/NM
enzalutamide	Xtandi	2012	I 438422		S/NM
erlotinib hydrochloride	Tarceva	2004	ARMC 40	454	S/NM
fadrozole HCl	Afema	1995	ARMC 31	342	S/NM

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Table 9. continued

generic name	trade name	year introduced	volume	page	source
gefitinib	Iressa	2002	ARMC 38	358	S/NM
imatinib mesilate	Gleevec	2001	DNP 15	38	S/NM
lapatinib ditosylate	Tykerb	2007	ARMC 43	475	S/NM
letrazole	Femara	1996	ARMC 32	311	S/NM
nilotinib hydrochloride	Tasigna	2007	ARMC 43	480	S/NM
pazopanib	Votrient	2009	DNP 23	18	S/NM
sunitinib malate	Sutent	2006	DNP 20	27	S/NM
temoporfin	Foscan	2002	I 158118		S/NM
toremifene	Fareston	1989	ARMC 25	319	S/NM
azacytidine	Vidaza	2004	ARMC 40	447	S*
capecitabine	Xeloda	1998	ARMC 34	319	S*
carmofur	Mifurol	1981	I 091100		S*
clofarabine	Clolar	2005	DNP 19	44	S*
decitabine	Dacogen	2006	DNP 20	27	S*
doxifluridine	Furtulon	1987	ARMC 23	332	S*
enocitabine	Sunrabin	1983	ARMC 19	318	S*
fludarabine phosphate	Fludara	1991	ARMC 27	327	S*
gemcitabine HCl	Gemzar	1995	ARMC 31	344	S*
mitoxantrone HCI	Novantrone	1984	ARMC 20	321	S*
nelarabine	Arranon	2006	ARMC 42	528	S*
pixantrone dimaleate	Pixuri	2012	I 197776		S*
tipiracil hydrochloride	Lonsurf	2014	DT 51(1)	58	S*
abarelix	Plenaxis	2004	ARMC 40	446	S*/NM
afatinib	Gilotrif	2013	DT 50(1)	69	S*/NM
axitinib	Inlyta	2012	I 38296		S*/NM
belinostat	Beleodaq	2014	DT 51(1)	56	S*/NM
bexarotene	Targretine	2000	DNP 14	23	S*/NM
bosutinib	Bosulif	2012	I 301996		S*/NM
cabozantinib S-malate	Cometriq	2012	I 379934		S*/NM
crizotinib	Xalkori	2011	DT 48(1)	45	S*/NM
dabrafenib mesilate	Tafinlar	2013	DT 50(1)	69	S*/NM
degarelix	Firmagon	2009	DNP 22	16	S*/NM
ibrutinib	Imbruvica	2013	DT 50(1)	71	S*/NM
idelalisib	Zydelig	2014	DT 51(1)	54	S*/NM
pemetrexed disodium	Alimta	2004	ARMC 40	463	S*/NM
ponatinib	Iclusig	2013	DT 50(1)	70	S*/NM
radotinib	Supect	2012	I 395674		S*/NM
raltiterxed	Tomudex	1996	ARMC 32	315	S*/NM
regorafenib	Stivarga	2012	I 395674		S*/NM
ruxolitinib phosphate	Jakafi	2011	DT 48(1)	47	S*/NM
tamibarotene	Amnoid	2005	DNP 19	45	S*/NM
temozolomide	Temodal	1999	ARMC 35	350	S*/NM
trametinib DMSO	Mekinist	2013	DT 50(1)	69	S*/NM
vandetanib	Caprelsa	2011	DT 48(1)	45	S*/NM
vemurafenib	Zeboraf	2011	DT 48(1)	45	S*/NM
vorinostat	Zolinza	2006	DNP 20	27	S*/NM
	Cervarix	2007	I 309201		V
autologous tumor cell-BCG	OncoVAX	2008	DNP 22	17	V
bcg live	TheraCys	1990	DNP 04	104	V
melanoma theraccine	Melacine	2001	DNP 15	38	V
vitespen	Oncophage	2008	DNP 22	17	V

the well-known β-lactamase inhibitor tazobactam (**17b**); the third was the modified glycopeptide dalvabancin (**18**); and the fourth was another of this class, oritavancin (**19**). The two synthetic molecules included the first novel anti-TB scaffold for many years, bedaquiline (**20**), and another "floxacin", finafloxacin (**21**). Overall, in the antibacterial area, as shown in Table 7, small molecules account for 112 agents, with "N" and "ND" compounds accounting for just over 73% of the approved agents.

What should make biomedical scientists and physicians involved in antibacterial research in academia or industry very nervous is the recent report from Liu et al.,[124] in the journal *Lancet Infectious Disease* in the middle of November 2015, where they reported that the class of compounds used effectively as the last resort (the peptidic colistins) now have a resistance determinant known as mcr-1 appearing in microbes in treated patients and animals.

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Table 10. All Anticancer Drugs (Late 1930s to 12/31/2014) Organized Alphabetically by Generic Name within Source

generic name	year introduced	reference	page	source
131I-chTNT	2007	I 393351		B
alemtuzumab	2001	DNP 15	38	B
aldesleukin	1992	ARMC 25	314	B
bevacizumab	2004	ARMC 40	450	B
catumaxomab	2009	DNP 23	18	B
celmoleukin	1992	DNP 06	102	B
cetuximab	2003	ARMC 39	346	B
denileukin diftitox	1999	ARMC 35	338	B
H-101	2005	DNP 19	46	B
ibritumomab	2002	ARMC 38	359	B
interferon alfa2a	1986	I 204503		B
interferon, gamma-1a	1992	ARMC 28	332	B
interleukin-2	1989	ARMC 25	314	B
ipilimumab	2011	DT 48(1)	45	B
mobenakin	1999	ARMC 35	345	B
mogamulizumab	2012	I 433141		B
nimotuzumab	2006	DNP 20	29	B
nivolumab	2014	DT 51(1)	56	B
obinutuzumab	2013	DT 50(1)	70	B
ofatumumab	2009	DNP 23	18	B
panitumumab	2006	DNP 20	28	B
pegaspargase	1994	ARMC 30	306	B
pembrolizumab	2014	DT 51(1)	56	B
pertuzumab	2012	I 300439		B
racotumomab	2013	DT 50(1)	72	B
ramucirumab	2014	DT 51(1)	55	B
Rexin-G (trade name)	2007	I 346431		B
rituximab	1997	DNP 11	25	B
sipuleucel-T	2010	I 259673		B
tasonermin	1999	ARMC 35	349	B
teceleukin	1992	DNP 06	102	B
tositumomab	2003	ARMC 39	364	B
trastuzumab	1998	DNP 12	35	B
PICN (Trade Name)	2014	DT 51(1)	58	N
aclarubicin	1981	I 090013		N
actinomycin D	1964	FDA		N
angiotensin II	1994	ARMC 30	296	N
arglabin	1999	ARMC 35	335	N
asparaginase	1969	FDA		N
bleomycin	1966	FDA		N
carzinophilin	1954	Japan Antibiotics		N
chromomycin A3	1961	Japan Antibiotics		N
daunomycin	1967	FDA		N
doxorubicin	1966	FDA		N
homoharringtonine	2012	I 090682		N
ingenol mebutate	2012	I 328987		N
leucovorin	1950	FDA		N
masoprocol	1992	ARMC 28	333	N
mithramycin	1961	FDA		N
mitomycin C	1956	FDA		N
neocarzinostatin	1976	Japan Antibiotics		N
paclitaxel	1993	ARMC 29	342	N
paclitaxel nanopart (Abraxane)	2005	DNP 19	45	N
paclitaxel nanopart (Nanoxel)	2007	I 422122		N
paclitaxel nanopart (Genexol-PM)	2007	I 811264		N
pentostatin	1992	ARMC 28	334	N
peplomycin	1981	I 090889		N
romidepsin	2010	DNP 23	18	N
sarkomycin	1954	FDA		N
streptozocin	pre-1977	Carter		N
testosterone	pre-1970	Cole		N

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Table 10. continued

generic name	year introduced	reference	page	source
trabectedin	2007	ARMC 43	492	N
vinblastine	1965	FDA		N
vincristine	1963	FDA		N
solamargines	1989	DNP 03	25	NB
abiratenone acetate	2011	DT 48(1)	44	ND
alitretinoin	1999	ARMC 35	333	ND
aminolevulinic-CO_2CH_3	2001	DNP 15	34	ND
amrubicin HCl	2002	ARMC 38	349	ND
belotecan hydrochloride	2004	ARMC 40	449	ND
bf-200 ala	2012	I 431098		ND
brentuximab vedotin	2011	DT 48(1)	45	ND
cabazitaxel	2010	I 287186		ND
calusterone	1973	FDA		ND
carfilzomib	2012	I 413092		ND
cladribine	1993	ARMC 29	335	ND
cytarabine ocfosfate	1993	ARMC 29	335	ND
dexamethasone	1958	FDA		ND
docetaxel	1995	ARMC 31	341	ND
dromostanolone	1961	FDA		ND
elliptinium acetate	1983	P091123		ND
epirubicin HCI	1984	ARMC 20	318	ND
eribulin	2010	I 287199		ND
estramustine	1980	FDA		ND
ethinyl estradiol	pre-1970	Cole		ND
etoposide	1980	FDA		ND
etoposide phosphate	1996	DNP 10	13	ND
exemestane	1999	DNP 13	46	ND
fluoxymesterone	pre-1970	Cole		ND
formestane	1993	ARMC 29	337	ND
fosfestrol	pre-1977	Carter		ND
fulvestrant	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	2000	DNP 14	23	ND
hexyl aminolevulinate	2004	I 300211		ND
histrelin	2004	I 109865		ND
hydroxyprogesterone	pre-1970	Cole		ND
idarubicin hydrochloride	1990	ARMC 26	303	ND
irinotecan hydrochloride	1994	ARMC 30	301	ND
ixabepilone	2007	ARMC 43	473	ND
medroxyprogesterone acetate	1958	FDA		ND
megesterol acetate	1971	FDA		ND
methylprednisolone	1955	FDA		ND
methyltestosterone	1974	FDA		ND
mifamurtide	2010	DNP 23	18	ND
miltefosine	1993	ARMC 29	340	ND
mitobronitol	1979	FDA		ND
nadrolone phenylpropionate	1959	FDA		ND
norethindrone acetate	pre-1977	Carter		ND
pirarubicin	1988	ARMC 24	309	ND
pralatrexate	2009	DNP 23	18	ND
prednisolone	pre-1977	Carter		ND
prednisone	pre-1970	Cole		ND
talaporfin sodium	2004	ARMC 40	469	ND
temsirolimus	2007	ARMC 43	490	ND
teniposide	1967	FDA		ND
testolactone	1969	FDA		ND
topotecan HCl	1996	ARMC 32	320	ND
trastuzumab emtansine	2013	DT 50(1)	69	ND
triamcinolone	1958	FDA		ND
triptorelin	1986	I 090485		ND
valrubicin	1999	ARMC 35	350	ND
vapreotide acetate	2004	I 135014		ND

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Table 10. continued

generic name	year introduced	reference	page	source
vindesine	1979	FDA		ND
vinflunine	2010	I 219585		ND
vinorelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	1994	ARMC 30	313	ND
amsacrine	1987	ARMC 23	327	S
arsenic trioxide	2000	DNP 14	23	S
bisantrene hydrochloride	1990	ARMC 26	300	S
busulfan	1954	FDA		S
carboplatin	1986	ARMC 22	318	S
carmustine (BCNU)	1977	FDA		S
chlorambucil	1956	FDA		S
chlortrianisene	pre-1981	Boyd		S
cis-diamminedichloroplatinum	1979	FDA		S
cyclophosphamide	1957	FDA		S
dacarbazine	1975	FDA		S
diethylstilbestrol	pre-1970	Cole		S
flutamide	1983	ARMC 19	318	S
fotemustine	1989	ARMC 25	313	S
heptaplatin/SK-2053R	1999	ARMC 35	348	S
hexamethylmelamine	1979	FDA		S
hydroxyurea	1968	FDA		S
ifosfamide	1976	FDA		S
levamisole	pre-1981	Boyd		S
lobaplatin	1998	DNP 12	35	S
lomustine (CCNU)	1976	FDA		S
lonidamine	1987	ARMC 23	337	S
mechlorethanamine	1958	FDA		S
melphalan	1961	FDA		S
miriplatin hydrate	2010	DNP 23	17	S
mitotane	1970	FDA		S
nedaplatin	1995	ARMC 31	347	S
nilutamide	1987	ARMC 23	338	S
nimustine hydrochloride	pre-1981	Boyd		S
oxaliplatin	1996	ARMC 32	313	S
pamidronate	1987	ARMC 23	326	S
pipobroman	1966	FDA		S
plerixafor hydrochloride	2009	DNP 22	17	S
porfimer sodium	1993	ARMC 29	343	S
procarbazine	1969	FDA		S
ranimustine	1987	ARMC 23	341	S
razoxane	pre-1977	Carter		S
semustine (MCCNU)	pre-1977	Carter		S
sobuzoxane	1994	ARMC 30	310	S
sorafenib	2005	DNP 19	45	S
thiotepa	1959	FDA		S
triethylenemelamine	pre-1981	Boyd		S
zoledronic acid	2000	DNP 14	24	S
alectinib hydrochloride	2014	DT 51(1)	56	S/NM
anastrozole	1995	ARMC 31	338	S/NM
apatinib mesylate	2014	DT 51(1)	56	S/NM
bicalutamide	1995	ARMC 31	338	S/NM
bortezomib	2003	ARMC 39	345	S/NM
camostat mesylate	1985	ARMC 21	325	S/NM
dasatinib	2006	DNP 20	27	S/NM
enzalutamide	2012	I 438422		S/NM
erlotinib hydrochloride	2004	ARMC 40	454	S/NM
fadrozole HCl	1995	ARMC 31	342	S/NM
gefitinib	2002	ARMC 38	358	S/NM
imatinib mesilate	2001	DNP 15	38	S/NM
lapatinib ditosylate	2007	ARMC 43	475	S/NM
letrazole	1996	ARMC 32	311	S/NM

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Table 10. continued

generic name	year introduced	reference	page	source
nafoxidine	pre-1977	Carter		S/NM
nilotinib hydrochloride	2007	ARMC 43	480	S/NM
pazopanib	2009	DNP 23	18	S/NM
sunitinib malate	2006	DNP 20	27	S/NM
tamoxifen	1973	FDA		S/NM
temoporfin	2002	I 158118		S/NM
toremifene	1989	ARMC 25	319	S/NM
aminoglutethimide	1981(?)	FDA		S*
azacytidine	2004	ARMC 40	447	S*
capecitabine	1998	ARMC 34	319	S*
carmofur	1981	I 091100		S*
clofarabine	2005	DNP 19	44	S*
cytosine arabinoside	1969	FDA		S*
decitabine	2006	DNP 20	27	S*
doxifluridine	1987	ARMC 23	332	S*
enocitabine	1983	ARMC 19	318	S*
floxuridine	1971	FDA		S*
fludarabine phosphate	1991	ARMC 27	327	S*
fluorouracil	1962	FDA		S*
ftorafur	1972	FDA		S*
gemcitabine HCl	1995	ARMC 31	344	S*
mercaptopurine	1953	FDA		S*
methotrexate	1954	FDA		S*
mitoxantrone HCI	1984	ARMC 20	321	S*
nelarabine	2006	ARMC 42	528	S*
pixantrone dimaleate	2012	I 197776		S*
thioguanine	1966	FDA		S*
tipiracil hydrochloride	2014	DT 51(1)	58	S*
uracil mustard	1966	FDA		S*
abarelix	2004	ARMC 40	446	S*/NM
afatinib	2013	DT 50(1)	69	S*/NM
axitinib	2012	I 38296		S*/NM
belinostat	2014	DT 51(1)	56	S*/NM
bexarotene	2000	DNP 14	23	S*/NM
bosutinib	2012	I 301996		S*/NM
cabozantinib S-malate	2012	I 301996		S*/NM
crizotinib	2012	I 379934		S*/NM
dabrafenib mesilate	2011	DT 48(1)	45	S*/NM
degarelix	2009	DNP 22	16	S*/NM
ibrutinib	2013	DT 50(1)	71	S*/NM
idelalisib	2014	DT 51(1)	54	S*/NM
pemetrexed disodium	2004	ARMC 40	463	S*/NM
ponatinib	2013	DT 50(1)	70	S*/NM
radotinib	2012	I 395674		S*/NM
raltiterxed	1996	ARMC 32	315	S*/NM
regorafenib	2012	I 395674		S*/NM
ruxolitinib phosphate	2011	DT 48(1)	47	S*/NM
tamibarotene	2005	DNP 19	45	S*/NM
Temozolomide	1999	ARMC 35	350	S*/NM
trametinib DMSO	2013	DT 50(1)	69	S*/NM
vandetanib	2011	DT 48(1)	45	S*/NM
vemurafenib	2011	DT 48(1)	45	S*/NM
vorinostat	2006	DNP 20	27	S*/NM
autologous tumor cell-BCG	2008	DNP 22	17	V
bcg live	1990	DNP 04	104	V
Cervarix (trade name)	2007	I 309201		V
melanoma theraccine	2001	DNP 15	38	V
vitespen	2008	DNP 22	17	V

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Table 11. Antidiabetic Drugs from 01.01.1981 to 12.31.2014 Organized Alphabetically by Generic Name within Source/Year

generic name	trade name	year introduced	volume	page	source
isophane insulin	Humulin N	1982	I 091583		B
porcine isophane insulin	Pork Insulatard	1982	I 302757		B
human insulin Zn suspension	Humulin L	1985	I 302828		B
human insulin zinc suspension	Humulin Zn	1985	I 091584		B
soluble insulin	Velosulin BR	1986	I 091581		B
human neutral insulin	Novolin R	1991	I 182551		B
hu neutral insulin	Insuman	1992	I 255451		B
mecasermin	Somazon	1994	DNP 08	28	B
insulin lispro	Humalog	1996	ARMC 32	310	B
porcine neutral insulin	Pork Actrapid	1998	I 302749		B
insulin aspart	NovoRapid	1999	DNP 13	41	B
insulin glargine	Lantus	2000	DNP 14	19	B
insulin aspart/IA protamine	NovoMix 30	2001	DNP 15	34	B
insulin determir	Levemir	2004	DNP 18	27	B
insulin glulisine	Apidra	2005	DNP 19	39	B
oral insulin	Oral-lyn	2005	DNP 19	39	B
pulmonary insulin	Exubera	2006	DNP 20	23	B
insulin degludec/ insulin aspar	DegludecPlus	2012	I 419438		B
insulin degludec	Degludec	2012	I 470782		B
pulmonary insulin	Afrezza	2014	DT 51(1)	45	B
albiglutide	Eperzan	2014	DT 51(1)	45	B
dulaglutide	Trulicity	2014	DT 51(1)	45	B
voglibose	Basen	1994	ARMC 30	313	N
acarbose	Glucobay	1990	DNP 03	23	ND
miglitol	Diastabol	1998	ARMC 34	325	ND
extenatide	Byetta	2005	DNP 19	40	ND
triproamylin acetate	Normylin	2005	DNP 19	40	ND
liraglutide	Victoza	2009	DNP 23	13	ND
lixisenatide	Lyxumia	2013	DT 50(1)	60	ND
glimepiride	Amaryl	1995	ARMC 31	344	S
repaglinide	Prandin	1998	ARMC 34	329	S
pioglitazone NCl	Actos	1999	ARMC 35	346	S
mitiglinide calcium hydrate	Glufast	2004	ARMC 40	460	S
epalrestat	Kinedak	1992	ARMC 28	330	S/ NM
troglitazone	Rezulin	1997	ARMC 33	344	S/ NM
rosiglitazone maleate	Avandia	1999	ARMC 35	348	S/ NM
sitagliptin	Januvia	2006	DNP 20	23	S/ NM
vildagliptin	Galvus	2007	ARMC 43	494	S/ NM
saxagliptin	Onglyza	2009	DNP 23	13	S/ NM
alogliptin benzoate	Nesina	2010	I 405286		S/ NM
linagliptin	Tradjenta	2011	DT 48(1)	39	S/ NM
teneligliptin hydrobromide	Tenelia	2012	I 343981		S/ NM
anagliptin	Suiny	2012	I 426247		S/ NM
tolrestat	Alredase	1989	ARMC 25	319	S/ NM
nateglinide	Starsis	1999	ARMC 35	344	S*
dapagliflozin	Forxiga	2012	I 356099		S*/ NM
canagliflozin	Invokana	2013	DT 50(1)	60	S*/ NM
empagliflozin	Jardiance	2014	DT 51(1)	45	S*/ NM
ipragliflozin proline	Suglat	2014	DT 51(1)	45	S*/ NM
tofogliflozin	Apleway	2014	DT 51(1)	45	S*/ NM
luseogliflozin	Lusefi	2014	DT 51(1)	45	S*/ NM

Antifungal Agents. In this area, two drugs were approved in the 2011 to 2014 time frame. These were two synthetic compounds, one the azole antifungal efinaconazole (**22**) ,and the other, tavaborole (**23**), is the first example of this novel skeleton containing boron. It should be noted, however, that a natural product, boromycin, a complex macrolide first isolated from *Streptomyces antibioticus*, was reported by the Zahner group[125] in 1967 with antibacterial activity, and then in 1996, it was reisolated by Kohno et al.[126] as an anti-HIV agent from an unspeciated streptomycete. Its probable mode of action is as a specialized ionophore. In contrast to the antibacterial agents, the majority of antifungal agents in the years from 1981 to 2014 are synthetic in origin, as can be seen from inspection of Table 8, with 28 of the 31 approved drugs (90%) being classified as other than natural product based. The paucity of natural product sources can be seen in the modern treatment regimens that still use agents such as amphotericin and griseofulvin, which are both listed in the *Integrity* database as being launched in 1958.

Antiviral Drugs. In this area, as mentioned earlier, a significant number of the agents are vaccines, predominately directed against various serotypes of influenza, as would be expected from the avian flu outbreaks. In the time frame 2011 to 2014, and looking only at small molecules, 16 drugs were approved for basically two viral diseases, HIV, as would be expected, and hepatitis C (HCV), with drugs directed against specific RNA polymerases and HCV proteases. There were no drugs formally from the "N*" categories, but eight fell into the "S*" or "S*/NM" classifications. In 2011, two "S*/NM" drugs were approved, boceprevir (**24**) and telaprevir (**25**), both directed against HCV proteases. None in this classification were approved in 2012. However, as mentioned above, in 2013 one "S*" drug, sofosbuvir (**14**), was approved for use against HCV. This particular drug, a "masked nucleotide", has the potential to

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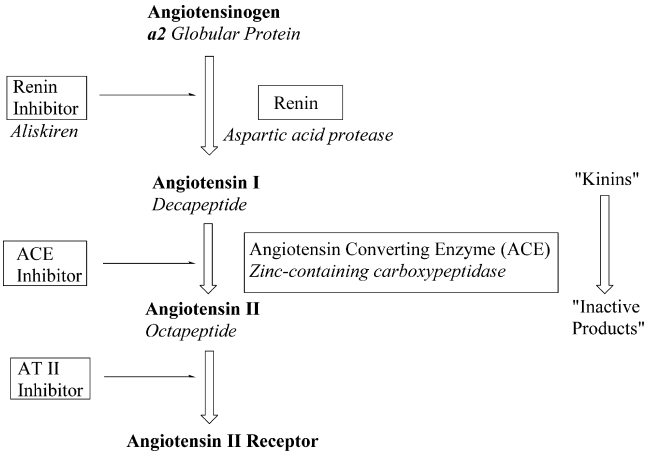
Scheme 1



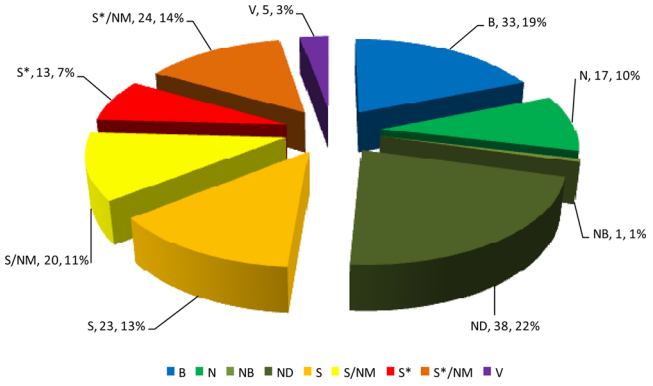
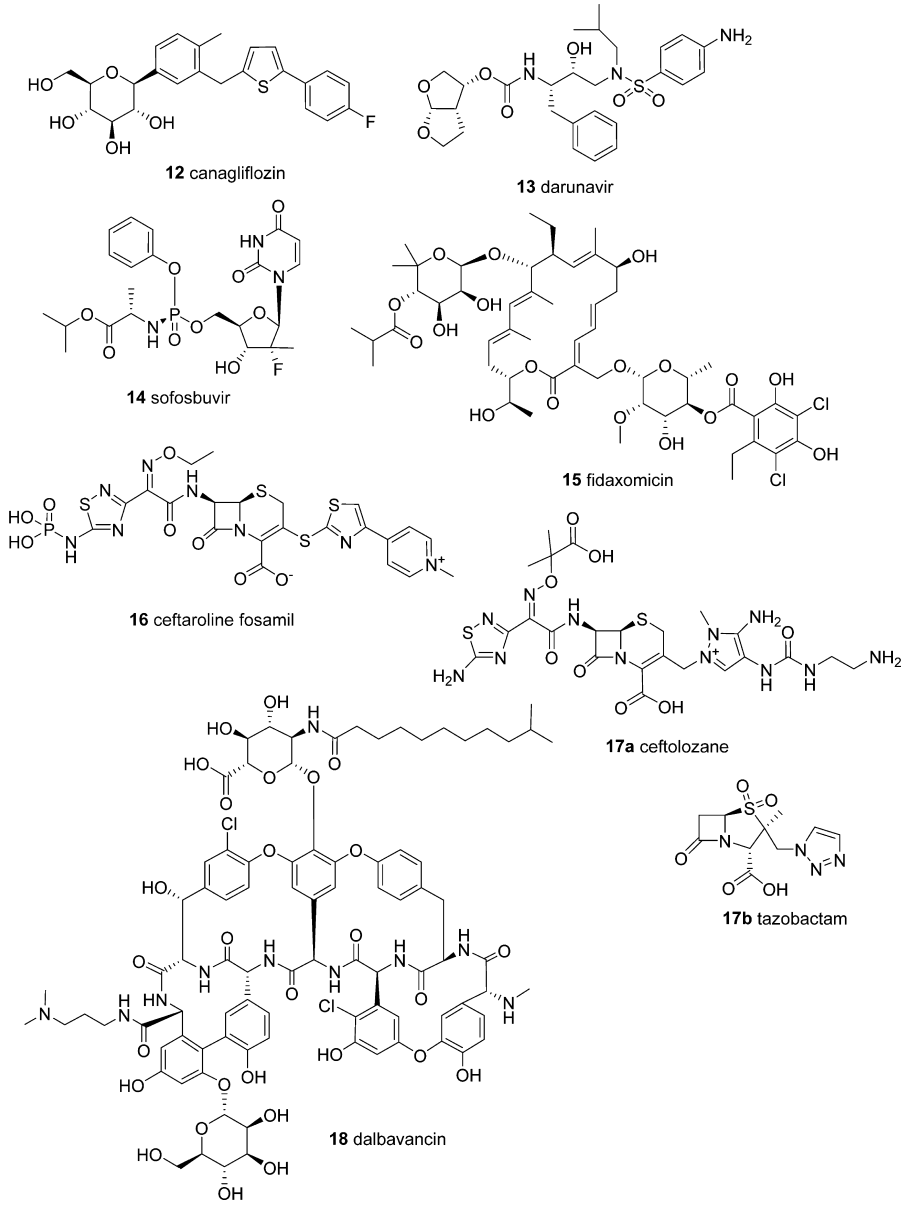


Figure 8. All anticancer drugs 1981−2014; n = 174.

become the best-selling drug of all time, as it currently is the only drug that cures HCV infections in roughly two months. However, its current nominal cost for this treatment is close to

Chart 2



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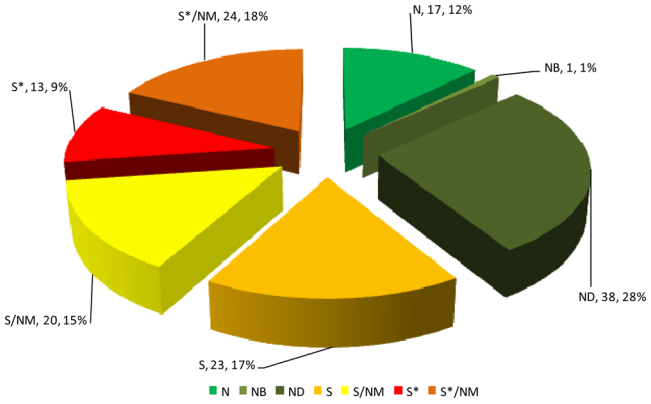

Figure 9. Small-molecule anticancer drugs 1940s–2014; n = 136.

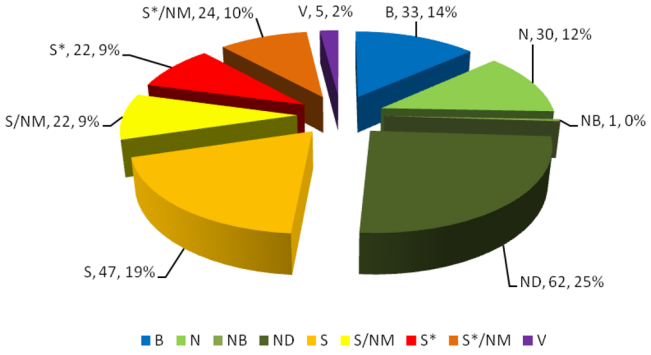

Figure 10. All anticancer drugs 1940s–2014 by source; n = 246.

$90 000 per patient. The only other curative treatment for patients with HCV once a severe stage is reached is a liver transplant. Also in the same year, the "S*/NM" classified drug simeprevir (**26**) was approved and acts against HCV proteases.

In 2014, however, there was a relative flood of approvals including one very unusual action by the FDA. The outlier, before this action is covered, was the approval of the anti-influenza small-molecule drug favipiravir (**27**). In 2014, the FDA approved a combination therapy known as Viekira Pak against HCV proteases. Normally, this combination therapy would not have been included in the listings, but in this case, the FDA effectively approved two clinical candidates, ombitasvir (**28**), then in phase II, and paritaprevir (**29**), then in phase III, in a combination with the 1996-approved drug ritonavir (**30**), also a compound falling into the "S*/NM" classification. Finally, under this category, the HCV protease inhibitor vaniprevir (**31**) was also approved in 2014.

If we now move to the synthetic area for the time period 2011 to 2014, there were five drugs in the "S" classification and three in the "S/NM" classification. In the "S" classification, there was one approval in 2011 of rilpivirine (**32**), a reverse-transcriptase inhibitor, and none in 2012, but in 2013 there were two drugs approved as HIV integrase inhibitors, dolutegravir (**33**) and elvitegravir (**34**). Then, in 2014, two more anti-HCV drugs, daclatasvir (**35**) and dasabuvir (**36**), were approved. Under the "S/NM" classification, three drugs were approved, none in 2011 and 2012, one [cobicistat (**37**)] in 2013 as an HIV protease inhibitor, and then two anti-HCV drugs in 2014, asunaprevir (**38**) and ledipasvir (**39**). The latter drug is unusual in that it is part of a combination therapy with sofosbuvir (**14**) under the trade name Harvoni and thus may be in direct competition with the earlier drug.

To sum up, in contrast to the antibacterial and antifungal areas, in the antiviral case, as shown in Table 7, small molecules accounted for 64 drugs, with only four (or 6%) in the 34 years of coverage falling into the "ND" category. However, as mentioned earlier, we have consistently placed modified nucleosides, peptidomimetics, etc., into the "S*" or "S*/NM" category. If these are added to the four drugs mentioned above, then the other than synthetic molecules account for 45, or 70% overall.

Disease Areas without Current Natural Product Drugs. As reported in our earlier analyses,[1−4] there are still disease areas where at the present time the available drugs are totally synthetic in origin. These include antihistamines, diuretics, and hypnotics for indications with four or more approved drugs (cf., Table 2), and, as found in the earlier reviews, there are still a substantial number of indications in which there are three or less approved drugs that are also totally synthetic.

Disease Areas with "*/NM" Classified Drugs. As mentioned in our earlier reviews,[2−4] due to the introduction of the "NM" subcategory, indications such as antidepressants,

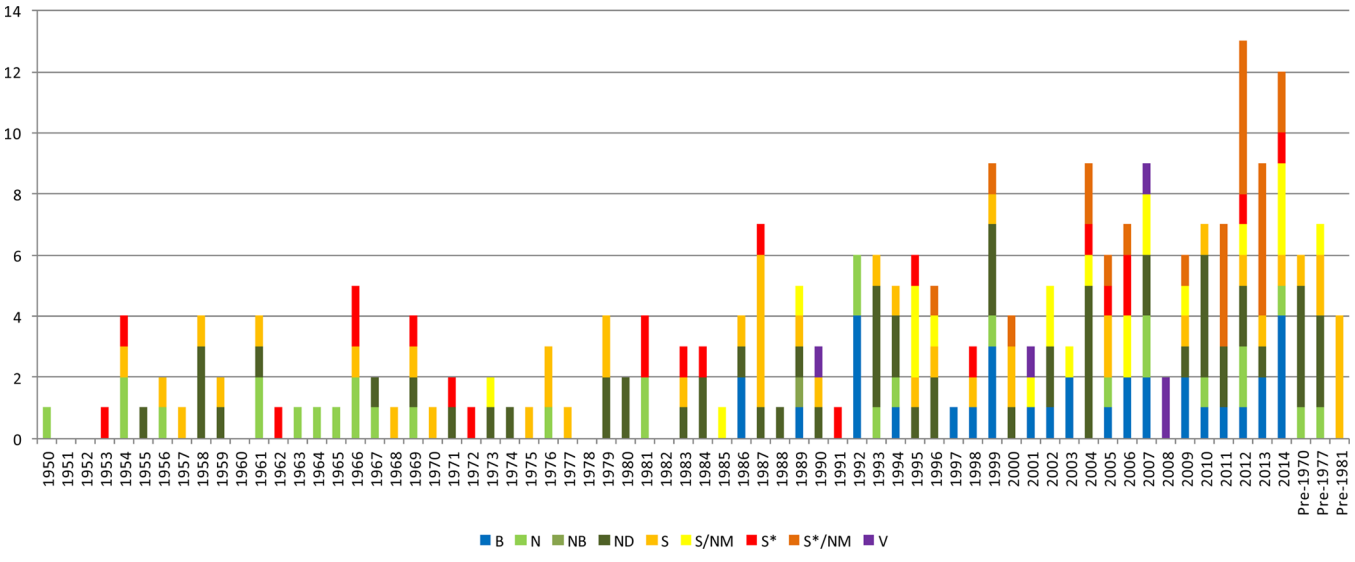

Figure 11. All anticancer drugs 1940s–2014 by source/year; n = 246.

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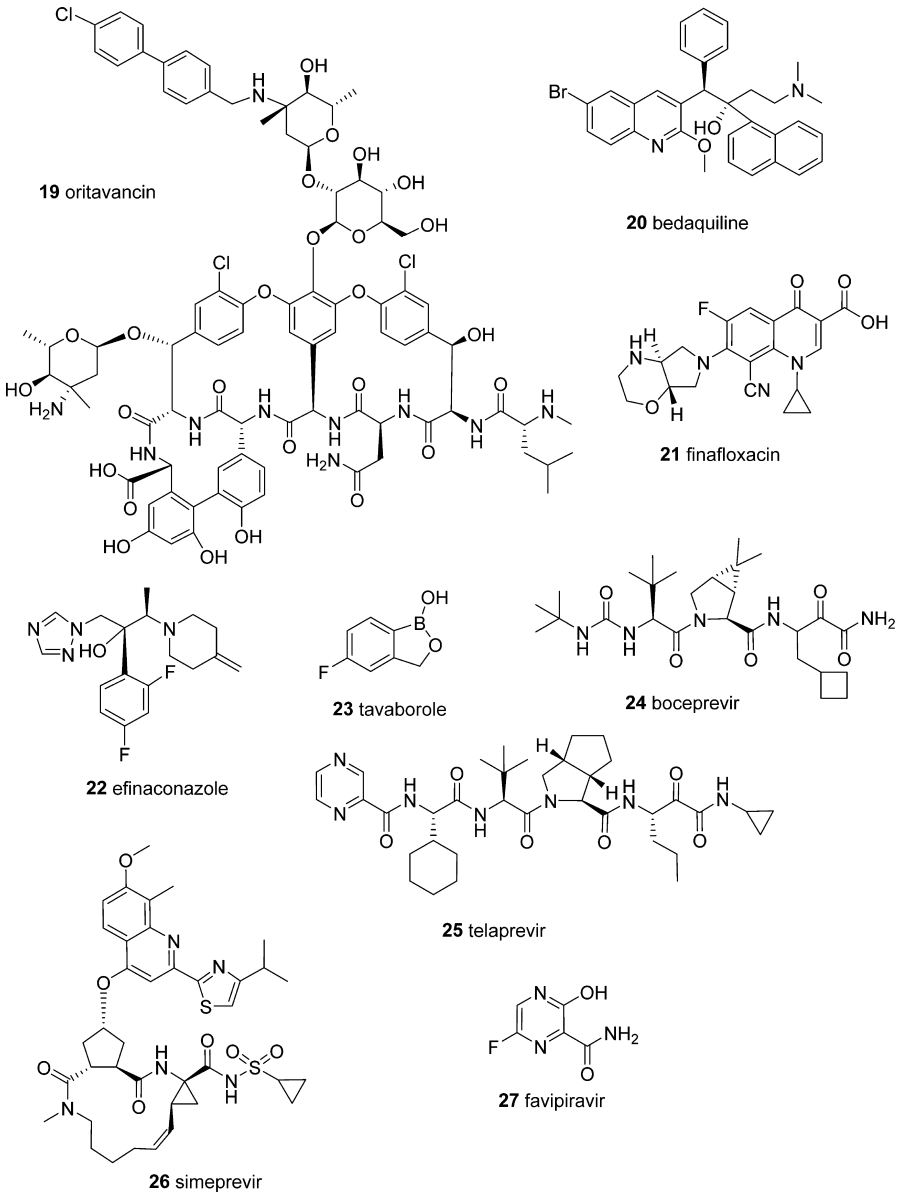
Chart 3



bronchodilators, and cardiotonics now have substantial numbers that, although formally "S" or "S*", fall into the "S/NM" or "S*/NM" subcategory, as the information in the literature points to their interactions at active sites as competitive inhibitors.

Anticancer Drugs 1981−2014. In this disease area (Table 9), in the time frame covered (01/1981−12/2014) there were 174 NCEs in total, with the number of nonbiologicals, aka small molecules, being 136 (78%), effectively the same percentage as the value of 77% in the last review.[4] Using the total of 136 as being equal to 100%, the breakdown was as follows, with the values from the last review inserted for comparison: "N" (17, 13% {11, 11%}), "NB" (1, 1% {1, 1%}), "ND" (38, 28% {32, 32%}), "S" (23, 17%, {20, 20%}), "S/NM" (20, 15% {16, 16% }), "S*" (13, 10% {11, 11%}), and "S*/NM" (24, 18% {8, 8%}). Thus, using our criteria, only 17% of the total number of small-molecule anticancer drugs were classifiable into the "S" (synthetic) category. Expressed as a proportion of the non-biologicals/vaccines, then 113 of 136 (83%) were either natural products *per se* or were based thereon, or mimicked natural products in one form or another.

From a natural products perspective, in the antitumor area there were some significant aspects in the four years from 2011 to 2014. Another nanoparticular, paclitaxel (PICN), was approved in India in 2014 as the fourth variation on this drug delivery approach, and two plant-derived agents, omacetaxine mepesuccinate (homoharringtonine) (**40**) and ingenol mebutate (**41**) (as an agent against actinic keratosis, a precancerous condition, that if untreated usually leads to a melanoma), were approved in 2012 by the FDA. The history of homoharringtonine was described by Camp[127] and Kantarjian et al.,[128] and that of the diterpenoid ingenol by a number of publications from Baran's group,[129−131] all showing the levels to which researchers had gone to develop these agents. From an "ND" aspect, abiraterone[132] (**42**) was approved in 2011 with Adcetris, a dolastatin 10 derivative linked to an anti-CD33 monoclonal,[133,134] being approved the same year. In 2012, the aminolaevulinic acid conjugate Ameluz was approved for photodynamic therapy,[135] and the same year saw the approval of carfilzomib[136] (**43**), the proteasome derivative that evolved from the work of Craig Crews[137] at Yale University. Then, in 2013 the maytansine−herceptin linked monoclonal

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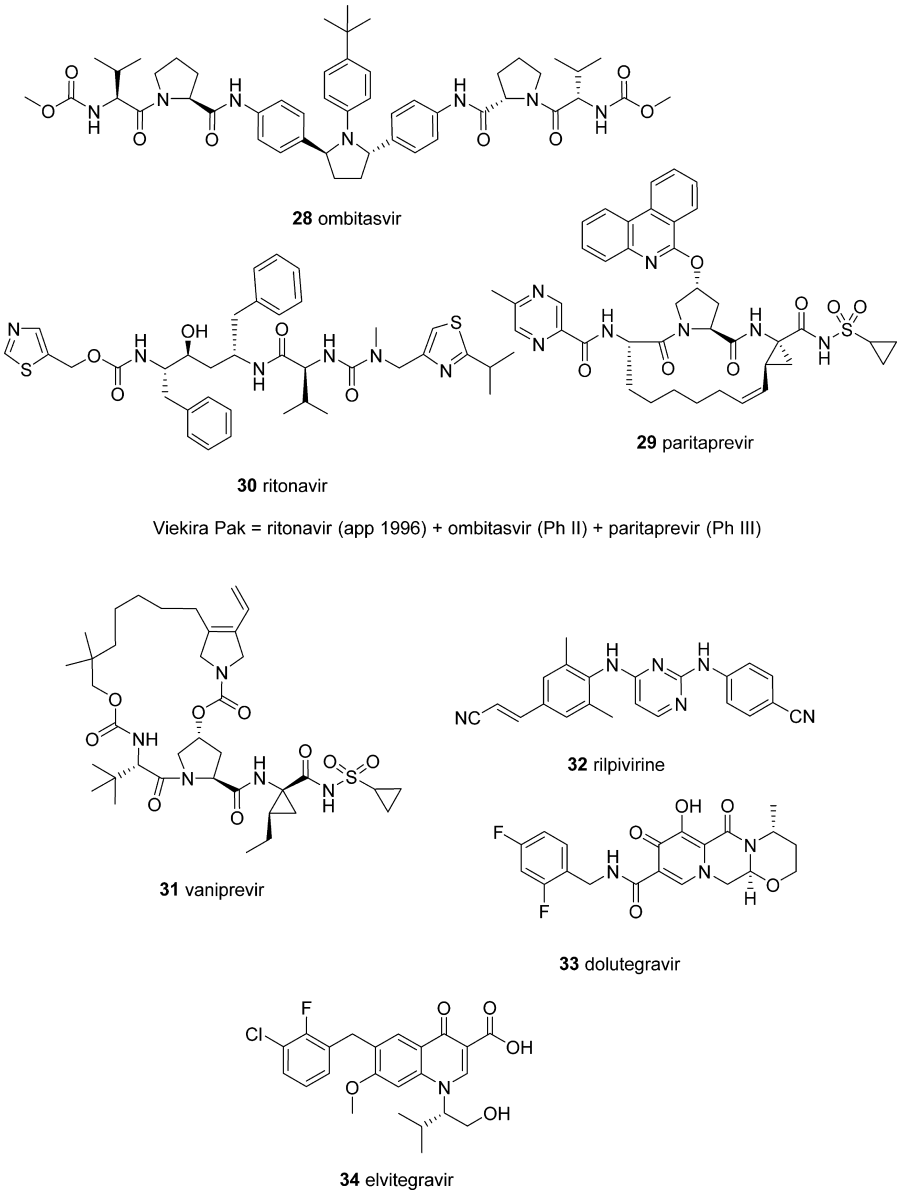
Chart 4



antibody Kadcyla was approved.[138,139] From the "S*" category, pixantrone[140] (**44**) was approved in 2012, with the uridine derivative tipiracil[141] (**45**) approved in 2014. Inspection of Table 9 shows that a significant number of PTKs were also approved in these years, with the numbers being predominately under the "S*/NM" category, although the HDAC inhibitor belinostat[142] (**46**) also was approved in 2014 and fell into the same category; thus the influence of natural products in the synthetic arena is still obvious.

Anticancer Drugs, Late 1930s to 2014. In this current review, we have continued as in our previous contributions[2−4] to reassess the influence of natural products and their mimics as leads to anticancer drugs from the beginnings of antitumor chemotherapy in the very late 1930s to the early 1940s. Using data from the FDA listings of antitumor drugs, plus our earlier data sources and with help from colleagues based worldwide, we have been able to specify the years in which all but 17 of the 246 drugs listed in Table 10 were approved. We then identified these 17 agents by inspection of three time-relevant textbooks on antitumor treatment,[103−105] and these were added to the overall listings using the names of the lead authors as the source citation.

Inspection of Figure 10 and Table 10 shows that, over the whole category of anticancer drugs approved worldwide, the 246 approved agents can be categorized as follows, with the figures for the 2012 review[4] (n = 206) being included for comparison: "B" (33, 13% {26; 13%}), "N" (30, 12% {27; 13%}), "NB" (1, 1% {1; 1%}), "ND" (62, 25% {57; 28%}), "S" (47, 19% {44; 21%}), "S/NM" (22, 9% {18; 9%}), "S*" (22, 9% {20; 10%}), "S*/NM" (24, 10% {8; 4%}), and "V" (5, 2% {5; 2%}). Removing the high-molecular-weight materials (biologicals and vaccines) reduces the overall number to 207 (100%). If we then use the number of nonsynthetics but include the naturally inspired agents (i.e., "N", "ND", "S/NM", "S*", "S*/NM"), this number is 160, or 77% of the total small molecules (having removed categories "B", "NB", and "V" from the overall total), effectively the same percentage as the 75% figure from the 2012 review.[4] If the two "/NM" categories are also removed, then the figure drops to 114, or 55%, compared to the 60% in our earlier reviews. This can be attributed to the large number of protein kinase inhibitors that

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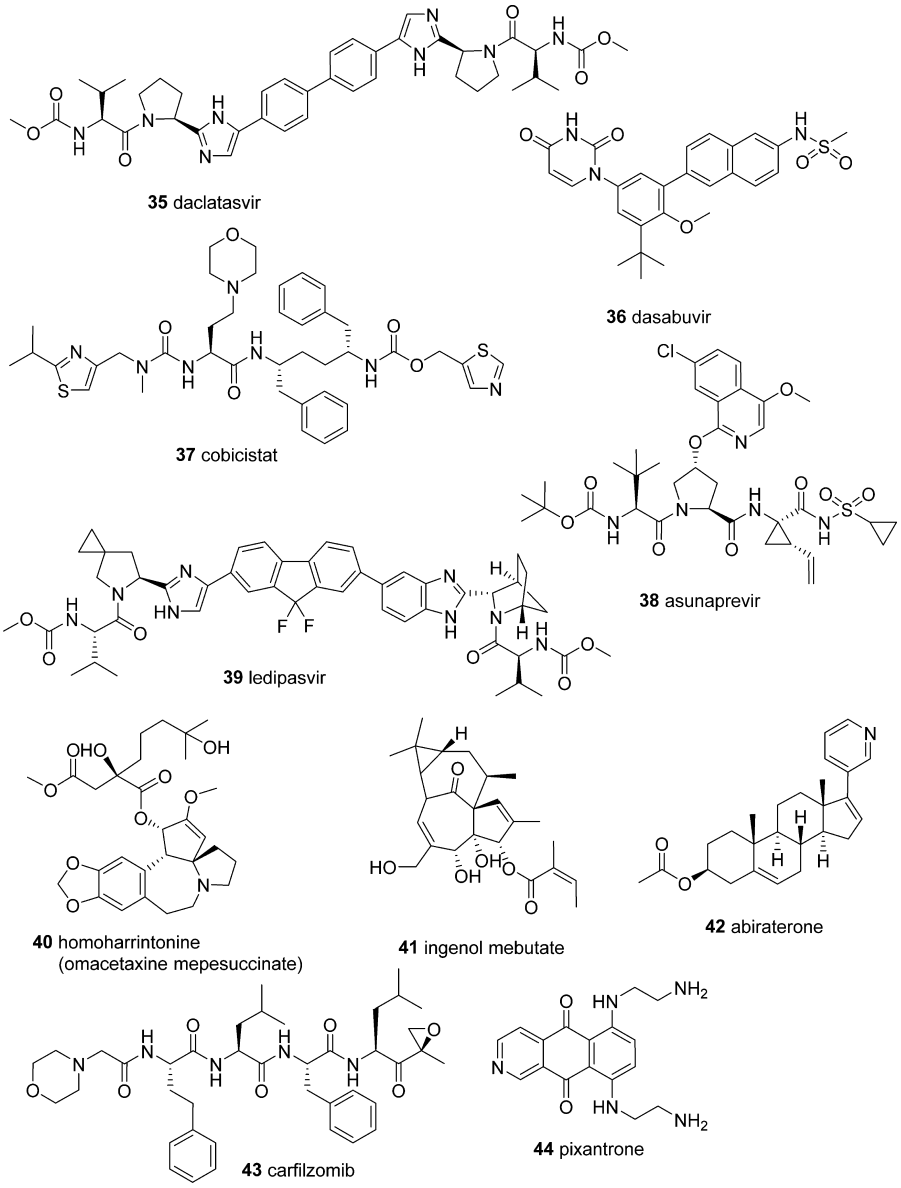
Chart 5



fell into the "/SM" classifications in the last four years, thus increasing the denominator for small molecules. Etoposide phosphate and various nanopaticle formulations of Taxol have been included for the sake of completeness. It should again be pointed out that the 17 antitumor drugs shown on the right in Figure 11 are not duplicated in the rest of the bar graph; we simply have not been able to locate accurate data on their initial approval dates.

Small-Molecule Antidiabetic Drugs. In the case of these drugs and looking only at small molecules for both diabetes I and II, the numbers since our last review have increased by 10 to 29 (Table 11). One, lixisentide (**47**), approved in 2013, fell into the "ND" classification, as it, like extenatide (Byetta), is a derivative of exendin-4.[143] Under the classification "S/NM", there were three approvals of drugs all targeted at the same enzyme complex, dipeptidyl peptidase IV (DPP-IV). The first was linagliptin[144] (**48**) in 2011, with the next two in 2012, teneligliptin[145] (**49**) and anagliptin[146] (**50**).

However, for "pride of place", one cannot beat the six sodium-dependent glucose transporter inhibitors (SGLTi's) that were approved between 2012 and 2014, all falling into the "S*/NM" classification. In 2012, dapagliflozin[147] (**51**) was approved in the EU; this was followed in 2013 by canagliflozin[148] (**12**) in the USA. In 2014, there were no less than four drugs launched all directed against this target. In alphabetical order, they were empaglifozin[149] (**52**) in the EU and the USA almost simultaneously, with the next three, ipragliflozin cocrystallized with L-proline[150] (**53**), luseogliflozin[151] (**54**), and tofoglflozin[152] (**55**), launched in Japan.

DISCUSSION

In contrast to the situation referred to in our previous three reviews,[2−4] the decline or leveling of the output of the R&D programs of the pharmaceutical companies may have begun to turn around when compared to earlier years in the 21st century. The figures for drugs of all types had dropped in 2006 to 40 NCEs launched, of which 19 (48%) were classified in the "other than small molecules", being in the "B/V" categories.

Increases in Biologicals and Vaccines from 2007. In the eight years 2007−2014 as shown in the bar graph in Figure 2, the

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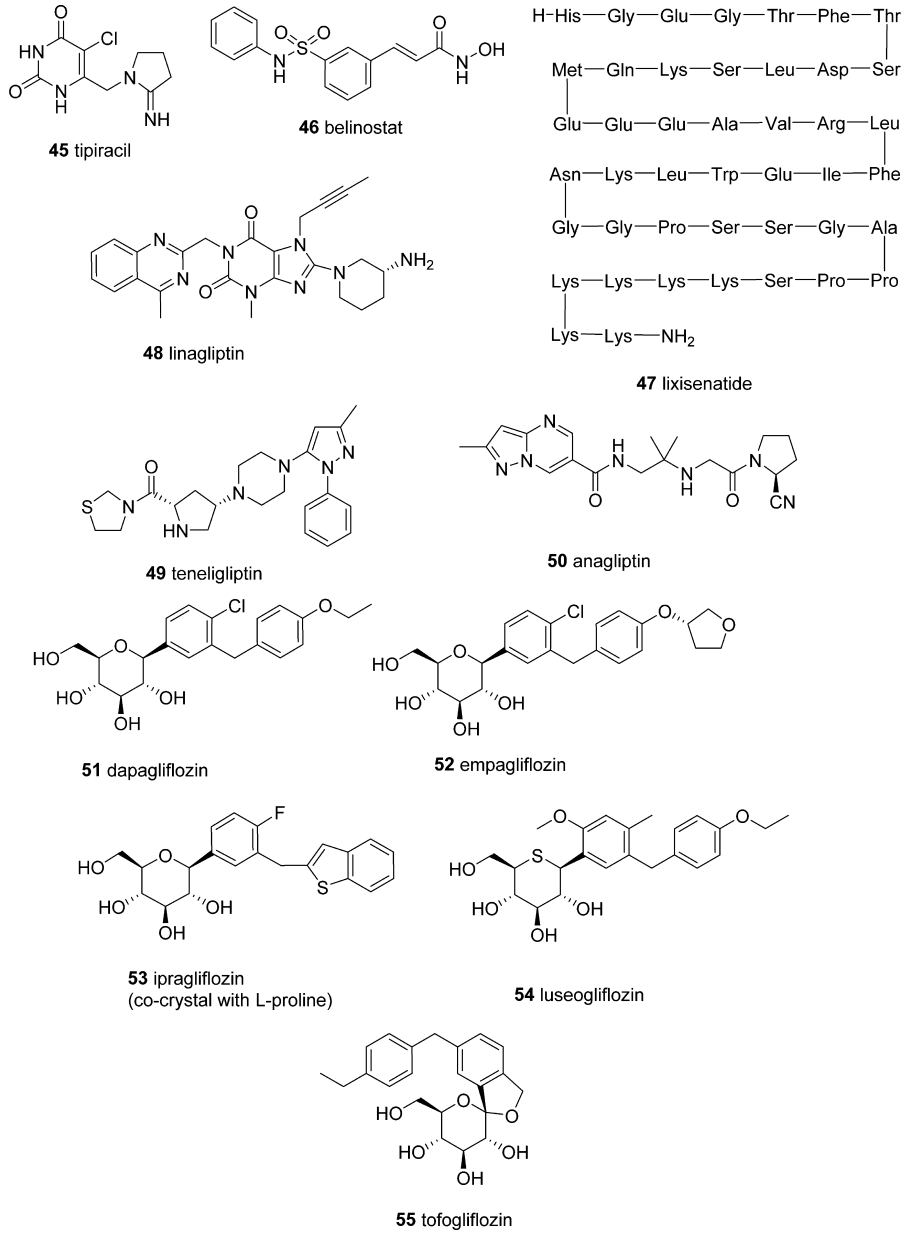
Chart 6



corresponding figures are as follows. In 2007, there were 44 NCEs launched, with 18 (41%) classified as "B/V". In 2008, 38 NCEs were launched, with 14 (37%) classified as "B/V". In 2009, 42 NCEs were launched, with 18 (43%) classified as "B/V". Then, in 2010, there was a dip, where only 33 NCEs were launched, with 13 (39%) classified as "B/V". In 2011, there was an increase of 1 to 34, with 7 (20%) classified as "B/V"; however the proportion of small molecules increased that year, so the divisor increased. In 2012, there was almost a doubling of NCEs to 60, but 25 (42%) fell into the "B/V" categories. This increase in 2012 in approved vaccines was due predominately to "avian influenza" treatments. In 2013, there was a drop to 47 NCEs, with 16 (34%) still attributable to the "B/V" categories. However, in 2014, the trend line for small-molecule NCEs began to move upward again, with 65 NCEs approved, of which 21 (32%) were in the "B/V" categories. Thus, one can see that, overall, of the total of 363 NCEs in these years, 132 (36%) fell into the "B/V" categories. However, as shown in Figure 7, although there were fluctuations in the overall numbers, a reasonable to substantial proportion of all small-molecule NCEs fell into the "N*" category; thus even in these days of advances in immunopharmacology-based treatments, natural-product-based small molecules are still in play.

Potential Sources of Natural Product Skeletons. Although combinatorial chemistry continues to play a major role in the drug development process, as mentioned earlier, it is noteworthy that the trend toward the synthesis of complex natural-product-like libraries has continued. Even including these newer methodologies, we still cannot find other *de novo* combinatorial compounds approved anywhere in the world than the three compounds (**1**–**3**) referred to earlier, although reliable data are still not available on approvals in Russia and the People's Republic of China at this time.

A rapid analysis of the small-molecule entities approved from 2011 to 2014 has indicated that there were significant numbers of antitumor, antibacterial, and antifungal agents approved, as

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mentioned above. The antibacterial compounds were either NPs or based on their skeletons, although, as is now, "the norm" antifungal agents were synthetic in origin.

Genomic Sources of Novel NP Skeletons. If one asks the question "where will novel natural product skeletons come from in the future?", the answer, we think, is from the massive amounts of genetic information now being amassed from microbial sources. There was always the comment made in previous years that only a very small proportion of the microbial world can be fermented. However, two excellent papers in the last two years have shown that genetic information can be "abstracted" from as yet uncultured microbes from sessile marine organisms. These were the "tour de force" by the Piel group in 2014, demonstrating that 31 of the then 32 known bioactive metabolites from the sponge *Theonella swinhoei* Y (yellow variant) were produced by a totally novel biochemical mechanism in an as yet uncultured microbe.[153] This was followed a year later by proof in the middle of 2015 from the Sherman group[154] that the source of the approved antitumor drug Yondelis, or Et743, is an as yet uncultured microbe in the tunicate *Ecteinascidia turbinata*, from which the Et743 complex was first isolated. Does this mean only from invertebrate sources? No, we consider that the information now coming from investigations on free-living microbes from often extreme sources (cold, hot, high pressure, etc.) will also provide novel skeletons for further work.[5,8−11]

Similarly, if one moves to the plant kingdom, there is now a significant volume of published work that indicates that a fair number of what were thought to be "plant-derived" natural products are in fact produced "in part" and in some cases, such as maytansine, totally[155,156] by interactions with endophytic microbes, frequently fungi. We currently say "in part" because the evidence for total production only by the isolated microbe is not yet finalized, and one cannot rule out horizontal gene transfer at this moment. However, the recent work by the Oberlies group[157] on the production of silybins by an endophytic fungus from the leaves of the milk thistle *Silybum marianum* demonstrated that these metabolites were produced by the isolated fungus when supplemented by a sterilized extract from the plant, a supplementation strategy well known in the days of antibiotic discovery but generally not used today by newer investigators studying these types of systems. People interested in this aspect of microbiology should also read the recent article from the Spiteller group demonstrating the production of cyclopeptides by a *Fusarium* species as "cross-talk" agents in plants, as this demonstrates the type of interaction we are referring to.[158]

Very recently, a series of reviews in the journal *Natural Product Reports* have further demonstrated the capabilities of modern techniques to help unlock the genomes of both cultivatable and "as yet uncultured" microbes from all sources. These should be read in conjunction with the articles referred to above on microbes isolated from marine invertebrates and plants, since together these aptly demonstrate the new technologies that can be brought to bear on the search for novel scaffolds from nature.[159−162]

In the period since our last review, other authors prominent in the natural product community have also published excellent reviews on natural products as drugs,[163,164] and these, together with the review by Butler et al.,[165] on natural product-based compounds in clinical trials, should also be read in conjunction with this review. In addition there were two very interesting reviews on small molecules, including natural products and close relatives, as protein−protein interaction inhibitors, which we also recommend reading to see how the role of NPs has expanded.[166,167]

That synthetic chemists are not letting opportunities go by can be seen from the 2014 essay by Nicolaou[168] and a series of papers that cover synthetic approaches to the new drugs from 2009 to 2013.[169−173] It is highly probable that in the near future totally synthetic variations on complex natural products will be part of the therapeutic arsenal used by physicians. One has only to look at the extremely elegant syntheses of complex natural products reported recently by Baran and his co-workers to visualize the potential of coupling very active and interesting natural products with the skills of synthetic chemists in academia and industry.[131]

Two recent papers of interest to drug discovery and development that are quite relevant to the discussion are as follows. The first, which is quite sobering to read, intimates, with data, that the actual productivity of the pharmaceutical industry from a development aspect is lower than is evident from the press releases and other outlets that are often used to demonstrate success.[174] The second may be quite beneficial as far as natural products and/or their derivatives are concerned, as it now appears that phenotypic screening using high-content methodologies may be making a comeback over "targeted screening systems".[175]

It is often not fully appreciated that the major hurdle in bringing a natural-product-based complex molecule to market is not the isolation, basic semisynthesis, or total synthesis, but the immense supply problems faced by process chemists in translating research laboratory discoveries to commercial items. Some recent examples of how these problems were overcome with natural products or their derivatives are given in a recent short review by one of the present authors.[176]

In this review, as we stated in 2003, 2007, and 2012,[2−4] we have *yet again* demonstrated that natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases. As we mentioned in earlier articles, some of our colleagues argued (though not in press, only in personal conversations at various fora) that the introduction of categories such as "S/NM" and "S*/NM" may well cause an overstatement of the role played by natural products in the drug discovery process. On the contrary, we would still argue that these further serve to illustrate the inspiration provided by Nature to receptive organic chemists in devising ingenious syntheses of structural mimics to compete with Mother Nature's longstanding substrates. Even if we discount these categories, the continuing and overwhelming contribution of natural products to the expansion of the chemotherapeutic armamentarium is clearly evident, as demonstrated in Figures 6 and 7, and as we stated in our earlier papers, much of Nature's "treasure trove of small molecules" remains to be explored, particularly from the marine and microbial environments.

To us, a multidisciplinary approach to drug discovery, involving the generation of truly novel molecular diversity from natural product sources, combined with total and combinatorial synthetic methodologies and including the manipulation of biosynthetic pathways, will continue to provide the best solution to the current productivity crisis facing the scientific community engaged in drug discovery and development.

Finally, the award of half of the 2015 Nobel Prize for Physiology or Medicine to Drs. Ŏmura and Campbell for their discovery and development of the avermectin/ivermectin complexes, with the other half being awarded to Prof. Tu for

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her discovery and development of artemisinin, is truly excellent news for the general public, as they may now begin to understand where these significant drugs were sourced. Two very recent publications cover some of the work that led to the awarding of this Nobel prize. The first by McKerrow[177] is a short description of the work performed by the three scientists, and the second, by Wang et al.,[178] demonstrates the multiplicity of targets in the malaria parasite *Plasmodium falciparum* for artemisinin, none of which would have been recognized but for this agent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01055.

The drug data set (PDF)

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Notes

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■ DEDICATION

Dedicated to Professors John Blunt and Murray Munro, of the University of Canterbury, for their pioneering work on bioactive marine natural products.

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