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FURTHER STUDY ON INVENTIVE STEP (PART III)

Document prepared by the Secretariat

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INTRODUCTION

1. At the twenty-second session of the Standing Committee on the Law of Patents (SCP), held in Geneva from July 27 to 31, 2015, the Committee discussed a study on inventive step prepared by the Secretariat (document SCP/22/3). The study addressed the definition of a person skilled in the art, methodologies employed for evaluating inventive step and the level of the inventive step. At its twenty-seventh session, held in Geneva from December 11 to 15, 2017, the SCP agreed that the Secretariat would prepare a further study on inventive step, giving a particular attention to the topics suggested in paragraph 8 of document SCP/24/3 (Proposal by the Delegation of Spain). That paragraph lists the following topics that may be included in a study or studies by the Secretariat: (i) common general knowledge: its combination with the state of the art; (ii) combination: juxtaposition vs synergic effects; (iii) the danger of hindsight analysis; (iv) secondary indicia; (v) selection inventions; (vi) problem invention; and (vii) the assessment of inventive step in the chemical sector (Markush claims, enantiomers. etc.).

2. Consequently, the Secretariat invited Member States and Regional Patent Offices, through its Note C. 8728, dated February 9, 2018,[1] to submit to the International Bureau examination guidelines and manuals, as well as summaries of the most important case law or interpretive decisions concerning the suggested topics for the preparation of such a study.

3. Taking into account the information submitted by the Member States and Regional Patent Offices in response to Note C.8728, the Secretariat prepared the first part of a further study on inventive step, which was submitted to the twenty-eighth session (document SCP/28/4). The Further Study on Inventive Step (Part I) focuses on the topics (i) to (iii) referred to in paragraph 1, above (i.e., (i) common general knowledge: its combination with the state of the art; (ii) combination: juxtaposition vs synergic effects; and (iii) the danger of hindsight analysis). At the said session, the Committee agreed that the Secretariat would prepare a Further Study on Inventive Step (Part II), giving a particular attention to the topics suggested in paragraph 8 of document SCP/24/3.

4. Following that agreement, the Secretariat submitted the Further Study to the twenty-ninth session (document SCP/29/4), with a particular focus on the topics (iv) to (vi) referred to in paragraph 1, above (i.e., secondary indicia, selection inventions and problem inventions). At the said session, the Committee agreed that the Secretariat would prepare a Further Study on Inventive Step (Part III), giving a particular attention to the topics suggested in paragraph 8 of document SCP/24/3.

5. This document contains the Further Study on Inventive Step (Part III), which focuses on the last topic referred to in paragraph 1, above, namely, the assessment of inventive step in the chemical sector. In preparing this document, the Secretariat took into account the information submitted by the Member States and Regional Patent Offices in response to Note C.8828 dated January 7, 2019[2] and to earlier Note C.8728.

6. Part III of the Further Study on Inventive Step covers inventions in the field of organic and inorganic chemistry, including pharmaceutical application. It is built on the earlier studies contained in SCP/22/3, SCP/28/4 and SCP/29/4, and therefore, they should be read together for the comprehensive understanding of the topic. Furthermore, since this study focuses on the inventive step assessment, this document does not cover other pertinent patentability issues that may be specifically relates to chemistry inventions. Those issues may include the

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1 The information submitted by Member States and regional offices is available in full on the website of the SCP electronic forum at: http://www.wipo.int/scp/en/meetings/session_28/comments_received.html.

2 The information submitted by Member States and regional offices is available in full on the website of the SCP electronic forum at: http://www.wipo.int/scp/en/meetings/session_30/comments_received.html.

requirements on novelty, industrial applicability (utility), enabling requirement, support requirement and unity of invention. In addition, certain exclusions from patentable subject matter, such as discoveries or diagnostic, therapeutic and surgical methods for treatment of humans or animals, as well as issues that relate to clarity and conciseness of claims and allowable claim formats are not dealt with in this document. For example, in some countries, a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, or a new use, or new medical use, of a known substance may be considered not patentable, on the grounds of non-patentable subject matter or lack of industrial applicability under the applicable patent law. Those issues outside the inventive step questions, however, are not addressed in this document. Moreover, while claim construction determines the scope of claims and has relevance to the assessment of inventive step, that issue is outside the scope of this Study.

ASSESSMENT OF INVENTIVE STEP IN THE CHEMICAL SECTOR

7. For the purpose of assessment of inventive step, chemical inventions are considered in the same light as other technical inventions. Consequently, the general guidance and methodologies for the assessment of inventive step, which have been developed in each jurisdiction and described in the earlier Studies, also apply to chemistry inventions.

8. Such general guidelines prepared by patent offices sometimes contain examples with respect to chemistry inventions. In addition, since the general methodologies and guidelines provide general principles, and not stringent rules, to be applied in each specific case, in some jurisdictions, patent offices supplement the general guidance with more detailed and specific guidance as to how to apply those general guidance to the assessment of inventive step in the field of chemistry inventions. Case laws also provide useful guidance on the particular issues relating to assessment of inventive step arising from chemical inventions.

9. For example, the submission by Austria to the SCP states that Austrian case law uses the problem-solution approach as developed by the European Patent Office (EPO) to determine the inventive step. While, in principle, that approach was also applied to inventions in the field of chemistry, Austrian courts recognize that the formal application of the problem-solution approach according to the usual scheme can be problematic, and therefore it does not necessarily have to be applied in every case. According to the case law of the Boards of Appeal of the European Patent Office, in a number of chemistry decisions, the problem and solution approach involves the following steps: (i) establishing the closest prior art; (ii) defining the problem in the light of that prior art; (iii) identifying the solution; (iv) demonstrating the success of the solution; (v) optionally reformulating the problem; (vi) examining the obviousness of the solution in view of the state of the art.[3] Demonstrating the success of the solution and reformulating the problem are particularly important steps (see T231/97 and T355/97).

10. Those supplementary guidance may be considered particularly useful in the chemistry field, because art of chemistry may be characterized by its experimental nature. Research outcomes in the chemistry sector are less predictable, in comparison to electronic or mechanical field. For example, it is not always easy to predict technical effects of a chemical compound only from its structure, and thus the technical effects need to be verified and confirmed by experimental data. It may be possible to define a chemical product by its properties, or by a method of preparing such a chemical product, even if its structure has not

[3] Case Law of the Boards of Appeal of the European Patent Office (8th edition), Part I.D, 2016.

been clearly defined. In addition, compared to other fields of technology, a chemical product with a particular structure could have a number of different and unpredicted properties (or utilities), while the functionality and utility of, for example, a hock could be predictably defined by its physical structure.

11. Having said that, as stressed by some case laws and guidelines, the fundamental legal requirement on inventive step is what is prescribed in the applicable law, i.e., whether the claimed invention is obvious to a person skilled in the art, having regard to the prior art.

A. Claimed Invention as a Whole

12. It is well established that in considering obviousness, the question is whether the claimed invention "as a whole" would have been obvious.[4] If the inventive step of a claimed invention is based on a given technical effect, it should be achievable over the whole area claimed. Technical problems could only be taken into account in the assessment of inventive step if it is successfully solved by all the claimed compounds, and not some of them.[5]

13. For example, T939/92 (OJ1996, 309) contained fundamental rulings by the Board of Appeal of the European Patent Office (EPO) on broad claims in the field of chemistry. The Board held that in view of the state of the art, the technical problem which the patent in suit addressed was the provision of further chemical compounds with herbicidal activity. Hence, it was necessary for all the claimed compounds to possess this activity. Moreover, the question as to whether or not such a technical effect was achieved by all the chemical compounds covered by such a claim might properly arise under the assessment of inventive step, if that technical effect turned out to be the sole reason for the alleged inventiveness of these compounds. The appellants' submission that the test results contained in the description showed that some of the claimed compounds were indeed herbicidal active could not be regarded as sufficient evidence to lead to the inference that substantially all the claimed compounds possessed this property. In such a case, the burden of proof rested with the appellants. The Board therefore held that the inventive step requirement had not therefore been met.[6]

14. It flows from the above general principle that where the claimed compounds are defined in the Markush format, all the compounds covered by the Markush grouping should demonstrate the involvement of the inventive step. In other words, a given technical effect that distinguishes the claimed invention with prior art should reside in all compounds covered by such a claim (see also Part N (Markush claims) of this document).

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4 See SCP/22/3, paragraph 98.

5 Case Law of the Boards of Appeal of the European Patent Office (8th edition), Part I.D, 9.8.3, 2016. See T939/92, OJ1996, 309; T694/92, OJ1997, 408; T583/93, OJ1996, 496.

6 See T268/00, T1188/00,T320/01,T1064/01,T924/02.

B. Product and its Manufacturing Process

(i) Prior art references without disclosure of a manufacturing method of a claimed compound

15. In Australia, if the compounds cannot be prepared by the prior art method, or there is no method of preparation given in the prior art, then there may be an inventive step in preparing the compounds.[7]

16. According to the submission by Germany to the SCP, in special cases, the inventive step can also be demonstrated from the fact that, although the existence of a substance (e.g., an enantiomer) was obvious to the skilled person, he could not produce it without major difficulties (see also Part E(i) of this document on enantiomers).[8]

17. Similarly, the court in the United States of America stated that if the prior art had failed to disclose a method for making a claimed compound at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. The absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious based on the close structural relationship between the claimed compounds and the prior art compounds.[9]

18. The case T595/90(OJ1994, 695) before the Board of Appeal of the EPO was concerned with the inventiveness of a product which could be envisaged as such but for which no known method of manufacture existed. The Board ruled that a product which could be envisaged as such with all characteristics determining its identity including its properties in use, i.e., an otherwise obvious entity, might nevertheless become non-obvious and claimable as such, if there was no known way or analogous method in the art for making it, and the claimed methods for its preparation were therefore the first to achieve this and do so in an inventive manner (T268/98 andT441/02). In T233/93, the combination of properties defining the claimed products had been a desideratum which the skilled community had striven to achieve. These properties, however had been considered to be irreconcilable. The Board stated that such a desired product, which may appear obvious *per se*, may be considered non-obvious and be claimable as such, if there is no known method in the art to make it and the claimed methods for its preparation are the first to produce it and do so in an inventive manner (T1195/00).

(ii) Analogy process (known and obvious manufacturing process for new and inventive product)

19. In certain countries, in general, analogy processes, which themselves would otherwise not involve inventive step, are nevertheless patentable to the extent that they provide a novel and inventive product.

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7 Submission by Australia to the SCP.
8 BGH, Xa ZR 130/07 (2009) – *Escitalopram*, GRUR 2010, 123.
9 *In re Hoeksema*,399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA1968). MPEP §2144.09, IV.

Argentina

20. The patentability of products and processes should be evaluated according to the properties and characteristics of those products or processes, which should be considered separately. Synthesis or manufacturing processes that are not novel and inventive must be considered unpatentable as such, regardless of whether the starting materials, intermediates or the final product are novel and inventive. An example is the new salting of a known product.[10]

Brazil

21. The Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, issued by INPI, Brazil[11] define the analogous processes as processes comprising starting materials and end-products that present novelty and inventive step relative to the prior art, although such processes involve the combination or use of procedures known to the prior art. With novelty and inventive step having been identified for the starting materials and end-products, it is not necessary to investigate such requirements for their respective claims of analogous processes, provided that they are linked to the main claim for the starting material or end-product.

22. Accordingly, analogous process claims can be generically interpreted as accessory claims, because, by definition, the novelty and inventive step is attributed to the presence of these requirements in the end-product and/or starting material. In addition to analogous processes related to the synthesis of chemical compounds that have novelty and inventive activity, the concept can also be extrapolated to those processes related to the production of pharmaceutical compositions, agrochemicals, drugs, catalysts, lubricants, pesticides or herbicides, among others.

23. If the examination leads to the conclusion that the starting materials and/or end-products are devoid of novelty and/or inventive step, the claimed analogous processes would not be accepted due to lack of novelty and/or inventive step, having regard to the prior art. In another situation, if the examination leads to the conclusion that the starting materials and/or end-products are devoid of novelty and/or inventive step but considers that the claimed processes are new and/or involve inventive steps, such process claims should be examined as common process claims. Since the steps involved in analogous processes are generally well known to a person skilled in the art, it may be sufficient to mention them generically in the description.

Germany

24. In Germany, in general, the production process of a substance that is as such new and inventive need not be inventive in itself, it can be a customary method of isolation and synthesis. In special cases, however, as stated in paragraph 16 of this document, a claimed invention may involve an inventive step if, although the existence of a substance was obvious to the skilled person, he could not produce it without major difficulties.[12]

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10 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

11 Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, 8, INPI, Brazil, 2017.

12 BGH, Xa ZR 130/07 (2009) – Escitalopram, GRUR 2010, 123.

EPO

25. The Case Law of the Boards of Appeal of the EPO describes a couple of cases where the Boards assessed the inventive step of analogy processes.[13] It is well-established that analogy processes are patentable insofar as they provide a novel and inventive product. According to T2/83 (OJ1984, 265), so-called analogy processes in chemistry are only claimable if the problem, i.e. the need to produce certain patentable products as their effect, is not yet within the state of the art. This is because all the features of the analogy process can only be derived from an effect which is as yet unknown and unsuspected (problem invention). If, on the other hand, the effect is wholly or partially known, e.g. the product is old or is a novel modification of an old structural part, the invention, i.e. the process or the intermediate should not merely consist of features which are already necessarily and readily derivable from the known part (or effect) in an obvious manner, having regard to the state of the art (T119/82, OJ1984, 217; see also T65/82, OJ1983, 327) (see also Part L (Intermediates) of this document). Likewise, in T1131/05, the Board deemed a process claim directed to an analogy process to be new and inventive.

(iii) Process parameters

26. In T 73/85, the Board of Appeal of the EPO stated that the very fact that the problem of improving the property in question was solved not by means of a specific change in structural parameters, but by amending process parameters, had in fact to be considered surprising. In that case, it did not matter that the individual reaction conditions claimed in the disputed patent were known *per se*; more important was whether the skilled person, in expectation of the sought-after optimization had suggested, or in the absence of possible predictions, had tried as a matter of priority, the combination of measures known *per se* claimed. In T 500/89, the Board established that the fact that individual parameter areas taken *per se* were known did not imply that it was obvious to combine them specifically to solve the problem according to the contested patent. The combination of the individual parameter areas was not the result of merely routine optimization of the process according to document 1, as there was nothing in said document to suggest this combination. See also Part G (Combination and Synergy) of this document.

C. Prior Art Citation without Disclosure of The Particular Property or Use of the Claimed Compound

27. The submission by Australia to the SCP noted that where a claim is directed to compounds *per se*, the problem addressed by the specification will usually be “to provide compounds suitable for a specific use”. This may be the biological activity of the compounds or use as intermediates in the synthesis of other compounds. If a prospective citation does not disclose the particular property or use of the compounds relevant to the problem, then it probably does not solve the problem and would not be an inventive step citation (*American Home Products Corporation Application [1994] APO 58*).

28. Likewise, the jurisprudence of the United States of America shows that if the prior art does not teach any specific or significant utility for the disclosed compounds, the prior art is unlikely to render structurally similar claims *prima facie* obvious in the absence of any reason for one of ordinary skill in the art to make the reference compounds or any structurally related compounds.[14]

29. In the same token, the court in the United States of America stated that if prior art compounds have utility only as intermediates, the claimed structurally similar compounds may

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13 The Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D, 9.17.

14 *In re Stemniski*, 444 F.2d 581,170 USPQ 343 (CCPA 1971). MPEP §2144.09, VI.

not be *prima facie* obvious over the prior art. If the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not ordinarily stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses (see also Part L (Intermediates) of this document).[15]

30. The German Federal Court of Justice found that, when examining whether the specific application of a pharmaceutical substance involves an inventive step, due account has to be taken of practices that are obvious to a person skilled in the art, for example, part of the standard medical repertoire, on the priority date (cf. standard measures).[16]

31. In relation to the case law established by the Boards of Appeal of the EPO, in T 725/11, the invention was directed to a pharmaceutical co-formulation in the form of a tablet comprising two active ingredients for HIV therapy. The board did not acknowledge an inventive step over an announcement by the patentee of a clinical trial of that combination therapy in an industry journal article. The patentee argued that this journal article was not the closest prior art because it was silent on efficacy and did not provide any technical details. The Board disagreed and stated that the journal article amounted to a concrete plan to develop a commercially viable product with a usable level of efficacy. Furthermore, the article was a public statement of intent made by the patentee's CEO and its Executive Vice President of research and development which would not be dismissed by the skilled person as mere speculation.

D. Obvious to Try – Expectation of Success

32. In some jurisdictions, one of the factors that may be taken into account for the assessment of inventive step is whether a person skilled in the art, equipped with the common general knowledge and prior art knowledge, would obviously think of carrying out certain steps with a reasonable expectation of success, and would be led to the claimed invention (obvious to try).[17] Due to the unpredictable nature of chemistry art, the obvious to try (or a similar kind of) argument is one of the rationales that may be widely used to support a conclusion of obviousness.

Australia

33. The submission by Australia to the SCP states that there is no invention in mere verification of a result suggested by the prior art. Accordingly, if the prior art indicates that certain compounds can be made by a particular reaction and suggests that other compounds could also be made by the same process, it is not inventive to verify that result (*Sharp & Dohme Inc v Boots Pure Drug Co Ltd (1928) 45 RPC 153 at 192*).

15 *In re Lalu*, 747 F.2d 703,223 USPQ 1257 (Fed. Cir. 1984). MPEP §2144.09, VI.
16 BGH, X ZB 6/13 (2014) – Kollagenase II, GRUR 2014, 464.
17 SCP/28/4, paragraph 58 and SCP/29/4, footnote 26.

China

34. The Guidelines for Patent Examination prepared by the China National Intellectual Property Administration (CNIPA)[18] provide an example of lack of inventive step where general suggestions in the prior art suggest a person skilled in the art to try it out. It states that if the effect of a technical solution is caused by something known and inevitable, the technical solution does not involve an inventive step. For example, an insecticide A-R is in the prior art, wherein R is C_{1-3} alkyl. The prior art states that the effectiveness of insecticide is improved with the increase in the number of atom in the alkyl. If the claimed invention is an insecticide A-C_4H_9, the insecticide effect compared with the prior art would obviously increase. Therefore, the claimed invention does not involve an inventive step, since the improved insecticide effect is inevitable from the prior art.

India

35. The Guidelines[19] of India indicate that obviousness cannot be avoided simply by showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.[20] Obviousness does not require absolute predictability of success. All that is required is a reasonable expectation of success.[21] Regarding pharmaceutical inventions, structural and functional similarity of the product provides the motivation to combine the teachings of the prior arts. A surprising effect, synergistic outcome of the combinations, prior art prejudice etc. usually demonstrates the non-obvious nature of the invention. However, choosing a better alternative/substitute from the known alternative from the prior art to obtain the known results would not go beyond what may be normally expected from a person skilled in the art. Thus, when the solution is from a limited number of identified predictable solutions, which is obvious to try, even the demonstration of surprising effects etc. do not provide any answer to the obviousness.

United Kingdom

36. According to the practice in the United Kingdom, in the chemical field, obvious to try objections are most frequently encountered in situations where an alternative set of reagents/reaction conditions may be used to achieve the same result with some expectation of either an improvement or other advantage in trying the alternative conditions. An important aspect of any obvious to try argument is that the means of enablement for the alternative (material, compound etc.) must also be obvious. Thus, whilst it may be obvious to try to make a chemical compound, the claim to that compound will only be obvious if a method for its preparation is also obvious.[22] In general, an invention can only be deemed “obvious to try” if

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18 Guidelines for Patent Examination, State Intellectual Property Office of the Republic of China, Part II, Chapter 10, 6.1.

19 Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.8, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

20 IPAB in *M/s. Beckton Dickinson and Company vs Controller of Patents & Designs*, [OA/7/2008/PT/DEL) [280-2012], paragraph 32.

21 IPAB in *Ajanta Pharma Limited vs Allergan Inc.*, ORA/20/2011/PT/KOL, ORDER (No.172 of 2013), paragraph 93.

22 Examining Patent Applications relating to Chemical Inventions, paragraph 69, UKIPO, June 2017. In *Boehringer Mannheim v Genzyme [1993] FSR 716* (at page 726), the court held that “thus for a claim to the product to be held obvious the skilled man must not only envisage 4,6 blocked G5-p-NP to be a product, but also be able to obtain it or produce it without any step or thought that was not obvious.”

there is a reasonable expectation of success.[23] In *Teva UK Ltd v Leo Pharma A/S [2015] EWCA Civ 779 (July 28, 2015)*, the Court of Appeal noted that the notion of something being obvious to try was useful only in a case in which there was a fair expectation of success, which requires more than the fact that a compound is worth including in a research program.

United States of America

37. In the United States of America, the *KSR* Supreme Court decision states that the rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under § 103."[24] Since the KSR decision, the case law in that area is developing quickly in the chemical arts. The Federal Circuit cautioned that an obviousness inquiry based on an obvious to try rationale must always be undertaken in the context of the subject matter in question, "including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest."[25] The Manual of Patent Examining Procedure (MPEP) illustrates a number of court cases in this regard.

Example 1: Choice of one salt from the limited number of candidates[26]

38. The claimed invention in *Pfizer, Inc. v. Apotex, Inc., 480 F.3d1348, 82 USPQ2d 1321 (Fed. Cir. 2007)*, was directed to the amlodipine besylate drug product. Amlodipine and the use of besylate anions were both known at the time of the invention. Amlodipine was known to have the same therapeutic properties as were being claimed for the amlodipine besylate, but the inventor discovered that the besylate form had better manufacturing properties (e.g., reduced "stickiness"). The court found that one of ordinary skill in the art having problems with the machinability of amlodipine would have looked to forming a salt of the compound and would have been able to narrow the group of potential salt-formers to a group of 53 anions known to form pharmaceutically acceptable salts. Consequently, there were only a finite number of salts to be tested for improved property with "a reasonable expectation of success" (see also Part E(ii) of this document on salts).

Example 2: Not obvious to try because of many options (closest prior art teaches away)

39. In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d1350, 83 USPQ2d 1169 (Fed. Cir. 2007)*, the claimed compound was pioglitazone, a member of a class of drugs known as thiazolidinediones (TZDs) for the treatment of Type 2 diabetes. As an infringement defense, the defendant argued that a two-step modification (involving homologation and ring-walking) of a known compound identified as "compound b" would have produced pioglitazone, and that it was therefore obvious.

40. The district court found that there would have been no reason to select the compound b as a lead compound. There were a large number ("hundreds of millions") of similar prior art TZD compounds generally disclosed. Although the parties agreed that compound b represented the closest prior art, one reference taught certain disadvantageous properties

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23 Examining Patent Applications relating to Chemical Inventions, paragraph 73, UKIPO, June 2017. See *MedImmune v Novartis*.

24 KSR, 550 U.S. at 421,82 USPQ2d at 1397.

25 Abbott Labs. v. Sandoz, Inc., 544 F.3d1341, 1352, 89 USPQ2d 1161, 1171 (Fed. Cir.2008).

26 See also Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014, which includes a similar example.

associated with compound b, which, according to the district court, would have taught the skilled artisan not to select that compound as a lead compound. The Federal Circuit affirmed the decision of the district court that the claimed invention is non-obvious. There were numerous known TZD compounds, and although one clearly represented the closest prior art, its known disadvantages rendered it unsuitable as a starting point for further research, and taught the skilled artisan away from its use. Furthermore, even if there had been reasons to select the compound b, there had been no reasonable expectation of success associated with the particular modifications necessary to transform the compound b into the claimed compound pioglitazone.

Example 3: Unexpected discovery of new property without any hint

41. *In Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.,520 F.3d 1358, 86 USPQ2d 1196 (Fed. Cir. 2008)*, the claimed subject matter was topiramate, which is used as an anti-convulsant. In the course of working toward a new anti-diabetic drug, the inventor had unexpectedly discovered that a reaction intermediate had anti-convulsant properties. The Federal Circuit affirmed the decision of the district court that the claimed invention is not obvious. It pointed out that there was no apparent reason that a person of ordinary skill would have chosen the particular starting compound or the particular synthetic pathway that led to topiramate. Furthermore, there would have been no reason to test topiramate for anti-convulsant properties if treating diabetes had been the goal.

Example 4: Prior art leads to a small number of options to try

42. In *Bayer Schering Pharma A.G. v. Barr Labs., Inc., 575 F.3d1341, 91 USPQ2d 1569 (Fed. Cir. 2009)*, the claimed invention was an oral contraceptive containing micronized drospirenone. The prior art compound drospirenone was known to be a poorly water-soluble, acid-sensitive compound with contraceptive effects. With that prior art knowledge, the patentee compared the bioavailability of unprotected drospirenone, enteric-coated formulation and the intravenous delivery. It found that despite the observation that drospirenone would quickly isomerize in a highly acidic environment, the normal pill and enteric-coated pill resulted in the same bioavailability. Consequently, the patentee developed micronized drospirenone in a normal pill, since it was known in the art that micronization improves the solubility of poorly water soluble drugs.

43. The district court found that a person having ordinary skill in the art would have considered the prior art result that a structurally related compound, spirorenone, though acid-sensitive, would nevertheless absorb *in vivo*, and would have suggested the same result for drospirenone. It also found that while another reference taught that drospirenone isomerizes *in vitro* when exposed to acid simulating the human stomach, a person of ordinary skill would have been aware of the study's shortcomings. The person of ordinary skill would have verified the findings as suggested by a treatise on the science of dosage form design, which would have then showed that no enteric coating was necessary. The Federal Circuit held that the patent was invalid because the claimed formulation was obvious. The Federal Circuit reasoned that the prior art would have funneled the formulator toward two options. Thus, the formulator would not have been required to try all possibilities in a field unreduced by the prior art. The prior art was not vague in pointing toward a general approach or area of exploration, but rather guided the formulator precisely to the use of either a normal pill or an enteric-coated pill. See also Part H (Dosage Regimen and Formulations) and Part I (Particle Size) in this document.

EPO

44. In accordance with the case law of the Boards of Appeal, a course of action can be considered obvious, if the skilled person would have carried it out in expectation of some improvement or advantage (T 2/83, OJ 1984, 265). In other words, obviousness is not only at hand when the results are clearly predictable but also when there is a reasonable expectation of success (T 149/93). It is not necessary to establish that the success of an envisaged solution of a technical problem was predictable with certainty. The Board in T 1577/11 concluded that, given the superior efficacy of anastrozole, as compared with tamoxifen, in treating advanced breast cancer, there was a reasonable expectation it would also improve the treatment of early breast cancer, as compared with that achieved with tamoxifen.

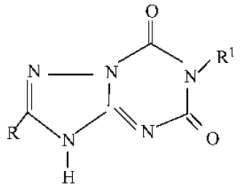
45. According to a further approach developed by the Boards of Appeal, the skilled person "would have had either some expectations of success or, at worst, no particular expectations of any sort, but a 'try and see' attitude, which ... does not equate with an absence of a reasonable expectation of success" (cf. T 1127/06, point 13 of the Reasons). In a few cases, inventive step was denied by the Boards of Appeal because the skilled person was in a "try and see" situation. Such a situation was considered to have occurred if the skilled person, in view of the teaching in the prior art, had already clearly envisaged a group of compounds or a compound and then determined by routine tests whether such compound/s had the desired effect (T 889/02, T 542/03, T 1241/03, T 1599/06 and T 1364/08).

E. Chemical Compounds – Structure and Property

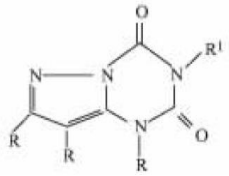
46. In general, to assess the inventive step of a new chemical compound that has a structural similarity with another compound found in the prior art, not only the extent of the similarity of the structure of those compounds but also the predictability of the property, utility, advantages or technical effects of the claimed compound are taken into account. Many court cases and Guidelines elaborate on this aspect, as described in the following paragraphs.

China

47. According to the Guidelines for Patent Examination by CNIPA, when a compound is novel, not similar in structure to a known compound and has a certain use or effect, the examiner may deem it to involve an inventive step without requiring that it shall have an unexpected use or effect. For example, where the structures of the prior art compound and the claimed invention are as shown in (1a) and (1b), respectively, there structures are not similar, as they do not have the identical basic core structure or basic rings. For the determination of inventive step of (1b), no evidence is necessary to show that (1b) has an unexpected use or effect compared with (1a).



(1a) Prior art



(1b) Claimed invention

48. For a compound that is similar in structure to a known compound, it must have an unexpected use or effect. The said unexpected use or effect may be: (i) a use different from that of the known compound; (ii) the substantive progress or improvement of a known effect of a known compound; or (iii) a use or effect which is not clearly part of the common general

knowledge or cannot be deduced from the common general knowledge.[27] For example, the prior art compound is N_2N-C_6H_4-SO_2NHR_1, sulfonamide (IIa) and the claimed invention is H_2N-C_6H_4-SO_2-$NHCONHR_1$, sulfonylurea (IIb). Sulfonamide (IIa) is an antibiotics and sulfonylurea (IIb) is an antidiabetic. They are similar in structure but different in pharmaceutical effect. Sulfonylurea (IIb) involves an inventive step, because it has unexpected use or effect compared with the prior art, sulfonylurea.

49. Conversely, for example, if the prior art compound is amino-sulfonylurea H_2N-C_6H_4-$SO_2NHCONHR_1$ (IIIa) and the claimed invention is metyl-sulfonyolurea H_3C-C_6H_4-$SO_2NHCONHR_1$ (IIIb), the structure of amino-sulfonylurea (IIIa) is similar to that of metyl-sulfonyolurea (IIIb). The difference lies in NH_2 and CH_3 only. Being short of unexpected use or effect, the claimed invention (IIIb) does not involve an inventive step.

50. The inventive step of a compound should not be denied simply on the grounds of structural similarity. In order to demonstrate that the claimed invention is obvious, it is necessary to further establish that its use or effect can be expected or predictable by a person skilled in the art, or based on the prior art, a person skilled in the art would be led to the claimed invention by logical analysis, inference or limited experiment.

Germany

51. The submission by Germany to the SCP noted that the inventive step of chemical substances or natural substances is generally based on the surprising properties and effects which the new substance possesses compared to comparable known substances and which the skilled person could not have expected.[28] The absence of those can be an obstacle to the grant of a patent.[29]

52. Similar to the chemical compounds that has surprising properties, the invention of a medicinal product may involve an inventive step if a skilled person would not have created the new medicinal product or other medicinal substance because he/she would not have expected its beneficial effects. However, for the skilled person wishing to provide a composition with beneficial effects on health risk factors, it is generally obvious to first give attention to compositions known for these effects, to identify their active substances and to charge them, in particular where there is evidence of an improvement of the effect through a higher dose of the active substance.[30] Thus, even a surprising synergy effect cannot confer inventive step if the measures resulting in this effect were themselves obvious (see also Part H of this document on dosage regimen).[31]

India

53. The Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, published by the Intellectual Property India, provide examples as to the assessment of inventive step where a claimed compound and a prior art compound have a similar structure.[32]
The first example shows a case where the claimed compound has a surprising effect, and the second example illustrate the case where the prior art teaches away a person skilled in the art from the claimed invention.

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27 Guidelines for Patent Examination, CNIPA, Part II, Chapter 10, 6.1.

28 BGH, X ZB 11/68 (1969) – *Disiloxan*, GRUR 1969, 265; BGH, X ZB 3/69 (1970) – *Anthradipyrazol,* GRUR 1970, 408.

29 BGH, X ZR 2/66 (1969) – *Geflügelfutter*, GRUR 1969, 531.

30 BGH, Xa ZR 28/08 (2010) – Fettsäurezusammensetzung, GRUR 2010, 607.

31 BGH X, ZR 50/09 (2012) – Ebastin, IBRRS 2012.

32 The Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

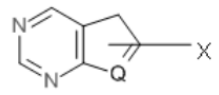
Example 1 – Similar structure/surprising effect

The claimed invention is a compound represented by the formula Py-B_3, in which Py stands for a specific pyrazolone skeleton and B stands for ethyl. The compounds of the invention possess analgesic properties. The closest prior art describes Py-B_3, wherein B stands for methyl. The compound of the prior art was not known to possess any therapeutic activity.

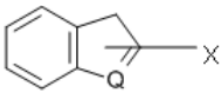
The prior art compound, although structurally very close, does not provide any clue to the skilled person that the resultant compounds with a very nominal change would be successful as a pharmaceutical product. Changing from methyl to ethyl would have been obvious to the skilled person, but the said change would not suggest achieving any pharmacological property of the modified compound. In other words, there was no coherent thread leading from the prior art to arrive to the invention. Alternatively, it may be said that there was no prior art motivation. The invention is therefore non-obvious.

Exercise 2 – Similar structure but teach away

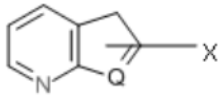
The claimed invention is a selective COX-II inhibitor nonsteroidal anti-inflammatory drug (NSAIDs) represented by the formula Hy-X (see the structure, below). Hy represents a complex heterocyclic structure, whereas X represents substituents. Cyclooxygenase I and II play vital roles in pharmacological activities of NSAIDs. Early NSAIDs are known to cause gastric irritations and life threatening ulcers. Selective COX II inhibitors, developed later, are shown to inhibit gastric secretions and thereby proved to be a better choice as NSAID. The object of the invention is to provide a class of COX II inhibitors.



Prior art D1 teaches compounds with the following structure:



Prior art D2 teaches compounds with following structure:



Both compounds of D1 and D2 are non-steroidal anti-inflammatory drugs and have disadvantage of gastric acid secretions. D2 is known to display higher level of gastric acid secretion as compared to D1.

Compared with D1, the claimed invention required two successive changes in the annular positions. However, after reaching to D2 and after finding that the resultant compound does not display any selective COX II inhibiting properties, the skilled person would not feel motivated to make any further change in D2 to reach to the compound of the present invention. Therefore, the prior art teaches away from the invention. Consequently, the invention is non-obvious.

Republic of Korea

54. The Patent Examination Guidelines of the Korean Intellectual Property Office (KIPO) state that inventive step of a chemical compound invention is determined by two features: (i) structural formula; and (ii) special technical effect of the chemical compound.[33] Inventive step of a chemical compound invention shall be determined based on the peculiarity of a chemical structure and the uniqueness of its property or use.

55. Since it is not always easy to predict the technical effects of a chemical compound from its chemical structure, improved effects accomplished by the claimed compound compared to that of a prior art compound is very important in determining inventive step. An examiner should not deny inventive step on the grounds of mere similarity in the structures of the claimed invention and the prior art chemical compound. For the assessment of inventive step, whether there are unexpected technical advantages in terms of the final result, chemical features, purpose or use of the claimed invention should be considered. If the claimed compound has unexpected or extraordinary characteristics, which cannot be easily derived from the prior art, inventive step may be acknowledged.

56. In short, the inventive step shall be recognized if:

- the claimed compound has a totally different chemical structure compared with the prior art compound;

- the claimed compound has extraordinary property which cannot be predicted from the prior art compound even though both have a similar structure; or

- even though the structure of the claimed invention is predictable from the similar structure of the prior art compound, the claimed invention has exceptional property that is not obvious to a person skilled in the art.

Otherwise, inventive step cannot be recognized (see Verdict 2007HEO2261 sentenced by Patent Court, January 17, 2008).

57. A medical invention is deemed to have inventive step if its medical effect is so creative and effective that a person skilled in the art cannot obviously be led to that effect from the chemical structure of the active compound or composition, or cannot identify it from the prior art references.[34]

Russian Federation

58. The Examination Guidelines of ROSPATENT[35] provide guidance as to the determination of inventive step for a compound invention having a similar structure to the prior art compounds. The determination of whether an invention relating to a chemical compound (or a group of chemical compounds) complies with the inventive step requirement is based on an analysis of the structure of the compound from the point of view of the obvious manifestation of its utilitarian property as indicated in the description of the invention. A negative conclusion may be drawn if, for example, the prior art shows compounds that are structurally similar to, and have the same property as, the claimed compound, and if on the basis of that information, a person skilled in the art would have expected the claimed compound to have such a property.

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33 Patent Examination Guidelines, Part IX, Chapter 5, 2.2, KIPO.
34 Patent Examination Guidelines, Part IX, Chapter 2, 2.3, KIPO.
35 Examination Guidelines for Invention Applications, Part 3.9, ROSPATENT.

This conclusion may be rebutted by the applicant if, for example, he/she provides evidence that the claimed compound has useful properties that the prior art compounds do not possess, or that it possesses the quantitatively superior property.

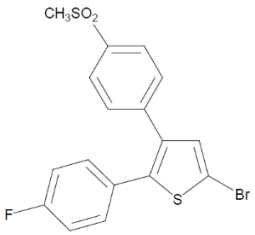
59. Close structural analogues are usually understood to be compounds that differ slightly in structure from one another. It is assumed that such structural differences should not lead to a significant change in the properties of the molecule as a whole (for example, its polarity, hydrophobicity, etc.) and, consequently, to a change in its properties. For example, compounds distinguished by the presence or absence of -CH_2-group (homologues), replacement of halogen atoms of one type with another (e.g. chlorine with fluorine), isomers, simple derivatives (e.g., salts or esters) of known compounds can be recognized as close structural analogues. The degree of structural proximity is a matter for a person skilled in the art to decide on a case-by-case basis.

60. Where the claims relate to compounds described by a general structural formula and one of the compounds in the group is known, it may be concluded that the other compounds do not meet the requirement of inventive step, unless they possess new qualitative or quantitative properties in relation to that known compound. See also Part A (Claimed Invention as a Whole) in this document.

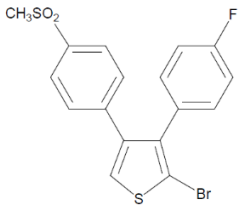
61. If the difference in properties between the claimed and known compounds consists in the difference in the quantitative indicators (for example, an increase in herbicide activity), particular attention should be paid to the extent of such difference. It cannot be regarded as a manifestation of new properties, in quantitative terms, if the difference in a particular parameter is within the margin of experimental error. The difference in properties should not be obvious and should be supported by a comparison of data under the same conditions, if the prior art does not provide information about the quantitative property of the known compound or if the property of the known compound was studied under the very different conditions so that no comparison of data is possible.

United Kingdom

62. The Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), published by the UKIPO, refer to *Pharmacia v Merck*[36], where the judge affirmed that it was obvious to investigate analogues (in this instance, regioisomers of known Cox II inhibitors as anti-inflammatory agents) of known pharmaceutically active compounds to determine their structure/activity relationship.[37]



DuP 697



Example 2

36 *Pharmacia v Merck [2002] RPC 41* (at paragraph 141).

37 Guidelines on Examining Patent Applications relating to Chemical Inventions, paragraph 70, UKIPO (updated June 2017).

63. Structurally, there is a clear similarity between DuP 697 and its close 3,4-disubstituted analogues. The judge considered that it was a matter of reasonable prediction that they would have similar activity. In arriving at that conclusion, he observed that a medical chemist wishing to investigate the structure/activity relationship of DuP 697 would think of making its 3,4-diaryl analogues, with a view to seeing whether they are active. The judge was also of the view that confronted with DuP 697 and required to develop a novel compound of similar activity, the 3,4-diaryl substitution is one of the first things which would occur to the medical chemist. In conclusion, all the evidence gave the judge the clear picture that the 3,4 diaryl compounds were obvious to try for any skilled person knowing of DuP 697(see also Parts D and E(i) on obvious to try and isomers, respectively).

United States of America

64. One of the exemplary rationale that may support a conclusion of obviousness is "a simple substitution of one known element for another to obtain predictable results".[38] The MPEP explains that, in order to reject a claim based on this rationale, the Graham factual inquiries be resolved. Then, the following steps must be articulated:

> (i) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components;
>
> (ii) a finding that the substituted components and their functions were known in the art;
>
> (iii) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable; and
>
> (iv) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

This rationale to support a conclusion that the claimed invention would have been obvious is that the substitution of one known element for another yields predictable results to one of ordinary skill in the art.

65. In the chemical arts, the cases involving so-called "lead compounds" form an important subgroup of the obviousness cases that are based on substitution. From the perspective of the law of obviousness, any known compound might possibly serve as a lead compound. In *Eisai*,[39] the Federal Circuit stated that "Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." Thus, the MPEP highlights that Office personnel should recognize that a proper obviousness rejection of a claimed compound that is useful as a drug might be made beginning with an inactive compound, if, for example, the reasons for modifying a prior art compound to arrive at the claimed compound have nothing to do with pharmaceutical activity. The inactive compound would not be considered to be a lead compound by pharmaceutical chemists, but could potentially be used as such when considering obviousness. In the same light, an obviousness rejection might be based on a known compound that pharmaceutical chemists would not select as a lead compound due to expense, handling issues, or other business considerations. However, there must be some reason for starting with that lead compound other than the mere fact that the "lead compound" merely exists.[40]

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38 MPEP §2143, I, B.

39 *Eisai, 533 F.3d at 1357, 87 USPQ2d at 1455.*

40 MPEP §2143, I, B.

66. The following case analyzing the issues such as the selection of a lead compound, the need to provide a reason for any proposed modification and the predictability of the result, is found in the MPEP as an example.

Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.[41]

The case concerns the pharmaceutical compound rabeprazole. Rabeprazole is a proton pump inhibitor for treating stomach ulcers and related disorders. The Federal Circuit affirmed the district court's summary judgment of non-obviousness, stating that no reason had been advanced to modify the prior art compound in a way that would destroy an advantageous property.

The defendant based its obviousness argument on the structural similarity between rabeprazole and lansoprazole. The compounds were recognized as sharing a common core, and the Federal Circuit characterized lansoprazole as a "lead compound." The prior art compound lansoprazole was useful for the same indications as rabeprazole, and differed from rabeprazole only in that lansoprazole has a trifluoroethoxy substituent at the 4-position of the pyridine ring, while rabeprazole has a methoxypropoxy substituent. The trifluoro substituent oflansoprazole was known to be a beneficial feature because it conferred lipophilicity to the compound. The ability of a person of ordinary skill to carry out the modification to introduce the methoxypropoxy substituent, and the predictability of the result were not addressed.

Despite the significant similarity between the structures, the Federal Circuit did not find any reason to modify the lead compound. According to the Federal Circuit: Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. […] In keeping with the flexible nature of the obviousness inquiry, the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship […] to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old."

The prior art taught that introducing a fluorinated substituent was known to increase lipophilicity, so a skilled artisan would have expected that replacing the trifluoroethoxy substituent with a methoxypropoxy substituent would have reduced the lipophilicity of the compound. Thus, the prior art created the expectation that rabeprazole would be less useful than lansoprazole as a drug for treating stomach ulcers and related disorders because the proposed modification would have destroyed an advantageous property of the prior art compound. The compound was not obvious, because, upon consideration of all of the facts of the case, a person of ordinary skill in the art at the time of the invention would not have had a reason to modify lansoprazole to form rabeprazole.

67. In general, a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.[42] "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties."[43] Compounds which are homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2-groups) are generally of

41 *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 87USPQ2d 1452 (Fed. Cir. 2008).*
42 MPEP §2144.09, I.
43 *In re Payne*, 606 F.2d 303,313, 203 USPQ 245, 254 (CCPA 1979).

sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. Homology, however, should not be automatically equated with *prima facie* obviousness, because the claimed invention and the prior art must each be viewed "as a whole", with all relevant facts other than the structural similarity.[44] For example, homologs which are far removed from adjacent homologs may not be expected to have similar properties. In *In re Mills*,[45] prior art disclosure of C_8 to C_{12} alkyl sulfates was not sufficient to render the claimed C_1 alkyl sulfate *prima facie* obvious.

EPO

68. To deny inventive step for novel chemical compounds because of their structural similarity to known chemical compounds amounted to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means for solving the technical problem underlying the application in question. Such an expectation would be justified, if the skilled person knew, be it from common general knowledge or from some specific disclosure, that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on those properties, which were important for solving the said technical problem and could be disregarded (T852/91, see also T358/04).[46]

69. In T643/96, the Board held that the concept of bioisosterism did form part of the common general knowledge of those skilled in the art, but that it had to be applied with caution when deciding upon inventive step. In the field of drug design, any structural modification of a pharmacologically active compound was, in the absence of an established correlation between structural features and activity, expected *a priori* to disturb the pharmacological activity profile of the initial structure (see T643/96, T548/91). This also held true for an alleged case of bioisosterism, which was one option of a structure-activity relationship, as long as it was not an established case of bioisosterism. In T643/96, it was held that, when deciding upon inventive step in relation to pharmacologically active compounds, what was essential was not whether a particular substructure of a chemical compound was replaced by another known isosteric one, but whether information was available on the impact of such a replacement on the pharmacological activity profile of the specific (group of) compound(s) concerned (see also T467/94 and T156/95).

70. In T 989/93, the Board stated that, in the absence of the appropriate common general knowledge, no conclusions are possible on the basis of the known properties of one group of chemical compounds (here, benzene derivatives) regarding the properties of a different group of chemical compounds (here, naphthalene derivatives).

71. With respect to improvement of properties,[47] the Board stated that if a product is required to manifest a particular property (in this case, a highly fungicidal effect) under various conditions, the superiority of the invention will depend on whether or not that property is improved under all conditions liable to be encountered in practice and particularly under the various conditions evolved in order to test it (in this case, exposure to water and wind) (T 57/84 (OJ 1987, 53)). In addition, it was stated in T254/86 (OJ1989, 115) that an invention which relied on a substantial and surprising improvement of a particular property did not also need to

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44 MPEP §2144.09, II.

45 *In re Mills*, 281 F.2d 218, 126 USPQ 513 (CCPA 1960).

46 Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D, 9.8.2 Structural similarity.

47 Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D), 9.13 Need to improve properties.

show advantages over the prior art with regard to other properties relevant to its use, provided the latter were maintained at a reasonable level so that the improvement was not completely offset by disadvantages in other respects to an unacceptable degree or in a manner which contradicted the disclosure of the invention fundamentally (see also T155/85, OJ1988,87).

72. In T 38/84 (OJ 1984, 368), the Board of Appeal pointed out that the achievement of a numerically small improvement in a process commercially used on a large scale (here enhanced yield of 0.5%) represented a worthwhile technical problem which should not be disregarded in assessing the inventive step of its solution as claimed (see also T 466/88 and T 332/90). In T 155/85 (OJ 1988, 87) the Board added that even small improvements in yield or other industrial characteristics could mean a very relevant improvement in large-scale production, but the improvement had to be significant and therefore above margins of error and normal fluctuations in the field in consequence of other parameters.

(i) Isomers, including enantiomers

73. The example described in paragraphs 62 and 63, above, related to a regioisomer invention where the inventive step was denied on the basis of the “obvious to try” argument. Other jurisdictions also provide examples of the inventive step analysis where the claimed inventions relates to isomers, including enantiomers. Isomers are molecules with identical chemical formulae, but having distinct structures, i.e., the different sequence of bonding or different special arrangements. Isomers do not necessarily share the same properties. Two main forms of isomerism are structural isomerism (or constitutional isomerism) and stereoisomerism (or spatial isomerism). Structural isomers are a type of isomers in which molecules with the same molecular formula have different bonding patterns and atomic organization. Stereoisomers have the same bond structure, but the geometrical positioning of atoms and functional groups in space differs. Enantiomers is one of stereoisomers that are mirror images of each other, such as left and right hands having a mirror image along one axis. In general, enantiomers have identical chemical and physical properties except for their ability to rotate plane-polarized light (+/−) by equal amounts but in opposite directions. Chemical synthesis of enantiomeric substances produces racemic mixture (racemate), which contains equal parts of (+) and (-) enantiomers. Enantiomer members often have different chemical reactions with other enantiomer substances. Since many biological molecules are enantiomers, in medicines, it is not rare that one of the enantiomers have desired pharmacological property, while the other enantiomer is less active, inactive, or sometimes having adverse effects.

74. The assessment of inventive step with respect to inventions on one specific enantiomeric form (pure enantiomer) boils down to a question as to whether it was obvious for a person skilled in the art to invent such a pure enantiomer, based on the prior art, including the common general knowledge. The paragraphs below provide information on inventive step assessment of inventions concerning isomers in different jurisdictions.

Argentina

75. When the molecular structure of a racemic compound is revealed in the prior art, the novelty of the enantiomeric compounds that form the racemate is also lost, since the knowledge of the molecular formula (whether or not it is written in three-dimensional form) is necessarily revealed in the prior art reference for the person skilled in the art. The existence of the enantiomers and diasteroisomers are therefore not patentable, even where different properties are described in the application. However, a patent could be obtained for processes for the

production of individual enantiomers, if they are novel, involve inventive step and are clearly described, and the result obtained from them is perfectly characterized by means of spectroscopic data.[48]

Australia

76. Where a racemic mixture is known for a specific use and the problem is to find a compound having that property in an enhanced level, or the same property with less side-effects, the question arises whether one of the isomers in isolation is an obvious solution. It can generally be presumed that it is common general knowledge that one isomer is often more active than the other. The single isomer will be an obvious solution, if it would have been a matter of routine to prepare the single isomer and test its activity. If the isomer is prepared by routine separation techniques, the single isomer will be an obvious solution. This is true even if it was not obvious beforehand which of the isomers would be more active.[49]

77. In contrast, enantiomers have been found by the court to be inventive where it was not obvious to seek to resolve the racemate and resolution was challenging and only achieved after many years of effort.[50]

Brazil

78. In relation to stereoisomers, the Guidelines for the examination of patent applications in the area of chemistry[51] state that when the purpose of the prior art compound is known, there is an expectation that the pure stereoisomer of this compound should have this same purpose. Thus, it is considered that a person skilled in the art would be motivated to obtain this stereoisomer in order to identify the most appropriate form for industrial use, such as, for example, the most active stereoisomeric form. The same reasoning should be applied to analysis of the inventive step of compositions (in relation to compositions, see Part G (Combination and Synergy) of this document).

Philippines

79. The Guidelines of the Intellectual Property Office of the Philippines (IPOPHL)[52] provide an example with respect to pure enantiomer, as follows:

> INVENTION: A substantially pure (+) enantiomer of compound F and non-toxic acid addition salts thereof, which is a selective serotonin reuptake inhibitor (SSRI) used in the treatment of depression.
>
> PRIOR ART: A racemic mixture of compound F and descriptions of techniques available to separate enantiomers from their racemates. The difficulty of separating enantiomers and the unpredictability of their properties are not known.
>
> COMMENT: The substantially pure (+) enantiomer of compound F may not be considered a mere discovery when the known difficulty of separating enantiomers and the unpredictability of their properties are not disclosed in the prior art. It may be deemed

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48 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

49 See, e.g., *Apotex Pty Ltd v Sanofi-Aventis [2009] FCAFC 134; Rhone-Poulenc Rorer S.A.'s Application [1995] APO 50*.

50 *Alphapharm Pty Ltd v H Lundbeck A/S [2008] FCA 559.*

51 Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, 3.4, INPI, Brazil, 2017.

52 Revised Guidelines on the Examination of Pharmaceutical Applications involving Known Substances, Section 9 (January 2018), Example 12, IPOPHIL.

inventive when the enhancement of efficacy is shown to be unexpected. In this case, where the therapeutic properties of the compound F would reside in its (+) enantiomer resulting in having twice the potency of the racemic compound, the enhancement of efficacy cannot be foreseen by a person skilled in the art. Lastly, the prior art would not have provided the skilled person with a reasonable expectation of success at separating the enantiomers of the compound F, where the difficulty involved in the separation would not have motivated the skilled person to develop new compounds or divert his attention to another research of interest.

Republic of Korea

80. The Examination Guidelines of KIPO[53] state that if an enantiomer is not disclosed in the prior art in detail, its inventive step shall be determined by considering whether it has extraordinary effect with its chemical and physical property compared to the prior art racemic mixture (racemate) disclosed.

81. If the use of enantiomers is not disclosed in the prior art in detail, its inventive step shall be recognized by considering that it has extraordinary effect with its chemical and physical property compared to the use of racemate disclosed.

Case from the Supreme Court[54] where the inventive step is recognized

It is well known that in the chemistry art, if racemate is disclosed, a fixed number of enantiomers are present depending on the number of asymmetric carbon (chiral center). Therefore, a use invention of specific enantiomers can be patented only if: (i) the prior art publications, etc. stating use of racemate do not disclose the use of the enatiomer in detail; and (ii) the enatiomer has different effect from the use of the racemate qualitatively or quantitatively, based on its specific physical and chemical property. In determining whether the sufficiently different effect is present, if the enantiomer has various effects in relation to its use, it is not required that all of the effects of the enatiomer have differences from those of the disclosed racemate. It is enough that some of the effects of the entiomer have differences from those of the disclosed racemate. The difference in the effect cannot be denied even if a person skilled in the art could possibly finds out its effect through repetition of a simple test. Even though it has been already well known that a specific enantiomer has better medicinal effect than that of racemate or the other enantiomer, it cannot be expected that (S) enantiomer in claim 6 of the claimed invention has better medicinal effect than that of the racemic racemate or the other (R) enantiomer which is stated in the publications. Therefore, it may not be easy for a person skilled in the art to recognize medicinal use of claim 6 of the claimed invention, based on general technical knowledge at the time of filing and from the medicinal use of the racemate mentioned above, in which two enantiomers were not separated.

United Kingdom

82. The examination guidelines relating to chemical inventions[55] issued by UKIPO state that, in most cases a single enantiomer is rendered obvious by prior disclosure of the racemate. An exception to this is where there is a technical prejudice such that the enantiomer cannot be straightforwardly prepared by standard resolution/separation techniques, even though the desirability of resolution/separation is known, as decided in *Generics (UK) Limited v H*

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53 Patent Examination Guidelines, Part IX, Chapter 5, 2.3, KIPO.

54 See Verdict 2002HU1935 sentenced by the Supreme Court, October 23, 2003.

55 Guidelines on Examining Patent Applications Relating to Chemical Inventions (updated June 2017), paragraph 55, UKIPO.

Lundbeck A/S. This practice was reaffirmed in *Novartis AG v Generics (UK) Limited* where it was held that the skilled team would consider resolution as a routine step. In this case Kitchen LJ stated: The skilled team would consider that resolution of the racemate might bring practical benefits and would see resolution as a routine step.[56]

83. The above decision, *Novartis AG v Generics (UK) Ltd,* is also a pharmaceutical example of an obvious to try decision.[57] This decision concerned the (-) enantiomer of N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl-carbamate for the treatment of Alzheimer's disease. The racemate (RA7) had previously been disclosed in two earlier publications as one of a number of compounds proposed for the treatment of Alzheimer's disease. The issues to be decided were: whether it would have been obvious to select RA7 for further development from the compounds listed in the prior art; would it have then been obvious to resolve it; and lastly, would it have been obvious to use the (-) enantiomer as a pharmaceutical in the treatment of Alzheimer's disease. Floyd J concluded that: there was nothing inventive in deciding to resolve and test RA7 to see if there were advantages or disadvantages associated with one of its enantiomers; and a pharmaceutical composition for the treatment of Alzheimer's disease comprising the (-) enantiomer was conceptually obvious and thus held that the patent was invalid. The decision in the lower court was appealed. It was contended that in using the "obvious to try" test, there had been a failure to consider whether the skilled team would have had a reasonable expectation that the (-) enantiomer would successfully treat Alzheimer's disease. It was argued that the "obvious to try" test was not applicable, as it only applies to cases where it is more or less self-evident that what is being tested should work. However, the Court of Appeal considered the approach taken by Floyd J was consistent with the principles set out in *MedImmune v Novartis,* and dismissed the appeal.

United States of America

84. In general, compounds which are position isomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. However, isomers having the same empirical formula but different structures are not necessarily considered equivalent by chemists skilled in the art and therefore are not necessarily suggestive of each other.[58] In *Ex parte Mowry*,[59] the court held that the claimed cyclohexylstyrene was not *prima facie* obvious over prior art isohexylstyrene. As in the case of homology, determining the obviousness of isomerism involving close structural similarity with the prior art reference must be considered with all other relevant factors.

85. One of the exemplary rationales that may support a conclusion of obviousness is "obvious to try" (see Part D of this document). The MPEP provides an example of applying the "obvious to try" test to a dextrorotary isomer from racemate.[60] In *Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075,89 USPQ2d 1370 (Fed. Cir. 2008)*, the claimed compound was clopidogrel, which is the dextrorotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate. Clopidogrel is an anti-thrombotic compound used to treat or prevent heart attack or stroke. The racemate, or mixture of dextrorotatory and levorotatory (D- and L-) isomers of the compound, was known in the prior art. The two forms had not previously been separated, and although the mixture was known to have anti-thrombotic properties, the extent to which each of the individual isomers contributed to the observed properties of the racemate was not known and was not predictable.

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56 Kitchen LJ in Novartis AG v Generics (UK) Limited (t/a Mylan) [2012] EWCA Civ 1623.

57 Guidelines on Examining Patent Applications relating to Chemical Inventions (updated June 2017), paragraphs 63 and 64, UKIPO. See Part D of this document, Obvious to Try – Expectation of Success.

58 MPEP §2144.09, II.

59 *Ex parte Mowry*, 91 USPQ 219 (Bd. App. 1950).

60 See MPEP §2143, I, E, Example 7.

86. At trial, the experts for both parties testified that persons of ordinary skill in the art could not have predicted the degree to which the isomers would have exhibited different levels of therapeutic activity and toxicity. Both parties' experts also agreed that the isomer with greater therapeutic activity would most likely have had greater toxicity. They also agreed that it was difficult to separate isomers at the time of the invention. Nevertheless, when the patentee ultimately undertook the task of separating the isomers, it found that they had the "rare characteristic of "absolute stereoselectivity", whereby the D-isomer provided all of the favorable therapeutic activity but no significant toxicity, while the L-isomer produced no therapeutic activity but virtually all of the toxicity. Based on this record, the district court concluded that the defendant had not met its burden of proving by clear and convincing evidence that the patent was invalid for obviousness. The Federal Circuit affirmed the district court's conclusion.

87. In relation to the exemplary rationale that may support a conclusion of obviousness "a simple substitution of one known element for another to obtain predictable results" (see the discussions on structural similarity between the claimed compound and prior art in Part E of this document), the MPEP mentions *Aventis Pharma Deutschland v. Lupin Ltd.*, which relates to the purification of a single stereoisomer, as an example of applying the said rationale.

88. In *Aventis Pharma Deutschland v. Lupin Ltd., 499 F.3d 1293,84 USPQ2d 1197 (Fed. Cir. 2007)*, the claims were drawn to the 5(S) stereoisomer of the blood pressure drug ramipril in stereochemically pure form, and to compositions and methods requiring 5(S) ramipril. The 5(S) stereoisomer is one in which all five stereocenters in the ramipril molecule are in the S rather than the R configuration. A mixture of various stereoisomers including 5(S) ramipril had been taught by the prior art. The question before the court was whether the purified single stereoisomer would have been obvious over the known mixture of stereoisomers.

89. The record showed that the presence of multiple S stereocentersin drugs similar to ramipril was known to be associated with enhanced therapeutic efficacy. For example, when all of the stereocenters were in the S form in the related drug enalapril (SSS enalapril) as compared with only two stereocenters in the S form (SSR enalapril), the therapeutic potency was 700 times as great. There was also evidence to indicate that conventional methods could be used to separate the various stereoisomers of ramipril.

90. The district court considered that there was no clear motivation in the prior art to isolate 5(S) ramipril. However, the Federal Circuit disagreed, and found that the claims would have been obvious. The Federal Circuit cautioned that requiring a clearly stated motivation in the prior art to isolate 5(S) ramipril ran counter to the Supreme Court's decision in KSR. The court also relied on the settled principle that in chemical cases, structural similarity can provide the necessary reason to modify prior art teachings. The Federal Circuit addressed the kind of teaching that would be sufficient in the absence of an explicitly stated prior art-based motivation, explaining that an expectation of similar properties in light of the prior art can be sufficient, even without an explicit teaching that the compound will have a particular utility.

91. In another case[61] referred to in the MPEP, the court considered the claimed invention non-obvious, because while there are similarity in the structures of isomers, there is no reason for a person skilled in the art to select it as the lead compound and modify it.

92. The compound at issue was risedronate. Risedronate is an example of a bisphosphonate, which is a class of compounds known to inhibit bone resorption. When the patentee sued the defendant for patent infringement, the latter defended by arguing invalidity for obviousness over one of the patentee's earlier patents. The prior art patent did not teach

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61 *Procter & Gamble Co. v. Teva Pharm. USA,Inc., 566 F.3d 989, 90 USPQ2d 1947 (Fed. Cir. 2009).*

risedronate, but instead taught thirty-six other similar compounds including 2-pyr EHDP that were potentially useful with regard to osteoporosis. The defendant argued obviousness on the basis of structural similarity to 2-pyr EHDP, which is a positional isomer of risedronate.

93. The district court found no reason to select 2-pyr EHDP as a lead compound in light of the unpredictable nature of the art, and no reason to modify it so as to obtain risedronate. In addition, there were unexpected results as to potency and toxicity. Therefore, the district court found that the defendant had not made a *prima facie* case, and even if it had, it was rebutted by evidence of unexpected results. The Federal Circuit affirmed the district court's decision. The Federal Circuit reasoned that, if 2-pyr EHDP is presumed to be an appropriate lead compound, there must be both a reason to modify it so as to make risedronate and a reasonable expectation of success. Here, there was no evidence that the necessary modifications would have been routine, so there would have been no reasonable expectation of success.

(ii) Esters, salts, N-oxides and ethers

94. Where new chemical compounds are, for example, salts, N-oxides, esters and ethers, other structurally similar compounds having the same base, functional group etc. may be found in the prior art. Some guidelines and case laws provide guidance for the assessment of inventive step where the claimed inventions cover those types of compounds.

Argentina

95. New salts of known active ingredients, esters of known alcohols, and other derivatives of known substances (such as amides and complexes) will be considered as the same substance already known by the state of the art and are not patentable.[62]

Australia

96. The submission by Australia to the SCP noted that there is a limited amount of judicial consideration of salts in Australia. Conventional salts of a (not novel or inventive) compound have been found to be obvious (*Apotex Pty Ltd v Sanofi-Aventis [2009] FCAFC 134*).

Brazil

97. The Guidelines[63] state that salts, N-oxides, esters and ethers are usually developed to provide a new compound with properties that enable more appropriate conditions suitable for its industrial application, such as solubility, dissolution, stability and appropriate organoleptic properties. If a certain salt, N-oxide, ester or ether can alter the properties of the base compound in a way that is not obvious to a person skilled in the art, such salt, N-oxide, ester or ether will be considered as having an inventive step. However, the mere description of a salt/ N-oxide/ester/ether alternative of a known compound, which is devoid of any non-obvious property or an unexpected technical effect relative to the prior art, does not represent an inventive step.

98. Normally, the process of producing a salt, N-oxide, ether or ester involves a combination of known and conventional procedures in the prior art, since all the reactions for producing these classes of compounds are described in the literature and are therefore obvious to a person skilled in the art. However, while salts, N-oxides, ethers or esters are considered

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62 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

63 Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, 2.4, INPI, Brazil, 2017.

patentable, the processes for producing them cannot be analyzed as analogous processes, and consequently, are also subject to patentability requirements (see also Part B(iii) (Analogy process) of this document).

India

99. The Guidelines[64] provide an example of a claimed invention, which is a mere conversion to monoester of a known compound with an anticipated effect.

> The claimed invention relates to monoester of a known diol compound for treating cancer diseases using amino acids selected from lysine, valine, leucine and the like, as an esterifying agent. Due to poor oral bioavailability, the diol was unable to use as oral delivery system. To improve the oral bioavailability one of the hydroxyl group in the diol was converted into a monoester using said amino acids. Prior art disclosed monoalcohol with similar structure having poor oral bioavailability was converted into an ester using amino acids selected from lysine, valine, leucine and the like, as an esterifying agent, which exhibit improved oral bioavailability in the treatment of cancer diseases. Amino acid used in the prior art as well as in the claimed invention is lysine.
>
> Prior art addressed poor oral bioavailability for substantially similar structure of monoalcohol. The problem was solved by converting the monoalcohol into ester using lysine as an esterifying agent.

Prior Art	**Claimed Invention**
$R\text{-}CH_2\text{-}OH$ ↓ $R\text{-}CH_2\text{-}OR'$ R' is lysine, valine, leucine and the like	$HO\text{–}CH_2\text{-}R\text{-}CH_2\text{-}OH$ ↓ $HO\text{–}CH_2\text{-}R\text{-}CH_2\text{-}OR'$ R' is lysine, valine, leucine and the like

> A person skilled in the art can be motivated with teachings of the prior art to use the amino acid for improving the oral bioavailability by converting diol into monoester of diol to solve similar kind of problem. Therefore, there is no technical advancement involved in the claimed invention.

100. The Guidelines also provide another example[65] of the inventive step analysis using an invention on specific salt, which is substantially similar to the example given in paragraph 38 of this document.

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64 Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Example 5, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

65 Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Example 3, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

F. Polymorphic Forms and Crystalline

Argentina

101. Polymorphism is an inherent property of the solid state of drugs used in the pharmaceutical industry: in other words, it is not a man-made invention but a property of the substance. When reference is made to the phenomenon of polymorphism in a solid compound, it refers to different crystalline forms of the same substance, which depend on the conditions of the environment in which it is generated (pressure, temperature, concentration, among others). Therefore, the presence of different crystalline forms corresponds to different arrangements of the molecules in their internal structure, in accordance with the proper physical conditions that govern during their formation, and is independent of human action. Consequently, whenever claims to polymorphs result from mere identification and/or characterization of a new crystalline form of a substance already known in the state of the art, even when they present differences in pharmacokinetics or stability in relation to solid forms already known of the same substance (amorphous and / or crystalline), such claims are not admissible. The processes of obtaining polymorphs constitute a routine experiment in drug preparation. They are not patentable because it is obvious to try to obtain the most pharmaceutically suitable polymorph by using the conventional methods.[66]

Australia

102. The submission by Australia to the SCP noted that there is a limited amount of judicial consideration on polymorphs in Australia. However, where a claimed crystal form of a known compound solved a problem (hygroscopicity) associated with a prior crystal form, and the prior art did not lead a person skilled in the art to the claimed form, the claimed polymorph was found to be inventive (*Bristol-Myers Squibb Company v Apotex Pty Ltd [2015] FCAFC 2*).

Brazil

103. With respect to assessment of inventive step on polymorph inventions, the Guidelines[67] state that although the same chemical substance is involved, and the possibility of the formation of different crystalline networks is a peculiar property of solids, polymorphic forms may have different physicochemical properties both in the product preparation processes and in shelf life or even in terms of chemical effects.

104. However, the Guidelines emphasize that the search for crystalline solids of a compound is a common practice of the industry to improve the physicochemical characteristics of compounds in general. Consequently, the mere description and characterization of an alternative crystalline solid of a known compound that is devoid of any non-obvious property of the solid or of any technical advance relative to the prior art would not satisfy the requirement of an inventive step.

105. In relation to solvates, clathrates and co-crystals, if the claimed invention is in a crystalline form (clathrate, co-crystal or crystalline form of the solvate), it must be physically and chemically characterized through the techniques described in accordance with the “Polymorph” section of the Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals and the INPI Patent Application Examination Guidelines, Part II.[68]

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66 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

67 Guidelines for the Examination of Patent Applications – Aspects related to the Examination of Patent Applications in the Area of Chemistry, 4.4, INPI, Brazil, 2017.

68 Guidelines for the Examination of Patent Applications – Aspects related to the Examination of Patent Applications in the Area of Chemistry, 5, INPI, Brazil, 2017.

Costa Rica

106. The Guidelines for the Assessment of Inventions in the Chemical and Pharmaceutical Sectors (2013) were updated in 2017 for the assessment of inventions relating to crystalline forms. Crystalline forms may have features that are not considered inventions under the Guidelines. To determine whether features produce results not obvious for a person skilled in the art, the patentability requirements must be studied and the following points be considered:

– If the routine research of a person skilled in the art on an active ingredient and the resulting polymorphs leads to a new, alternative crystalline form (e.g., another polymorph), the mere provision of this alternative is considered an obvious solution to the technical problem, so there is no inventive step.

– In the case of a different form of a known compound with different and unexpected pharmacological properties relative to the state of the art, if the person skilled in the art had no basis for anticipating those different and unexpected properties, the provision of the crystalline form to solve the technical problem claimed would not be obvious. Inventive step is therefore recognized.

– The solution to a technical problem is considered obvious if a person skilled in the art can follow the principles of the existing art with reasonable expectations of success.

– Crystalline products are generally easier to isolate, purify, dry, etc. Therefore, in the absence of an unexpected feature, the mere provision of a crystalline form based on a known active ingredient cannot be considered inventive.

– Some of the arguments used to establish absence of inventive step when considering patent applications for new polymorphs are as follows:

(i) It is necessary to demonstrate the existence of an unexpected effect or technical advantage by providing comparative data on the claimed compound relative to the closest prior art;

(ii) Experimental techniques and processes for the selection of polymorphs are a routine part of the pharmaceutical development process;

(iii) The crystallization and recrystallization processes used to obtain polymorphs are common and therefore obvious for a person with ordinary skill in the art;

(iv) It is common knowledge for a person with average knowledge of the subject matter that hydrates are usually purer and more soluble.

Republic of Korea

107. In case where a new crystal form of a known chemical compound is claimed, and prior art shows a different crystal form of the chemical compound, the new crystal form is considered having inventive step, insofar as its effect is qualitatively different with that of prior art, or insofar as it demonstrates quantitatively greater effect than the prior art, regardless of any qualitative effect of the invention.[69]

[69] Patent Examination Guidelines, Part IX, Chapter 5, 2.2, KIPO.

108. In the medicinal field, it is well known in the technical field of medicinal compound that different crystal forms (polymorphic forms) may have different features, such as solubility or stability. It is therefore common to review the existence of polymorphic forms of the compound in the medicinal compound research. Accordingly, a claimed invention in the medicinal field, involving a compound with a specific crystal form different from the prior art crystal form of the same compound, is considered involving inventive step, if it has clearly different qualitative effect compared to the compound disclosed in the prior art, or if it has clearly different quantitative effect compared to that in the prior art, regardless of its qualitative effect. For the positive determination of inventive step, that effect of the claimed invention shall be stated clearly in the description part of the application.[70]

109. Manufacturing a crystal using mixed solvents is well-known or commonly used art, since the target substance melts in one solvent better than in another one. Therefore, it is considered as having no inventive step. However, if the effect of the invention, compared with the prior art, is much better than expected by a person skilled in the art, inventive step is acknowledged.[71]

United Kingdom

110. In general, the mere provision of a compound in a crystalline form is not considered inventive (in the absence of a technical prejudice).[72] In T 1555/1277 the Board commented that "the mere provision of a crystalline form is not regarded as involving an inventive step. Investigation of whether active compounds are prone to crystalline transformation and characterization of such crystalline forms is routine practice in the pharmaceutical industry." A similar conclusion was reached in the earlier decision T 0777/08 (see below under the "EPO"). Thus, where the prior art teaches the existence of an amorphous (or undisclosed) form of the compound, the provision of a crystalline polymorphic form is unlikely to be inventive without an unexpected technical effect.

EPO

111. In T 777/08 (OJ2011, 633), the Board assessed whether a crystalline form of a known compound that improved the technical effect of the amorphous form of that compound involves an inventive step.[73] The claims in question related to a particular polymorph (form IV) of crystalline atorvastatin hydrate. The Board considered that the amorphous form of atorvastatin, as obtained according to the processes of documents (1) and (2) represented the closest state of the art. The appellant defined the problem to be solved in view of this prior art as the provision of atorvastatin in a form having improved filterability and drying characteristics. Having regard to the experimental results reported in document (25), which demonstrated shorter filtration and drying times for form IV compared to the amorphous form, the Board was satisfied that this problem had been solved. It also found that the skilled person in the field of pharmaceutical drug development would have been aware of the fact that instances of polymorphism were commonplace in molecules of interest to the pharmaceutical industry, and have known it to be advisable to screen for polymorphs early on in the drug development process. Moreover, he/she would be familiar with routine methods of screening. Consequently, in the absence of any technical prejudice and in the absence of any unexpected property, the mere provision of a crystalline form of a known pharmaceutically active compound could not be regarded as involving an inventive step.

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70 See Verdict 2010HU2865 sentenced by Supreme Court, July 14. 2011.

71 Patent Examination Guidelines, Part IX, Chapter 2, 2.3, KIPO.

72 Guidelines on Examining Patent Applications Relating to Chemical Inventions (updated June 2017), paragraph 56, UKIPO.

73 Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D, 9.8.5.

G. Combination and Synergy

112. The Further Study on Inventive Step (Part I) (document SCP/28/4) dealt with the assessment of inventive step where two pieces of prior art information are combined. It also looked at "true" combination inventions on one hand and a mere juxtaposition or aggregation of known features on the other hand. While general principles described in document SCP/28/4 are also applicable to chemistry inventions, this document provides complementary information and examples in this regard in the area of chemistry.

Argentina

113. In some cases, claims on combination of previously known active principles indicate which specific compounds they comprise and the amounts they cover, while in others, reference is made only to one category of therapeutic compounds, such as antacids and antivirals, without specifying which compounds it includes. Most combinations have already been tested in medical practice by administering the components separately. Claims for combinations of known active principles in practical terms are equivalent to claims for medical treatments, for which patentability is excluded.[74]

Brazil

114. In the particular case of inventions related to combinations, the interaction between the associated compounds must produce a non-obvious effect, such as a synergistic or supra-additive effect, which does not correspond to an additive effect, i.e., the mere sum of the individual effects of each compound that makes up the said combination.[75] Thus, when the result of the association of two or more known compounds is a sum of the effects that would be expected for each compound used alone, the claimed combination will be considered devoid of inventive step, since the said combination corresponds to a predictable association of known compounds to generate an expected technical effect.

115. Evidence of the non-obvious effect of a combination often involves the presentation of data that allow a comparison to be made between the effects observed with the respective compounds when used alone and those obtained from the combination of these compounds under the same experimental conditions. It should be noted that the claimed non-obvious effect cannot be suggested in the state of the art, such as, for example, in combinations of compounds of the same class as the compounds of the combination under analysis.[76]

Philippines

116. The following examples with respect to the assessment of inventive step for inventions combining known compounds are provided in the Revised Guidelines on the Examination of Pharmaceutical Applications involving Known Substances, Section B.9 (January 2018), IPOPHIL.

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74 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

75 Guidelines for the Examination of Patent Applications – Aspects related to the Examination of Patent Applications in the Area of Chemistry, 7, INPI, Brazil, 2017.

76 Guidelines for the Examination of Patent Applications, II, paragraph 7.19.

Example 9

Invention:
A synergistic combination of Compound M, or a pharmaceutically acceptable salt thereof and Compound N, or a pharmaceutically acceptable salt thereof.

Overview of the Description of the Invention:
The inventors found out that Compound N actually inhibits a liver enzyme-ctyochrome P450 which metabolizes protease inhibitors. The bioavailability of Compound M is twice the value it had when administered alone. The combination is superior in terms of potency and shown to be a beneficial treatment as shown in the pharmacological data provided in the description as filed.

Prior Art:
Compound M is a remarkable antiretroviral drug from the protease inhibitor class used to treat HIV and AIDS. Compound N has been shown to be a potent secondary protease inhibitor. Specifically, Compound N has been shown to exhibit a booster effect for Compound X. The mechanism behind the booster effect is not known. In addition, HIV protease inhibitors are known to be metabolized by cytochrome P450 monooxygenase, a liver enzyme.

Comment:
First, the claimed combination is drawn to the analysis of a patent eligible subject matter:

> Step 1: Is the claim directed to new form of a known compound?
> Yes
>
> Step 2: Is the new form inherent?
> No. Although each of the compound are being used in the treatment of HIV and AIDS, the combination is not an inevitable and not a necessary result of performing methods explicitly mentioned in the prior art.
>
> Step 3: Has the new form resulted to enhancement of known efficacy?
> Yes. The composition provided a synergism which could not be predicted by a person skilled in the art.
>
> Step 4: Is the enhancement inherent?
> No. The synergy of the two compounds is not an accidental result nor implicitly intended result from the explicit disclosures of the prior art. A person skilled in the art could not predict, at the time of filing, that a superior potency is attained when the combination is used to treat HIV and AIDS since the mechanism of the booster effect of Compound N was not yet known at the time of the claimed invention.

Second, the claim is deemed to be not inherent and novel as the combination is not disclosed in the prior art.

Third, the enhancement of efficacy, which in this case is the unexpected superior potency, should be assessed whether it could demonstrate inventive step. Following the problem solution approach, the closest prior art is taken to be the document disclosing the combination of Compound N with Compound X. The technical problem is seen to be the provision of an alternative HIV drug which is superior in potency. Based on the disclosure in the prior art, the booster effect of Compound N has already been shown with Compound X, another protease inhibitor.

Even though the mechanism or scientific principle behind the booster effect of Compound N is not yet known at the time the claimed invention was filed, a person skilled in the art would be motivated to look for other combinations comprising Compound N, with the expectation of success, in order to arrive at the claimed combination. Such endeavor falls within the normal routine work within his ordinary skill and common sense. Hence, the claimed combination, although offers an unexpected superior enhanced efficacy, should still be deemed obvious.

Example 10

Invention:
Synergistic combination of Compound O and Compound P useful as antibacterial with no toxic side effects.

Overview of Description of the Invention:
Compound O, was discovered by the inventors to have a very high gram-negative activity, including moderate activity against pseudomonas aeruginosa while most anaerobic pathogens and several gram-positive strains are moderately susceptible to it. Compound P, a nitroimidazole, has an antibacterial spectrum that includes most of anaerobes. To increase the spectrum and to lessen the chances of resistance, it was combined with Compound O, a nitroimidazole which has an antibacterial spectrum that includes most of anaerobes. The additive advantage over monotherapy is that both drugs act on DNA and provide sequential block on bacterial DNA to contribute to synergistic activity. Compound P showed antioxidant potential and offers no obvious toxicity as compared to individual treatment. Pharmacological data is provided in the description as filed.

Prior Art:
Compound O, which is a broad antibacterial spectrum of quinolones, and Compound P, a nitroimidazole are known compounds. Monotherapy with both compounds caused mild to moderate hepatoxicity and nephrotoxicity. Both drugs have similar pharmacokinetic profile with long half-lives suitable for parenteral administration. An undue experimentation and inventive skill would require a person skilled in the art to combine said compounds based on his common knowledge.

Comment:
A fixed dose combination of Compound O and Compound P could be considered to involve inventive step if the combination is superior in terms of potency and spectrum and shown to be a beneficial treatment than individual therapy of said drugs. Each of the components enhances the therapeutic effect of each other, an enhancement which could not be predicted by a person skilled in the art in light of the prior art documents.

Russian Federation

117. The Examination Guidelines[77] state that where the invention relates to a composition of at least two known ingredients which provides a synergistic effect that the state of the art does not imply, the invention is considered to involve an inventive step.

[77] Examination Guidelines for Invention Applications, Part 3.9, ROSPATENT.

Example

A pharmacologically active agent, which is an analgesic and an antiseptic, consisting of "A" and "B" in a ratio of 20-40 and 60-80 wt%, respectively, is claimed (a tablet contains 0.01g "A" and 0.03g "B").

It is known that "A" is used as an analgesic and "B" as an antiseptic, but in tablets containing only "A" its quantity is 0.05g, and in tablets containing only "B" its quantity is 0.06g.

Based on the above information, in the claimed invention, "A" and "B" both show a higher activity of their inherent character (as a result of which it has become possible to significantly reduce their content in the tablet, compared to the medicines known from the prior art, while achieving the same therapeutic effect). Such an invention involves inventive step, since it creates a synergistic effect.

118. When considering compositions, it is necessary to ensure that the technical result specified by the applicant can be achieved over the entire range of the claimed ingredient content. This is particularly important where the minimum and maximum values of the claimed intervals differ significantly, for example, from 0.1 to 100 g/l. In such situations, it is necessary to make sure that the description of the invention contains information that supports the achievement of the technical result, for example, at the boundaries of the claimed range (see also Part A (Claimed Invention as a Whole) in this document).

United Kingdom

119. The Guidelines on Examining Patent Applications Relating to Chemical Inventions provide guidance on the inventive step assessment regarding a specific combination of two compounds or polymers in a composition.[78] In BL O/220/13 which centered on two applications for vitamin supplement compositions, the first for bone health maintenance and the second for postnatal health and lactation. The hearing officer considered that, for such compositions to be inventive, there had to be some degree of synergy between the constituents. Neither of the applications, however, provided any suggestion that the constituents interacted with each other in any way. It was considered that although there was an inevitable degree of interaction when present in the human body, this was quite unintentional and incidental to the operation of the composition. Assessment of inventive step was therefore conducted on the basis of each of the constituents individually. As each constituent was well known in the art for use in dietary supplements, the invention was considered to be an obvious collocation and both applications were refused for lack of inventive step.

120. Synergistic effects are most often encountered in the chemical arts when active compounds are combined in pharmaceutical formulations. However they also appear in other applied chemistry fields. For some inventions, the synergistic effect may not be clear-cut and thus careful consideration of the examples will be necessary. Collocation arguments may not be appropriate in some multi-component compositions, for example, toiletries products where, despite the fact that each component is essentially acting in its normal fashion, its presence in the composition may require 'tuning' of the proportions of the other components to counter any undesirable properties of the component. UK case law currently states that the synergistic effect must be plausible on the basis of the application as filed.[79]

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78 Guidelines on Examining Patent Applications Relating to Chemical Inventions (updated June 2017), paragraphs 87 and 88 UKIPO.

79 *Glaxo Group Ltd's Patent [2004] RPC 43*; *Richardson-Vicks Inc.'s Patent [1995] RPC 568 at 581*.

121. Therefore, when assessing if a composition claim may be obvious, it is important to consider the nature of the disclosure in the prior art. In general, the mere fact that each of the required components for a particular compositional claim are present in lists of possible ingredients within one document should not be regarded as destroying the inventiveness of that composition. Instead, search and examination should generally concentrate on those prior art disclosures where the exemplified compositions have much in common with the claimed compositions, but differ in only one or a few respects. The extent to which the prior art examples and the claimed compositions differ and yet a valid inventiveness argument can be made will depend in large part on the art. In compositional cases, what forms part of the common general knowledge or would be regarded as routine laboratory modification should be considered. For instance, a prior art example composition sharing the bulk of the required ingredients, but possessing the missing ingredients in a short preferred list of obvious replacements for a given example ingredient, or a prior art example with all of the required components, but where not all of the components are present in the required proportions, should generally be used as the basis of obviousness objections. Equally, a prior composition, where the missing components are merely standard additives for the end use, may form the basis of a strong inventive step argument (e.g., carbon black added as a UV stabiliser). The applicant may then put forward arguments with respect to whether the replacements or alteration of proportions required is indeed inventive.

122. The Examination Guidelines also provide guidance on inventiveness of combined use of two or more known medicaments in the pharmaceutical field.[80] Claims related to the combined use of two or more known medicaments may be in the form of *per se* composition claims or first or second medical use claims, and may also define a kit of parts for simultaneous or sequential administration. Following the practice established by the House of Lords in *SABAF v MFI Furniture Centres*, the first question that must be addressed is whether – for the purpose of assessing inventive step – the claim in question relates to a single invention or plural inventions. If the two (or more) ingredients simply perform their usual function in the body, and there is no synergy between them, then the claim relates to two separate inventions, and there is no inventiveness in combining them. The Hearing Officer in *Lalvani et al's Applications* applied this practice to dietary supplement compositions with multiple ingredients, with no evidence in the application of any synergy between them. On the facts of the case, he considered that each of the ingredients was either a known or obvious ingredient of compositions intended for the uses in question, and so the applications were refused on grounds of lack of an inventive step.

123. Moreover, synergistic effects between the components must be identified in the specification. Evidence of synergy provided after the filing date cannot be used to demonstrate inventiveness, if there is no indication of such synergy in the specification as filed (*Glaxo Group's Patent* [2004] RPC 43). Moreover, evidence of unexpected synergy between the two components does not render a combination inventive if the combination would in any case be obvious to the skilled person. In particular, if it is known to combine two categories of active agent (such as an analgesic and a decongestant), it is unlikely to be inventive to merely substitute a newer, more effective agent of one or other category in the combined preparation. If the synergy demonstrated by the new combination is no greater than the equivalent prior art combination, then it does not provide evidence of inventiveness.

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[80] Examination Guidelines for Patent Examination relating to Medical Inventions in the Intellectual Property Office (April 2016), paragraphs 227 to 230, UKIPO.

124. In *Richardson-Vicks' Patent*,[81] the argument was made that combined preparations faced particular difficulties in obtaining regulatory approval, and this would constitute a prejudice away from a new combination. This was rejected by the judge: any perceived regulatory difficulty is considered irrelevant for inventiveness. On the other hand, if there is a technical prejudice that would point away from the combination in question, then inventiveness may be acknowledged, even if the combination is superficially obvious.

United States of America

125. One of the exemplary rationale that may support a conclusion of obviousness is "combining prior art elements according to known methods to yield predictable results". The MPEP[82] explains that, in order to reject a claim based on this rationale, the Graham factual inquiries be resolved. Then, the following steps must be articulated:

> (i) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;
>
> (ii) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;
>
> (iii) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
>
> (iv) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art.

126. The case of *In re Omeprazole Patent Litigation, 536 F.3d 1361,87 USPQ2d 1865 (Fed. Cir. 2008)* is one in which the claims were found to be nonobvious in the context of an argument to combine prior art elements. The invention involved applying enteric coatings to a drug, omeprazole, in pill form for the purpose of ensuring that the drug did not disintegrate before reaching its intended site of action. The claimed formulation included two layers of coatings over the active ingredient.

127. The district court found that the patent in suit was infringed by the defendants. The district court rejected the defendants' argument that the patents were invalid for obviousness. The defendants had argued that the claimed invention was obvious because coated omeprazole tablets were known from a prior art reference, and because secondary subcoatings in pharmaceutical preparations generally were also known. There was no evidence of unpredictability associated with applying two different enteric coatings to omeprazole. However, the patentee's reason for applying an intervening sub-coating between the prior art coating and omeprazole had been that the prior art coating was actually interacting with

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81 *Richardson-Vicks Inc.'s Patent [1995] RPC 568*.

82 MPEP §2143, I, A (Combining prior art elements according to known methods to yield predictable results).

omeprazole, thereby contributing to undesirable degradation of the active ingredient. This degradation of omeprazole by interaction with the prior art coating had not been recognized in the prior art. Therefore, the district court reasoned that based on the evidence available, a person of ordinary skill in the art would have had no reason to include a sub-coating in an omeprazole pill formulation.

128. The Federal Circuit affirmed the district court's decision that the claimed invention was not obvious. Even though sub-coatings for enteric drug formulation were known, and there was no evidence of undue technical hurdles or lack of a reasonable expectation of success, the formulation was nevertheless not obvious because the flaws in the prior art formulation that had prompted the modification had not been recognized. Thus, there would have been no reason to modify the initial formulation, even though the modification could have been done. Moreover, a person of skill in the art likely would have chosen a different modification even if they had recognized the problem.

129. The above Omeprazole case can also be analyzed in view of the discovery of a previously unknown problem by the patentee, i.e., "problem inventions" which are discussed in the Further Study on Inventive Step (Part II) (document SCP/29/4). See also Part H of this document on formulations.

130. In addition, MPEP §2144.04, II.A addresses obviousness analysis related to a claimed invention that eliminate a step or an element and its function from a prior art composition. In *Ex parte Wu*,[83] claims at issue were directed to a method for inhibiting corrosion on metal surfaces using a composition consisting of epoxy resin, petroleum sulfonate, and hydrocarbon diluent. The claims were rejected over a primary reference which disclosed an anticorrosion composition of epoxy resin, hydrocarbon diluent, and polybasic acid salts wherein said salts were taught to be beneficial when employed in a freshwater environment, in view of secondary references which clearly suggested the addition of petroleum sulfonate to corrosion inhibiting compositions. The Board affirmed the rejection, holding that it would have been obvious to omit the polybasic acid salts of the primary reference where the function attributed to such salt is not desired or required, such as in compositions for providing corrosion resistance in environments which do not encounter fresh water.

EPO

131. In T 1814/11, the problem to be solved was to provide an alternative synergistically active fungicidal composition based on prothioconazole. The Board concluded that synergistic effects were not foreseeable, i.e., even if a combination of two specific compositions had a synergistic effect as in document 1, such synergy could not necessarily be expected if the structure of one of the two compositions were modified. Synergy was not in principle foreseeable and therefore could not be attributed to a specific mechanism of action and/or structure. The Board dismissed the respondent's suggestion of trial-and-error experimentation as inappropriate in this case.

H. Dosage Regimen and Formulations

Argentina

132. In some cases, a claimed formulation is associated with certain effects, as a controlled release of the drug at a particular site in the body. Achieving such effects is part of the usual ability of a knowledgeable person in the formulation of pharmaceutical products, who can select from manuals the right excipient to achieve the desired effect. The formulation techniques and

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83 *Ex parte Wu, 10 USPQ 2031 (Bd. Pat. App. & Inter.1989).*

the set of components that can be used to develop pharmaceutical products in their different forms are elements well known to a technically trained person. For example, it is not inventive to use stabilizing agents in particular (such as pH regulators) or the use of some components to modify the bioavailability of the drug (term indicating the measurement of the actual velocity and the total amount of drug that reaches the general circulation from the pharmaceutical form administered), given that it is widely known that the pharmaceutical form used may affect bioavailability.[84]

133. New formulations and compositions as well as the processes for preparing them should be considered as a general rule obvious, in view of the prior art. Similarly, claims relating to the pharmacokinetic parameters (such as Tmax, Cmax, concentration plasma), the micronization of a known product or the distribution by particle size should not be considered admissible (see also Part I of this document on a particle size). As an exception, claims on a formulation could be acceptable when a long-standing problem is solved in a non-obvious way. In that case, the description of the tests and the results obtained should be included in the description.[85]

134. While dosage claims are sometimes drafted as product claims, they are equivalent to claims on methods for medical treatment, since dosage is not a product or process, but the dosage of the product with which the therapeutic action for that use is obtained. They are therefore not patentable.[86]

Philippines

135. The Revised Guidelines on the Examination of Pharmaceutical Applications involving Known Substances[87] provide an example of the inventive step analysis using an invention relating to an extended release formulation of an antibiotic drug compound, as follows:

> Invention:
> An extended release pharmaceutical composition comprising compound R (a derivative of the known compound Q) and a pharmaceutically acceptable polymer, for reducing gastrointestinal side-effects, whereby after ingestion certain specified parameters (pK limitations) of drug bioavailability are met.
>
> Prior Art:
> A combination of references that disclosed: (a) extended release formulations of compound Q; (b) extended release formulations of compound S (another derivative of the known compound Q) and their pK profiles; and (c) extended release of a drug including compound R as an alginate salt.
>
> Comment:
> An extended release formulation of the antibiotic drug compound R, which aims to extend the period of drug effectiveness after ingestion and thereby reduce the requisite frequency of dosage, is considered to involve inventive step when the claimed pK limitations were not disclosed in any of the prior art as well as that there was no motivation for a skilled person to combine the teachings of the prior art references and come up with a reasonable expectation of success, i.e., a skilled artisan would not have predicted which formulation that might be selected from the prior art would provide the

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84 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

85 *Idem.*

86 *Idem.*

87 Revised Guidelines on the Examination of Pharmaceutical Applications involving Known Substances (January 2018), Section B.9, Example 11, IPOPHIL.

required pharmacokinetics; also, when there are dissimilarities in the pharmacokinetic properties and that the bioavailability of the formulations in the invention are not predictable from the prior art. When the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option, the pursuit of the known option may be obvious even in the absence of a "teaching, suggestion, or motivation" concerning that option. If this leads to the anticipated success, it likely is the product of ordinary skill and common sense, and not of innovation.

Republic of Korea

136. With respect to the inventive step assessment with the consideration in dosage regimen or dose, the inventive step may be acknowledged only where the dosage regimen or dose has a prominent or heterogeneous effect that cannot be expected by a person skilled in the art.[88]

Example 1: The invention relates to a pharmacological composition for prevention or treatment of hepatitis B. Claim 1 claims Compound A of 0.5-1.0 mg administered once a day and attached to the surface of a carrier disposition. The closest prior art discloses a pharmacological composition for treatment of hepatitis B, with compound A of 0.5-2.5 mg being orally administered as active component, and to improve pharmacological effects and for the convenience of administration/medicine taking. Since optimization of the unit administration volume and of administration method is a general technical consideration for a person skilled in the art in the medical field, based on the closest prior art, a person skilled in the art may reasonably predict that the effect can be arisen even if compound A is administered only once a day within the smaller range of 0.5-1.0 mg dosage. In addition, the claimed invention does not exhibit a prominent, unpredictable effect compared with the closest prior art. [2014hue768]

Example 2: The claimed invention relates to a pharmacological composition for prevention or treatment of osteoporosis, with Compound C of 100mg to around 150 mg as active component, being orally administered once a month. The closest prior art discloses that it is useful to treat osteoporosis with Compound C of 2.5 to 5.0 mg as an active component, administered once a day, and that it is possible to administer Compound C with 35 mg every week. Based on the prior art, a person skilled in the art could easily select the option of administering Compound C with 150 mg every month to treat osteoporosis. Even though a patent applicant asserts that administering Compound C with 150 mg shows superior bioavailability compared to lower dosage, and that after one year of administration, 150 mg administration per month is superior to 2.5 mg administration every day in terms of bone density improvement, it can be rationally expected that the higher dosage administration (150 mg per month during one year) would provide a superior effect compared to lower dosage administration (2.5 mg per day during one year). Therefore, it shall be considered that no unexpectedly striking difference has been made by the invention.

United Kingdom

137. The Examination Guidelines for Patent Applications Relating to Medical Inventions in the Intellectual Property Office[89] refer to a number of cases relating to dosage regimen. Following the decision of the Court of Appeal in *Actavis v Merck*, second medical use claims which are defined by a new dosage regime (where the substance or composition, and the disease treated, are both known in the prior art) are in principle allowable. In this decision, Jacob LJ highlighted

88 Patent Examination Guidelines, Part IX, Chapter 2, 2.3, KIPO.

89 Examination Guidelines for Patent Applications Relating to Medical Inventions in the Intellectual Property Office (April 2016), paragraphs 146 to 148 and 224 to 225, UKIPO.

the fact that investigating dosage regimes is standard practice in the art, and so only in an unusual case (such as the existence of a technical prejudice pointing away from the claimed dosage regime) would a new dosage regime alone confer inventiveness to a claim. In a review of an Office Opinion, the Hearing Officer in *InterMune's Patent* held that the above comments provided useful guidance on determining obviousness, rather than establishing a binding legal principle that there is a general presumption that there must be a clear technical prejudice pointing away from the claimed dosage regime to confer validity on such a claim. Nevertheless, on the facts of the case, the Hearing Officer declined to overturn the Opinion that the patent lacked inventive step.

138. In *Hospira v Genentech* (2014), the inventiveness of a new dosage schedule for an anti-cancer drug was considered. Birss J rejected the argument that the skilled person would not consider the new schedule, pointing out that the skilled person would be aware that changes to dosage regimes were a routine aspect of the development of existing drug treatments. He also held that there was nothing in the prior art or the common general knowledge to suggest the new dosage regime should not be trialed, and it would be obvious to run a small clinical trial of the new schedule – on the facts of the case, he considered that it would have a reasonable expectation of success. This decision was upheld at the Court of Appeal, where it was pointed out that it was not necessary for the skilled person to know the new dosage schedule would work – all that was required was that the prospects of success were sufficiently good to warrant a small clinical trial. Similarly, in *Novartis v Focus* and *Accord Healthcare v Medac*, it was considered obvious to conduct trials of the claimed dosage regimes and in both cases, the patents were revoked for lack of inventive step. In *Accord Healthcare v Medac*, it was held that the skilled team would include a drug formulator as well as a clinician, and it would be obvious to the formulator to investigate dosages to reduce undesirable effects (in this case, injection pain).

139. The decision of the Hearing Officer in *Advance Biofactures of Curacao's Application* illustrates some of the factors which might, exceptionally, lead to a new dosage form being considered both novel and inventive. The active agent was present at substantially higher concentration than the prior art, and it was impossible in practice to deliver the required dose with the prior art solutions. Moreover, the person skilled in the art would have considered this higher concentration to have unacceptable side effects, and the concentrated composition was successful in treating a group of patients who did not benefit from treatment with the prior art compositions.

140. A unit dosage form consists of a tablet, suppository, ampoule or other device, containing a definite amount of a drug, the whole of which is intended to be administered as a single dose. It is thus distinguished from a supply of an indefinite amount of a medicament, for example, a bottle of medicine from which a dose has to be measured out. In cases where the required dosage for a new medical use is markedly different from that for the known use, it may be possible to allow a claim to a unit dosage form containing the known active ingredient in such an amount that the unit dosage form is novel and not obvious to have been made up in that amount for the prior art use. Thus, if the new medical use requires a dose of, for example, ten times (or one tenth) that for the prior art use, a claim to a unit dosage form might be judged to be novel and inventive and allowable. In assessing the inventiveness of such claims, it should be remembered that dosages required are usually related to body weight so that children's doses are smaller than those for adults. It is also well known in medicine for patients to be asked to take more than one tablet at a time and it is known for half tablets to be taken.

141. In *Actavis Group PTC EHF and others v ICOS Corporation and another [2019] UKSC 15*, the Supreme Court reviewed a case that involved the assessment of inventive step with respect to an invention claiming a specific dosage form of a known medicine. The patent in question is directed to the use of tadalafil in 1 to 5 mg of daily dosage for the treatment of erectile

dysfunction (ED). The exclusive licensee of the patent asserted that the essence of the invention is the effective treatment of ED with tadalafil at a low dose and with minimal side effects. It stated that the patented invention has allowed the medicine to be taken daily (for chronic use) rather than on demand. Use of tadalafil for the treatment of ED was already disclosed in an earlier patent ("Daugan" patent), which state that the dose of radalafil for such treatment will generally be in the range of 0.5 mg to 800 mg daily. The central question was whether the claims of the patent in question is obvious in light of the Daugan patent and the common general knowledge.

142. The Supreme Court presented a number of factors which are relevant considerations in that case as follows: (i) whether, at the priority date, something is "obvious to try"; (ii) the routine nature of the research and any established practice of following such research; (iii) the burden and cost of the research program; (iv) the necessity for and the nature of the value judgements that the skilled team would have; (v) whether alternative or multiple paths of research exist; (vi) the motive of the skilled person; (vii) whether the results of research are unexpected or surprising; (viii) hindsight; (ix) whether a feature of a claimed invention is an added benefit in a context in which the claimed invention is obvious for another purpose; and (x) the nature of the invention.

143. In view of those factors, the Supreme Court considered that the task which the notional skilled team would undertake was that of implementing the Daugan patent. The target of the skilled team would be to ascertain the appropriate dose, which would usually be the lowest effective dose. The skilled team would know of that target from the outset of research. The pre-clinical and clinical trial tests involved familiar and routine procedures and normally progressed to the discovery of the dose-response relationship in Phase IIb of the clinical trial. The Supreme Court further noted that the fact that tadalafil at the dose of 5mg, while remaining effective as a treatment of ED, also, and unexpectedly, had the additional benefit of reduced side effects was an added benefit which does not prevent the identification of 5mg as the appropriate dose from being obvious. The Court thus concluded that the patented claims lack inventive step.

United States of America

144. In the context of the "obvious to try" argument, the MPEP refers to *Alza Corp. v. Mylan Labs. Inc.*,[90] in which the claimed invention was drawn to sustained-release formulations of the drug oxybutynin, where the drug is released at a specified rate over a 24-hour period.[91] Oxybutynin was known to be highly water-soluble, and the specification had pointed out that development of sustained-release formulations of such drugs presented particular problems. Prior art D1 had taught sustained-release compositions of highly water-soluble drugs, including oxybutynin. Prior art D2 had taught a sustained-release formulation of oxybutynin that had a different release rate than the claimed invention. Finally, prior art D3 had taught a generally applicable method for delivery of drugs over a 24-hour period. D3 mentioned applicability of the disclosed method to several categories of drugs to which oxybutynin belonged.

145. The court found that because the absorption properties of oxybutynin would have been reasonably predictable at the time of the invention, there would have been a reasonable expectation of successful development of a sustained-release formulation of oxybutynin as claimed. The prior art had suggested a finite number of ways to overcome these obstacles. The claims were obvious because it would have been obvious to try the known methods for formulating sustained-release compositions, with a reasonable expectation of success (see also Part D of this document on obvious to try).

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90 *Alza Corp. v. Mylan Labs., Inc., 464F.3d 1286, 80 USPQ2d 1001 (Fed. Cir. 2006)*.

91 MPEP §2143, I, E, Example 2.

I. Particle Size

146. The Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals[92] provide the following example which involves a mere change of prior art in its particle size with anticipated effects.

> The claimed invention relates to a pharmaceutical composition comprising first active agent in an amount from about 2 mg to about 4 mg corresponding to a daily dosage and second active agent in an amount from about 0.01 mg to about 0.05 mg corresponding to a daily dosage together with one or more pharmaceutically acceptable carriers or excipients. The composition consists of a number of separately packaged and individually removable daily dosage units placed in a packaging unit and intended for oral administration for a period of at least 21 consecutive days. The first active agent present in the composition is in micronized form or sprayed from a solution onto particles of an inert carrier.
>
> Prior art D1 indicates that the first and second active agents together with combination of those agents are known in the art. Prior art D2 states that micronization for poorly soluble similar drugs is also known in the art for improved drug delivery.
>
> Micronized form of first active agent is novel aspect in the present composition. Dose and dosage regimen of first and second active agents in combination and micronization for poorly soluble similar type of drugs are known in the art. Therefore, it is obvious to a person skilled in the art to convert poorly soluble active ingredient into micronized form for improved drug delivery. Further, changing the particle size is mere modification in the physical form of the active agent for improved and anticipated effect and therefore the claimed invention is obvious.

J. New Use of Known Substance

Brazil

147. In the case of inventions of new medical use, some aspects must be observed when assessing the requirement of inventive step:[93]

> – The mechanism of action of the compound involved in the new use should not be inferred from its mechanism of action for the medical use already revealed in the prior art;
>
> – The new use should refer to the treatment of a disease whose etiology is different from that of the disease related to the use revealed in the prior art;
>
> – The new use cannot be inferred from the structure-activity relationship of the drug in comparison with structurally related molecules, i.e., from structural analogy with other compounds that present the same activity currently claimed and already revealed in the prior art;
>
> – The new use cannot be inferred from the revelation of known adverse effects of the prior art for the drug in question;

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92 Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Example 6, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

93 Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, 9.1.2, INPI, Brazil, 2017.

– The new use cannot be inferred from the use of the compound for the treatment of a symptom of a disease already revealed in the state of the art, even if the claimed use refers to a different disease.

China

148. In China, the invention relating to the use of a chemical product is made on the basis of discovery of a new property of the product and the use of such property.[94] Therefore, the use invention is an invention of a process, and its claim is a process claim. As to the determination of inventive step of use invention of chemical compound, a use invention of a new chemical product is regarded as involving inventive step, if the use cannot be expected from the known product having a similar structure or composition. Where it is a use of a known product, it involves an inventive step if the new use cannot be derived or expected from the structure, composition, molecular weight, known physical/chemical property and existent use of the product, but utilizes a newly discovered property of the product and produces with an unexpected technical effect.

Philippines

149. Where the known substance has been used to treat a related condition, inventive step of the claim should be assessed carefully taking into account the merits of each application. If the diseases have a common origin, causative factors or mechanism, the claim may lack inventive step.[95]

Example

[Invention]
The use of prenyl ketone compound of formula (I) …… for the preparation of a medicament for the treatment or prophylaxis of inflammation of the gastric mucosa.

[Overview of the Description of the Invention]
The technical problem to be solved in relation to the prior art is to extend the field of therapeutic application of the prenyl ketone and that the solution proposed by the application is the use for the preparation of a medicament for the treatment of gastritis.

[Prior Art]
(a) The anti-ulcer effect of the prenyl ketone of the claim, i.e., geranylgeranylacetone (GGA), on experimentally induced gastric and duodenal ulcers in rats was disclosed.
(b) The protecting effect of GGA against ulcer and to its protection against gastric mucosal damage in general induced by acetylsalicylic acid was also known. It was also disclosed that gastritis and ulcer are considered as distinct diseases characterized by different pathology.

[Comment]
It is known that certain drugs such as aspirin and other non-steroidal anti-inflammatory drugs predispose to formation of an ulcer. It is also known that aspirin or other anti-inflammatory agents can generate gastritis. Though gastritis and ulcer are distinct diseases, they have common aspects in relation to their “causative factors”. Thus, the skilled person would expect that the cytoprotective activity of GGA applies to any kind of attack by a mucous breaker aggressive agent such as acetylsalicylic acid, regardless of whether it eventually leads to gastritis or ulcer.

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94 Guidelines for Patent Examination, Part II, Chapter 10, 6.2, CNIPA.

95 Revised Guidelines on the Examination of Pharmaceutical Applications involving Known Substances (January 2018), Section 12 and Example 20, IPOPHIL.

United Kingdom

150. The Examination Guidelines for Patent Applications Relating to Medical Inventions in the Intellectual Property Office discuss the issues regarding inventiveness in a claim to a new medical use for a known substance or composition.[96] Very often, in the case law relating to new medical uses of known substances or compositions, the final step in the Windsurfing/Pozzoli test – assessing whether the invention is obvious – is framed as a question as to whether it would be obvious to try to use the agent for the claimed purpose. As discussed in *MedImmune v Novartis*, in pharmaceuticals and biotechnology, there may be many possible avenues to explore with little indication which, if any, will prove fruitful. Nevertheless, particularly given the potential rewards of inventing a successful treatment, they are pursued, and this would plainly not happen if the prospects of success were so low as not to make them worthwhile. However, denial of patent protection in all such cases would act as a significant deterrent to research. For this reason, obviousness in these circumstances is only found where it is considered obvious to try with a reasonable or fair expectation of success, and the Court of Appeal gave some general guidance as to how this might be assessed: "Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way."[97]

151. This approach was endorsed in relation to a second medical use claim by the Court of Appeal in *Regeneron Pharmaceuticals v Genentech*, and has been applied by the courts in many decisions since then. In *Actavis v Eli Lilly* (2015), it was pointed out that logically, the question of whether the new use is obvious to try should be addressed first, and then, if necessary, whether there would be a reasonable expectation of success. On the facts of the case, it was decided that it was not obvious to try to use the agent in question for the new use at all, and had it been there would have been no expectation of success. "Success" in second medical use cases means achieving the claimed therapeutic effect, the criteria by which this would be assessed may vary according to the disclosure in the specification, and so what exactly the skilled person is said to be "trying" may also vary.

152. In some cases, such as *Hospira v Genentech* (2014) and *Teva v AstraZeneca*, the question was whether it would be obvious to undertake a clinical trial with a fair expectation of success, whereas in *Generics v Warner-Lambert* and *Merck Sharp & Dohme v Ono,* the question was whether it would be obvious to perform specified animal tests with a fair expectation of success. In *Hospira v Genentech* (2015), Arnold J considered some of the factors which would determine whether it was obvious to run a clinical trial with a reasonable expectation of success. These included: the level of motivation to find a new or improved treatment for the condition; whether the trial would be of routine design; whether it would be technically difficult (as opposed to merely time-consuming and expensive); what risk to patients it would present; the failure rate in such trials; whether the specification overcame any "lions in the path" that would have deterred the skilled person from carrying out the trial; and how promising the skilled person would consider the prior art disclosure to be in light of the common general knowledge.

153. If the agent in question in a second medical use claim has been used to treat a related condition, this disclosure may form the basis of an inventive step objection. This will obviously have to be dealt with on a case-by-case basis, but some guidance may be derived from the decision of the EPO Board of Appeal in T 913/94. The first question to be asked is whether the

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96 Examination Guidelines for Patent Applications Relating to Medical Inventions in the Intellectual Property Office (April 2016), paragraphs 132 to 136 and 144 to 145, UKIPO.

97 *MedImmune v Novartis [2010 EWCA Civ 1234, [2013] RPC 27*.

diseases have a common origin, causative factors or mechanism. If this is the case, it does not automatically mean that the claim lacks inventiveness. However, if the symptoms of the disease already treated in the prior art are shared with, and are more serious than, the claimed condition, then this strongly suggests that the agent will be effective in the latter case as well.

154. In relation to cancer treatments, the Board of Appeal in T 385/07 argued that different types of cancer have very different causes and characteristics, and there are no "magic bullets" which successfully treat all cancers. The disclosure that a particular treatment is effective against one or more cancer types would not normally indicate a "reasonable expectation of success" in the treatment of an unrelated form of cancer. Nevertheless, this will need to be assessed on the facts of the case, as there are cancer treatments which exert their effect by targeting a mechanism common to many, if not all cancers – one such treatment was at issue in *Merck Sharp & Dohme v Ono*.

EPO

155. In T112/92 (OJ1994,192), document (1), as the closest prior art, referred to the use of glucomannan as a thickener for an ungelled processed food product, but did not mention its function as a stabilizer. The Board applied the principles set out in T59/87 (OJ1991, 561) to the present case, and stated that even if glucomannan did act as an emulsion stabilizer in preparing the product in accordance with document (1), this use would have been a hidden use. It came to the conclusion that the use of a substance as a stabilizer for emulsions, if not inextricably linked with its use as a thickening agent, was at least very closely related. The Board held that it would have been obvious for the skilled person, knowing that glucomannan was effective as a thickening agent for emulsions, at least to try to find out if it was also effective as a stabilizer. Although T59/87 had found that a claim to an inherent but hidden later use of a known substance could be novel, the subject-matter of such a claim would still lack inventive step if the prior art indicated a well-established link between the earlier and later uses (see also T544/94).[98]

K. Catalyst

India

156. The Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals[99], provide an example of obvious use of catalyst, as follows:

> The claimed invention relates to a process for the preparation of Compound C by treating Compound A and Compound B in the presence of platinum catalyst. All the features of the invention are disclosed in the prior art except the platinum as a catalyst explicitly, but it was mentioned as noble metal catalysts. Prior art generically disclosed platinum as noble element, which is also an equivalent element used in the art for similar purposes and obvious to the skilled person. Therefore, it is application of known feature in the prior art into claimed invention in an obvious way.

98 Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D, 9.12.

99 The Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 8.10, Example 4, Intellectual Property India, Office of the Controller General of Patents, Designs and Trademarks, October 2014.

Republic of Korea

157. Even though a prior art reference discloses catalyst having the identical or similar composition to the catalyst of the invention, if the reaction in which the catalyst is used is not same or the type is different, and the effect of catalyst of the invention is recognized compared to the case without catalyst, it is deemed that the invention involves inventive step.[100] If the identical or similar composition of catalyst is not disclosed in prior art, the assessment of inventive step is made by comparing an effect of the claimed catalyst with a case without the catalyst.

158. Although a catalyst supporter may have no catalytic activity, it is used for various purposes, such as to produce catalyst having an effective catalytic reaction, to reduce cost of preparation and to improve mechanical property. In order to assess the inventive step of the selection of supported or unsupported catalyst, its technical effects stated in the specification or its extraordinary effect should be considered.[101]

L. Intermediates

Brazil

159. The Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry[102] note that where an intermediate is a main invention, the inventive step of the intermediate should be analyzed based on its function as an intermediate and its differences relative to compounds in the prior art. Thus, if the closest prior art discloses compounds similar to the claimed intermediate but gives no indication of their function in producing other compounds, i.e., their function as intermediates, it would understandably not be obvious or evident for a person skilled in the art to use compounds similar to those in the prior art as synthesis intermediates.

160. In the case where the compounds of the closest prior art function as intermediates, the differences between the claimed (intermediate) compound and those of the prior art should be observed, in order to determine whether these differences are obvious, taking into account the intermediate function of the claimed compound.

161. Where an intermediate is an accessory invention (the main invention being a final chemical compound or a process for producing the chemical compound), it is not possible to extrapolate the novelty and inventive step of the principal invention to the intermediate, since the effects/activities/purposes of the main invention and the intermediate are different. If the intermediate is not the main invention, it should be determined whether the intermediate and the process for producing it belong to the same inventive concept as the main invention, which is a final compound product and/or its production process.[103]

162. A process for producing an intermediate may be the main invention of the patent application. However, such processes are usually an accessory invention to the main invention of a final compound or even an intermediate. If a process of producing the intermediate is the main invention, the process claims must define: (i) the starting material, the end-product and the means of transforming the former into the latter; and (ii) the various steps necessary to achieve the set objective.

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100 Patent Examination Guidelines, Part IX, Chapter 5, 2.3, KIPO.

101 See Verdict 2008HEO13732 sentenced by the Patent Court, Oct. 9. 2009.

102 Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry, 2.6, INPI, Brazil, 2017.

103 See also Guidelines for Examination of Patent Applications, Part I, paragraphs 3.119 to 3.125.

United States of America

163. In *In re Lalu*,[104] the US court ruled that if prior art compounds have utility only as intermediates, the claimed structurally similar compounds may not be *prima facie* obvious over the prior art. (see paragraph 29 of this document).

EPO

164. The Boards of Appeal of the EPO have assessed a number of cases with respect to intermediates.[105] In decision T22/82 (OJ1982, 341), the Board ruled that the preparation of new intermediates for a surprisingly advantageous complete process for the preparation of known and desired end products was inventive.

165. Again in T163/84 (OJ1987, 301), intermediate chemical products were held to be patentable on the grounds that their further processing to the known end products involved an inventive step. The Board however held that a new chemical intermediate did not become inventive merely because it was prepared in the course of an inventive multi-stage process and was further processed to a known end-product; there had to be other factors as well, such as that the process for preparing the new intermediate had enabled it to be prepared for the first time and had done so inventively and other methods of preparing it had appeared to be ruled out.

166. In T648/88 (OJ1991, 292), the Board disagreed with the view expressed in T163/84, pursuing instead the line taken in T22/82. An intermediate intended for the preparation of a known end-product was deemed to be inventive if its preparation took place in connection with inventive preparation or inventive further processing or in the course of an inventive complete process (confirmed in T1239/01).

167. In T65/82 (OJ1983, 327), it was explained that new intermediates which take part in (non-inventive) analogy processes for sequent products (i.e., end products or intermediates of various kinds), must − in order to qualify as intermediates − provide a structural contribution to the subsequent products. Even where this condition is met, such intermediates are not thereby unconditionally inventive, i.e., not without taking the state of the art into consideration. As to the state of the art in relation to intermediates, there are two different areas to be taken into account. One is the “close-to-the-intermediate” state of the art. These are all compounds close to the intermediates as identified from their chemical composition. On the other hand, the “close-to-the-product” state of the art must also be taken into account, i.e., those compounds close to the subsequent products as identified from their chemical composition.

168. In T18/88 (OJ1992,107), the applicants had argued that the insecticidal activity of the known end products was significantly superior to that of another known insecticide with a similar structure, and that this was sufficient to establish an inventive step for the intermediate products, even if the end products were not novel and/or inventive. The Board, referring to T65/82 (OJ1983, 327), rejected the applicants’ argument on the following grounds: claimed intermediates must themselves be based on an inventive step to be patentable. Whether, under certain circumstances, new and inventive subsequent products might support an inventive step of intermediates was not the question here, because the subsequent products in this case were either not novel or not inventive. The superior effect of subsequent products which were neither novel nor inventive was not sufficient to render the intermediates inventive (T697/96, T51/98).

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104 *In re Lalu*, 747 F.2d 703,223 USPQ 1257 (Fed. Cir. 1984). MPEP §2144.09, VI.

105 Case Law of the Boards of Appeal of the European Patent Office (8th edition), 2016, Part I.D, 9.8.4 (Intermediate products).

M. Selection Inventions and Ranges

169. In general, a selection invention may involve, for example, the selection of individual elements, sub-sets or sub-ranges, which are within the larger set or range in the prior art but have not been specifically disclosed in the prior art. The Further Study on Inventive Step (Part II) (document SCP/29/4) dealt with the assessment of inventive step in relation to selection inventions. While general principles described in document SCP/29/4 are applicable to selection inventions in the chemistry art, the following paragraphs provide the complimentary explanations and examples in this regard in the area of chemistry.

170. Although it is outside the scope of this document, a clear distinction should be made between the novelty requirement and inventive step requirement in relation to selection inventions. As explained in the submission by Chile to the SCP, a generic description of the prior art does not normally affect the novelty of a specific form of the invention, even if that specific form is included within the terms of the generic disclosure, as long as such specific form is not explicitly mentioned in the prior art. In contrast, a specific description affects the novelty of a generic claim covering the specific description. For example, a description of “copper” affects the novelty of “metal” as a generic term, but not the novelty of any metal other than copper. Similarly, a description of “rivets” affects the novelty of “fastening device” as a general term, but not the novelty of any other fastening device. However, the Guidelines[106] of Argentina notes that the disclosure of a group of chemical compounds in a prior art reference, even in a generic form, reveals all of the components of that group, which become part of the state of the art. Consequently, there is no novelty in the selection of an element(s) already disclosed by the state of the art, even if the selected element(s) have differentiated properties, or have not been previously demonstrated. Similarly, the discovery of a differentiated or superior characteristic or property of a certain element(s), already known from the state of the art, does not meet the novelty.

171. Another example found in the submission by Chile is a selection invention pertaining to a range of values. For instance, a prior art document defines a chemical procedure that can be performed within a temperature range of 10° and 100°C, including examples at 20°, 40°, 60° and 80°C. Later, it is discovered that between 68º and 72ºC, the process is, unexpectedly, much more efficient, yields better performance, emits fewer pollutants or produces other technical benefits. If an application is filed claiming the procedure between 68º and 72ºC, i.e., an interval within the temperature range that has already been disclosed, whereas this selected interval was not explicitly described in the prior art document, novelty can only be evaluated through a limited interpretation of the prior art as a process normally conducted between 10º and 100ºC and at intermediate temperatures of 20º, 40º, 60º and 80º. Consequently, given that the prior art documentation does not specifically state that the process operates differently at another or other temperatures (within or outside the described range) − in this case, a procedure between 68º and 72ºC − the claimed values shall not be considered as disclosed and the invention will have novelty.

Australia

172. A generic structural formula represents all the specific structural formulae encompassed by the generic formula. The compounds that are within the scope of the generic formula are clearly put forward as possessing the same properties as any specifically disclosed compounds. In the absence of selection (e.g., identification of a compound or compounds having a surprising or unexpected advantage) or the lack of an enabling disclosure, it is immediately

106 Guidelines for the Patentability Examination of Applications on Chemical-Pharmaceutical Inventions (approved by the Joint Resolution 118/2012, 546/2012 and 107/2012), 2012.

obvious that the compounds within the scope of the generic formula would be expected to have the same properties as the specifically disclosed compounds and there is no inventive step in merely preparing those compounds in the manner suggested and verifying their properties (*Rohm and Haas Co v Nippon Kayaku Kabushiki Kaisha and Sankyo Co, Ltd [1997] APO 40; University of Georgia Research Foundation, Inc v Biochem Pharma, Inc [2000] APO 68*).

Brazil

173. While the procedures for the technical examination of patent applications for a selection of chemical compounds are detailed in the Patent Application Examination Guidelines, Part II, paragraphs 4.19 to 4.25 and 5.31 to 5.34, Part 2.8 of the Guidelines for the Examination of Patent Applications – Aspects Related to the Examination of Patent Applications in the Area of Chemistry provide some examples regarding the inventive step assessment of selection inventions relating to chemical compounds.

174. In general terms, to be considered new, the selected chemical compound must not be specifically disclosed in the prior art in the form of examples, tests, results, lists, tables, nomenclature, individualized structural formula or method of preparation. With respect to inventive step, the selection of said compound may not be obvious or evident to a person skilled in the art based on the teachings of the prior art. Invariably, because it is a selection of compounds already described generally in an earlier document, evaluation of the inventive step requirement of the patent for a selection of compounds involves the presentation of comparative data relative to the prior art. The closest prior art would correspond to the compound(s) with the greatest structural similarity specifically disclosed in the prior art.

175. Example of selected compounds that have novelty but lack inventive step:

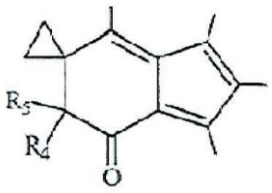
Invention

The patent application refers to analogous illudin compounds with antiproliferative properties for the treatment of tumors in mammals.

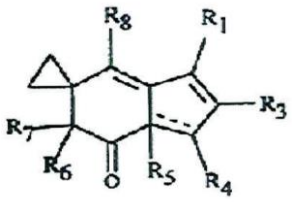
Prior art

The prior art generically describes, in Markush formula, substances analogous to illudin and useful as antiproliferative agents.

Invention



Prior art



Technical analysis

The selected compounds represent a restricted group among the compounds generically disclosed in the prior art document. However, since they were not specifically disclosed (Patent Application Examination Guidelines, Part II, paragraphs 4.21 to 4.23), they are considered to have novelty.

The applicant presented test results comparing the antiproliferative activity of the claimed compounds and that of specifically disclosed compounds with greater structural similarity in the prior art. The results presented did not demonstrate a non-obvious effect relative to the prior art, since the antiproliferative activity of the claimed compounds was very similar

to that of the compounds disclosed in the prior art (Patent Application Examination Guidelines, Part II, paragraph 5.33). Thus, although the claimed compounds are considered novel, they fail to satisfy the inventive step requirement.

176. Example of selected compounds that have both novelty and inventive step:

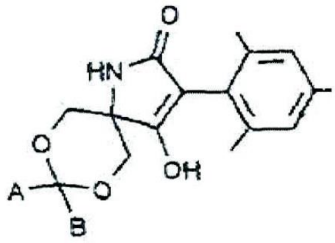
Invention

The patent application relates to phenyl-substituted cyclic ketoenols, processes for their preparation and their use in pesticidal and herbicidal compositions.

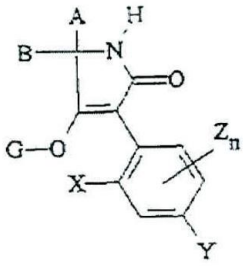
Prior art

The prior art provides a generic description of cyclic ketoenols with pesticidal and herbicidal activity, which includes the compounds selected in the patent application under review.

Invention



Prior art



Technical analysis

The compounds claimed in the patent application are considered to have novelty because, although they are chemical derivatives generically presented in Markush formula in the prior art document, they have not been specifically disclosed (Patent Application Examination Guidelines, Part II, paragraphs 4.21 to 4.23).

In order to prove the inventive step of the subject matter, test data was presented that clearly demonstrated the non-obvious technical effect of the claimed compounds relative to compounds with greater structural similarity specifically disclosed in the prior art. Hence, the selected compounds were considered to be not obvious to a person skilled in the art (Patent Application Examination Guidelines, Part II, paragraph 5.34).

Republic of Korea

177. Where the prior art discloses only the generic concept, while the claimed invention covers the species of prior art genus, the claimed invention involves inventive step if all the species have different effect from that of the prior art invention qualitatively or quantitatively.[107]

Example 1: Inventions are lacking inventive step, since specific chemical compounds are merely selected among a wide range of chemical compounds.

(i) There is no description that the claimed chemical compound, selected from the wide range of prior art chemical compounds, has a favorable effect compared to the prior art chemical compounds.

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107 Patent Examination Guidelines, Part IX, Chapter 5, 2.3, KIPO.

(ii) The claimed chemical compound, selected from the wide range of prior art chemical compounds, has a favorable effect compared to the prior art chemical compounds, but the claimed compound would be easily selected by a person skilled in the art, since the property of the chemical compound is predictable.

Example 2: Inventions comprising specific chemical compounds selected from a wide range of chemical compounds have unexpected favorable properties.

The claim pertains to a chemical compound with a specific substituent selected from the R group disclosed in the prior art and it is not expected that a person skilled in the art would select that specific chemical compound from the generally described chemical compounds in the prior art in order to obtain favorable properties.

Russian Federation

178. The Examination Guidelines[108] state that the methodology of analyzing inventive step of selection inventions in general corresponds to that of other chemical compounds. The difference in properties of the claimed and known compounds sharing a common structural formula as well as the degree of such difference are taken into account (see paragraphs 58 to 61, above).

Example

A chemical compound is claimed (no purpose is indicated in the claims). The description of the invention provides information about its toxicity and the possibility of using it to control ticks on the animal's body. The said substance is a particular case (selection) of a group of the known compounds characterized by common structural formula. A prior art reference states that their toxicity is sufficient to destroy ticks, but that their use is impossible due to their increased toxicity to animals. Since this compound has not been described previously as obtained and studied, it is regarded as a new compound. The inventor was the first to determine that the level of toxicity of the claimed compound allows for the killing of ticks, but does not cause any harm to animals. Thus, the prior art does not imply that the claimed compound could achieve the technical result as described in the application, and the claimed compound exhibits a new property unknown to that group.

United Kingdom

179. The decision of the UK Court of Appeal in *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd.*[109] utilized an approach based on EPO Boards of Appeal decisions (in particular T 939/92 AGREVO/Triazoles and T 133/01 WYETH) wherein the contribution of the application was considered and a selection would be regarded as obvious, if it had made no real technical advance.[110] The question to be asked is whether the invention makes a hitherto unknown technical contribution or is merely an arbitrary selection. If it is merely an arbitrary selection, the invention is obvious.[111]

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108 Examination Guidelines for Invention Applications, Part 3.9, ROSPATENT.

109 "[…] it regards what can fairly be regarded as a mere arbitrary selection from a class as obvious. If there is no more than an arbitrary selection then there is simply no technical contribution provided by the patentee." *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2010] RPC 9 (at paragraph 44).

110 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 78, UKIPO.

111 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 79, UKIPO.

180. The nature of the selection will frequently not be so readily determined where, for example, a sub-range is being selected from a larger range. In this regard, the position following the Court of Appeal judgement in *Generics [UK] Ltd v Yeda Research and Development Co. Ltd*. includes:[112]

(i) If the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used for the purposes of judging obviousness. In such circumstances, the claim must either be restricted to the subject matter which makes the technical contribution, or a different contribution common to the whole claim must be found;

(ii) A selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious, because it does not make a real technical advance;

(iii) A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step;

(iv) Later evidence may be cited to support a technical effect made plausible by the specification.

181. The judgment in *Generics [UK] Ltd v Yeda Research and Development Co. Ltd.* also addressed the question of what happens if the technical property or effect made plausible by the specification does not exist in fact. The lower court had held that since later evidence cannot be used to support a technical effect not indicated in the specification, neither can it be used to refute such an effect. The Court of Appeal held, however, that in considering later evidence on this issue, one is not judging the obviousness of the invention by reference to later evidence; one is simply defining by evidence what the invention is. The Court allowed the admission of later evidence which, according to the plaintiff, showed that the composition as claimed did not demonstrate the relied upon technical effect. The Court however found that the evidence provided did not prove the absence of the technical effect and rejected the appeal.[113]

182. EPO Technical Board of Appeal decision T 181/82 suggests that where comparative tests are submitted as evidence of an unexpected technical effect, there must be the closest possible structural approximation between the prior art compound tested and the subject-matter of the invention; and that only known substances − not notionally described ones − qualify for use in comparisons of compounds.[114]

183. The Guidelines on Examining Patent Applications Relating to Chemical Inventions also state that the technical significance of the parameters by which the product or process is selected should be considered. Where unusual parameters are used in a claim, it may be difficult to prove whether or not the prior art would have inevitably exhibited those parameters. If arbitrary parameters are used, they are considered to be non-technical and may be ignored in the assessment of obviousness (and by extension novelty).[115]

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112 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 80, UKIPO.

113 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 82, UKIPO.

114 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 84, UKIPO.

115 Guidelines on Examining Patent Applications Relating to Chemical Inventions (Updated June 2017), paragraph 85, UKIPO.

184. In relation to the overlapping scope of a claim and a prior art reference, there could be a case where a claim comprises a Markush structure which is of overlapping scope to a Markush structure contained in the prior art. The Guidelines of the UKIPO[116] state that it is the Office practice, in contrast to that of the EPO, to object to the claim as lacking an inventive step rather than novelty. Thus, the Markush structures are treated in effect as defining classes of compounds. Rather than determining the extent to which one group might be considered to be coterminous with another (and thus whether novelty is appropriate) it has been deemed pragmatic to simply object under obviousness. Nevertheless, the strength of this objection will in part depend on matters such as the intended use (whether explicitly mentioned in the claim being examined or not) and on the extent of the overlap (for example, do the two Markush structures share a common core or. in the case of polymers, do they share the same groups pendant from the polymer backbone?). In situations where there is a clear, supported selection invention, an obviousness objection need not be pursued.

United States of America

185. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a *prima facie* case of obviousness exists.[117] In *In re Woodruff*,[118] the prior art taught carbon monoxide concentrations of "about 1-5%", while the claim was limited to "more than 5%." The court held that "about 1-5%" allowed for concentrations slightly above 5% thus the ranges overlapped. Similarly, in *In re Geisler*,[119] the claim reciting thickness of a protective layer as falling within a range of "50 to 100 Angstroms" was considered *prima facie* obvious in view of prior art reference teaching that "for suitable protection, the thickness of the protective layer should be not less than about 10 nm [i.e., 100 Angstroms]." The court stated that "by stating that 'suitable protection' is provided if the protective layer is 'about' 100 Angstroms thick, [the prior art reference] directly teaches the use of a thickness within [applicant's] claimed range."

186. Likewise, a *prima facie* case of obviousness exists where the claimed ranges or amounts do not overlap with the prior art but are merely close. In *Titanium Metals Corp. of America v. Banner*,[120] the court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium: "The proportions are so close that *prima facie* one skilled in the art would have expected them to have the same properties.".

187. Applicants can rebut a *prima facie* case of obviousness by showing the criticality of the range. For example, a presumption of obviousness may be rebuttable by showing that the claimed range achieves unexpected results relative to the prior art range, or that the prior art teaches away from the claimed invention.[121]

188. Where the difference between the claimed invention and the prior art reference resides in concentration or temperature, such difference would not support the patentability of subject matter, unless there is evidence indicating that such concentration or temperature is critical.

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116 Guidelines on Examining Patent Applications relating to Chemical Inventions (Updated June 2017), paragraph 90, UKIPO.
117 MPEP, §2144.05, I.
118 *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).
119 *In re Geisler*, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362,1365-66 (Fed. Cir. 1997).
120 *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775,783, 227 USPQ 773, 779 (Fed. Cir. 1985).
121 MPEP, §2144.05, III.

Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.[122] It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions.[123]

189. With respect to obviousness of species when prior art teaches genus,[124] the obviousness of a claim to a specific compound, species, or subgenus embraced by a prior art genus should be analyzed no differently than any other claim. In determining whether one of ordinary skill in the art would have been motivated to select the claimed compound, species or subgenus, various factors of prior art teaching should be taken into account. In this regard, the MPEP provides the non-exclusive factors as follows:

(i) Consider the size of the prior art genus, bearing in mind that size alone cannot support an obviousness rejection.

For example, in *In re Petering,* the court stated that "a simple calculation will show that, excluding isomerism within certain of the R groups, the limited class we find in Karrer contains only 20 compounds. However, we wish to point out that it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved, including such factors as the limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus. With these circumstances in mind, it is our opinion that Karrer has described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name."

(ii) Consider the express teachings in the prior art reference that teaches a particular reason to select the claimed species or subgenus.

For example, claims directed to diuretic compositions comprising a specific mixture of amiloride and hydrochlorothiazide were obvious over a prior art reference expressly teaching that amiloride was apyrazinoylguanidine which could be co-administered with potassium excreting diuretic agents, including hydrochlorothiazide which was a named example, to produce a diuretic with desirable sodium and potassium eliminating properties.[125]

(iii) Consider any teachings of a "typical," "preferred," or "optimum" species or subgenus within the disclosed genus. If such a prior art species or subgenus is structurally similar to that claimed, its disclosure may provide a reason for one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties.

(iv) Consider the properties and utilities of the structurally similar prior art species or subgenus. It is the properties and utilities that provide real world motivation for a person of ordinary skill to make species structurally similar to those in the prior art. Conversely, lack of any known useful properties weighs against a finding of motivation to make or select a species or subgenus.

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122 MPEP, §2144.05, II.
123 *In re Williams*,36 F.2d 436, 438 (CCPA 1929).
124 MPEP, §2144.08.
125 *Merck & Co. v. Biocraft Labs*., 874 F.2d 804,807, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989).

(v) Consider the predictability of the technology. If the technology is unpredictable, it is less likely that structurally similar species will render a claimed species obvious, because it may not be reasonable to infer that they would share similar properties.

For example, *prima facie* obviousness of claimed analgesic compound based on structurally similar prior art isomer was rebutted with evidence demonstrating that analgesia and addiction properties could not be reliably predicted on the basis of chemical structure.[126]

EPO

190. In the Guidelines for Examination,[127] examples of non-inventive or inventive selection inventions are provided as follows:

[Obvious and consequently non-inventive selection]

The invention consists merely in selecting particular chemical compounds or compositions (including alloys) from a broad field.

Example: The prior art includes disclosure of a chemical compound characterised by a specified structure including a substituent group designated “R”. This substituent “R” is defined so as to embrace entire ranges of broadly-defined radical groups such as all alkyl or aryl radicals either unsubstituted or substituted by halogen and/or hydroxy, although for practical reasons only a very small number of specific examples are given. The invention consists in the selection of a particular radical or particular group of radicals from amongst those referred to as the substituent “R” (the selected radical or group of radicals not being specifically disclosed in the prior-art document since the question would then be one of lack of novelty rather than obviousness). The resulting compounds:

(a) are neither described as having nor shown to possess any advantageous properties not possessed by the prior-art examples; or

(b) are described as possessing advantageous properties compared with the compounds specifically referred to in the prior art, but these properties are ones which the person skilled in the art would expect such compounds to possess, so that he/she is likely to be led to make this selection.

[Not obvious and consequently inventive selection]

(i) The invention consists in selecting particular chemical compounds or compositions (including alloys) from a broad field, such compounds or compositions having unexpected advantages.

Example: In the above example of a substituted chemical compound, the invention again resides in the selection of the substituent radical “R” from the total field of possibilities defined in the prior disclosure. In this case, however, not only does the selection embrace a particular area of the possible field, and result in compounds that can be shown to possess advantageous properties but there are no indications which would lead the person skilled in the art to this particular selection rather than any other in order to achieve the advantageous properties.

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126 *In re May*, 574 F.2d 1082, 1094, 197 USPQ 601, 611 (CCPA1978).

127 Guidelines for Examination, Part G, Chapter VII, Annex.

(ii) The invention involves special selection in a process of particular operating conditions (e.g., temperature and pressure) within a known range, such selection producing unexpected effects in the operation of the process or the properties of the resulting product.

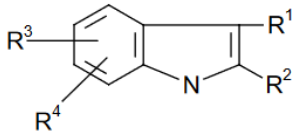
Example: In a process where substance A and substance B are transformed at high temperature into substance C, it was known that there is in general a constantly increased yield of substance C as the temperature increases in the range between 50 and 130 °C. It is now found that in the temperature range from 63 to 65 °C, which previously had not been explored, the yield of substance C was considerably higher than expected.

N. Markush Claims

191. Many jurisdictions allow a single patent claim to contain alternative elements. A "Markush" claim recites a list of alternatively usable members in one claim.[128] In other words, typically, a Markush claim covers a list of alternatives from which a selection is to be made. It is named after *Ex parte Markush* in the United States of America.[129] The listing of specified alternatives within a Markush claim is referred to as a Markush group or Markush grouping.

192. In general, alternatives in a Markush claim may be recited as "X selected from the group consisting of a, b and c": for example, "A metal selected from the group consisting of copper, gold and iron". Where the Markush claim defines a group of chemical compounds by a chemical formula, it may be expressed as follows:

Claim 1. A compound of the formula:



wherein R^1 is selected from the group consisting of phenyl, pyridyl, thiazolyl, triazinyl, alkylthio, alkoxy and methyl; R^2–R^4 are methyl, benzyl or phenyl.

193. Claims in a Markush grouping are most frequently used for defining inventions in metallurgy, chemistry and biology. When a Markush grouping is used in a chemical formula, it allows a group of chemical compounds having a common structural element to be covered in one claim. However, inventions in other fields of technology, such as those involving pure mechanical features or process steps, can also be claimed in the Markush style.[130]

194. The Markush style of claiming allows a patent drafter to include more than one alternative members in one claim, instead of drafting plurality of claims that cover each alternative member. If properly used, a Markush claim assists a person skilled in the art to grasp the entire scope of alternatives in a single claim, instead of reading and analyzing many claims that define

128 MPEP, §2117.

129 *Ex parte Markush*, 1925 Dec. Comm'r Pat. 126, 127 (1924).

130 MPEP, §2117 provides the following example: a claim to a hemodialysis apparatus comprising "at least one unit selected from the group consisting of (i) a dialysate-preparation unit, (ii) a dialysate-circulation unit, (iii) an ultrafiltrate-removal unit, and (iv) a dialysate-monitoring unit" and a user/machine interface operably connected thereto.

each alternative. In addition, the Markush style of claiming allows the patent drafter to group together the alternatives that do not have otherwise a well-defined generic name. For example, in the case of “a metal selected from the group consisting of copper, gold and iron”, there is no proper generic word that covers only copper, gold and iron.

195. In general, a Markush claim is allowable in many countries, provided that the number and presentation of alternatives in a single claim does not make the claim obscure or difficult to construe and provided that the claim meets the requirements for the unity of invention. In certain circumstances, a Markush group may be so expansive that a person skilled in the art would not be able to determine the scope of the claimed invention. The claim may lack clarity and conciseness, or it may not be supported by the description, or the description may not disclose the claimed invention in a manner sufficiently clear and complete so that a person skilled in the art is able to carry out the entire scope of the claimed invention. Whether each alternative member expressed in the Markush grouping meets the unity of invention or not is another question that may be raised. However, those are the issues outside the inventive step requirement.

196. In relation to the inventive step requirement, whether alternatives are expressed in a single Markush claim or in the plurality of claims, each of which defining each alternative, is not relevant to the assessment of inventive step *per se.* Therefore, if a chemical invention is claimed in a Markush formula, it is not surprising that the general rules and practices on the inventive step analysis of chemical inventions apply to such an invention.

197. For example, the Examination Guidelines of INPI, Brazil[131] state that, in general, the compounds defined in a new Markush formula will meet the inventive step requirement if, based on the prior art, a person skilled in the art would not be motivated to carry out the claimed structural modifications. In cases of structural similarity with prior art, the evaluation of the inventive step involves the recognition of the existence of an unexpected technical effect, often evidences by comparative data in relation to the state of the art. In the same token, referring to the Andean Patent Manual, the submission by Ecuador to the SCP states that compounds claimed in the Markush format involve inventive step when: (i) "the compounds have an unexpected structure (rare case); or (ii) produce an unexpected effect (most frequent case, especially if the compounds are similar to others in the prior art. The unexpected effect may be completely different from those described for similar known compounds, or it may be the same but with improved results).”

198. Similarly, following the well-established principle that the claimed invention “as a whole” should be non-obvious to meet the inventive step requirement, the submission by Malaysia to the SCP notes that in case of claims in the Markush format, the claimed invention is not considered inventive if at least one embodiment of Markush alternatives appears not to involve an inventive step over the prior art. For example, if the claimed invention relates to neuroprotective chrommanol compounds including various chemical compounds as alternatives, all embodiments of the chemical compounds should have a remarkable effect over prior art in order for the claimed invention to be patented. Likewise, the submission by Costa Rica to the SCP states that Markush formulae need to be very well defined and the essential distinctive technical feature relative to the prior art must be present in all alternative compounds. In addition, the submission by Ecuador to the SCP refers to the Andean Patent Manual, which states that for the recognition of inventive step, all compounds included in the Markush formula must fulfill the conditions, otherwise only those whose structure or unexpected effect has been demonstrated by the applicant are accepted.

131 Guidelines for Examination of Patent Applications, Part II, paragraphs 6.7 and 6.8, INPI, Brazil.

199. A number of examples illustrated in Parts A to M of this document use Markush grouping to define the claimed invention or to describe the prior art reference. Those concrete examples may provide a general impression about how Markush claims are used in the chemical arts.

[End of document]