MILLION-CARD MONTE: REFORMING THE MARKUSH CLAIM POST-AIA TO SAVE SYNTHETIC CHEMICAL INNOVATION

ADAM SUSSMAN

ABSTRACT

The Markush patent claim arose as a solution to the challenging problem of describing inventions that could not be defined any other way than by a list of the members of a group. The original Markush group, claimed in 1923, listed only three alternatives; in the years since, the populations of these groups have swelled to totals beyond calculation, as pharmaceutical companies took advantage of the opportunity to claim multitudes of alternative chemical compounds by systematically iterating the functional groups at various molecular positions. However, without completing the now-impossible task of synthesizing and testing each of innumerable chemical compounds for patentable utility, how can a patent applicant realistically have fulfilled the statutory requirements to obtain a patent? Is the United States now protecting the mere ability to conceive of possible compounds that may never be synthesized or tested? As the AIA converts our patent system to a first-to-file structure, and the numbers of Markush group members threaten to bloat even more in the rush to preserve priority, we must reconsider and reform the Markush claim before the ability to invent chemical compounds becomes synonymous with the ability to conceive.

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MILLION-CARD MONTE: REFORMING THE MARKUSH CLAIM POST-AIA TO SAVE SYNTHETIC CHEMICAL INNOVATION

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“Step right up.” “Three-Card Monte is the name of the game.” “Five dollars to anyone who can find the Red Queen.” Imagine this scenario, but before you bet, the dealer changes the rules by keeping the cards face up for the entire length of the game. If that seems deceivingly favorable, it’s because you haven’t heard the catch—you won’t be selecting the Red Queen from among three cards, but from among one million cards, all of which randomly change positions. And to make the game even more interesting, the dealer will not tell you which card you have to select in order to win. Ready to place your bet?

Chemical and pharmaceutical researchers and manufacturers currently face similar insurmountable odds under U.S. Patent Law. In the United States, patent claims “particularly point out and distinctly claim the subject matter which the inventor regards as the invention” and define the boundaries of patent protection. Patent claims involving chemical compounds often employ Markush groups. Such claims enable inventors to include several combinations of subject matter, usually constituent molecules, without defining particular combinations of

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1 See DUANE SWIERCZYŃSKI, THE COMPLETE IDIOT’S GUIDE TO FRAUDS, SCAMS, AND CON’S 96 (2003).

2 In Great Britain, it’s known as “Find the Lady.” The French call it “Bonneteau.” Here in the states, it goes by a slightly more rough-and-tumble name: three-card monte. The rules are simple: There are three cards, slightly arched at the middle so they’ll be easy to grab. One of those cards is a Queen; the other two are not. The dealer shows you the Queen, then starts moving the cards around. Your job, as the player, is to keep your eyes on that Queen no matter what. If you can guess which is the Queen after the dealer shuffles the cards, you win the pot. The thing is: no player ever wins.

3 Id. 35 U.S.C. § 112(b) (2012).

4 8 DONALD S. CHISUM, CHISUM ON PATENTS § 8.06[2] (2012). (“The Markush doctrine developed as an exception to the . . . ban on alternative language. With chemical compounds, there may be no suitable phrase to cover the alternatives. . . . [A] claimant could use [a] . . . coined subgeneric group in the form of ‘material selected from the group consisting of X, Y, and Z.’”) (quoting Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1280 (Fed. Cir. 2003)).
the group members. While Markush-type claims began as a convenient shorthand for including various combinations, their use has exploded beyond the Patent Office's expectations, not only wreaking havoc on chemical manufacturers facing potential infringement suits, but also stifling innovation.

Part I of this comment will explain the role Markush-type claims play in patent law, as well as key fundamentals required of every patent application. Part II proceeds by applying current provisions of the law to a modern chemical Markush group to illustrate problems created by Markush groups having innumerable combinations. Part III will review recent attempts to reform Markush-type claims and suggest a novel approach to limit their breadth in the interest of furthering scientific innovation.

I. BACKGROUND

This background section provides a brief history of the Markush decision and the subsequent development of alternative claiming, followed by a simple Markush group example. Then, several requirements for United States patent applications are briefly discussed, each of which raises unique practical problems for the analysis of Markush-type claims, which is demonstrated in the next section.

A. The Origin of Markush-Type Claims

The original, allowed Markush patent claim was a solution built on compromise. In 1923, Eugene Markush filed a patent application with the United States Patent and Trademark Office (“USPTO”) covering his original, organic chemical compounds. To avoid filing multiple applications on closely related compounds, each of which may not have individually supported a patent, Markush

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4 8 CHISUM, supra note 3, § 8.06[2] (“Markush phrasing . . . is a clear and effective form for claiming classes of chemical compounds.”).

5 Steve Gardner & Andy Vintner, Stronger Protection for New Drugs, PHARMA, May–June 2010, at 46, 46 (“Markush patterns in some Composition of Matter filings have exploded to the point where it is effectively impossible to verify the millions of structures presented.”). As early as 1934, the Commissioner of Patents grew concerned about the growing trend of applicants taking advantage of the Markush group. Ex parte Dahlen, 1934 Dec. Comm'r Pat. 9, 10.


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[T]his [Markush] formula has been taken advantage of by many applicants to multiply their claims far beyond reasonable bounds. The abuse of the Markush formula has, in many instances, been carried to such excess as to defeat the very purpose for which a set of claims is intended. In the mass of verbiage presented by the claims, the invention is effectively concealed rather than clearly pointed out. It is quite apparent that proper and sensible restrictions must be imposed on the use of this unusual form of claim, which is distinctly a child of emergency, and intended for special relief only.

Id.
attempted to claim in the alternative. The patent Examiner objected to the alternative claim structure, so Markush substituted the original terminology with one generic term. When the Examiner rejected this term as too broad, Markush coined the language that has come to characterize the claim format named for him: “material selected from the group consisting of.” The Commissioner of Patents eventually allowed this phrase upon petition, with Markush’s original three alternatives listed as group members. However, the Commissioner’s decision came with a proviso: Group members were allowed only inasmuch as each could actually replace the others as the selected material.

When claims are written in the alternative, such as in Markush-type claims, the scope and clarity of the claims must be precise and unambiguous. Markush-type claims are not automatically considered indefinite merely because they include large numbers of species. However, if a Markush group is so vastly populated that one skilled in the art cannot accurately measure the boundaries of the claimed invention, an Examiner may reject the claim for indefiniteness. Alternatively, an examiner may reject a Markush group under the “improper

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8 Markush, 1925 Dec. Comm.’r at 127. Markush originally claimed “a diazotized solution of aniline or its homologues or halogen substitutes.” Id.
9 Id. Markush substituted his original claim language with the simple term “mono-amine.” Id.
10 Id. Markush rewrote the claim phrase as “material selected from the group consisting of aniline, homologues of aniline and halogen substitutes of aniline.” Id. Homologues of aniline are defined as “bodies in which one or more atoms of the hydrogen of the benzene-nucleus are replaced by a corresponding number of atoms of methyl or other radical,” which practically amounts to an extensive variety of compounds in and of itself. ALFRED HENRY ALLEN, AMINES & AMMONIUM BASES, HYDRAZINES, BASES FROM TAR, VEGETABLE ALKALOIDS 51 (Kessinger Publishing ed. 2009) (1892).
11 Markush, 1925 Dec. Comm.’r at 128 (“[W]here the validity of the claim is not involved, the paucity of the language may necessitate a waiver of technical rules of this Office, to the end that an applicant may properly protect his real invention.”).
12 Id.
15 Supplementary Guidelines, supra note 14, at 7166. (“For example, a Markush group that encompasses a massive number of alternative species may be indefinite under § 112, ¶ 2 if one skilled in the art cannot determine the metes and bounds of the claim due to an inability to envision all of the members of the Markush group.”).
16 In re Harnisch, 631 F.2d 716, 721–22 (C.C.P.A. 1980). An examiner should maintain a rejection on the basis of “improper Markush grouping” until the applicant amends the language and limits the claim to those species sharing a “singular structural similarity and a common use,” or
Markush grouping” doctrine if: “(1) The species of the Markush group do not share a ‘single structural similarity,’ or (2) the species do not share a common use.”

B. A Simple Example

To illustrate the utility of a simple Markush group, consider a U.S. patent application having independent claim 1 directed to a chemical compound X-R. Now consider dependent claim 2 directed to a compound according to claim 1, wherein R is “selected from the group consisting of A, B, and C.” This single dependent claim using a Markush group could be rewritten as three dependent claims:

2. A compound according to claim 1, wherein R is compound A.

3. A compound according to claim 1, wherein R is compound B.

4. A compound according to claim 1, wherein R is compound C.

So long as group members A, B, and C “belong to a recognized physical or chemical class or to an art-related class,” the Examiner would likely have allowed the Markush group.

C. Statutory Requirements Under 112

In the centuries since its inception, the USPTO has adopted strict regulatory and administrative rules to aid implementation of statutory provisions and to govern the drafting and examination of U.S. patent claim language. Chief among the

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17 MPEP, supra note 13, § 803.02. Examiners may not refuse to examine the subject matter applicants regard as their inventions, unless the claimed invention lacks “unity of invention.” See In re Weber, 580 F.2d 455, 458 (C.C.P.A. 1978); In re Haas, 580 F.2d 461, 464 (C.C.P.A. 1978). Compounds in a Markush group generally satisfy the unity of invention standard when they have a common utility, and possess a structural feature critical to such utility. MPEP, supra note 13, § 803.02.

18 Harnisch, 631 F.2d at 723; Supplementary Guidelines, supra note 14, at 7166 (“Members of a Markush group share a ‘single structural similarity’ when they belong to the same recognized physical or chemical class or to the same art-recognized class.”).

19 Supplementary Guidelines, supra note 14, at 7166 (“Members of a Markush group share a common use when they are disclosed in the specification or known in the art to be functionally equivalent.”).

20 MPEP, supra note 13, § 2173.05(h).

statutory requirements is adherence to 35 U.S.C. § 112, which supplies the general framework for patent claims defining an applicant’s invention.\textsuperscript{22} According to the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.\textsuperscript{23}

Examination of claim language often turns on analyses of the requirements of the first paragraph of § 112: “(A) A written description of the invention; (B) The manner and process of making and using the invention (the enablement requirement); and (C) The best mode contemplated by the inventor of carrying out his invention.”\textsuperscript{24} These requirements guarantee that exclusionary rights of patents depend on the exchange with the public of information enhancing scientific and technological development.\textsuperscript{25}

1. The Written Description Requirement

The written description requirement serves several purposes. First, it demonstrates that the applicant has indeed invented the claimed subject matter.\textsuperscript{26} Second, it “ensures that the inventor had possession of . . . the specific subject matter later claimed by him or her.”\textsuperscript{27} Third, the requirement promotes the progress of science\textsuperscript{28} by ensuring that patentees adequately describe their inventions to the public in return for their exclusionary rights.\textsuperscript{29}

To satisfy the written description requirement, the specification “must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.”\textsuperscript{30} Possession can be demonstrated in several different ways, including actually reducing the invention to practice or offering proof conclusive of actual possession.\textsuperscript{31} Conforming to the requirement is a “fact-based inquiry” dependent upon the subject matter of the

\textsuperscript{22} See 35 U.S.C. § 112.
\textsuperscript{23} Id. § 112(a).
\textsuperscript{24} Id. § 2161.
\textsuperscript{25} Id. § 2162.
\textsuperscript{26} Id. § 2163(I); In re Barker, 559 F.2d 588, 592 n.4 (C.C.P.A. 1977).
\textsuperscript{27} MPEP, supra note 13, § 2161(I); In re Herschler, 591 F.2d 693, 700–01 (C.C.P.A. 1979).
\textsuperscript{28} U.S. CONST. art. I, § 8, cl. 8.
\textsuperscript{29} MPEP, supra note 13, § 2163(I).
\textsuperscript{30} Id.; Moha, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319 (Fed. Cir. 2003).
\textsuperscript{31} MPEP, supra note 13, § 2163(I). An applicant demonstrates possession by “words, structures, figures, diagrams, and formulas” that fully delineate the claimed invention. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997). One may establish possession through proof of actual reduction to practice, by submitting drawings or structural chemical formulas illustrating that the invention was complete, or by providing distinctive, identifying details sufficient to prove possession of the invention. Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68 (1998).
A chemical compound, for example, must be defined by its distinguishing characteristics.\textsuperscript{32} The written description of the claimed subject matter receives a strong presumption of adequacy upon the filing of a patent application.\textsuperscript{33} The Patent Examiner carries the burden of proving the written description inadequate.\textsuperscript{34} The Manual of Patent Examining Procedure ("MPEP"), an Examiner’s bible, dictates a three-step methodology for the analysis of descriptive adequacy:\textsuperscript{35} (1) determine what each claim covers as a whole;\textsuperscript{36} (2) ensure that applicant provides support for each element or step of the claimed invention;\textsuperscript{37} and (3) conclude whether a skilled artisan would be informed that applicant possessed the entire claimed invention as of the application filing date.\textsuperscript{38}

\textsuperscript{32} MPEP, \textit{supra} note 13, § 2163(I) (quoting Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 969–70 (Fed. Cir. 2002)).

\textsuperscript{33} Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) ("[I]t is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.").

\textsuperscript{34} MPEP, \textit{supra} note 13, § 2163(I)(A).

\textsuperscript{35} \textit{In re Wertheim}, 541 F.2d 257, 263 (C.C.P.A. 1976) ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.").

\textsuperscript{36} MPEP, \textit{supra} note 13, § 2163(II)(A).

\textsuperscript{37} Id. § 2163(II)(A)(1). Claim interpretation is fundamental to the examination of applications. Every claim must be individually evaluated and afforded the “broadest reasonable interpretation” corresponding with the description. \textit{In re Morris}, 127 F.3d 1048, 1053–54 (Fed. Cir. 1997). The examiner must evaluate all limitations within the preamble, transition, and body of the claim, and the limitations of each must derive satisfactory support from the written description. \textit{Lockwood v. Am. Airlines, Inc.}, 107 F.3d 1565, 1572 (Fed. Cir. 1997). An examiner may issue a rejection citing inadequate written description if each claim does not recite appropriate structures, acts, or functions to define its scope and meaning. MPEP, \textit{supra} note 13, § 2163(II)(A)(1).

\textsuperscript{38} MPEP, \textit{supra} note 13, § 2163(II)(A)(2). If those of ordinary skill in the art would consider an element of the invention necessary to establish possession, the element may be essential. See Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1206 (Fed. Cir. 1991). The examiner must compare the scopes of the claim and the description in order to evaluate whether the applicant has established possession, and must perform this comparison according to the level of skill in the art as of the application filing date. See \textit{Wang Labs. v. Toshiba Corp.}, 993 F.2d 858, 865 (Fed. Cir. 1993). The disclosure generally requires less specificity to satisfy written description requirement as the level of skill in the art increases. See \textit{Hybritech, Inc. v. Monoclonal Antibodies, Inc.}, 802 F.2d 1367, 1379–80 (Fed. Cir. 1986).

\textsuperscript{39} MPEP, \textit{supra} note 13, § 2163(II)(A)(3)(a). As long as one of ordinary skill in the art could conclude that the applicant possessed the claimed invention, any detailed disclosure of distinguishing characteristics providing evidence of such possession satisfies the written description requirement. \textit{Purdue Pharma L.P. v. Faulding Inc.}, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Examples of such disclosures include “complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.” Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002). Chemical inventions are only adequately described if exactly defined by name, structure, formula, or specific properties, rather than by a mere, prospective synthetic plan. See \textit{Univ. of Rochester v. G.D. Searle & Co.}, 358 F.3d 916, 927 (Fed. Cir. 2004).
2. The Enablement Requirement

Patent applications must also be enabling; that is, they must “enable any person skilled in the art . . . to make and use the [invention].” This requirement meaningfully informs the interested public of the subject matter of the invention. The standard analysis for compliance with the enablement requirement is whether the claimed invention can be made without “undue experimentation,” which is informed by several factors. Moreover, the enablement requirement is deemed satisfied if the specification discloses one method to make and use the claimed invention that “bears a reasonable correlation to the entire scope of the claim.”

The extent of information required to enable an invention decreases as the “knowledge in the state of the art” and the level of predictability in the field increase. If there is predictability in the art, one skilled in the art should be able to apply known results in the prior art to the claimed invention, and less information is required for the patent application to be enabling. Certain subject matter, including chemical reactions, is inherently and famously unpredictable, and necessitates a disclosure enabling more than one species.

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41 MPEP, supra note 13, § 2164.
42 Id. § 2164.01; In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Undue experimentation factors:

[I]nclude, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP, supra note 13, § 2164.01(a).
43 Id. § 2164.01(b); In re Fisher, 427 F.2d 833, 839 (C.C.P.A. 1970).
44 MPEP, supra note 13, § 2164.03; Fisher, 427 F.2d at 839.
45 MPEP, supra note 13, § 2164.03.

[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.

Id. This inherent unpredictability of chemical reactions warrants that a disclosure enables more than one species. Fisher, 427 F.2d at 839.
3. The Best Mode Requirement

In addition to describing a claimed invention with sufficient detail and enabling one skilled in the art to make and use the invention, a patent applicant must also disclose the best mode of carrying out an invention. This requirement guarantees that applicants will offer full disclosures when attempting to obtain patent protection by prohibiting the active and knowing concealment of the best embodiments of their inventions.

Compliance is evaluated based on a two-pronged analysis: If the inventor possesses a best mode as of the application filing date, then the written description must disclose that mode. Every applicant must disclose the best mode contemplated, even if that applicant did not discover that mode. Prior to enactment of the America Invents Act (“AIA”), failure to disclose the best mode was grounds for invalidating a patent. However, the AIA expressly removes non-compliance as grounds for invalidation. Applicants also need not specify which embodiments they consider to be their best.

4. The Definiteness Requirement

According to 35 U.S.C. § 112(b), the claims must clearly indicate and specifically define the boundaries of the subject matter to be protected by the patent grant. This requirement is objective and evaluated based on definiteness, or clarity of the claim boundaries to one of ordinary skill in the art. The definiteness requirement

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48 MPEP, supra note 13, § 2165; In re Nelson, 280 F.2d 172, 184 (C.C.P.A. 1960) (“[T]he ‘best mode’ requirement does not permit an inventor to disclose only what he knows to be his second-best embodiment, retaining the best for himself.”).
49 MPEP, supra note 13, § 2165; Eli Lilly & Co. v. Barr Labs. Inc., 251 F.3d 955, 963 (Fed. Cir. 2001) (categorizing this analysis as “a subjective inquiry which focuses on the inventor’s state of mind at the time of filing.”).
50 MPEP, supra note 13, § 2165; Eli Lilly, 251 F.3d at 963 (“This is an objective inquiry, focusing on the scope of the claimed invention and the level of skill in the art.”).
51 Benger Labs. Ltd. v. R.K. Laros Co., 209 F. Supp. 639, 644 (E.D. Pa. 1962) (“[I]f [the applicant] knows at the time the application is filed, of a better method to practice the invention and knows it for the best, it would make no difference whether or not he was the discoverer of that method.”).
52 See, e.g., Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1537 (Fed. Cir. 1987) (holding noncompliance with best mode requirement where inventors of a laser did not disclose a preferred TiCuSil brazing method, which was not found in the prior art nor common criteria for literature use of TiCuSil); Dana Corp. v. IPC Ltd. P’ship, 860 F.2d 415, 420 (Fed. Cir. 1988) (finding violation of the best mode requirement because the inventor failed to disclose a known treatment that he knew was necessary to successful performance of his invention).
55 MPEP, supra note 13, § 2171.
56 Id. Examination protocols establish not only the novelty and nonobviousness of the claimed invention over the prior art, but whether the claim language is “precise, clear, correct, and unambiguous.” Id. § 2171. Examination as to patentability considers only the applicant’s
demands analysis in light of the particular application contents, the prior art, and the interpretations of the claim language that would be made by one skilled in the art.\textsuperscript{57}

\textbf{D. The Evolving Markush Group}

In the ninety years since the Markush claim was conceived, its prevalence in chemical and pharmaceutical patents has led to format-specific claim examination protocols.\textsuperscript{58} However, whereas Markush limited his claimed group to three alternative members, modern Markush groups have grown exponentially such that a single claim can cover countless combinations of compounds.\textsuperscript{59} Current supplementary examination guidelines do not forestall the real, alarming possibility that Markush claim groups may continue to swell in size.\textsuperscript{60} The U.S. has now adopted a first-inventor-to-file system and largely abandoned the best mode requirement under the AIA.\textsuperscript{61} The prospective danger of such a system surrounds the fate of a yet-undiscovered, potentially important or revolutionary chemical compound, claimed among the multitudes of combinations in a single Markush group.\textsuperscript{62} A future miracle-drug may be the next anonymous “Red Queen” one is forced to blindly select in a hand of Million-Card Monte. With the statutory requirements of §112 in mind, the following section will analyze an allowed Markush-type claim that calls for serious alarm given current Markush group doctrine.

\textsuperscript{57} MPEP, supra note 13, § 2173.02. The examiner must analyze each claim as a whole for definiteness. See Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379 (Fed. Cir. 2000). Rejection should result if one of ordinary skill in the art could not discern the boundaries of a claim in attempting to avoid potential infringement. See Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1470 (Fed. Cir. 1993).

\textsuperscript{58} MPEP, supra note 13, § 2173.05(h).


\textsuperscript{60} Gardner & Vinter, supra note 5, at 46.

\textsuperscript{61} Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 3, 125 Stat. 284, 285–93 (2011) (adopting a “first inventor to file” patent system); Id. § 15(a), 125 Stat. at 328 (“F]ailure to disclose the best mode shall not be a basis on which any claim of a patent may be cancelled or held invalid or otherwise unenforceable.”).

\textsuperscript{62} Gardner & Vinter, supra note 5, at 46 (“As early as 1935, the United States Patent and Trademark Office (USPTO) noted that the misuse of Markush structures was ‘like a fire which had spread beyond control.’”) (quoting V. I. Richard, Claims Under the Markush Formula, 17 J. PATENT OFFICE SOC. 179, 190 (1935)).
II. ANALYSIS

Though it may be a scam, and it may be illegal, Three-Card Monte is a persisting fact of urban life.63 Similarly, the USPTO has permitted patent applicants to host legitimate games of Million-Card Monte time and again over the last ninety years through the use of Markush claims.64

The analysis that follows highlights the problems inherent in conventional evaluation of chemical inventions by examining a Markush claim that the USPTO allowed, but should have rejected. As shown below, this Markush claim fails to meet any of the statutory or regulatory requirements discussed earlier. Currently implemented interpretations of these requirements also present serious logistical problems and implicate profound consequences for the fate of claimed, yet technically undiscovered chemical inventions.

A. A Not-so Simple Example

The first claim of U.S. Patent No. 5,866,572, “Quinazoline Derivatives,” exemplifies a Markush group structure by representing a vast array of organic compounds that share the general framework of compound I depicted below.65 Each

![Diagram of compound I](image)

wherein $X^1$ is a direct link;
wherein $Q^1$ is a 5-membered heteroaryl moiety containing one heteroatom selected from oxygen and sulphur, which heterocyclic moiety is a single ring or is fused to a benzo ring, and $Q^1$ optionally bears up to 3 substituents selected from halogeno, hydroxyl, amino, trifluoromethoxy, trifluoromethyl, cyano, nitro, carboxy, carbamoyl, (1–4C)alkoxycarbonyl, (1–4C)alkyl, (1–4C)alkoxy, (2–4C)alkenyloxy, (2–4C)alkynylloxy, (1–3C)alklenedioxy, (1–4C)alkylamino, di-[1–4C]alkylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-(1–4C)alkylpiperazin-1-yl, (2–4C)alkanoylamino, N-(1–4C)alkyl carbamoyl, N,N-di-[1–4C]alkyl carbamoyl, amino-(1–4C)alkyl, (1–4C)alkylamino-(1–4C)alkyl, di-[1–4C]alkylamino-(1–4C)alkyl, pyrrolidin-1-yl-(1–4C)alkyl, piperidino-(1–4C)alkyl, morpholino-(1–4C)alkyl, piperazin-1-yl-(1–4C)alkyl, 4-(1–4C)alkylpiperazin-1-yl-(1–4C)alkyl, halogeno-(2–4C)alkoxy, hydroxy-(2–4C)alkoxy, (1–4C)alkoxy-(2–4C)alkoxy, amino-(2–4C)alkoxy, (1–4C)alkylamino-(2–4C)alkoxy, di-[1–4C]alkylamino-(2–4C)alkoxy, pyrrolidin-1-yl-(2–4C)alkoxy, piperidino-(2–4C)alkoxy, morpholino-(2–4C)alkoxy, piperazin-1-yl-(2–4C)alkoxy, 4-(1–
of the labels \( Q^1, Q^2, X^1, \) and \( R^1 \) represents a different menu of chemical functional

\[
\begin{align*}
&\text{4C)alkylpiperazin-1-yl-(2-4C)alkoxy, (1-4C)alkylthio-(2-4C)alkoxy, (1-}
\text{4C)alkylsulphinyl-(2-4C)alkoxy, (1-4C)alkylsulphonyl-(2-4C)alkoxy, halogeno-(2-}
\text{4C)alkylamino, hydroxy-(2-4C)alkylamino, (1-4C)alkoxo-(2-4C)alkylamino, amino-(2-}
\text{4C)alkylamino, (1-4C)alkylamino-(2-4C)alkylamino, di-[1-}
\text{4C)alkylamino-(2-4C)alkylamino, pyrrolidin-1-yl-(2-4C)alkylamino, piperidino-(2-}
\text{4C)alkylamino, morpholino-(2-4C)alkylamino, piperazin-1-yl-(2-4C)alkylamino, 4-(1-}
\text{4C)alkylpiperazin-1-yl-(2-4C)alkylamino, N-(1-4C)alkylhalogeno-(2-4C)alkylamino, N-(1-}
\text{4C)alkyl-(1-4C)alkoxy-(2-4C)alkylamino, halogeno-(2-4C)alkanoylamino, haloxy-(2-}
\text{4C)alkanoylamino, (1-4C)alkoxy-(2-4C)alkanoylamino, (3-}
\text{4C)alkenylamino, (3-4C)alkynylamino, amino-(2-4C)alkenylamino, (1-}
\text{4C)alkenylamino-(2-4C)alkenylamino, di-[1-}
\text{4C)alkenylamino-(2-4C)alkenylamino, pyrrolidin-1-yl-(2-4C)alkenylamino, piperidino-(2-}
\text{4C)alkenylamino, morpholino-(2-4C)alkenylamino, piperazin-1-yl-(2-4C)alkenylamino and 4-(1-}
\text{4C)alkylpiperazin-1-yl-(2-4C)alkenylamino, and wherein any of the above-mentioned substituents comprising a CH2 (methylene) group which is not attached to a halogeno, SO or SO2 group or to a N, O or S atom optionally bears on said CH2 group a substituent selected from hydroxyl, amino, (1-4C)alkoxy, (1-4C)alkylamino and di-[1-4C)alkylamino;}
\end{align*}
\]

wherein \( m \) is 1 or 2 and each \( R^1 \) is independently hydrogen, halogeno, trifluoromethyl, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-4C)alkoxycarbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[1-4C)alkylamino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl or N,N-di-[1-4C)alkylcarbamoyl;}

and wherein \( Q^2 \) is phenyl optionally bearing up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxyl, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[1-4C)alkylamino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl, and N,N-di-[1-4C)alkylcarbamoyl, or \( Q^2 \) is a group of the formula II

![Diagram](attachment://diagram.png)

wherein \( X^2 \) is a group of the formula CO, C(R^2=), CH(OR^2), C(R^2=)-C(R^2=), C(R^2=)=C(R^2=), C=O, CH(CN), O, S, SO, SO2, N(R^2), CON(R^2), SO2N(R^2), N(R^2)CO, N(R^2)=SO2, OC(R^2=), SC(R^2=), C(R^2=)O or C(R^2=)S wherein each \( R^2 \) is independently hydrogen or (1-4C)alkyl, \( Q^2 \) is phenyl or naphthyl or a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heteroaryl moiety is a single ring or is fused to a benzo ring, and wherein said phenyl or naphthyl group or heteroaryl moiety optionally bears up to 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxyl, amino, nitro, carboxy, carbamoyl, (1-4C)alkoxycarbonyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[1-4C)alkylamino, (2-4C)alkanoylamino, N-(1-4C)alkylcarbamoyl and N,N-di-[1-4C)alkylcarbamoyl, \( n \) is 1, 2 or 3 and each \( R^4 \) is independently hydrogen, halogeno, trifluoromethyl, cyano, hydroxyl, amino, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-[1-4C)alkylamino or (2-4C)alkanoylamino;}

or a pharmaceutically-acceptable salt thereof.

Id.
groups that may be alternatively selected for attachment to the structure of \( \text{1} \) at the indicated positions.\(^{66}\)

\[
\begin{array}{c}
\text{HN-} \\
\text{N} \\
\text{X}_1 \text{Q}_1 \\
\text{X}_2 \text{Q}^2 \\
\text{(R)}_m
\end{array}
\]

For example, compounds \( \text{2} \) through \( \text{5} \) are very different compounds claimed in the Markush group under common structure \( \text{1}. \)^{67} Substituting different functional groups imparts different properties to each compound.\(^{68}\)

The entire range of compounds covered in the Markush group of this single patent claim exceeds \( 10^{24} \) different permutations—more than a mole of different

\(^{66}\) Id.

\(^{67}\) Id.

B. Describe This!

The breadth of this exemplary Markush group might make one raise an eyebrow in light of the purposes for the written description requirement. It is extremely unlikely that the applicant claiming this group has definitively “invented” or “had possession of the claimed subject matter.” The indicated methods of demonstrating possession for chemical compounds include proof of actual reduction to practice or definition according to distinguishing characteristics, including descriptions of how to

possibilities. Even present patent claim examination and restriction practices do not provide for rejection of this claim; the nature of the chemical Markush group stymies evaluation by revealing practical fallacies in the tests themselves.

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69 '572 Patent, supra note 59, col.40 l.27. Though seemingly incredulous, 1.4562•10²⁴ compounds is actually a conservative estimate. The basic aromatic ring structure of Q, for example, can be in five different forms with two different points of attachment to formula I. According to the claim language, each of these ten aromatic ring structures can optionally be substituted with up to three different substituents, resulting in 570 possibilities for the basic structure of Q.

For example, where the claim recites “(1-4)alkyl,” the language refers to single-bonded alkyl groups containing one to four carbons. There are eight possibilities: methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl, and isobutyl (the additional methyleclopropyl and cyclobutyl moieties were not included due to the associated ring strains and inherent impracticality). The claim language recites that these may be possibilities within a functional group that is optionally substituted at up to three positions on Q; at minimum, this means 512 possibilities. When there are multiple “(1-4C)” groups claimed in a substituent, such as in “di-(1-4C)alkylamino-(2-4C)alkoxy,” which quotes two independent 1-4C groups each chosen from among the above listed eight possibilities, and additionally seven possibilities for 2-4C alkyl groups, 448 combinations of groups exist that can optionally be substituted 570 different ways on Q. For that one substituent, the number grows to at least 255,360 such possibilities.

Similarly, a conservative estimate of Q includes 345,573 different substituents that can be arranged 570 distinct ways, for a total of 196,976,610 possibilities. The R group, which can occupy either of two, or both of two, positions on I encompasses 187 different possibilities, for a total of 35,343 iterations. The groups X, R, and Q respectively include conservatively estimated populations of 441, 4160, and 114,018, resulting in a subtotal of 209,172,878,076 possibilities for Q². The three subtotals for Q, R, and Q, when multiplied together, produce 1.4562•10²⁴.

The overall sum does not take into account the range of heteroaryl moieties represented by Q of formula II, because unlike most other functional groups listed, it is unclear which of these heteroaryl moieties are actually stable enough to exist and provide the claimed utility. Inclusion of even two or three such moieties could further multiply the combinations exponentially. Additionally, stereochemistry has not been considered at all; each and every alkyl, alkenyl, and alkynyl group that includes three- or four-carbon substituents includes the possibility of stereoisomeric compounds. For example, each sec-butyl group exists in two stereochemical orientations; having n different sec-butyl groups in one structure results in 2ⁿ different diastereomeric compounds, which must be multiplied into the overall count.

70 See MARTIN S. SILBERBERG, CHEMISTRY: THE MOLECULAR NATURE OF MATTER AND CHANGE 90 (5th ed., McGraw-Hill Higher Education 2009). The mole (abbreviated mol) is the International System of Units unit for the amount of a substance. One mole represents the amount of a substance containing the same number of entities as there are atoms in exactly 12 g of carbon-12. One mole (1 mol) contains Avogadro’s number of constituents, or 6.022•10²³ entities. Id.

71 Supplementary Guidelines, supra note 14, at 7166.

72 MPEP, supra note 13, § 2163(I); In re Barker, 559 F.2d 588, 592 n.4 (C.C.P.A. 1977).

73 MPEP, supra note 13, § 2161(I); In re Herschler, 591 F.2d 693, 700–01 (C.C.P.A. 1979).
obtain the compounds. It is nearly certain to be impractical for even the most robust pharmaceutical companies to finance separate syntheses of an excess of $10^{24}$ different compounds, especially as these molecules are presumably suited to the same use given that they are claimed together. However, for each compound to be individually obtained with purity, each would indeed require an independent synthetic strategy from starting materials to the claimed product compound. Unfortunately, even the most efficient synthetic strategies proposed on paper often present unworkable dead-ends in the laboratory, continuously challenging a chemist to revise the original plan.

The specification of this particular patent gives general and specific examples of how these compounds might be synthesized; however, each synthesis must be tailored to the chemical compound synthesized, and functional groups must be prudently installed so as not to interfere with subsequent functionalization reactions. Though one of ordinary skill in the art of synthetic organic chemistry might be able to similarly plan a synthesis on paper, such a chemist would still be forced to perform the actual route to obtain the compound, selecting from the suggested varieties of listed reagents by trial-and-error. Therefore, a patent claim

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74 See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68 (1998) (demonstrating possession by actual reduction to practice); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) (indicating possession by characterizing compounds according to unique characteristics, including the method of obtaining the compound).

75 Robert Burns Woodward, *Synthesis, in Perspectives in Organic Chemistry* 155, 165 (Alexander R. Todd ed., 1956) ("While analytical and degradative work must always be primary, it is often synthesis which provides the simplest, most rigorous, and final proof.").


77 *572 Patent, supra note 59, col.18 l.29* ("Any reducing agent known in the art for promoting a reductive amination reaction may be employed. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminum hydride such as lithium aluminum hydride, or preferably an alkali metal borohydride. . ."). The patent specification provides specific procedures for the preparation of forty compounds, sixty-five percent of which contain the named substituent "3-chloro-4-fluoroanilino"; this indicates that the range of specific, synthesized examples is miniscule compared to the range of potential substituents claimed.


79 *572 Patent, supra note 59, col.15 l.39* ("A suitable catalyst for the reaction includes, for example, a metal catalyst such as a palladium(0), palladium(II), nickel(0) or nickel(II) catalyst, for example tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride, palladium(II) bromide, bis(triphenylphosphine)palladium(II) chloride, tetrakis(triphenylphosphine)nickel(0), nickel(II) chloride, nickel(II) bromide or bis(triphenylphosphine)nickel(II) chloride."). Entire books have been written about transition-metal catalysis, which is characteristically delicate and temperamental; realistically, catalytic success for a specific reaction is much more complex than choosing one option
covering an excess of $10^{24}$ compounds would extravagantly burden those of ordinary skill in the art with the task of "undue experimentation" by forcing them to specifically determine how to obtain each compound, rather than making the applicant perform this necessary research.

The first element in the analysis of descriptive adequacy involves establishing what a claim covers. Unfortunately, language such as, "a 5- or 6-membered heteroaryl moiety containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur, which heteroaryl moiety is a single ring or is fused to a benzo ring, and . . . optionally bears up to 3 substituents," covers such a variety of possible heteroaromatic functional groups that the full extent of these groups was difficult to fathom or consider in the $10^{24}$ calculation. If one skilled in the art has initial difficulty in ascertaining the full scope of a claim, comparing the scope of the claim to that of the written description becomes technically impossible. Only by individually synthesizing and analyzing each of these claimed compounds could one hope to determine their physical and chemical properties, the specific relationship between structure and reactivity for each compound, and, ultimately, possession of the

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80 MPEP, supra note 13, § 2163(II)(A)(1).
81 '572 Patent, supra note 59, col.41 l.42.
82 Id. It is unclear exactly how many and which heterocycles containing nitrogen, oxygen, or sulfur, separately or in combination, would be of sufficient stability to provide the claimed utility. Prudence warrants actual synthesis and analysis of the properties and reactivities of the claimed compounds with these substituents.
83 Wang Labs. v. Toshiba Corp., 993 F.2d 858, 865 (Fed. Cir. 1993).
84 FRANCIS A. CAREY & ROBERT M. GUILLIANO, ORGANIC CHEMISTRY 26–27 (8th ed., McGraw-Hill 2011). Though several physical and chemical properties can be estimated by comparison to other compounds previously synthesized and tested, this is at best an extrapolation. Id. Every compound has a unique set of properties, including the molecular dipole moment, which results from the three-dimensional vector sum of all of the individual bond dipole moments. Id. at 28. Consequently, water (H$_2$O) has a bent shape so that the two oxygen bonds that aggregate to form strong positive and negative molecular poles as a result of electronegativity differences, whereas carbon dioxide (CO$_2$) has a linear shape so that the two carbon-oxygen double bonds cancel. Id. at 27. Water molecules bind together like small magnets such that they are more difficult to separate and require heat to separate into individual molecules in the gas phase. SILBERBERG, supra note 70, at 451. By contrast, carbon dioxide molecules are in the gas phase at room temperature because each is nonpolar and therefore not as heavily attracted to other molecules. Id. at 399. One can imagine that as molecular complexity increases, structure affects chemical and physical properties in progressively more subtle and complex ways. Id.
85 Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002). The ortho-para- and meta-directing influences of aromatic functional groups represent one of the earliest defined structure-reactivity correlations; certain substituents promote substitution of the aromatic ring at ortho and para positions, while others deactivate the ring and result in meta substitution. CAREY & SUNDBERG, supra note 68, at 218. Electron-donating $p$-amino and $p$-methoxy group substituents on an aromatic ring increase the stability of the benzylic cation, whereas electron-withdrawing groups such as $p$-cyano and $p$-nitro groups destabilize the cation; cationic stability determines the reaction rate of substitution. Robert W. Taft et al., The Relationship Between Substituent-Induced Energy and Charge Effects in Proton-Transfer Equilibria, 103 J. AM. CHEMICAL SOC’Y 1344, 1346–47 (1981). For addition of cyanide to aromatic aldehydes, the electronic nature and position of the aromatic substituent influence the reaction equilibrium. Wei-Mei Ching & Roland G. Kallen, Mechanism of Carbamion Addition to Carbonyl Compounds, 100 J. AM. CHEMICAL SOC’Y 6119, 6122 (1978). Conformation and substituent orientation can have significant effects on reactivity; while oxidation of cis-4-t-butylcyclohexanol is faster than that of the trans diastereomer, acetylation of the
entire claimed invention. Because the test for descriptive adequacy scientifically fails, an Examiner should have issued a rejection; instead, listing suitable possible reagents and general methods for synthesizing compounds which may never have been, and which may never be, actually synthesized substitutes for proof of actual possession by the inventor.

C. Unable to Enable

The pure-science, heuristic aspect of synthetic organic chemistry centers around the journey from inexpensive, simple starting materials (“A”) toward a complex, active, desired final product (“Z”). A chemist can plan a synthetic route using well-known chemical reactions to transform A into a series of intermediates (“B”, “C”, etc.) along the path to Z. Just as in the application of general statutes to specific cases, a well-established reaction with literature precedent may or may not have previously been applied to specific starting materials or advanced intermediates. However, even synthetic roadmaps that are based entirely on efficient, preceded reactions

\[ \text{cis diastereomer is faster than that of the trans.} \]

Ernest L. Eliel et al., Conformational Analysis. XI. Configurational Equilibria and Chromic Acid Oxidation Rates of Alkylcyclohexanols. Deformation Effects, 88 J. AM. CHEMICAL Soc’Y 3327, 3331–32 (1966); Ernest L. Eliel & Francis J. Biros, Conformational Analysis. XII. Acetylation Rates of Substituted Cyclohexanols. The Kinetic Method of Conformational Analysis, 88 J. AM. CHEMICAL Soc’Y 3334, 3341–42 (1966). The cyclohexanone carbonyl group experiences an asymmetric environment in its chair conformation; small nucleophiles prefer axial attack of the carbonyl even though the approach is more sterically hindered. Benjamin W. Gung, Diastereofacial Selection in Nucleophilic Additions to Unsymmetrically Substituted Trigonal Carbons, 52 TETRAHEDRON 5263, 5270 (1996). Steric hindrance refers to the destabilization resulting from two hydrocarbon chains being too close to one another, and is the major factor determining relative rates of nucleophilic substitution at substituted methylene groups. Marvin Charton, Steric Effects. III: Bimolecular Nucleophilic Substitution, 97 J. AM. CHEMICAL Soc’Y 3694, 3694 (1975). Severe angle strain inherent in molecules such as cyclopropane leads to rapid ring-opening reactions with electrophiles to relieve the strain and release energy. Joseph B. Lambert et al., Corner Bromination of Cyclopropane, 106 J. AM. CHEMICAL Soc’Y 792, 793 (1984). Molecular torsional strain results from eclipsing of bonds on adjacent carbons; cyclohexanone can be reduced by sodium borohydride twenty-three times faster than cyclopentanone because of the respective favorable and unfavorable changes in torsional strain. Herbert C. Brown & K. Ichikawa, Chemical Effects of Steric Strains—XIV: The Effect of Ring Size on the Rate of Reaction of the Cyclanones with Sodium Borohydride, 1 TETRAHEDRON 221, 225 (1957).


Hong Lin & Samuel J. Danishefsky, Gelsemine: A Thought-Provoking Target for Total Synthesis, 42 ANGEWANDE CHEMIE, INT'L EDITION IN ENG. 36, 37 (2003) (“[S]ynthesis is the expression of our collective understanding of the underlying science of chemistry. It is not unlikely that these forays will be of greater consequence than the total syntheses themselves.”).

Stephen Hanessian, Target-Driven Organic Synthesis: Reflections on the Past, Prospects for the Future, in CHEMICAL SYNTHESIS: GNOSIS TO PROGNOSIS 61, 71 (Chryssostomos Chatgilialoglu & Victor Snieckus eds., Springer 1996) (“Target-driven synthesis implies that the prime objective is to reach the intended target by the most expedient, practical, and hopefully innovative method. Achieving such an objective without heavily ‘borrowing’ from already tested synthetic methods may be a very tall order.”).

Lin & Danishefsky, supra note 87, at 45 (employing a common reaction, called a “Claisen rearrangement,” to provide surprising reactivity en route to the target structure of gelsemine).
may suffer from unforeseen stereochemical, regiochemical, or isolation and purification challenges.

A chemist must always wield the most efficient and practical weapon in his arsenal—actually performing a proposed synthetic route from A to Z and adapting to the difficulties of the process along the way. Practically speaking, for one of ordinary skill in the art of synthetic chemistry, no amount of experimentation is "undue" with respect to synthesizing a novel chemical target molecule, especially as federal case law has conceded the considerable unpredictability of chemical reactions. The “quantity of experimentation” metric must then directly relate to the amount of practice needed to actually produce and isolate a synthetic target with reasonable purity in order to enable one successfully. With such a vast number of compounds claimed in the Markush group given as an example, each of which bears its own unique set of functional groups and consequent synthetic challenges, a specification cannot possibly disclose one representative method to make these compounds that would correlate to the entire claimed invention. Therefore, the

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90 CAREY & SUNDBERG, supra note 68, at 97. Racemization occurs when both possible enantiomers, the non-superimposable mirror-image stereoisomers of a chiral compound, of a product are generated from a single reactant compound. Id. A reaction may result in complete or partial racemization depending on whether it produces a racemic mixture or enantiomeric excess. Id. Epimerization involves the inversion of one of multiple stereocenters in a stereoisomer. Id. THOMAS H. LOWRY & KATHLEEN SCHUeller RICHARDSON, MECHANISM AND THEORY IN ORGANIC CHEMISTRY 135 (3d ed. HarperCollins Publishers 1987) ("The terms regioselective and regiospecific refer to reactions in which bonds can be made or broken in two or more different orientations. If one orientation is significantly favored, the reaction is regioselective; if one orientation occurs to the exclusion of the others, the reaction is regiospecific."). Rather than use "regioselective," the adjectives "high" or "low" can be used as modifiers for "regiospecific." Alfred Hassner, Regiospecificity. Useful Terminology in Addition and Elimination Reactions, 33 J. ORGANIC CHEMISTRY 2684, 2685 (1968).

92 CAREY & SUNDBERG, supra note 78, at 847 ("When a reaction is not completely stereoselective, the product will contain one or more diastereomers of the desired product. This requires ... some manipulation to correct the stereochemistry. Fortunately, diastereomers are usually separable, but the overall efficiency of the synthesis is decreased with each such separation.").

93 Hanessian, supra note 88, at 64.

Target molecules may be related to natural products or they may be totally "unnatural", arising from a knowledge of the three dimensional X-ray structure of an enzyme’s active site for example. Extensive structure-activity data on a series of compounds in combination with X-ray crystallography, molecular modeling, and computational techniques may suggest a "lead compound" for synthesis. Indeed, it is through this type of total synthesis that molecules exhibiting nanomolar levels of biological activity in vitro and in vivo have been attained. The emphasis on total synthesis has therefore shifted in part from real natural products such as those offered by fermentation, etc. to man-made molecules based on biological or physicochemical parameters.

Id. (citation omitted).

94 MPEP, supra note 13, § 2164.01; In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).
96 MPEP, supra note 13, § 2164.01(a).
97 '572 Patent, supra note 59, col. 40 l. 27.
98 MPEP, supra note 13, § 2164.01(b); Fisher, 427 F.2d at 839.
specification would not meet the enablement requirement without disclosing the actual method of synthesizing each individual claimed compound.

D. Will the Real “Best Mode” Please Stand Up?

As more cards get added to our initial game of Three-Card Monte, the Red Queen can more easily hide in plain sight. Similarly, though at least one member of a Markush group had to have been sufficiently conceived and possessed to allow the claim, common claim-drafting practice involves listing vast libraries of alternative potential functional groups.99 Plausibly, only one or a handful out of endless possible claimed combinations may have actually been synthesized and tested.100

Principal to the reactivity and function of any chemical compound is its chemical structure.101 The structure of a compound influences its characteristic physical properties and reactivity through the three-dimensional, relative arrangements of component atoms and molecular electron distributions.102 Minute differences in the structures of different compounds can result in profound differences in their physical properties and reactivities.103

Markush claim-drafting practice, in light of the structure-reactivity relationship, presents two practical concerns. First, we must grapple with the possibility that the

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99 Steve Gardner & Andy Vinter, Beyond Markush—Protecting Activity not Chemical Structure, INNOVATIONS IN PHARMACEUTICAL TECH. 1 (Sept. 2009), available at http://www.cresset-group.com/publications/Beyond_Markush.pdf (“[I]t has become routine to have multiple R-groups each with hundreds of defined substituents, generating millions (or billions) of potential compounds.”).

100 Gardner & Vinter, supra note 5, at 46.

101 See supra note 85 and accompanying text.

102 CAREY & GIULIANO, supra note 84, at 1024–28.

Stereochemistry is the key to understanding carbohydrate structure, a fact that was clearly appreciated by the German chemist Emil Fischer. . . . Aldopentoses have three chirality centers. The eight stereoisomers are divided into a set of four D-aldopentoses and an enantiomeric set of four L-aldopentoses. The aldopentoses are named ribose, arabinose, xylose, and lyxose. . . . [A]ll of these diastereomers have the same configuration at C-4 and...this configuration is analogues to that of (+)-D-glyceraldehyde. Among the aldopentoses, D-ribose is a component of many biologically important substances, most notably the ribonucleic acids. D-Xylose is very abundant and is isolated by hydrolysis of the polysaccharides present in corn cobs and the wood of trees. The aldohexoses include some of the most familiar of the monosaccharides, as well as one of the most abundant organic compounds on Earth, (+)-D-glucose. With four chirality centers, 16 stereoisomeric aldohexoses are possible; 8 belong to the D series and 8 to the L series. All are known, either as naturally occurring substances or as the products of synthesis.

Id.; A. J. KIRBY, STEREORELECTRONIC EFFECTS 1 (Oxford University Press, Inc. 1996) (“A molecule’s bonding electrons serve not only as its skeleton, but also as a rudimentary nervous system. . . . Every nucleus in a molecule can sense the presence of a strongly electronegative atom or group, or the approach of another molecule, or the changes in electron density. . . . when bonds are made or broken.”).

103 See supra note 84 and accompanying text.
“best mode contemplated” is not necessarily the best mode in practice.\textsuperscript{104} By disclosing the best mode, the inventor highlights a particular embodiment to those of ordinary skill in the art as that best suited to practicing the claimed utility.\textsuperscript{105} If the inventor legitimately expects others to innovate from the claimed invention, professional responsibility accompanies such a proclamation. No one, including the inventor or examiner, can responsibly contemplate which of the multitudes of compounds constitutes the best mode—short of synthesizing and testing the properties and reactivity of each and every different compound.\textsuperscript{106} Without having performed scientific analyses on each claimed compound, only a small likelihood exists that the inventor has actually even discovered the true best mode among all of the available alternatives. Thus, disclosing the best mode reduces to irresponsible, uninformed guessing. Consequently, knowing whether the inventor possessed a best mode\textsuperscript{107} to begin with becomes a murky and challenging determination, and the test for compliance with the best mode requirement fails.\textsuperscript{108}

The second concern stems from the exhaustive listing of alternative, substituent functional groups commonly practiced in drafting Markush claims. In claiming such a vast number of alternatives, the drafting process could result in the claiming of a compound that, if actually synthesized and tested, might ultimately prove to be better than the contemplated best mode. Even if not a better compound for the claimed utility, such a claimed alternative compound could have a unique, novel, and miraculous reactivity; however, as a mere alternative, the compound, though claimed, might never be synthesized, tested, or discovered.

\textbf{E. Definitely Maybe}

It’s quite probable that as Three-Card Monte bloats into Million-Card Monte you would begin to feel utterly defeated by trying to keep track of the Red Queen. Though a Markush group may encapsulate more than $10^{24}$ compounds and nevertheless clearly define its boundaries,\textsuperscript{109} even one of ordinary skill in the art could reasonably lose track of the boundaries of such a claim.\textsuperscript{110} In fact, Supplementary Examination Guidelines cite such failure to envision all the members of a Markush group as grounds for potentially rejecting the claim.\textsuperscript{111} Certainly, however, the benchmark for such a rejection based on indefiniteness need not be the

\textsuperscript{104} MPEP, \textit{supra} note 13, § 2165; \textit{In re Nelson}, 280 F.2d 172, 184 (C.C.P.A. 1960).

\textsuperscript{105} MPEP, \textit{supra} note 13, § 2165; \textit{Eli Lilly & Co. v. Barr Labs. Inc.}, 251 F.3d 955, 963 (Fed. Cir. 2001) ("[T]he public receives knowledge of the preferred embodiments for practicing the claimed invention.").

\textsuperscript{106} MPEP, \textit{supra} note 13, § 2165.03 ("The examiner should assume that the best mode is disclosed in the application, unless evidence is presented that is inconsistent with that assumption. . . . The information that is necessary to form the basis for a rejection based on the failure to set forth the best mode is rarely accessible to the examiner . . ."); see \textit{supra} note 85 and accompanying text.

\textsuperscript{107} MPEP, \textit{supra} note 13, § 2165; \textit{Eli Lilly & Co. v. Barr Labs. Inc.}, 251 F.3d 955, 963 (Fed. Cir. 2001).

\textsuperscript{108} MPEP, \textit{supra} note 13, § 2165.

\textsuperscript{109} Id. § 2171.


\textsuperscript{111} \textit{Supplementary Guidelines, supra} note 14, at 7166.
point at which confusion arises or the power to envision all possible group members fails; Markush groups can serve their purpose to claim in the alternative without being so large as to trigger such analyses.  

Current supplementary guidelines reveal additional problems with respect to effectively rejecting Markush groups under the “improper Markush grouping” doctrine or restricting them.  Though all group members may share a “single structural similarity,” problems arise with determining whether all group members share a common use. Short of synthesizing and testing each group member, the properties imparted to the members by the various functional groups raise doubts as to common utility.

F. So What’s The Big Deal?

A hypothetical example best illustrates the danger of broad Markush claiming. Suppose sixty-five years ago, a pharmaceutical company conducted promising chemotherapeutic clinical trials and found a structural pattern among a handful of effective compounds. In an effort to protect its research, the company broadly claimed in the alternative every conceivable structural variation, inadvertently included in which were the anthracyclines. Though unknown at the time and far afield of the company’s focus or interest, the anthracyclines that were claimed included doxorubicin (“DXR”), commonly used today in chemotherapy to effectively treat a variety of cancers. When other researchers later discovered and tested

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112 N,N-Diacylpiperazine Tachykinin Antagonists, U.S. Patent No. 5,344,830 col.59 l.34 (filed Dec. 10, 1992) (issued as the first claim: “A compound which is selected from the group consisting of: 1) 4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-carbamoyl)-N-[3-(4-morpholinyl)propyl]-2-piperazinecarboxamide; 2) 4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-carbamoyl)-N-[2-(4-morpholinyl)ethyl]-2-piperazinecarboxamide; 3) 4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-carbamoyl)-N-[2-(1-piperidinyl)ethyl]-2-piperazinecarboxamide; 4) 4-(N,N-di-n-pentylcarbamoyl)-1-(N,N-diphenyl-carbamoyl)-N-[2-(acetamide)ethyl]-2-piperazinecarboxamide; ... 22) (S)-4-(N,N-di-n-pentylcarbamoyl)-2-(2-N-(benzoyloxy)carbonylmethyl)-N-methylamino)(ethylaminoacarbonyl)piperazine; or a pharmaceutically acceptable salt thereof.” The total number of compounds claimed in this Markush group was twenty-two. Id.

113 See In re Harnisch, 631 F.2d 716, 721–22 (C.C.P.A. 1980) (rejecting claims under “improper Markush grouping” doctrine); MPEP, supra note 13, § 803.02 (delineating Markush group restriction practices).

114 Harnisch, 631 F.2d at 723; Supplementary Guidelines, supra note 14, at 7166.

115 Supplementary Guidelines, supra note 14, at 7166.

116 A. Fujiwara et al. Anthracycline Antibiotics, 3 CRITICAL REVIEWS IN BIOTECHNOLOGY 133, 133 (1985). The anthracyclines include several of the most effective anticancer treatments ever discovered, and have demonstrated results against more types of cancer than any other known category of chemotherapeutic compounds. R.B. Weiss, The anthracyclines: will we ever find a better doxorubicin? 19 SEMINARS IN ONCOLOGY 670, 671 (1992).

DXR, determined its efficacy in treating cancers, elucidated its structure, and filed a patent application, the USPTO Examiner would have rejected their claims, citing the earlier Markush claim. How much further effort, time, or resources could these researchers or their benefactors then justify in studying chemical compounds given that all closely related analogues had already been protected? In abandoning their research as unprofitable, these scientists would potentially sacrifice the use of DXR to effectively treat cancer patients worldwide over the last forty years.  

III. PROPOSAL

The game of Million-Card Monte guarantees that the player loses his money when he bets. Though odds weigh heavily against completely eradicating this swindle, modifying the rules could reduce the player’s odds of losing.

This proposal highlights a recent, legislative attempt to control the expanding sizes of Markush groups. Though initially unsuccessful, and inherently problematic, the USPTO did subsequently adopt guidelines to curtail broad Markush claiming. The real solution to the problem ultimately could stem from one of several attractive alternatives.

A. One Pebble In A River

In August 2007, the USPTO proposed changes to its treatment of claims containing alternative language, including Markush claims. The USPTO grew concerned about the time that it was taking for examiners to analyze Markush group alternatives and attempted to shift the burden of proving the “relatedness” of alternatives back to the applicant.

The proposed rules limited each claim to a single invention. For subject matter reading on multiple species with alternative language, a single invention occurs when all species share a substantial feature required for common utility, or all


118 F. Arcamone et al., Adriamycin, 14-hydroxydaunomycin, a new antitumor antibiotic from S. peucetius var. caesius, 11 BIOTECHNOLOGY & BIOENGINEERING 1101, 1101 (1969).


120 Application of Weber, 580 F.2d 455, 458 (C.C.P.A. 1978) (“The struggle to balance the needs of inventors...with those of the Office for search and examination responsibilities commensurate...with resources is a long-standing one. The Office ‘must have some means for controlling...examiners’ caseloads and the...searching done per filing fee.’”). The USPTO expected that more drastic measures were required to ameliorate examination difficulties incurred by the use of Markush groups than by simply monitoring the extent of searching per filing fee. Proposed Rules, supra note 119, at 44,994. According to the USPTO, more thorough and more reliable examination would stem from demanding that applicants using alternative language maintain relatedness among the claimed alternatives. Id. at 44,992.
species are obvious over one another. The changes required that the number and presentation of alternatives not detract from comprehension of the claim language, and that each alternative in a list be substitutable for each other. Finally, the rules eliminated overlapping of alternatives, which creates difficulty in concluding whether a claim contains more than one invention.

The USPTO subsequently solicited comments from the public on the proposed changes. The comments, received from intellectual property organizations, corporations, associations, law firms, and individuals, recognized the cited problems but generally criticized the approach taken by the proposed rules. Eventually, the

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121 Proposed Rules, supra note 119, at 44,996 (“The [substantial] feature could be a common structure, material, or act necessary for at least one shared specific, substantial, and credible utility. . . . The second definition codifies the long-standing principle that it is improper to restrict between species that are prima facie obvious over each other.”).

122 Id. This suggestion stems from the assertion in In re Driscoll, 562 F.2d 1245, 1249 (C.C.P.A. 1977) (“[M]embers of [a] Markush group are . . . alternatively usable for the purposes of the invention.”).

123 Id. Alternatives may fully overlap, for example, in a claim stating “selected from the group consisting of an adhesive agent, tape, and glue,” or partially overlap, such as “selected from the group consisting of citrus fruits and tropical fruits.” Id. at 44,997. The rules proposed that applicants file multiple claims ranging in scope from the broadest to which they believed they are entitled to the narrowest that they are willing to take, which would eliminate the practice of appearing to narrow claim scope by “nest[ing] sets of overlapping alternatives.” Id.


Fee-based differentiation of this type is a preferable and fairer means for assuring that inventors whose inventions may be best protected through extensive use of alternative claiming practices can do so—provided that they pay their own way through the patent examining process. If alternative claiming practices mean that a single claim in a single patent application entails the equivalent workload for a patent examiner of examining 10, 100, or more typical patent applications, then
USPTO adopted Supplementary Examination Guidelines in 2011 containing similar provisions to assist Office personnel with examination of claims for compliance with 35 U.S.C. § 112.126

B. Alternative Alternatives

As illustrated in the Analysis, attempts to evaluate Markush claim language, even under the Supplementary Guidelines, raised practical problems where some of the alternative claimed chemical compounds had never been synthesized or tested and a “common use” of such alternatives could only be constructively determined.127 Therefore, the possibility of an undiscovered but claimed miracle compound that does not actually have the requisite “common use” remains. The proposed rules and adopted guidelines endeavored to reduce the sizes of Markush groups in order to ease the work performed by examiners, rather than concentrating on the consequences that Markush claims posed for innovation and claimed but unknown alternatives.

1. The Sledgehammer Approach

Typically, only a hardline approach avoids the slack that has led to the slippery slope of Markush group claiming over the last century. The simplest and most logical approach to the problem would be to eliminate the Markush claim completely. At first blush this approach may appear harsh and superfluous. Certainly, examples have illustrated the possibility of claiming in the alternative at a level at which one of ordinary skill could reasonably presume that every Markush group member had been reduced to practice or otherwise possessed, and evaluated the claimed utility.128 Therefore, no need should exist for claiming more than those alternatives for which an applicant has demonstrated possession and the claimed utility. Markush groups remain unique aberrations, tolerated by the USPTO despite the fact that applicants claim subject matter extending far beyond what their patent applications indicate they have possessed. Applicants should not be allowed broad claims for multitudes of chemical compounds beyond that which they have actually discovered simply by claiming in the alternative.

2. Hit Them Where It Hurts

Short of completely abandoning the Markush claim, another appealing option incentivizes smaller, more refined Markush groups while simultaneously rewarding

the fees for examination should reflect the magnitude of the differential examination work being requested by the inventor.

Id. (emphasis in original).

126 Supplementary Guidelines, supra note 14, at 7162.
127 See supra Part II.E.
128 ’316 Patent, supra note 7, at col.4 l.31; ’830 Patent, supra note 112, at col.59 l.34.
the USPTO. Currently, applicants pay a flat fee for filing, search, and examination of a standard application encompassing a set number of patent claims, with surcharges added for each additional claim. Therefore, the applicant has a vested interest in claiming as many alternatives as possible in the claims that were initially purchased.

Markush groups would immediately and dramatically shrink in size if the USPTO adopted a system in which applicants paid a surcharge for each Markush group member. Applicants would negotiate balances between the desires to claim as broadly as possible in the alternative and to maintain minimal expense. The USPTO, a fee-based government office that raises funds primarily by charging patent applicants, would regularly enjoy the influx of revenue resulting from a pay-per-group-member system. Certainly, such a Markush surcharge system would require careful calibration to ensure that applicants would rather pay group-member surcharges than the fee for adding additional claims.

3. Applicant Guidance Suggested

If abandoning Markush claiming or changing the pay structure for these claims seem impractical, a third alternative would supplement current descriptive requirements. An applicant wishing to continue to claim multitudes of alternatives in Markush groups without paying any more than others who claim single inventions should at least make a greater attempt to distinguish between alternatives that are better suited to the claimed utility of their inventions.

Even if many of the claimed chemical alternatives have never been synthesized or tested, an applicant has resources at his disposable to make predictions based on current scientific evidence as to which alternatives are more or less likely to possess the claimed utility. The burden of such predictive analysis should fall upon the

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129 MPEP, supra note 13, § 607 (“37 CFR 1.16(h) sets forth the excess claims fee for each independent claim in excess of three. 37 CFR 1.16(g) sets forth the excess claims fee for each claim (whether independent or dependent) in excess of twenty.”).


applicant, who seeks to benefit from the patenting process, rather than the person skilled in art within the public who hopes to make and use the claimed subject matter and subsequently innovate.

CONCLUSION

The foregoing argument sets forth the statutory and administrative technical requirements that an invention must meet before an applicant is granted a patent, and introduces the Markush claim as a mechanism by which inventors can claim large groups of similar compounds in the alternative. Though Markush claims began as small groups of alternatives, their populations have increased exponentially. Analysis of large Markush groups of chemical compounds with innumerable alternatives under established guidelines have proven impracticable. Markush groups implicate dire consequences for innovation, but by modifying Markush practice, the USPTO may increase odds in favor of the next player trying to find the Red Queen.

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[M]olecular modeling in suitable computers in conjunction with appropriate displays has become a superior substitute for the use of mechanical models in situations where quantitative (as distinct from qualitative or semiquantitative) information about exact molecular shapes and intra- or intermolecular interactions is desired. Molecular modeling of this type had been used quite extensively to study the fit of enzymes with their substrates or of drug receptors with drugs. Assuming that an X-ray structure of the enzyme is available, and that the conformation in solution is close to that in the crystal, one can model both the enzyme and the (small) substrate and then try to “dock” the substrate in the active site of the enzyme. The approach is useful if one tries to devise enzyme inhibitors that must fit into the active site but should not undergo the subsequent chemical transformations that the natural substrate will undergo. If the structure of the enzyme is not known, or in the case of a drug receptor one can actually try to model the active site or receptor if one knows the structure of a number of substrates that interact with it. Then one can try to devise new substrates (drugs) that will fit the enzyme cavity or receptor as modeled.


133 Gardner & Vinter, supra note 5, at 46.