The Markush Challenge

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Received December 20, 1990

A summary of the use of extensive Markush structures is presented. The development of the Markush formula as we know it today is described, in addition to the advantages, disadvantages, and solutions associated with generic specifications.

INTRODUCTION

The patenting concept has been developed to encourage an inventor to disclose his invention to the public in return for protection against the use of the invention by others. The inventor receives the right to exclude others from practicing the invention for a specific period of time. Disclosure to the public seeks to add to the body of knowledge to which the technology belongs and thereby stimulate or facilitate innovation.

A patent specification must describe the invention in such detail that a person with ordinary skills in the art can practice, reproduce, or otherwise invoke the invention following the details of the disclosure. The portion of the patent which delineates what is legally covered by the patent is the list of claims. The format of the claims is determined by statute and/or convention.

In the United States, the U.S. Patent and Trademark Office (USPTO) does not allow alternative language in patent claims. A claim should not be a list of items which may be substitutes that accomplish essentially the same task or carry out the same function. For example, a claim should not state that A is attached to B with a bolt or a pin or a screw but should rather be stated as "A is attached to B by a fastening means".

The use of Markush structures is an exception to this policy. In Markush chemical structures, a single set of notations represents a variety of specific compounds through the use of defined variables. The variables may be clearly elucidated substructures such as methyl groups, keto groups, cyano groups, or less well-defined textual descriptions such as substituted phenol, heteroaryl, or carbocyclic.

The widespread use of the Markush formula began following a 1924 decision of the U.S. Patent Office (now the U.S. Patent and Trademark Office, USPTO). In this ruling, the USPTO accepted the use of claims describing chemical compounds or substituents of chemical compounds as a specified group of materials which do not belong to an otherwise definable class provided that the elements of the groups are equivalent.

Originally, the scope of Markush structures was limited. Markush claims were allowable only where nomenclature did not provide sufficient terms to adequately cover an applicant's invention or when the invention included rare substances which were not easily obtainable. Gradually, the acceptance of these structures was liberalized to permit subgenus claims.

Currently, Markush claims need only describe groups or members of a class which possess at least one common property and that property is responsible for their functional relationship. While Markush structures give the inventor a broad scope of legal coverage as well as several other advantages, a number of problems are inherent in describing chemical compounds as a group of related compounds rather than as specific molecules. The favorable business position Markush structures offer will be discussed as well as the problems their use or misuse causes. Possible solutions will then be explored.

ADVANTAGES

The use of Markush structures affords several advantages. The chemical industry is a capital intensive industry with a cost of research and development for new products ranging in the millions for a single chemical entity. In the pharmaceutical industry, the cost to bring new drugs to market is estimated between $75 and $100 million per compound. Further, effective product life is often eroded due to extensive regulatory requirements which must be met before a firm can market its product.

Patent protection must offer companies sufficient incentive to develop new products, recover investment, and realize a profit. The practice of writing generic structural representation helps to provide an inventor with broad patent coverage for an invention and protects incumbent rights in the market place. More specifically, broad claims provide expressed coverage for the compounds of interest, alleviating reliance upon judicial construction of the patent beyond its literal scope.

In addition, in the United States, an original generic specification builds a foundation for additional scientific developmental work and coverage of those innovations through continuations in part and divisional application filings. Broad coverage is especially important to the pharmaceutical industry because homologous series of compounds tend to show predictable biological activity. Broad coverage prevents competitors patenting minor modification of active compounds, and thus unfairly exploiting the original patentees' invention. Unless the modification shows unexpected activity or has a profound effect on some property such as potency, a generic Markush claim will block the modified compound on the basis of obviousness and/or novelty.

Broad Markush claims convey several business advantages to firms provided the claims are acceptable to the various patenting authorities. In the case of multiple international filings, generic claims allow a patentee to write one general specification and then refine claims according to the different patenting requirements of each patenting body involved. Simply, the onus is remanded to the patenting authority during the patenting process to inform the patentee what is acceptable and what is not. Thus, a generic set of claims may be wholly acceptable in one country but requires significant modification in another. Instead of writing five separate and distinct applications, one document may survive intact in three countries and only have to be revised in two. The savings in time and money can be significant.

Product or patent licensing has risen dramatically in the last several years. In the chemical process industry, licensing royalties are estimated at between $8 and $9 billion annually. In the pharmaceutical industry, the figure is probably higher augmented by the high cost of biological testing and extensive regulatory approval periods. The trend to license patented technology favors the use of broad claims particularly in the case of cross-licensing. With broadly and literally claimed inventions, the licensor has a better basis for the development of cross-licensing agreements where the licensor has some claim upon innovations developed by the licensee, based upon the licensor's original patented technology.

Furthermore, licensing is a tacit acceptance of the patentee's ownership of the subject technology and thus helps alleviate

0095-2338/91/1631-0002$02.50/0

The method of Claim 1 wherein said hydroxycarboxylic acid is hydroxymonocarboxylic acid having the following chemical structural formula:

$R \cdot (CR_2OH)_m(CH_2)_nCOOH$

wherein

R, R_2 = H, alkyl, aralkyl or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having up to 26 carbon atoms.

m = 1,2,3,4,5,6,7,8 or 9

n = 0 or a numerical number up to 23

present as free acid, lactone or salt form, and as optically active or inactive isomer such as D, L and DL forms: the hydrogen atom attached to the carbon atom may be substituted by a monfunctional F, Cl, Br, I or S atom or a lower alkyl or alkoxy saturated or unsaturated radical having 1 to 9 carbon atoms.

Figure 1.

the ever present threat of infringement or validity litigation. So, in looking at the advantages then, if I can summarize briefly, we have express coverage for inventions with broad Markush structures. There is foundation for further developmental work and then filing on that developmental work with continuations and divisions which prevents acceptance of patents that are minor modifications of implied compounds in the Markush. It may allow for fewer distinct and separate applications for multinational filings, and it enhances the development of cross-licensing agreements.

DISADVANTAGES

There are significant disadvantages to using broad Markush structures. Markush claims can provide an inventor with the most patent protection under the law. However, given the law, misuse of such claims can easily circumvent statutory and scientific boundaries, and actually become self-defeating.

Generic structures are allowed under the premise that a compound as a whole will exhibit specific activity regardless of what is substituted on the basic molecule. Clearly, where variable structure represents greater than three or four or ten million compounds, it is unreasonable to expect that so many compounds will exhibit activity similar to the activity shown by substances for which practical data is supplied.

The arguments which consider whether a Markush is scientifically reasonable or outside statutory limitations is an open-ended discussion which probably has no exactly correct or exactly incorrect answers. However, broad Markush characterizations have several practical disadvantages. Infinite variables are difficult to represent on computerized information systems because these systems are largely based upon specific discrete chemical entities for which there are specific connection relationships, rather than on an infinite permutation of a large number of specific or vaguely described chemical species. The potential restrictions on the scope and form of Markush structures is not based solely on whether these structures can be easily entered into a database since many extensive Markush structures could not be searched manually either. Classification systems are designed to separate documents for later search and retrieval. If a Markush structure is so broad that it cannot be classified, it becomes unusable information and its status as prior art is questionable.

Broad disclosure cannot be totally separated from the notion of retrieving the information contained in the disclosure. If a Markush is so broad, it becomes difficult to determine when a competitor is infringing or when a firm owning a patent is infringing technology known in the art. We have two figures which illustrate claims from a single patent, EP 273202.

Figure 1 cites several claims from EP 273202 as an example of a patent application that is nearly impossible to classify and

The method of Claim 1 wherein said compound is a hydroxydicarboxylic acid having the following chemical structural formula:

$$\begin{array}{l} (CH_2)_nCOOH \\ | \\ (CHOH)_mCOOH \end{array}$$

wherein

m = 1,2,3,4,5,6,7,8 or 9

n = 0 or a numerical number up to 23

present as free acid, lactone or salt form, and as optically active or inactive D, L and meso isomer: hydrogen atom attached to the carbon atom may be substituted by a nonfunctional F, Cl, Br, I or S atom or a lower alkyl or alkoxy saturated or unsaturated radical, having 1 to 9 carbon atoms.

Figure 2.

retrieve manually or by computerized means. Consider claim 4:

The method of claim 1 wherein said hydroxycarboxylic acid is hydroxymonocarboxylic acid having the following chemical structural formula:

$$R \cdot (CR_2OH)_m(CH_2)_nCOOH$$

wherein R *and* R_2 = *hydrogen, alkyl, aralkyl, or aryl group of saturated or unsaturated, straight or branched chain or cyclic form, having up to 25 carbon atoms*; $m = 1, 2, 3, 4, 5, 6, 7, 8,$ *or* 9; $n = 0$ *or a numerical number up to 23 present as free acid, lactone, or salt form, and as optically active isomer such as D, L, and DL forms*; *the hydrogen atom attached to the carbon atom may be substituted by a monfunctional* (sic) *fluorine, chlorine, bromine, iodine, or sulfur atom or a lower alkyl or alkoxy saturated or unsaturated radical having 1–9 carbon atoms.*

Now, there is an ambiguity when they state that the hydrogen atom is attached to the carbon atom. Which hydrogen atom is attached to which carbon atom when *n* is more than 1? So, right there we are not sure what structures are being delineated.

In Figure 2, claim 9 from the same patent reads as follows:

The method of claim 1 wherein said compound is a hydroxydicarboxylic acid having the following chemical structural formula:

$$HOOC(CH_2)_n(CHOH)_mCOOH$$

wherein $m = 1, 2, 3, 4, 5, 6, 7, 8,$ *or* 9; $n = 0$ *or a numerical number up to 23, present as free acid, lactone, or salt form, and as optically active or inactive D, L, and meso isomer*; *hydrogen atom attached to the carbon may be substituted by a nonfunctional fluorine, chlorine, bromine, iodine, or sulfur atom or a lower alkyl or alkoxy saturated or unsaturated radical, having 1–9 carbon atoms.*

While claims should not be disembodied from the entire specification, these two very generic claims merely represent hydroxycarboxylic acids. Little else can be reliably ascertained about their chemical nature or behavior. If one is clever enough to substitute decane rings for R in claim 4, make *m* equal 2 where there is a double bond between the two carbons and *n* equals 23, will this theoretical compound exhibit the same activity as those specifically enumerated in the dependent claims? Scientifically, it would appear that the postulated compound might experience steric difficulties and probably not exist at all. Carboxylic acids are routinely used in dermatological preparations. The art is known. Claims as broad as those illustrated in this example do not add to the body of knowledge. If a disclosure does not add to the body of knowledge and it is so vague that one ordinarily skilled in the art cannot determine what is feasibly covered by the invention, it would seem to violate at least two tenets of the patenting concept.

This same patent has been given the international classification code of A61K-047, "medicinal preparations characterized by a nonactive ingredient used for example, carriers and their additives". Equivalent published applications are also classified under A61K-007/00, "cosmetics and similar toilet preparations", and A61K-007/06, "preparations, for example, lotions or powders for the care of the hair, preparations to promote hair growth or to aid in hair removal for example shaving preparations". If the assignee of this patent wished to monitor the patents and patent applications in this area, the firm would have to monitor thousands of documents weekly. Assuming the classifications were also based upon the chemical structures claims, the firm would also have to monitor classes C07-059 to C07-065 which would add several thousand more documents to the current awareness responsibilities. The task, whether manual or computer assisted would require significant resources.

Declining classification in an accepted classification scheme, one computerized record of this patent has approximately 4500 fragmentation codes. Coding any hydroxycarboxylic acid will retrieve this document.

Unbridled use of Markush structures can also have the effect of undermining confidence in the validity of the prior art. Unfortunately, many young scientists are lead to believe that patents are an unreliable source of information. Describing compounds in unjustified unsubstantiated terms is not the sole reason for the perception, but no doubt has contributed to the myth. In addition to the difficulty inherent in policing exhaustively generic Markush claims, there is the practical consideration that very generic claims require more time to search and examine for patentability.

The previous example illustrates this point. The patent was applied for in the U.S. in 1986 and later a European filing was issued in 1988 without a search report. A search report was published in June 1990. A number of circumstances can cause delays in search and examination of an application, but searching and examining generic hydroxycarboxylic acids and the extensive body of prior art slows down the prosecution. A narrower claim will likely traverse the patenting process more quickly and possibly get to market sooner. Of course, the objective of all patenting strategy may not be new product introduction; however, the majority of patent applications are filed with new product introduction objectives.

The initial steps in the process of examination of Markush structures is often similar to the first steps employed in searching these representations. An examiner and a searcher both identify the most unique part of the molecule, that is, the portion of the molecule most likely to confer its special activity. Exhaustive Markush structures may cause the examiner to focus on a relatively unimportant aspect of the molecule and cite prior art, that while relative to that portion of the delineated species, it is not germane to the most unique or significant part of the substance described. The patentee has a recourse in such events. However, early effort to circumvent this potential problem benefits the patentee in resource conservation and detracts little from the protection available for an invention. Patent laws are liberal in the acceptance of generic structures often making extensive generic formulations unnecessary. Numerous compounds can be legitimately claimed in Markush formula whether or not they have been reduced to practice. Claiming or disclosing a great many compounds which have not been reduced to practice can afford a competitor a significant edge. If the competition reduces implied substances to practice, particularly outside of the United States, and these compounds show any variance in activity or properties, the competition may be allowed a patent, obviously limiting the scope of the claim to what has been or can easily be reduced to practice lessens this potential disadvantage of Markush claims.

So, in summarizing the disadvantages, in addition to those discussed by Sibley in the previous paper, these structures are difficult to search, and they are difficult to monitor for current awareness or infringement. The prosecution time is increased. They undermine the validity of the prior art, increase the possibility of examination errors, and encourage competitor copying of many compounds that have not been reduced to practice.

SOLUTIONS

Are there any solutions to these problems? The challenge of effectively using Markush formulas is a goal which patenting authorities, scientists, patent attorneys, and patent information professionals should consider with a commitment to providing tenable solutions. Patent offices must provide patent attorneys and scientists with sufficient motivation to voluntarily limit the scope of their Markush structures.

Acceptance of Markush structures as an exception to the dictum against using alternative language and patent claims has evolved significantly since the original Markush case. Perhaps patenting authorities, for example, the USPTO, can establish a middle ground between total nonacceptance of alternatives and total acceptance of infinite variability. One such criterion could be that if a structure represents at least one compound known in the art which has no utility for the use stated in the specification or contrary utility, then the entire Markush could be deemed too broad and not usable.

Another moderating stance could be that textual terms such as leaving groups or metabolically cleavable groups should not be allowed because they are too indistinct and too dependent upon individual molecular environments to qualify as members of subcategories. As to leaving groups, I say, well we can search Morrison and Boyd if we are just going to use leaving groups as R groups.

Patent attorneys should be more aware of the practical limitations broad Markush claims place upon the prosecution of their applications and the negative impacts that such claims place upon the goal of receiving a granted valid patent.

The practicing scientist's goal could be to study the possibilities of more sophisticated ways of describing molecules. For example, molecules could be described in terms of electron cloud conformations and densities and how these may effect biological activity. New methods of characterizing structure–activity relationships could obviate the need to endlessly list R group alternatives. Difficulty in representing Markush structures alone in computerized form is probably not sufficient reason to restrict or standardize the convention. The challenge to database producers is to design systems which can accommodate complex structures and yet be reasonably simple to search.

The ultimate challenge is for each occupational group involved in the intellectual property arena to work together in seeking solutions to these problems. Attorneys should join forces with information professionals and patent office personnel in developing computerized tools and classification systems which serve the attorney's need for extensive patent protection but at the same time make information retrievable and hence useful.

Recently, the European Patent Office has produced information products. Collaboration with patent offices and established information vendors can only benefit all intellectual property professionals. A truly innovative company would be one formed by the members of this panel or willing counterparts. Clear objectives, broad scientifically justifiable coverage, classification, and retrievability, and compliance with moderate legal requirements are not pipe dreams. Each goal is obtainable starting with fact finding discussions and forums such as this symposium and resulting in practical solutions to the Markush challenge.