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Protecting Chemistry Inventions: The Double-Edged Sword of Being an Unpredictable Art

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ABSTRACT: Recent decisions by the highest courts in the US in regard to written description and enablement as well as parallel restrictions previously established in Europe emphasize that applicants in the fields of chemistry/pharma/life sciences should strive to include as many examples, data, and guidance about how to extrapolate from the example(s) in the description. This holds in particular whenever a broad genus and/or functional features is/are to be protected. It is important to keep in mind that these data and this guidance must be disclosed in the application at the time of filing. Data collected at a later stage can only be used to further support data and evidence already present in the application as filed.

Inventions, i.e., novel and non-obvious substances, devices, or methods, can be protected by patents, irrespective of the field of technology from which they originate. A gearbox or a battery management method is subject to the same patentability requirements and the same sequence of examination as a chemical substance or a synthetic method. A summary of the relevant material patentability requirements and the examination sequence before the United States Patent Office (USPTO) and the European Patent Office (EPO), as applicable for *all* applications, can be found in Table 1.

Table 1. Patentability Requirements and Examination Sequence before USPTO and EPO[a]

patentability requirement	USPTO	EPO
patent eligible subject matter	35 U.S.C. § 101	Art. 52, 53 EPC
novelty	35 U.S.C. § 102	Art. 54 EPC
inventive step/non-obviousness	35 U.S.C. § 103	Art. 56 EPC
written description/enablement	35 U.S.C. § 112 (a)	Art. 83 EPC
clarity	35 U.S.C. § 112 (b)	Art. 84 EPC

[a]U.S.C.: United States Code. EPC: European Patent Convention.

However, in day-to-day practice, some of these patentability requirements are judged differently for the so-called "predictable" technology fields, such as mechanical and electrical engineering, than for the so-called "unpredictable" fields such as chemistry and biotechnology. This distinction presupposes that the electrical and mechanical arts lack unpredictable factors while the chemical arts lack predictability.

To illustrate this distinction, we refer to a famous historical example: Mathematicians Leverrier and Adams predicted the existence of the planet Neptune, based on irregularities of Uranus' orbit. When astronomer Galle found Neptune, the prediction of a planet "by pen" was a dramatic confirmation of Newton's law of gravitation. When Newton's law of gravitation failed to fully describe Mercury's orbit, Einstein's general theory of relativity resolved this discrepancy and established the reign of predictability in the fields of physics and engineering. By contrast, as we will see below, simple modifications to a modestly complex small molecule can lead to unpredictable changes in activity and hence may be the basis for an invention.

The fact that a skilled person cannot predict, with any certainty, which function or activity a substance may possess has several important repercussions on how an invention in the areas of chemistry and life sciences is examined for patentability. As a potential advantage, whenever a hitherto unknown (i.e., novel) substance is synthesized, typically a non-predictable effect or use can be ascribed to this substance. Generally, in this case the assumption is made that finding this substance (and its use) was not obvious to the skilled person, and hence, the statutory requirement of inventive step is met. However, by the same token, this assumption of non-predictability places an additional burden on an applicant in the case where a broader group of substances is claimed, for example, a generic compound class or a so-called "Markush-structure" (i.e., a structural formula with two or more residues that can vary independently). In this case, providing one synthetic route and the activity data of one compound may not be sufficient to support the assumption that all claimed permutations of this compound can be synthesized and are active. Recent case law from courts in the US and overseas in the area of chemistry and life sciences is used to illustrate the inventive step advantage and the increasing demand to provide a larger number of working compounds and activity data in the case where a broader class of substances is to be protected.

WHAT IS OBVIOUS AND PREDICTABLE IN ENGINEERING MAY NOT BE IN CHEMISTRY

The following case was decided by the German Federal Supreme Court[1] but stands as a representative example of how patent offices and courts throughout the world decide whether or not a new compound is obvious in view of the existing prior art. In this case, the prior art did disclose "generic" 4′-(*N*-methylpiperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (**1**) with the unspecified residues R_1 and R_2 (Figure 1).

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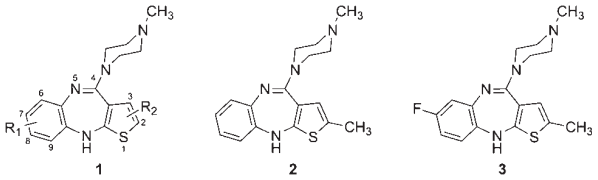

Figure 1. Generic formula **1**, Olanzapin (**2**), and Flumezapin (**3**).

The court had to decide whether (a) the claimed compound Olanzapin (**2**) falling under the generic formula **1** with R_1 = H and R_2 = methyl, is disclosed by said generic formula **1**, and if (a) is answered in the negative, whether (b) **2** is rendered obvious ("suggested") by the fluorine derivative Flumezapin (**3**), which was individualized in the same prior art document as **1**.

While logically, the generic formula **1** does include the compound Olanzapin, an important general principle in patent law as applicable to chemistry states that a generic structural formula does not necessarily inherently disclose the specific compounds falling under this formula (otherwise no future chemistry inventions would be possible since all conceivable new compounds fall under one known generic formula or another). Therefore, the court held that the general formula **1** does not disclose the specific compound Olanzapin.

Next was the question whether knowledge of Flumezapin suggests to the skilled person that the modification of the same would arrive at Olanzapin, in an obvious manner. Based on the activity data disclosed in the prior art, the reasonable expectation of a medicinal chemist would have been that the presence of the fluorine substituent in position 7 enhances the antipsychotic potency of the compound. Also, the prior art did not disclose any individualized compound falling under the generic formula **1** that is *not* halogenated. Therefore, the skilled person had no reason or incentive to modify Flumezapin to arrive at a compound that is not halogenated at all. This example shows that the intrinsic feature of lack of predictability helps to get compounds patented even if they are structurally closely related to a sister compound.

In 2007, the US Supreme Court had decided, in the famous KSR case[2] (from the area of engineering), that the teaching-motivation-success standard, previously used to determine whether or not claimed subject-matter is obvious, is too strict. Simply put, there needs to be no explicit motivation in the prior art to modify a given teaching to arrive at the claimed subject-matter. More specifically, the Supreme Court stated that when there is a need to solve a problem and there is a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the claimed solution, the same is likely an obvious product of ordinary skill and not the product of innovation. The subject-matter underlying the KSR decision is from the predicable art and relates to a mechanism for combining an electronic sensor with an adjustable automobile pedal. All elements as such and their function were known from the art, and the result of the combination was predictable and hence obvious.

For applicants in the unpredictable art, the question was whether the KSR decision would also make it easier to challenge chemistry patents as obvious. The consensus based on subsequent decisions by the next-highest court, i.e., the US Court of Appeal for the Federal Circuit (CAFC) is that this is not the case and that there still needs to be some reason (motivation) to modify a starting compound in order to arrive at the claimed compound. Among many similar decisions, the Rabeprazole case[3] illustrates this principle. Lansoprazole (**4**), the starting compound known from the art, is structurally rather similar to the claimed compound Rabeprazole (**5**). The compounds only differ in regard to the substituent at the 4-position of the pyridine ring (Figure 2).

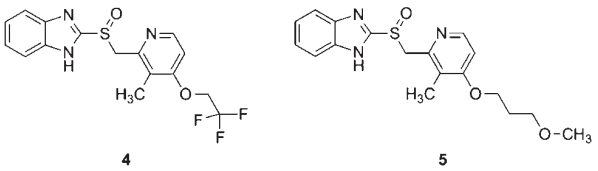

Figure 2. Structures of Lansoprazole (**4**) and Rabeprazole (**5**).

Although structurally similar, the CAFC could not find any motivation in the art to substitute the active groups. In particular, the court stated: "The record shows no discernible reason for a skilled artisan to begin with Lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property [lipophilicity]."

LACK OF PREDICTABILITY LIMITS THE BREADTH OF CHEMISTRY/BIOLOGICS CLAIMS

On the flip-side of the acknowledgment that activity found in one compound does not predetermine activity in a structurally similar compound, applicants for chemistry and life sciences applications generally have the burden of proof to show that, for a larger class of compounds (e.g., defined by a generic structure and/or a Markush structure), supported only by a few explicit examples; indeed all of the members of this larger class have the claimed activity or effect. In patent terms this means that an invention must be enabled (over the whole range claimed) and that the applicant must have had full possession of the invention on the filing date (written description requirement). Also, the activity underlying the claimed compounds must be present over the whole range claimed. Over the last years, these requirements have become particularly relevant in the unpredictable arts.

For example, in the 2014 decision *AbbVie v. Janssen Biotech*,[4] the CAFC held invalid a claim directed at a class of antibodies in which none of the antibodies was structurally defined, but only functionally in terms of a certain disassociation constant to a binding site. The claim was found invalid for lacking sufficient support in terms of written description since "the claimed scope reaches beyond what the inventors have contributed to the art," in particular since the inventors have not provided structural examples of antibodies that fulfill the claimed function.

Similarly, in the 2013 decision *Wyeth v. Abbott Laboratories*,[5] the CAFC declared invalid a broad genus claim directed at Rapamycin and its derivatives since the disclosure of the patent only supported one single compound falling within the scope of the claims (Sirolimus). As the description of the patent was silent on how to structurally modify Sirolimus to produce Rapamycin derivatives with the desired properties, the skilled person essentially has to synthesize and biologically evaluate thousands of compounds to determine which derivatives have the claimed properties and which do not. This was seen as an undue burden and the patent was declared to be invalid for lack of enablement.

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A similar case from a Board of Appeal of the European Patent Office is T 1151/04. The Board held invalid a reach-through-type of claim ("Use of activity-lowering effectors of dipeptidyl peptidase [for the] oral therapy of [diabetes mellitus]"). Such functional claims without a pointer to the identity/structure of the potential compounds are generally not allowable in proceedings before the EPO, not least because future, not-yet synthesized compounds are also encompassed. In response to this rejection, the patentee filed a generic structural claim ("Use of aminoacyl-thiazolidides or of alanine-pyrolidide as inhibitor of the enzyme activity of dipeptidyl peptidase [for the] oral therapy of [diabetes mellitus]"). Similar to the *Wyeth* decision above, the Board/Court held that an unmanageable pool of thousands of compounds is covered by the claim and that it would be an undue burden to test all claimed thiazolidides and pyrolidides for their effectiveness in inhibiting DPP-IV. In particular, the application provides no selection or guidance how to distinguish effective from noneffective compounds.

These decisions highlight the increasing demand, both in Europe and the US, for applications to not just provide one example but to cover as much breadth as possible with examples/data and to provide guidance in the description how to extrapolate from these examples/data to the remaining scope.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

The authors declare no competing financial interest.

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(4) US CAFC. *AbbVie Deutschland GmbH & Co. KG v. Janssen Biotech Inc.*; No. 13−1338 (Fed. Cir. July 1, 2014).

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