



Peter Blasi

Markush structures: Opportunities and risks

Peter Blasi, CAS, investigates the pros and cons of scientific intellectual property, specifically thinking about Markush structures and their complications under patent law.

In 1924, one patent authored by Eugene Markush forever changed the world of scientific intellectual property (IP). A short phrase in the following claim chartered new territory:

*“The process for the manufacture of dyes which comprizes coupling with a halogen-substituted pyrazolone, a diazotized unsophonated material **selected from the group consisting of aniline, homologues of aniline and halogen substitution products of aniline.**”*

The patent examiner initially rejected the expansive language. Markush appealed to the US Commissioner for Patents, however, and his arguments were accepted. Markush was granted US Patent Number 1506316 entitled “Pyrazolone Dye and Process of Making the Same”. Ever since, the practice of crafting claims in a more generic fashion has become the norm, and these structures now permit applicants to claim more than one chemical entity within one claim.

Markush structures are unique to chemistry but the concept is also relevant for engineers, mechanics, architects, and IT professionals alike; the claims provide a simplified way of describing a group of related structures, designs, styles, systems, skeletons or organizations that can all accomplish the same or a similar function. In an architectural drawing, an analogy might be a perpendicular line connected to an arc that represents a door. That doorway, as drawn, represents a structure of a certain size and location, but a door of any style fitting those dimensions (be it arched, wood, metal, glass, pocket, hinged, or bi-fold) might be

used. The door serves a function that many different constructions would satisfy. In chemistry, Markush structures represent a shorthand way of describing multiple different chemical constructions that achieve the same or comparable function. These structures become important when performing searches of the patent literature especially when you are researching patentability opportunities, when you want to identify additional similar structures or when looking for prior art claims to determine potential infringement.

A typical Markush structure is shown in **Figure 1**. The listed structure includes variables (A, D, X, and n) at specific positions that create implied structural variations. This means that any of the following chemical moieties and combinations thereof at those listed positions are included in the patent’s claims. A, D, and X are specific chemical groups and “n” indicates the number of times chemical group X may be repeated within the larger structure.

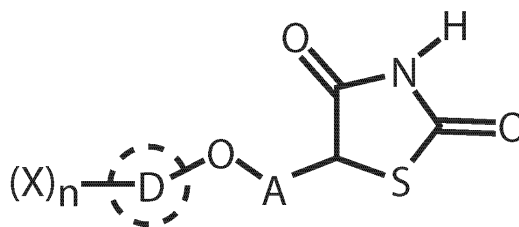


Figure 1. In which, A represents an alkylene group that may be substituted by up to three halogen atoms or is alkenylene substituted by 1-2 hydroxy groups; D represents optionally substituted aryl or heteroaryl group such as phenyl; X represents halo, alkyl, or alkoxy, and n = 0-5; or salts thereof.

The best way to demonstrate the importance of Markush structures is by example. Merck & Co.’s cholesterol-lowering agent Zetia® (ezetimibe) is scheduled to lose patent protection by April 2017, so generic drug manufacturers will contact an attorney to see what structural variants of the drug are already claimed by

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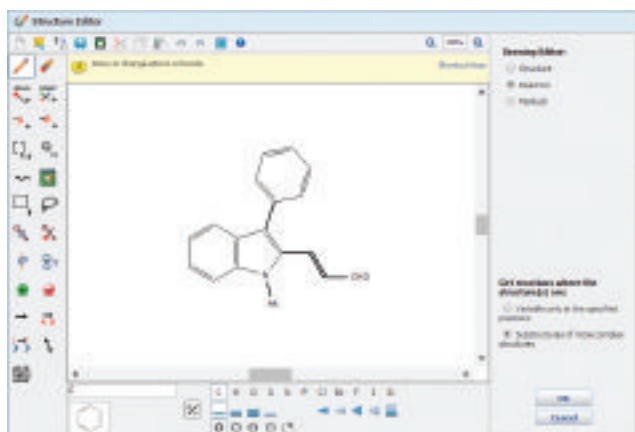
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Peter leads business development for the Science IP team, introducing clients to the value of Science IP search services and bringing them together with seasoned search professionals to meet their information needs. He has a background in biochemistry and is a registered U.S. patent attorney with professional search experience in chemical, biological, and mechanical arts.

others in the patent literature in order to establish freedom to operate. The manufacturer's attorney will perform this search on the exact Zetia structure in a registry of chemical structures, such as CAS REGISTRYSM, and will then look for functionally equivalent modifications of that structure in a Markush database such as MARPAT[®]. The attorney will review the retrieved references and send the client his or her opinion on the risk involved with marketing their generic candidate. If it turns out the attorney feels that their client's risk of pursuing a generic compound is high, the client may ask the attorney to evaluate the prior art in order to determine how it might be invalidated so that the client can proceed.

Searching a chemistry substance database as well as a Markush database is essential for a reason that is illustrated below. Pictured in **Figure 2A** is a precursor to a cholesterol-lowering statin drug marketed by Novartis. Example B is a variant of the structure shown in A and represents a hypothetical option for a generic manufacturer to pursue. In the case of structure A, both CAS REGISTRY and MARPAT will retrieve references for it, as this exact structure can be found specifically in the patent literature. For B, which includes a heterocycle variable on the ring that differentiates it from A, CAS REGISTRY retrieves no answers. A search in MARPAT, however, does retrieve references for this structure, which indicates that although the exact structure B has not yet been described in a patent, several patents have used Markush structures to generically cover it. Therefore, if a client is looking to create a generic version of the Novartis statin once it comes off patent, failing to use Markush structures in the search would mean missing this potential prior claim.

A



B

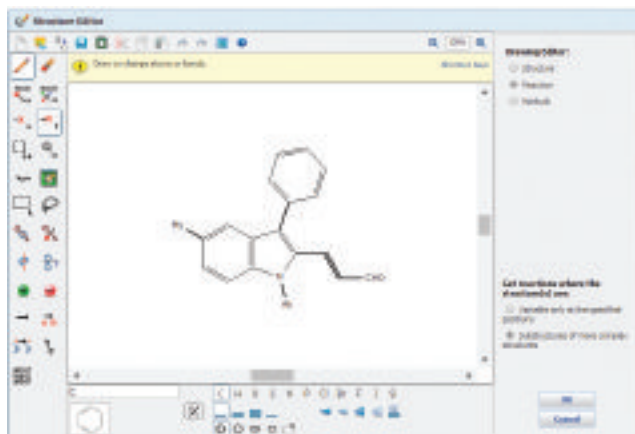


Figure 2A and B. A is a substituted indole that is a precursor to a cholesterol-lowering statin drug marketed by Novartis. B is a generic variation of A which is not covered in CAS REGISTRY but can be found in MARPAT.

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The use of Markush structures is not always straightforward and, in the past, has been controversial, as patent offices have tried to restrict the structures' scope against the wishes of chemical manufacturers worldwide. Even though the example above demonstrates why searches must cover both structure and Markush databases to be comprehensive, searching Markush structures is often a complicated endeavor. Markush structures in patents are becoming increasingly broad and difficult to interpret as patent assignees strive to cover as many functionally equivalent variants as possible. The sheer complexity and volume this entails makes finding specific structures within Markush databases time consuming, requiring experience and sophisticated search tools to reliably access the necessary information.

MARPAT is the Markush database produced by CAS and accessed by CAS solutions SciFinder[®] and STN[®]. It covers over 1.1 million searchable Markush structures entered from 1988 until the present and is updated daily. As of September 2016, the database includes more than 471,000 citations for Markush structure-containing patents. With both generic and atom-level variable structures, MARPAT works as an extension of CAS REGISTRY and consequently enables a searcher to access both CAS REGISTRY and MARPAT in order to get the most thorough, up-to-date information and avoid potential oversights.

Choosing to use both MARPAT and the expert MARPAT searchers at Science IP[®], the official research service of CAS provides clients with the most comprehensive choice possible when performing freedom to operate searches for generic chemicals. MARPAT is built, indexed and maintained by subject matter experts well versed in the complexities of Markush structures, and the professional searchers at Science IP know how to best access and interpret the information the database contains. MARPAT and Science IP provide clients with confidence that they are basing their business decisions on the most complete, dependable data possible.

Markush structures offer a shorthand way to represent an assortment of related structures. They can be difficult to search and analyze, however, especially for those without prior experience. Considering these structures is essential for generic drug manufacturers in order to perform a comprehensive freedom to operate search, which is why combining the extensive knowledge base of MARPAT with the Markush expertise of Science IP searchers ensures the best possible outcome.



Figure 3. A CAS subject matter expert indexing Markush structures from a Japanese-language patent for entry into the MARPAT database.