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Guidelines for the examination of patent applications relating to pharmaceuticals



Guidelines for Pharmaceutical Patent Examination:

Examining
Pharmaceutical Patents
from a Public Health
Perspective

Carlos M Correa



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Acronyms and Abbreviations

5ASA	5-aminosalicylic acid
5-FU	5-fluorouracil
AIDS	Acquired immune deficiency syndrome
AZT	Zidovudine
DAT	Dementia of the Alzheimer type
DCL	Descarboethoxyloratadine
EPO	European Patent Office
HIV	Human immunodeficiency virus
ICTSD	International Centre for Trade and Sustainable Development
IR	Infrared absorption spectrum
NIF	Neutrophil inhibitory factor
NMDA	N-methyl-D-aspartate
NMR	Nuclear magnetic resonance
NOS	Nitric oxide synthase
NRTIs	Nucleotide analogue reverse transcriptase inhibitors
R&D	Research & Development
SDG	Sustainable Development Goal
TRIPS	Trade-related Aspects of Intellectual Property Rights
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
USPTO	US Patent and Trademark Office
WHO	World Health Organization
WTO	World Trade Organization



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Acknowledgements

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This document represents a follow-up to an earlier document, *Guidelines for the Examination of Pharmaceutical Patents: Developing a Public Health Perspective*, which was published in 2007 as a working paper by the International Centre for Trade and Sustainable Development (ICTSD), the United Nations Conference on Trade and Development (UNCTAD) and the World Health Organization (WHO).

The present document takes into account developments since the publication of the ICTSD-UNCTAD-WHO working paper in 2007. It includes new examples of patent applications and/or grants, and analysis of and references to the initiatives of a number of countries that have adopted laws and/or policies that seek to factor in public health considerations in the examination of patent applications.

With this document, the aim is to provide guidance for the development or revision of guidelines on patent examination processes in developing countries in response to concerns about the rise of patent numbers in the pharmaceutical sector. For this purpose, a number of recommendations are made with regard to the examination of the patentability of applications relating to pharmaceutical products and processes.

The draft of this document was also reviewed by policy and technical experts from China, Indonesia, Malaysia, Thailand and Viet Nam during the Regional Consultation on Integrating Public Health Considerations in Pharmaceutical Patenting in Low- and Middle-Income Countries, held in Bangkok, Thailand, on 6–7 May 2015.

This document has had the benefit of an expert review process and comments and inputs from a number of experts in the field. They include Susana Piatti (Consultant, Argentina); Suchart Chongprasert (Food and Drug Authority, Thailand); Barbara Milani (Consultant, Geneva); and Srividya Ravi (Consultant, India). All of their contributions are gratefully acknowledged.



Foreword

One important lesson of the global AIDS response is that efforts to stimulate innovation and R&D for lifesaving treatments must be accompanied by measures to ensure timely and affordable access to such treatments.

The 2030 Agenda for Sustainable Development has embraced this lesson. In aspiring to ensure health and well-being for all, Sustainable Development Goal (SDG) 3 includes the target of ending epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases by 2030. In so doing, it recognizes that support for research and development is essential to achieving this target but that such support must be linked to affordable access.

SDG 3 further highlights the relationship between patents and access, specifying that access should be provided in accordance with the *“the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all ...”* This is a reflection of the growing consensus that an appropriate balance should be maintained between protecting the rights of inventors and incentivizing innovation, on the one hand, and promoting accessibility and affordability of treatments, on the other.

Recognizing the key role that patent offices and patent examiners play in safeguarding this balance, some countries have taken steps to provide guidance for how public health considerations may be factored into the examination of patent applications. This document examines initiatives in countries, such as Argentina, Ecuador, India and the Philippines, to integrate public health considerations into the procedures for the granting of patents on pharmaceuticals. It proposes a number of recommendations on guidelines that can be adopted as criteria for the examination of patent applications. Adoption of a clear criteria will ensure the public health perspective is properly integrated in the process of patent examination.

It is hoped that the recommended guidelines in this document will make a useful contribution to enhancing the functioning and transparency of the patent system in the public interest.

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Executive summary

The Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) establishes minimum standards for the protection of intellectual property rights by members of the World Trade Organization (WTO). Beyond these minimum standards, however, it leaves many ‘flexibilities’ that allow WTO members to define their own policies and standards on various matters.

One important flexibility allowed to WTO members is determining what is meant by ‘invention’– a concept that is not defined in the TRIPS Agreement. In fact, there is significant diversity in national laws and practices around the notion of invention, and to date, no complaint has been raised to the WTO regarding a definition of this concept. In particular, national laws may require a determination of whether an invention exists before entering into the analysis of compliance with the patentability requirements.

Similarly, the TRIPS Agreement obligates WTO members to grant a patent when patentability requirements are met, but it does not define those requirements. Thus WTO members may adopt different concepts of novelty (universal, local or a mix); inventive step or non-obviousness; and industrial applicability or utility.

Nothing prevents WTO members from applying rigorous patentability criteria to avoid low-quality patents. Similarly, WTO members retain flexibility to determine the rules applicable to the disclosure of the invention in order to ensure its reproducibility and to avoid broad, generic claims.

There has been growing attention, particularly in the area of public health and pharmaceuticals, to the need to ensure an appropriate balance between the interests of patent holders and technology users (as per the requirements of articles 7 and 8 of the TRIPS Agreement). In this respect, several countries (e.g. Argentina, Ecuador, India and the Philippines) have adopted legislation or policies for examining patent applications relating to pharmaceutical products and processes in a manner that accounts for public health considerations. Analysis of pharmaceutical patent claims has shown that the proper application of patentability standards can prevent the grant of ‘poor quality’ or trivial patents, which, by preventing the timely entry of generic competition, may harm public health.

This document, *Guidelines for the Examination of Patent Applications relating to Pharmaceuticals*, is intended as a contribution towards efforts to enhance the functioning and transparency of the patent system in the public interest. It proposes recommendations that can be adopted to incorporate public health perspectives in procedures for granting pharmaceutical patents.

It is important to note that the recommended guidelines do not intend to modify the standards of patentability established by patent law, or to add additional standards. Instead, they aim to ensure the correct application of those standards in view of the specific nature of the claimed subject matter and the public health relevance of the decisions. These guidelines thus advise patent examiners in assessing the patentability requirements of applications relating to pharmaceutical products and processes, as well as the use of pharmaceutical products.

The adoption of guidelines such as these is important for four reasons.

First, although pharmaceuticals share common features with other inventions, there are elements of patent claims relating to pharmaceuticals that are unique, determined by their intended use.

Second, a set of examination criteria will help speed up patent procedures, increase uniformity in the treatment of applications, and offer applicants greater certainty about the possible outcome of the procedures.



Third, there is a proliferation of patent applications in the field of pharmaceuticals claiming polymorphs, salts, formulations and so on, which are often made to prevent generic competition rather than to protect genuine inventions. So-called evergreening patents do not contribute to the technological pool and they limit the market entry of generic products.

Finally, given the impact of patents on the availability, accessibility and affordability of treatments and technologies, the manner in which pharmaceutical patent applications are examined can have critical implications for public health. Patent offices and examiners play vital roles in ensuring an appropriate balance between protecting inventions and incentivizing innovation on the one hand, and promoting accessibility and affordability of treatments and health technologies on the other. This balancing process is also important for achieving broader development priorities, from national efforts to promote research and development (R&D), technology transfer and pharmaceutical production, to achieving universal health coverage.



Summary of recommendations

- 1 **The concept of invention**
 - Materials found in nature (such as genes) and properties and forms newly found in known products (e.g. the crystalline form of a compound of medical use) should not be deemed inventions.
 - The concept of invention should be understood as encompassing a technical effect.
 - When it is determined that the patent application does not cover an invention, no further analysis of compliance with the patentability requirements is needed.

- 2 **Patentability standards**
 - Novelty**
 - An assessment of novelty requires consideration of what has been expressly, implicitly or inherently disclosed in the prior art. The discovery of a previously unknown property of a substance does not render the substance patentable. More than one document may be used to establish the lack of novelty.
 - The determination of novelty should include information disclosed in patent applications filed in the same country that are published on or after the filing date of the application being examined.
 - Inventive step**
 - Patents should only be granted when the claimed object is the result of an inventive activity. The fact that a solution has been found to a problem or that an advantage has been obtained, even if unexpected, is not sufficient to prove the existence of such activity.
 - A claimed invention should be assessed in the light of the knowledge of an expert, or a team of experts, with ordinary creativity in the technical field. A specific prior art document is not indispensable to prove that a claimed invention falls within the common knowledge, or that it is obvious for an expert in the field.
 - Industrial applicability/utility**
 - In countries that apply an industrial applicability standard, an invention must be capable of being made in industry in order to be patentable.
 - The use or methods of use of a medicine, including the specification of a certain dose, and processes that do not allow a person skilled in the art to obtain a product in industry, should be deemed as lacking industrial applicability.

- 3 **Sufficiency of disclosure**
 - The disclosure of the claimed invention should be precise and clear enough for a person with average knowledge in the field to reproduce the invention without undue burden of experimentation.
 - The required disclosure should be sufficient to implement all the embodiments of the invention.

- 4 **Flexibilities under the TRIPS Agreement**
 - National laws and patent office practices should use the flexibilities allowed by the TRIPS Agreement with regard to the concept of invention and in defining patentability standards and the sufficiency of disclosure.
 - Specific guidelines for examining pharmaceutical-related patent applications should be issued in order to protect the public against the grant of unwarranted patents that may unduly limit access to affordable medicines.



5 Typical claims relating to pharmaceuticals

1 Markush claims

- An application including a Markush claim should contain sufficient information to allow a person skilled in the art to perform the invention over the whole area claimed, using his common general knowledge, without undue burden and experimentation, and without needing inventive skill.
- The coverage of the patent should be limited to the claimed embodiments that are actually enabled by the disclosure in the specification.
- Claims of limited scope could be granted if evidence is provided that the same claimed function will be obtained through the substitution of any member within the same family class. Such evidence should include fusion point, infrared absorption spectrum (IR) or nuclear magnetic resonance (NMR) obtained through testing and experimentation, and other information needed to enable the reproduction by the disclosed method of each embodiment of the invention. Applicants may also be requested to submit electronic files to facilitate the prior art search.

2 Selection patents

- The selection of elements included in a disclosed group lacks novelty, such as in the case of compounds disclosed in a prior generic chemical structure or included within a numerical range. Patents should not be granted either in cases where a selection of elements is made from a list of known compounds, or where a selection is made of starting materials and alternative processes to obtain a compound.

3 Polymorphs

- Patents on polymorphs should be denied on the grounds of absence of a patentable invention or inventive activity. This conclusion may be reached even in cases where a document providing the basis for an inventive step analysis in relation to the specific claimed polymorph is not identified; obtaining a polymorph is a routine activity in pharmaceutical production, carried out through methods widely known to a person skilled in the art. However, a process used for the preparation of a polymorph, if novel and involving inventive step, may be patentable.

4 Enantiomers

- Isolated enantiomers should not be deemed patentable when the racemic mixture was previously disclosed. Processes for the separation and purification of enantiomers may only be patented if novel and inventive. Any difficulty in developing and applying such processes is not by itself sufficient to prove inventive activity.

5 Salts

- The preparation of salts with advantageous properties over the drug in its free base/acid form is part of the common knowledge of a person skilled in the art. Patent applications on particular salts will normally face an objection of lack of inventive step. Generic references to pharmaceutically acceptable salts in patent applications covering a compound should not be allowed either, as they would fail the sufficiency of disclosure requirement.

6. Ethers and esters

- The preparation of ethers or esters to achieve advantageous properties over the drug in its free base or acid form is part of the common knowledge of a person skilled in the art. Patent applications on particular ethers and esters will normally lack inventive step. Generic references to ethers or esters in patent applications covering an active ingredient or other subject matter should not be allowed.



7. Compositions

- The preparation of pharmaceutical compositions (formulations) requires the use of techniques and compounds commonly known to a person skilled in that field. Patent applications on compositions will normally confront an objection of lack of inventive step. Generic claims over compositions associated with new active ingredients, prodrugs, and so on, with unspecified carriers or excipients, will also be objectionable.

8. Doses

- Claims over the dose of a drug fail to comply with the industrial applicability requirement. They should be treated as a method of medical treatment, in spite of their appearance, for instance, as a composition (or combination) claim.

9. Combinations

- Combinations of known drugs may be considered a method of treatment and, hence, be deemed non-patentable because they lack industrial applicability or are excluded from protection under national law. In some cases, combination claims do not meet the novelty standard, such as when the combination was previously known and practised by the medical profession. In addition, such a combination will not satisfy the inventive step standard, unless a synergistic effect, justified by appropriate clinical tests, can be demonstrated. However, synergistic effects that may be reasonably expected from the combination of two or more drugs of known therapeutic classes do not meet the inventive step standard.

10. Prodrugs

- Examiners should, as the first step in examining claims over prodrugs, determine whether the patent on the basic drug covers the prodrug. If this is the case, the new application will not be admissible. A claim on a prodrug will generally fail to meet the inventive step standard unless evidence is provided that it overcomes pharmaceutical or pharmacokinetically based problems of the parent drug in a non-evident manner. Generic claims over specified prodrugs should not be allowed.

11. Metabolites

- Claims on metabolites are not admissible. They can be rejected on the grounds of absence of an invention or lack of novelty/inventive step.

12. New medical use

- Claims relating to the new use of a known drug can be rejected on various grounds:
 - a) it is the discovery of a property;
 - b) there is no invention, given the absence of a technical character;
 - c) there is no novelty, as the compound and its process of manufacture are known;
 - d) absence of industrial applicability, since the effects take place in the body; and
 - e) exclusion of methods of medical treatment, when such exclusion is provided for in a national patent law.



I. Introduction

These guidelines advise patent examiners in assessing the patentability requirements of applications relating to pharmaceutical products and processes, as well as the use¹ of pharmaceutical products. The adoption of guidelines such as these is important for four reasons.

First, although pharmaceuticals share common features with other inventions, there are elements in patent claims relating to pharmaceuticals that are unique, determined by their intended use.

Second, a set of examination criteria will help speed up patent procedures, increase uniformity in the treatment of applications, and offer applicants greater certainty about the possible outcome of the procedures.

Third, there is a proliferation of patent applications in the field of pharmaceuticals claiming polymorphs, salts, formulations and so on, which are often made to prevent generic competition rather than to protect genuine inventions. So-called evergreening patents² do not contribute to the technological pool, and they limit the market entry of generic products.

Fourth, given the impact of patents on the availability, accessibility and affordability of treatments and technologies, the manner in which pharmaceutical patent applications are examined can have critical implications for public health. Patent offices and examiners play vital roles in ensuring an appropriate balance between protecting inventions and incentivizing innovation on the one hand, and promoting accessibility and affordability of treatments and health technologies on the other. This balancing process is also important for achieving broader development priorities, from national efforts to promote research and development (R&D), technology transfer and pharmaceutical production, to achieving universal health coverage.

Several countries (e.g. Argentina, Ecuador, India and the Philippines) have adopted legislation or policies for examining patent applications relating to pharmaceutical products and processes in a manner that accounts for public health considerations. Analysis of pharmaceutical patent claims has shown that the proper application of patentability standards can prevent the grant of 'poor quality' or trivial patents, which, by preventing the timely entry of generic competition, may harm public health.

Importantly, these guidelines do not intend to modify the standards of patentability established by patent law, or to add additional standards. Instead, they aim to ensure the correct application of those standards in view of the specific nature of the claimed subject matter and the public health relevance of the decisions.

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1. The TRIPS (Trade-related Aspects of Intellectual Property Rights) Agreement does not oblige World Trade Organization members to grant patents claiming a particular use of a product; many countries do not grant patents for the second and subsequent uses of medicines (see below).
2. 'Evergreening' is a strategy by which pharmaceutical companies apply for patents over derivatives, formulations, dosage forms, etc. of known drugs in order to extend their exclusive rights beyond the expiry of the original patent.



II. General rules regarding patentability

1. The concept of invention

Most patent laws do not define ‘invention’,³ leaving the specific boundaries of this concept to patent offices and courts to determine. Generally, an invention may be understood as a technical development conceived by an inventor. This notion excludes something that has merely been discovered or otherwise found by chance or as a result of research. For example, a natural gene for which a function has been identified is a discovery, not an invention.⁴ In fact, many patent laws specifically exclude discoveries.⁵

The identification of particular properties or physical forms of a known product also does not amount to an invention, despite the efforts involved in identifying such properties or forms.⁶

India’s *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals* specifies that: it should be borne in mind that finding the new property of an already known substance does not make the substance novel and/or inventive.⁷

As discussed below, identifying the most suitable polymorph for a pharmaceutical product may not be deemed an invention either: a polymorph is an inherent characteristic of a compound in its solid form that is found, not invented. Similarly, finding a new use for a known medicine is not an invention.

The concept of invention may be seen as encompassing a *technical effect*, as is the case under European law. Although the European Patent Convention does not spell out this requirement, the technical character of an invention is generally considered an essential requirement for its patentability. The European Patent Office (EPO), for instance, held in decision T 154/04 (OJ 2008, 46) that “technical character” was an implicit requisite of an invention within the meaning of article 52(1) of the European Patent Convention.

Recommendations

Materials found in nature (such as genes) and properties and forms newly found in known products (e.g. the crystalline form of a compound of medical use) should not be deemed inventions. The concept of invention should be understood as encompassing a technical effect.

When it is determined that the patent application does not cover an invention, no further analysis of compliance with the patentability requirements is needed.

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3. Definitions of ‘invention’ are found in Indonesian Law No. 14 Year 2001 regarding patents (Article 1: invention is “an Inventor’s idea that is poured in any activity of solving a specific problem in the field of technology, either in the form of a product or process, or an improvement and development of a product or a process”), and in the Mexican Industrial Property Law of June 25, 1991 (Article 15: “Any human creation that allows matter or energy existing in nature to be transformed for use by man for the satisfaction of his specific needs shall be considered an invention.”).
4. The US Department of Justice argued in an amicus curiae submitted in a case relating to the patentability of claims over DNA that “the chemical structure of native human genes is a product of nature, and it is no less a product of nature when that structure is ‘isolated’ from its natural environment than are cotton fibers that have been separated from cotton seeds or coal that has been extracted from the earth.” Available at www.pubpat.org/assets/files/brca/CAFC/United%20States%20Amicus%20Brief.pdf.
5. See, e.g., article 52(2) of the European Patent Convention.
6. Significant efforts or difficulties in finding a technical solution are not evidence of inventive step, which requires an inventive activity, available at http://ipindia.nic.in/iponew/draft_Pharma_Guidelines_12August2014.pdf.
7. Office of the Controller General of Patents, Designs and Trademarks, *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*, 2014. para. 6.2, available at http://ipindia.nic.in/iponew/draft_Pharma_Guidelines_12August2014.pdf



2. Patentability standards

Novelty

Generally, universal (or absolute) novelty is required for a valid patent. The concept of novelty, however, may be applied in different ways, depending on the legislation and interpretation by patent offices and courts. In particular, there is room for national policies to determine the scope of what has been disclosed and is therefore part of the ‘prior art’.

The disclosure of an invention in the prior art may not have been made *expressis verbis*, but may be implicit in a prior art document. Implicit teachings can be considered part of the prior art, hence destroying the novelty of an invention. This approach is preferable to the ‘photographic’ approach to novelty, which is based on explicitly disclosed information. The photographic approach entails a rigid and formalistic assessment of novelty, which may lead to the unwarranted grant of patent rights. The EPO’s jurisprudence has clearly relied on implicit features to establish novelty. In T 0701/09, for instance, the EPO Board found that:

direct and unambiguous disclosure was not limited to explicit or literal statements, but equally included implicitly disclosed information which a reader skilled in the art would unequivocally gather from the overall context of a cited document.⁸

In accordance with the guidelines applied by the US Patent and Trademark Office (USPTO):

the express, *implicit*, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103.⁹

The Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals* note in this regard:

Implicit disclosure: The lack of novelty must normally be clearly apparent from the explicit teaching of the prior art. However, if the said prior art discloses the claimed subject-matter in such implicit manner that it leaves no doubt in the mind of the examiner as to the content of the prior art and the practical effect of its teaching, an objection regarding lack of novelty should be raised.¹⁰

Novelty may also be excluded when the information available in the prior art discloses the essential elements of an invention, regardless of whether data enabling the execution of the invention were available. Thus, novelty will be destroyed if a compound was made and tested, even if a clear description of its properties or a method of making it was not disclosed.

In *Enercon (India) Limited v. Aloys Wobben* ORA/6/2009/PT/CH, ORDER (No. 18 of 2013) the Intellectual Property Appellate Board of India noted that novelty may be denied on the basis of ‘inherent anticipation’. It stated:

the prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art. . . it is not necessary that inherent anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention.

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8. Available at www.epo.org/law-practice/case-law-appeals/recent/t090701du1.html.
9. USPTO, Requirements of Rejection Based on Inherency; Burden of Proof [R-08.2012], available at: www.uspto.gov/web/offices/pac/mpep/s2112.html (emphasis added).
10. Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, para. 7.4.



In accordance with US case law:

“the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.” *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable (*In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)).¹¹

The number of documents that examiners may consider in determining whether novelty has been destroyed is an important question. Although general practice has been to consider a single document, patent law does not rule out the possibility of considering more than one document.¹²

Many laws specify that the prior art should be deemed to include applications filed in the same country that are published on or after the filing date of the application being examined.¹³

Recommendations

An assessment of novelty requires consideration of what has been expressly, implicitly or inherently disclosed in the prior art. The discovery of a previously unknown property of a substance does not render the substance patentable. More than one document may be used to establish the lack of novelty.

The determination of novelty should include information disclosed in patent applications filed in the same country that are published on or after the filing date of the application being examined.

Inventive step

The patent system was devised to reward inventiveness, encourage technical progress and foster the dissemination of innovations. Restricting the free movement of ideas, as the granting of a patent entails, is only justified when the applicant has devised a new product or process as an outcome of an ‘inventive activity’ or ‘inventive step’.

Generally, patent laws define inventive step (or non-obviousness) based on a legal fiction. They assume a judgment made by a person skilled in the art, with ordinary knowledge or expertise in a given technical field. The determination of the knowledge and capability of such a person is crucial to ensuring that the patent system rewards those who contribute new technical solutions, and to avoiding the grant of patents over minor or trivial developments that may block innovation or exclude legitimate competition. This is particularly important in the pharmaceutical sector, where patents are often strategically used to deter the market entry of generic medicines at lower prices.

A patent system that rewards innovation should be based on an analysis of what is evident or obvious for an expert or a team of experts. In many cases, an invention requires technical contributions from specialists from different fields. Accordingly, considering the expert knowledge of one person would be insufficient. In a case relating to European patent EP 0 347 066 on two enantiomers of the antidepressant drug citalopram, for instance, the Tribunal

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11. See USPTO, Requirements of Rejection Based on Inherency; Burden of Proof [R-08.2012], available at www.uspto.gov/web/offices/pac/mpep/s2112.html.
12. The combination of publications to establish lack of novelty has been suggested in the *EAC Regional Intellectual Property Policy on the Utilisation of Public Health-Related WTO-TRIPS Flexibilities and the Approximation of National Intellectual Property Legislation*, 2013, available at www.cehurd.org/wp-content/uploads/downloads/2013/05/EAC-TRIPS-Policy.pdf.
13. See, e.g., article 3(3) of Indonesian patent law No. 14, 2001.



de Grande Instance of Paris (30-09-10) ruled that the ‘skilled person’ must be defined as a team composed of a medicinal chemist, a pharmacologist and a biochemist working in the pharmaceutical industry.¹⁴

Examiners should consider not only what is formally documented in the prior art, but also what an expert, such as a person trained and experienced in disciplines relevant to the pharmaceutical sector, could consider evident in the light of such prior art. Thus the identification of a pharmaceutically suitable salt to manufacture a medicine, or its formulation to ensure a certain release characteristic (e.g. slow release) of the active ingredient, are part of the common knowledge of people working in those fields. Only in very rare occasions will a salt or formulation, even if new, comply with a rigorously applied inventive-step requirement. In relation to US patent number 4,879,303 on the besylate of amlodipine salt, for instance, the US Court of Appeals for the Federal Circuit stated that:

a suggestion, teaching or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.¹⁵

In accordance with the EPO Guidelines for Examination:

[c]ommon general knowledge can come from various sources and does not necessarily depend on the publication of a specific document on a specific date. An assertion that something is common general knowledge need only be backed by documentary evidence (for example, a textbook) if this is contested.¹⁶

Although some patent laws refer to a person with an ‘average’ or ‘ordinary’ knowledge,¹⁷ this does not mean that he/she has no creativity. In *KSR v. Teleflex*, for instance, the US Supreme Court held that:

a person of ordinary skill is also a person of ordinary creativity, not an automaton.¹⁸

This means that the person skilled in the art should be deemed to be a person who can derive new knowledge from the prior art, even with experimentation when it does not entail methods unknown to an expert in the field. In accordance with the Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*:

[t]his hypothetical person [the person skilled in the art] is presumed to know all the prior arts as on that date, even non-patent prior art available to the public. He has knowledge of the technical advancement as on that date, and the skill to perform experiments with the knowledge of state of the art. He is not a dullard and has a certain modicum of creativity.¹⁹

In many cases, the examiner will have to consider whether it was obvious for a person skilled in the art to carry out certain activities, for instance, to obtain a salt or a polymorph of a compound of medical use. The ‘obvious to try’ test, as applied in some jurisdictions, requires consideration of the reasonable expectation of success, even when experimentation is required. For instance, the Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*, provide that:

the reasonable expectation of success embedded in the prior art which motivates the skilled person to reach to the invention, is the most crucial determining factor in ascertaining inventive step. Obviousness

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14. Société Ratiopharm GmbH v. Société H. Lundbeck AIS, available at http://kluwerpatentblog.com/files/2011/02/2010-09-30_TGI_Paris_Ratiopharm_vs_Lundbeck.pdf.

15. *Pfizer, Inc. v. Apotex, Inc.*, 2006-1261; March 22, 2007.

16. Available at www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vii_3_1.htm.

17. For instance, in the United States, non-obviousness is judged in the light of the knowledge of a “person having ordinary skill in the art” (35 U.S.C. § 103 (A)).

18. See *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).

19. Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals. para. 18.



cannot be avoided simply by showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. Obviousness does not require absolute predictability of success. All that is required is a reasonable expectation of success. In the matter of pharmaceutical inventions, structural and functional similarity of the product provides this 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.²⁰

In countries that apply what is known as the ‘problem-solution’ approach²¹ to determining inventive step, finding a solution to a problem is not sufficient to establish a patentable invention. The solution must be, in itself, the outcome of an inventive activity. In particular, a claim that the proposed solution offers certain advantages (for instance, increased bioavailability of a medicine) is not enough to establish an inventive step.

In some cases, the surprising or unexpected nature of the results obtainable with a new product may be an indicator of inventive step. However, this is not necessarily the case. The EPO Board of Appeals, for instance, decided that:

if, having regard to the state of the art, it would already have been obvious for a skilled person to arrive at something falling within the terms of a claim, because an advantageous effect could be expected to result from the combination of the teachings of the prior art documents, such claim lacked inventive step, irrespective of the circumstance that an extra effect (possibly unfore seen) was obtained (T 21/81).²²

Where, because of an essential part of the technical problem being addressed, the state of the art obliged a skilled person to adopt a certain solution, that solution was not automatically rendered inventive by the fact that it also unexpectedly solved part of the problem. Therefore, an unexpected bonus effect does not confer inventiveness on an obvious solution (T 231/97).²³

While some patent offices have limited the number of documents that may be considered in assessing inventive step, there is no rationale for such limitations. The assessment should include the prior art as a whole.

Recommendations

Patents should only be granted when the claimed object is the result of an inventive activity. The fact that a solution has been found to a problem or that an advantage has been obtained, even if unexpected, is not sufficient to prove the existence of such activity.

A claimed invention should be assessed in the light of the knowledge of an expert, or a team of experts, with ordinary creativity in the technical field. A specific prior art document is not indispensable to prove that a claimed invention falls within the common knowledge, or that it is obvious for an expert in the field.

Industrial applicability/utility

While some countries, such as the United States, only require that the utility of a claimed invention be shown in the patent application, most countries apply an industrial applicability standard. An industrial applicability standard imposes

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20. Ibid., para. 8.8.
21. This methodology was developed by the EPO pursuant to the European Patent Convention Rule 27(1)(c). It is applied by many countries whose practice has been influenced by the technical assistance and training offered by the EPO.
22. Available at www.epo.org/law-practice/legal-texts/html/caselaw/2013/e/clar_i_d_10_8.htm
23. Ibid.



a higher burden on the applicant than the utility standard, and it excludes the patentability of certain types of claims common in the pharmaceutical sector. Industrial applicability means that a product can be manufactured or a technical process applied in accordance with the teachings disclosed in a patent. Thus, a patent application describing a process that may be applied only in a laboratory, or how to use a medicine to achieve a certain therapeutic effect, would not be patentable.

Industrial applicability means that an invention can be made in industry.²⁴ An industrial applicability requirement rules out the patentability of inventions whose effects take place as the result of physiological or pharmacological actions that occur in the body. For instance, a new therapeutic use or changes in dosages of a known medicine would not be patentable.

Complex issues arise in determining the industrial applicability or utility of claims relating to new and as yet unproven drugs. Pharmaceutical companies generally file patent applications before completing clinical studies. Hence, the efficacy and safety of the drug has not been determined. Patent offices and courts generally accept this fact, but request that some evidence be provided to support an application. In the United States, for instance, the examiner is not expected to seek evidence on safety or efficacy of treatments for humans to demonstrate utility, but will examine the nature of disease in relation to the asserted utility. In the case of diseases known to be incurable at the time of filing, the examiner will review the asserted utility with this in mind. Claims for curing or preventing a disease generally require greater proof of utility compared to claims for method of treatment or treating a symptom; in the latter case, adequate test data can be sufficient evidence of utility.²⁵

Recommendations

In countries that apply an industrial applicability standard, an invention must be capable of being made in industry in order to be patentable.

The use or methods of use of a medicine, including the specification of a certain dose, and processes that do not allow a person skilled in the art to obtain a product in industry, should be deemed as lacking industrial applicability.

3. Sufficiency of disclosure

In addition to complying with patentability requirements, the grant of a patent is generally conditional upon the sufficient disclosure of the invention. In other words, the specifications should provide information to allow a person skilled in the art to make or practise the claimed invention. In accordance with Article 83 of the European Patent Convention, for instance, an application must “disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.” This requirement aims to ensure that an “actual technical contribution to the art” is made; it justifies the grant of a patent monopoly.²⁶ In the United States, the patent specification should allow a “person of ordinary skill in the art” to make and use the invention without “undue experimentation.”²⁷

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24. ‘Industry’ is broadly understood in accordance with article 1(3) of the Paris Convention for the Protection of Industrial Property, including what is applicable “to industry and commerce proper, but likewise to agricultural and extractive industries and to all manufactured or natural products, for example, wines, grain, tobacco leaf, fruit, cattle, minerals, mineral waters, beer, flowers and flour”.

25. Carlos Correa (editor), *A Guide to Pharmaceutical Patents*, South Centre, 2012, p. 103.

26. See, e.g., T 409/91, para. 155-156.



Lack of sufficient disclosure is often a reason for the refusal of a patent application or the revocation of a patent.²⁸ This is a matter of substance, not form. The Markush claims discussed below, for instance, raised an issue of insufficient disclosure: only a few examples of realization for a great number of compounds are disclosed. The same objection may be raised when a patent application generically claims formulations, salts, polymorphs, and so on without characterizing them, as discussed below.

The knowledge attributed to a person skilled in the art for assessing sufficiency of disclosure needs not be the same as the knowledge attributed for assessing inventive step. To ensure a description of the invention that is understandable to a person with average knowledge, “the skilled person, in the context of sufficiency of disclosure, should be a person who without undue burden of experimentation would be able to translate the specification into the technical reality.”²⁹

Recommendations

The disclosure of the claimed invention should be precise and clear enough for a person with average knowledge in the field to reproduce the invention without undue burden of experimentation.

The required disclosure should be sufficient to implement all the embodiments of the invention.

4. Flexibilities under the TRIPS Agreement

The Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS Agreement) establishes minimum standards for the protection of intellectual property rights by members of the World Trade Organization (WTO). However, it has left many ‘flexibilities’ that allow members to define their own policies and standards on various matters.

An important flexibility allowed to WTO members is to determine what is meant by ‘invention’, a concept that is not defined in the TRIPS Agreement. In fact, there is significant diversity in national laws and practices around the notion of invention, and to date, no complaint has been raised to the WTO regarding a definition of invention. In particular, national laws may require a determination of whether an invention exists before entering into the analysis of compliance with the patentability requirements.

Similarly, the TRIPS Agreement obligates WTO members to grant a patent when patentability requirements are met, but it does not define those requirements. Thus, WTO members may adopt different concepts of novelty (universal, local or a mix); inventive step or non-obviousness; and industrial applicability or utility. Nothing prevents WTO members from applying rigorous patentability criteria to avoid low-quality patents.³⁰ Similarly, WTO members retain

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27. 35 USC 112: “The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.”
28. See, e.g., Fuel Oils/EXXON [1994] OJEPO 653; Biogen v Medeva [1997] RPC 1 (HL). See generally on the subject under common law, Sivaramjani Thambisetty, The Evolution of Sufficiency in Common Law, LSE Law, Society and Economy Working Papers 6/2013 London School of Economics and Political Science, 2013, available at: www.lse.ac.uk/collections/law/wps/WPS2013-06_Thambisetty.pdf
29. India’s Intervention on a study on inventive step (SCP/22/3) at the World Intellectual Property Organization’s Standing Committee of Patents P/22, 28 July 2015, available at <http://keionline.org/node/2298>



flexibility to determine the rules applicable to the disclosure of the invention, in order to ensure its reproducibility and avoid broad, generic claims, as is the case with the Markush claims (see discussion below).

The UN High Commissioner for Human Rights has stated that:

[t]he requirements under the TRIPS Agreement for the grant of patents — novelty, inventive step and industrial applicability — are open to interpretation under national legislation and each country can decide according to local conditions. Consequently, the High Commissioner encourages interpretations of these requirements that do not lose sight of the public interest in the wide dissemination of knowledge.³¹

The World Health Organization (WHO) Commission on Intellectual Property Rights, Innovation and Public Health also noted that:

[t]he TRIPS Agreement allows countries a considerable degree of freedom in how they implement their patent laws, subject to meeting its minimum standards, including the criteria for patentability laid down in TRIPS. Since the benefits and costs of patents are unevenly distributed across countries, according to their level of development and scientific and technological capacity, countries may devise their patent systems to seek the best balance, in their own circumstances, between benefits and costs. Thus developing countries may determine in their own ways the definition of an invention, the criteria for judging patentability, the rights conferred on patent owners and what exceptions to patentability are permitted, provided these are consistent with the relevant articles of TRIPS (for WTO members).³²

The Doha Declaration on the TRIPS Agreement and Public Health confirmed the right of WTO members to use the TRIPS flexibilities.³³

Adopting specific guidelines in relation to the examination of patent applications for pharmaceuticals does not violate the non-discrimination clause contained in article 27.1 of the TRIPS Agreement. Countries that decide to develop and apply specific guidelines to ensure that patent applications relating to pharmaceuticals are rigorously examined act in conformity with the TRIPS Agreement. The *Declaration on Patent Protection: Regulatory Sovereignty under TRIPS* developed under the auspices of the Max Planck Institute for Innovation and Competition confirms that:

[e]very technology is more or less unique with regard to its exposure to market failure, its susceptibility to patent protection, and its socio-economic implications... Measures to accommodate these differences cannot be considered contrary to article 27(1) of the TRIPS Agreement. While that provision prohibits discrimination as to the field of technology, it does not prevent states from treating different situations differently. Differentiation that serves to level the actual conditions of competition across all fields of technology is not discriminatory but rather the opposite. It constitutes a necessary response to the

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30. The Global Commission on HIV and the Law, Risks, Rights and Health, New York, 2012, p. 80.
31. UN High Commissioner for Human Rights, The impact of the Agreement on Trade-related Aspects of Intellectual Property Rights on human rights: Report of the High Commissioner, E/CN.4/Sub.2/2001/13, 27 June 2001, para 62.
32. WHO Commission on Intellectual Property Rights, Innovation and Public Health, Report, 2006, p. 21, available at: www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf?ua=1.
33. Paragraph 4: "We agree that the TRIPS Agreement does not and should not prevent members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health and, in particular, to promote access to medicines for all. In this connection, we reaffirm the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose." Available at www.wto.org/english/thewto_e/minist_e/mino1_e/mindecl_trips_e.htm



diversity of technologies and, consequently, a *conditio sine qua non* for an intrinsically balanced system of protection that remains neutral in its effects on competition. Differentiation may relate to the requirements of patentability, patent eligibility and disclosure. . . , to the exclusion of subject matter from patentability, as well as to the scope of protection.³⁴

Recommendations

National laws and patent office practices should use the flexibilities allowed by the TRIPS Agreement with regard to the concept of invention and in defining patentability standards and the sufficiency of disclosure.

Specific guidelines for examining pharmaceutical-related patent applications should be issued in order to protect the public against the grant of unwarranted patents that may unduly limit access to affordable medicines.

Box 1. Example of Markush claim

1, 2, 4, 5-Tetrahydro-3H-benzazepine compounds and a process for their preparation and pharmaceutical compositions containing them.

Publication number: US 2009/0069296 A1 / Publication date: 12 March 2009

Abstract: Compounds of formula (I)

Claims:

1. Compound of formula (I): wherein: R₁ represents a hydrogen atom or a group selected from C₃-C₇cycloalkyl, benzyl and linear or branched C₁-C₆alkyl, the alkyl group being saturated or unsaturated and optionally substituted by a hydroxy or C₃-C₇cycloalkyl group or by one or more halogen atoms, R₂, R₃, R₄ and R₅, which may be the same or different, each represent a hydrogen atom or a hydroxy group; methyl group;—OSO₂R₁₀ group;—OCOR₁₀ group; or linear or branched, saturated or unsaturated C₁-C₆alkoxy group optionally substituted by a methoxy or —(CO)—NR₁₂R'₁₂ group, or R₂ and R₃, or R₃ and R₄, or R₄ and R₅ together form a group —O—(CH₂)_q—O—, —O—CH=CH—O— or —O—CH=CH—, R₆, R₇, R₈ and R₉, which may be the same or different, each represent a hydrogen atom or a linear or branched, saturated or unsaturated C₁-C₆alkoxy group, or R₆ and R₇, or R₇ and R₈, or R₈ and R₉ together form a group —O—(CH₂)_q—O—, R₁₀ represents a group selected from linear or branched C₁-C₆alkoxy, NR₁₁R'₁₁ and linear or branched C₁-C₆alkyl which is optionally substituted by one or more halogen atoms, R₁₁ and R'₁₁, which may be the same or different, each represent a hydrogen atom or a linear or branched C₁-C₆alkyl group, or R₁₁ and R'₁₁ together with the nitrogen atom carrying them form a monocyclic or bicyclic, 5- to 8-membered, nitrogen-containing heterocycle optionally containing another hetero atom selected from O and N, said heterocycle being optionally substituted by one or more halogen atoms, R₁₂ and R'₁₂, which may be the same or different, each represent a hydrogen atom or a linear or branched C₁-C₆alkyl group, X represents O, NH or CH₂, m and p, which may be the same or different, each represent 0 or 1, n and q, which may be the same or different, each represent 1 or 2, its optical isomers when they exist, and also addition salts thereof with a pharmaceutically acceptable acid.

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34. Available at www.ip.mpg.de/en/pub/news/patentdeclaration.cfm.



III. Typical claims relating to pharmaceuticals

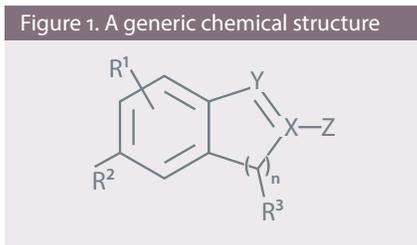
1. Markush claims

Markush claims³⁵ consist of a generic chemical structure with multiple alternatives that allow for the protection, under a single patent, of several variants of a claimed invention. The admission of pharmaceutical patents for such claims raises complex issues because a single patent may potentially block research and development and the commercialization of up to several million molecules.³⁶ Recent studies show a growing use of Markush claims in several developing countries, where such claims accounted for more than 50 percent of all patent applications relating to pharmaceuticals.³⁷

Figure 1 presents an example of a generic chemical structure, and Box 1 an example of a patent based on a Markush claim.

The compounds covered by a Markush claim may be determined by a combination of variations that can give rise to a potentially infinite set of alternatives. Variations include:

- substituent variation based on alternative values for an R-group.
- position variation depending on the point of attachment.
- frequency variation due to multiple occurrence of groups.
- homology variation depending on the attached groups (e.g. alkyl, methyl or ethyl).



Typically, patent applications based on Markush claims present a few implementation examples, while the general formula may cover thousands or millions of possible embodiments of the claimed invention. Hence, Markush claims raise issues concerning sufficiency of disclosure: it is impossible to know the peculiarities of the process for obtaining each of the non-exemplified embodiments and whether they will perform the disclosed functions.

Markush claims have become increasingly complex and excessively broad, for instance: “R₁ is a substituted or unsubstituted, mono-, di- or polycyclic, aromatic or non-aromatic carbocyclic or heterocyclic ring system, or . . .”³⁸ Such claims may disguise the true nature of the invention and cover compounds that lack the activity indicated in the patent application.

In addition, it is virtually impossible to make prior art searches to establish novelty and inventive step for thousands or millions of compounds. Although there are tools that may aide in the examination process, they do not permit a complete and accurate assessment. Several computer-based tools may be required for a comprehensive retrieval, but their use is complex and they do not guarantee accurate results.

Patent offices have adopted or proposed different measures aimed at reducing the scope of Markush-type

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35. Dr. Eugene A. Markush was the founder and president of Pharma Chemical Corporation of Bayonne, New Jersey. He was a leading manufacturer of dyes in the United States and held over 20 patents on synthetic dyes and related fields. In 1924, he obtained a patent on pyrazolone-based dyes (U.S. No. 1,506,316), which protected a generic chemical structure, in addition to the products already synthesized, using the expression “where R is a group selected from.” While Dr. Markush did not file the first patent with a generic chemical structure, he was involved in a precedent-setting legal case in the United States for this type of claim.

36. Eli Lilly’s patent CA 1,075,687 (1975), for instance, covered 15 trillion of compounds “useful in the treatment of mild anxiety states and certain kinds of psychotic conditions such as schizophrenia.”

37. See Carlos Correa (editor), *Pharmaceutical innovation, incremental patenting and compulsory licensing*, South Centre, Geneva, 2013, p. 18.

38. See J. F. Sibley, “Too broad generic disclosures: a problem for all”, *J. Chem. Inf. Comput. Sci.*, 1991, 31 (1) p. 5–8.



claims.³⁹ The Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*, for instance, requires that the complete specification be “critically examined;” specific guidance is also provided in the Argentine guidelines (see Box 2).

Box 2. Criteria for the examination of Markush claims

India

While examining Markush claims, the complete specification should be critically examined to determine whether (i) it discloses the best representatives, as known to the applicant, of the possible embodiments; (ii) such embodiments share a common use or property; (iii) such possible embodiments share common structure; (iv) physical and/ or chemical properties of claimed compound are disclosed; (v) test conducted for the representatives of such embodiments is provided. . . ; (vi) in case of product claims, at least one process for preparing the compounds should be disclosed provided that the process enables the whole scope of the invention.

Moreover, if any one of (i) to (vi) are not met, such a Markush claim may be objected depending upon the circumstances of the application so examined under ‘unity of invention’ and insufficiency of disclosure suitably.⁴⁰

When the Markush grouping is for alternatives of chemical compounds, the alternatives are regarded as being of a similar nature where the following criteria are fulfilled: (A) all alternatives have a common property or activity; and (B)(1) a common structure is present, that is, a significant structural element is shared by all of the alternatives; or (B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.⁴¹

Argentina

Compounds represented by a Markush formula shall be admissible only if unity of invention is demonstrated; if they comply with the requirements for patentability (novelty, inventive step and industrial application); and if the specification sufficiently describes how to obtain all of the compounds provided by the claimed Markush formula.

When an invention involves multiple compounds claimed under a Markush-type formula, a reasonably logical and proportional relationship between the scope of the claims and the related matter disclosed in the description shall be required. The description should include experimental procedures that, taking into account combinations of different substituents or reasonably acceptable equivalents thereof, are representative of the entire scope of the claimed matter. If the working examples are not sufficiently representative of the claimed scope of the invention, and therefore the claims lack sufficient support in the description, the applicant should be required to limit it.

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39. For instance, in 2007 the USPTO published proposed new rules, which were not finally enacted, for the “Examination of Patent Applications That Include Claims Containing Alternative Language.” Under these rules, nested Markush structures would be banned and an enumeration of alternatives would be required. The proposed rules also required that “the number and presentation of alternatives in the claim do not make the claim difficult to construe.” The Supplementary Guidelines for Determining Compliance with 35 U.S.C. 112 and for Treatment of Related Issues in Patent Applications, 76 Fed. Reg. 7,162 (9 February 2011) required a “single structural similarity” for the admissibility of Markush claims and clarified that “[m]embers of a Markush group share a ‘single structural similarity’ when they belong to the same recognized physical or chemical class or to the same art-recognized class.” It also stated that members of a Markush group share a common use “when they are disclosed in the specification or known in the art to be functionally equivalent.” See Kimberly J. Prior, “The USPTO’s Historic Struggle with Markush Claims: Will the 2011 Guidelines Provide Relief?” (2012), Student Scholarship, Paper 114. http://erepository.law.shu.edu/student_scholarship/114.

40. Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, 2014, para. 4.2.

41. *Ibid.*, para. 11.15.



/ box 2 continued

For a sufficient description of the compounds included in the claimed Markush formula, the embodiments of the invention described in the working examples should be representative of all the compounds to be protected. In all cases, these embodiments shall be perfectly exemplified by providing all the data characterizing the compound obtained by physico-chemical characterization techniques (such as melting point, boiling point, -IR- infrared spectrum, proton nuclear magnetic resonance -1HNMR- and carbon 13-13CRMN-), indicating whether polymorphic compounds have been detected.

Thus, the protection of Markush formulas should be limited to the matter supported by the description, that can be effectively reproduced by a person skilled in the art and whose industrial application comes up unambiguously from the description.⁴²

Recommendations ⁴³

An application including a Markush claim should contain sufficient information to allow a person skilled in the art to perform the invention over the whole area claimed, using his common general knowledge, without undue burden and experimentation, and without needing inventive skill.

The coverage of the patent should be limited to the claimed embodiments that are actually enabled by the disclosure in the specification.

Claims of limited scope could be granted if evidence is provided that the same claimed function will be obtained through the substitution of any member within the same family class. Such evidence should include fusion point, infrared absorption spectrum (IR) or nuclear magnetic resonance (NMR) obtained through testing and experimentation, and other information needed to enable the reproduction by the disclosed method of each embodiment of the invention. Applicants may also be requested to submit electronic files to facilitate the prior art search.

2. Selection patents

In some cases, a subgroup of elements is selected from a larger group and claimed on the grounds that a new, unexpected property has been found. For instance, if a Markush claim was admitted in relation to a set of pharmaceutical compounds, the patent owner might later file a new patent application covering one or more of such compounds. Thus, the patent owner may obtain a further 20-year monopoly simply by picking one or more compounds out of the generic formula.

Selection patents are also often filed when a starting compound is selected from a list and there is a choice of processes to obtain a final product. In T12/81, for instance, the EPO considered a case where the prior art listed 20 starting compounds and gave a choice among five processes for reducing ketones to their corresponding secondary alcohols, which could take two diastereomeric forms.⁴⁴

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42. Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute), Adoption of Guidelines for the Examination of Patent Applications of Chemical and Pharmaceutical Inventions, 2012, para. (1)(iv) (unofficial translation).

43. See Carlos Correa, Guidelines for the examination of pharmaceutical patents: developing a public health perspective, Working Paper, WHO, ICTSD and UNCTAD, Geneva, 2006, p. 12, available at: www.ictsd.org/themes/innovation-and-ip/research/guidelines-for-the-examination-of-pharmaceutical-patents.

44. Available at www.epo.org/law-practice/case-law-appeals/recent/t810012ep1.html.



In other cases, the selection may take place within a numerical range, for instance, when C₂ is selected from a previously disclosed compound including a chain range C₁-C₄.

Selection patents are examined in several jurisdictions using different criteria. For instance, in accordance with the EPO Guidelines for Examination, an application would be acceptable (provided that the patentability criteria are met) in the case of the selection of "individual chemical compounds from a known generic formula whereby the compound selected results from the selection of specific substituents from two or more 'lists' of substituents given in the known generic formula. The same applies to specific mixtures resulting from the selection of individual components from lists of components making up the prior art mixture."⁴⁵ Under the EPO rules and jurisprudence, the selection within a numerical range is also acceptable if (a) the selected subrange is narrow compared to the known range; (b) the selected subrange is sufficiently far removed from any specific examples disclosed in the prior art and from the end points of the known range; and (c) the selected range is not an arbitrary specimen of the prior art, i.e. not a mere embodiment of the prior art, but another invention (purposive selection, new technical teaching).⁴⁶ The EPO's admission of selection patents is based on a fiction of novelty: a prior *generic* disclosure is considered to not deprive the *specific* selected item from novelty.

In Germany, the novelty standard has been strictly applied, leading to the rejection of patentability of selections. The disclosure of a group of compounds, even if large, has been deemed to destroy the novelty of each component of the group. In the case of selections within a range, the Federal Supreme Court's decision in *Inkrustierungsinhibitoren - 2* - of 1999 established that the specification of a range of quantity or weight lacks novelty, as it is a simplified notation of the numerous possible values between the upper-limit value and the lower-limit value. Thus, a selection deemed patentable by the EPO may be regarded as non-eligible in Germany in the light of the same prior art. In the United Kingdom, it has traditionally been considered that in order to be patentable, the selection must possess a special advantage judged in the context of the inventive step requirement.⁴⁷ In Canada, the unexpected advantages are primarily treated as a matter of utility, under the 'promise doctrine' developed by the courts.⁴⁸

The variety of approaches to selection patents illustrates the flexibilities available to patent offices and courts when dealing with this issue. Importantly, WTO members are not obliged to consider that a selection of disclosed compounds is still eligible for patent protection based on the argument that a generic claim does not disclose its specific components.

The grant of selection patents, if allowed, implies that the coverage of a patent may be much wider than its disclosure. In other words, while the holder of the patent would get protection on all the embodiments of the basic patent, the subsequently selected elements (although protected) would be considered as not disclosed and, hence, novel. This argument was rejected by the Supreme Court of India in *Novartis AG v. Union of India & Others* (Judgment of 1 April 2013). The Court stated that:

a monopoly is granted to a private individual in exchange of the invention being made public so that, at the end of the patent term, the invention may belong to the people at large who may be benefited by it. To say that the coverage in a patent might go much beyond the disclosure thus seems to negate the fundamental rule underlying the grant of patents.⁴⁹

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44. Available at www.epo.org/law-practice/case-law-appeals/recent/t810012ep1.html.

45. *Ibid.*

46. *Ibid.*

47. See e.g., *Beecham v Bristol* (HL) [1978] RPC 521 at 579.

48. See, e.g., *Eli Lilly Canada Inc. v. Novopharm Limited*, Federal Court of Appeal Decisions, 21.7, 2010, available at: <http://decisions.fca-caf.gc.ca/fca-caf/decisions/en/item/36863/index.do>.

49. Available at <http://judis.nic.in/supremecourt/imgs1.aspx?filename=40212>.



Recommendations

The selection of elements included in a disclosed group lacks novelty, such as in the case of compounds disclosed in a prior generic chemical structure or included within a numerical range. Patents should not be granted either in cases where a selection of elements is made from a list of known compounds, or where a selection is made of starting materials and alternative processes to obtain a compound.

3. Polymorphs

Most drugs exhibit structural polymorphism, which appears in the solid state of a chemical compound. Polymorphism is the ability of the chemical molecules or ions to exist with different internal crystal structures.⁵⁰

The techniques to obtain and characterize polymorphs (including hydrates/solvates⁵¹) are well known to, and normally practised by, a person skilled in the pharmaceutical field.⁵² Such a person will generally seek to obtain the most thermodynamically stable polymorph of the drug⁵³ to assure a reproducible bioavailability over the drug's shelf life, including under a variety of storage conditions. Polymorphs of drug substances are obtained through standard crystallization methods with the intervention of variable thermodynamic and kinetic factors, such as temperature, humidity and time.

Polymorphism is an inherent property of a substance, hence polymorphs are not created but found. In some cases, polymorphs can occur unintentionally during production or storage of a drug.⁵⁴ One example was Abbott's molecule inhibitor of HIV protease (ritonavir) marketed as 'Norvir'. During the manufacture of ritonavir in 1998, unexpectedly, a new unmarked polymorph emerged, interrupting production.⁵⁵ In other cases, a polymorph is so unstable that it cannot be obtained in repeated laboratory attempts.⁵⁶ As noted in proceedings before a US court, "[b]y the early

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50. Two types of polymorphism are usually distinguished: packing polymorphism, which results from a difference in crystal packing, and conformational polymorphism, which results from different conformers of the same molecule.

51. See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), *Specifications: Test Procedures & Acceptance. Criteria for New Drug Substances and New Drug Products: Chemical substances Q6A*, 1999, available at www.ich.org/products/guidelines/quality/quality-single/article/specifications-test-procedures-and-acceptance-criteria-for-new-drug-substances-and-new-drug-product.html.

52. See, e.g., D. T. Guranda and G. N. Gil'deeva, 'Preparation of drug polymorphs (a review)', *Pharmaceutical Chemistry Journal*, May 2010, Vol. 44 Issue 5, p. 254; M. Sherry Ku, *Salt and Polymorph Selection Strategy Based on the Biopharmaceutical Classification System for Early Pharmaceutical Development*, 2010, available at www.americanpharmaceuticalreview.com/Featured-Articles/117500-Salt-and-Polymorph-Selection-Strategy-Based-on-the-Biopharmaceutical-Classification-System-for-Early-Pharmaceutical-Development/. The first observation of polymorphism is attributed to Friedrich Wohler and Justus Von Liebig in 1832 (see <http://chemistry.tutorvista.com/inorganic-chemistry/polymorphism.html>).

53. There are occasional situations in which the development of a meta-stable crystalline or amorphous form is sought, such as to achieve faster dissolution rates or higher concentrations, for instance, for rapid absorption. See, e.g., Maria Saifee, Nazma Inamdar, Dinesh L. Dhamecha and Amit A. Rathi, 'Drug Polymorphism: A Review', *International Journal of Health Research*, December 2009, Vol. 2 Issue 4, p. 291.

54. For instance, the US Food and Drug Administration Guideline indicated as early as 1987 that "the manufacturing process (or storage condition)" may produce "particular polymorphs or solvates." It also noted that "[r]outine storage conditions, as well as some conditions of product manufacture (e.g. tablet compression, or use of an organic solvent during granulation) may also cause [polymorphic] transformations."

55. See, e.g., John Bauer, Stephen Spanton, Rodger Henry, John Quick, Walter Dziki, William Porter and John Morris, 'Ritonavir: An Extraordinary Example of Conformational Polymorphism', *Pharmaceutical Research*, June 2001, Vol. 18, Issue 6, p. 859-866.



2000s, skilled artisans would have appreciated that drug products preferably contain a compound's most stable polymorph because metastable polymorphs may convert during manufacture or storage.⁵⁷

A large number of patents have been filed on polymorphs (see Box 3) and many were granted. However, patent offices and courts have become increasingly reluctant to grant such patents, and in some countries, they are rejected as a matter of course.⁵⁸ In decision T 777/08 of 24 May 2011, the EPO Technical Board of Appeal, for instance, held:

at the priority date of the patent in suit, it belonged to the routine tasks of the skilled person involved in the field of drug development to screen for solid-state forms of a drug substance. For the sake of completeness, the board therefore wishes to note that, in the absence of any technical prejudice, which has not been alleged by the appellant, the mere provision of a crystalline form of a known pharmaceutically active compound cannot be regarded as involving an inventive step. 'Crystalline products are generally the easiest to isolate, purify, dry and, in a batch process, handle and formulate.' Thus, in view of his general knowledge, as reflected in this excerpt from document (28), the skilled person, starting from the amorphous form of a pharmaceutically active compound as closest prior art, would have a clear expectation that a crystalline form thereof would provide a solution to the problem as defined [the provision of atorvastatin in a form having improved filterability and drying characteristics].⁵⁹

In applying this doctrine, the EPO refused a patent application (EP No. 01924250) covering lopinavir's crystalline forms on the grounds that there were no unexpected advantages over Abbott Laboratories' earlier patent for the amorphous form, and that no inventive step was present. It has also been noted that it is increasingly difficult to obtain a patent on a polymorph in the United States, or to defend its validity if challenged in court.⁶⁰ In India, the Supreme Court confirmed on 1 April 2013 the refusal of a patent filed by the Swiss pharmaceutical firm Novartis on a crystalline form of an anti-cancer drug (imatinib mesylate). The refusal was based on a finding that increased therapeutic efficacy had not been proven as required by section 3(d) of the Indian Patent Act.⁶¹

In some cases, patent applications generically refer to polymorphs of a drug without specifically describing them, as in WO0172687 (A1), Diphenyl ether compounds useful in therapy, published on 4 October 2001, covering a "compound of general formula (I), or pharmaceutically acceptable salts, solvates or polymorphs thereof. . .". Such references do not meet the sufficiency of disclosure requirement established by most patent laws. The same applies to generic references to salts, ethers/esters and prodrugs, as noted below.

Polymorphs cannot be conceived *a priori* by a person skilled in the art. They are simply found in the solid states of drugs using routine techniques and are characterized by conventional methods based on X-ray diffraction. Accordingly, polymorphs cannot be considered an invention as defined above. Even if, however, they were eligible for patent protection, they would not show inventive activity, as it is obvious for a person in the field to seek the most suitable polymorph for achieving properties desirable for pharmaceutical use.

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56. See, e.g., Jack D. Dunitz and Joel Bernstein, 'Disappearing Polymorphs', *Acc. Chem. Res.*, 1995, 28 (4), pp 193–200.

57. *Cephalon, Inc., Cephalon France, and Teva Sante Sas, v. Watson Laboratories, Inc., Sandoz, Inc., Lupin Limited, and Apotex, Inc.*, Brief of Defendant-Appellant Lupin Limited, United States Court of Appeals for the Federal Circuit, Case: 13-1360.

58. See, e.g., Argentine Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute), Adoption of Guidelines for the Examination of Patent Applications of Chemical and Pharmaceutical Inventions, 2012, para. (1)(iv).

59. Available at http://archive.epo.org/epo/pubs/oj011/12_11/12_6331.pdf.

60. See, e.g., P. Vure, 'Polymorph patents; how strong they are really?' *Int. J. of Intellectual Property Management*, vol.4, no.4, 2011, 297–306.

61. See <http://supremecourtindia.nic.in/outtoday/patent.pdf>.



Box 3. Examples of patents covering polymorphs

Example 1: Salts of an anti-migraine indole derivative

Publication number: WO9606842(A1) / Publication date: 7 March 1996.

Abstract: The invention relates to an alpha-polymorphic form of a compound of formula (I), to processes for the preparation thereof, to an intermediate beta-polymorphic form, and to pharmaceutical compositions and therapeutic uses thereof.

Claims:

1. A compound of formula (I)
2. A crystalline, α -polymorphic form of a compound according to claim 1 characterized by an infrared spectrum as a mull in nujol which shows significant absorption bands at $\nu = 3371, 3293, 2713, 2524, 1419, 1343, 1307, 1264, 1151, 1086, 1020, 1008, 999, 922, 900, 805, 758, 740, 728, 689, 672, 652, 640, 598, 581, 573, 531, 498, 465, 457, 443, 428, 422, 414$ and 399 cm

Example 2: Non-hydrated gabapentine polymorph, production process and utilization for producing pharmaceutical-grade gabapentine

Publication number: EP1083164 (A1) / Publication date: 14 March 2001.

Abstract: The non-hydrated gabapentine polymorph is obtained by desiccating by atomization or turbo-drying an aqueous solution of gabapentine; the invention also relates to its use in order to obtain gabapentine appropriate for pharmaceutical use; disclosed is a method which comprises subjecting the polymorph to a crystallization process in solvents.

Claims:

1. Non-hydrated gabapentin polymorph having substantially the following X-ray diffraction data: ...

Occasionally, a process to obtain a polymorph may be novel and inventive. However, these standards shall not be considered met simply because it has been difficult to implement such a process; the process should be non-obvious for an expert in the field.

Recommendations

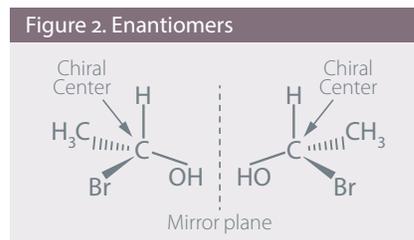
Patents on polymorphs should be denied on the grounds of absence of a patentable invention or inventive activity. This conclusion may be reached even in cases where a document providing the basis for an inventive-step analysis in relation to the specific claimed polymorph is not identified; obtaining a polymorph is a routine activity in pharmaceutical production, carried out through methods widely known to a person skilled in the art. However, a process used for the preparation of a polymorph, if novel and involving inventive step, may be patentable.

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62. 'Chiral' means that the molecules are mirror images of each other and they are not superimposable, i.e., they cannot be placed in the same space in such a way that they will overlap.



4. Enantiomers

Enantiomers are chiral molecules,⁶² meaning they are mirror images of one another (see figure 2). They have identical physical characteristics (energy, solubility in typical achiral solvents, boiling and melting points, NMR and IR spectra, etc.) except for their ability to rotate plane-polarized light (optical activity). A racemic mixture contains an equal amount of each enantiomer. The techniques applicable to separate enantiomers in a racemic mixture are well known.⁶³ They include the formation of diastereomeric salts and the use of chiral chromatography. Reactions can also be used (with chiral reagents or chiral catalysts) that are enantioselective.



A large proportion of the drugs on the market today are chiral. A person skilled in organic chemistry in the pharmaceutical sector is well aware that the individual enantiomers in a racemic mixture frequently differ in their biological/therapeutic effects, and that the mixture's pharmacological activity is normally attributable to one of the enantiomers. It is also known⁶⁴ that the inactive enantiomer may show undesired, or even toxic, side effects.⁶⁵

Patent applications often claim an isolated enantiomer and its method of isolation (see Box 4).

Box 4. Examples of patents covering enantiomers

Example 1: R-enantiomers of N-propargyl-aminoindan compounds, their preparation and pharmaceutical compositions containing them

Publication number: US5457133 (A) / Publication date: 10 October 1995.

Abstract: R(+)-N-propargyl-1-aminoindan, its preparation and use and pharmaceutical compositions containing it. The novel compound was found to be useful for the treatment of human patients for Parkinson's disease, memory disorders, dementia of the Alzheimer type (DAT), depression and hyperactive syndrome.

Claims: 1. (+)-N-propargyl-1-aminoindan having the structure: STR2 or a pharmaceutically acceptable acid addition salt thereof.

Example 2: Resolution of ibuprofen

Publication number: EP1083164 (A1) / Publication date: 14 March 2001.

Abstract: (S)-ibuprofen may be separated from a mixture of (S)-ibuprofen and (R)-ibuprofen in high yield and enantiomeric purity in a single resolution step using an N-alkyl-D-glucamine as the resolving agent.

Claims: 18 An (S)-ibuprofen N-alkyl-D-glucamine salt. 19 The salt of claim 18 which is the (S)-ibuprofen N-octyl-D-glucamine salt.

63. See, e.g., Y. Wang and A. Chen, 'Crystallization-Based Separation of Enantiomers', in *Stereoselective Synthesis of Drugs and Natural Products*, John Wiley & Sons, 2013, p. 1–20.

64. See, e.g., Bhupinder Singh Sekhon, 'Enantioseparation of Chiral Drugs – An Overview', *International Journal of PharmTech Research*, Vol.2, No.2, April-June 2010 p.1584-1594.

65. One classic example is thalidomide, synthesized in 1953 by Chemie Grünenthal, a West German company. Thalidomide's 'R' isomer has sedative effects while the 'S' enantiomer is teratogenic. It was found that when only one of the optical isomers is administered, both enantiomers are formed in a roughly equal mix in the blood (see, e.g., www.chm.bris.ac.uk/motm/thalidomide/opticalziso.html). Although withdrawn from the world market when its teratogenic effect was discovered, thalidomide was later reintroduced for use in various dermatologic conditions thought to have an autoimmune or inflammatory basis. See, e.g., Stephanie Tseng, Grace Pak, Kenneth Washenik, Miriam Keltz Pomeranz, and Jerome L Shupack, 'Rediscovering thalidomide: A review of its mechanism of action, side effects, and potential uses', *JAAD*, Vol. 35, Issue 6, p. 969–979.



There are several grounds for questioning the patentability of individual enantiomers when the racemic mixture is already known:

First, an enantiomer is necessarily present in, or inherent to, a racemic mixture. If the molecular structure of the racemic mixture is known, even in a bi-dimensional form, the presence of a chiral carbon necessarily discloses the existence of both enantiomers. The patentability of an isolated enantiomer may be refused on the grounds of the inherency doctrine, as noted above. In fact, the pharmacological/therapeutic effect of a racemic mixture is almost entirely or entirely based on the active enantiomer. Hence, an individual enantiomer lacks novelty.

Second, for a person skilled in pharmaceutical R&D, it is obvious to identify and isolate the therapeutically active enantiomer. The concept of 'obvious to try' is applicable here in assessing inventive step, independent of the availability of prior documents specifically referring to the particular compound.

Third, although the separation of enantiomers in a racemic mixture may be difficult (given that they have the same boiling point, melting point and solubility), overcoming these difficulties is not equivalent to showing inventive activity. The process for isolation of enantiomers may involve, in some circumstances, an inventive step when the claimed method incorporates unexpected or surprising elements. However, difficulty in isolating and purifying an enantiomer is not *per se* an indicator of inventive activity.

Litigation relating to enantiomers illustrates that, if correctly applied, the inventive step standard would disallow the protection of enantiomers. For instance, on 29 September 2009, the Full Court of the Federal Court of Australia found that all of the claims in Sanofi-Aventis' patent number 597784 were invalid for lack of inventive step. This included claims to a single enantiomer, particular clopidogrel salts and a process for preparing the enantiomer.⁶⁶

Recommendations

Isolated enantiomers should not be deemed patentable when the racemic mixture was previously disclosed. Processes for the separation and purification of enantiomers may only be patented if novel and inventive. Any difficulty in developing and applying such processes is not by itself sufficient to prove inventive activity.

5. Salts

Salts are generally sought when the drug is not sufficiently soluble or stable, or when it is difficult to purify, handle or process during manufacturing. Different salts may lead to different solubility, bioavailability and efficacy, and to different organoleptic characteristics or other properties.

The preparation of pharmaceutically suitable salts is a mature technical field. The individual salt-forming acids and bases, their relevant properties and the processes for their preparation are familiar to any person with ordinary training in the formulation of pharmaceuticals.⁶⁷ Regardless of whether salt screening studies follow trial-and-error procedures or other

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66. See www.genericsweb.com/download/DIF%20Clopidogrel.pdf

67. See, e.g., P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), *Pharmaceutical Salts: Properties, Selection, and Use*, 2nd Revised Edition, Wiley-VCH, 2011.



methods (such as high-throughput synthesis),⁶⁸ it would be hard to demonstrate that an inventive activity is involved.

It has been common in the pharmaceutical industry to file patent applications on particular salts as a means of evergreening (see Box 5).⁶⁹ If such patents are granted, generic drugs may be prevented from entering the market. For instance, Dr. Reddy's Laboratories sought marketing approval for amlodipine maleate in the United States. However, the US Court of Appeals for the Federal Circuit concluded⁷⁰ that Pfizer's basic patent for amlodipine was infringed, as it covered salt forms of the drug, including its maleate salt.⁷¹

The choice of a salt for a particular drug is important in obtaining certain desirable characteristics related to stability, bioavailability, manufacturability and route of administration to the patient.⁷² However, the fact that a particular salt has advantages over the free base/acid drug or other salts does not mean that it results from an inventive activity. Thus, while a salt may be novel and industrially applicable, it will very rarely comply with the requirement of inventive step.

Box 5. Examples of patents covering salts

Example 1: Mono- and dipotassium salts of azo compounds

Publication number: US5457133 (A) / Publication date: 10 October 1995.

Abstract: Mono- or dipotassium salts of azo compounds conforming to the formula (I) or one of its tautomeric structures where R and R' are independently OH, NH₂, NH-CN, acylamino or arylamino and R₁ and R₁' are independently -OH or -NH₂, and also their hydrates.

Claims: 1. A monopotassium salt monohydrate of an azo compound conforming to formula (I) or a tautomeric form thereof wherein R and R' are independently OH, NH₂, NH-CN, acylamino, or arylamino, and R₁ and R₁' are independently -OH or -NH₂.

Example 2: Sildenafil n-oxide as prodrug

Publication number: US 2009/0005395 A1 / Publication date: 23 June 2008.

Abstract: Embodiments of the present invention relate to a compound of formula (1A)

Claims: 1. A compound of formula (1A); or a pharmacologically acceptable salt, hydrate or solvate thereof.
2. The compound as claimed in claim 1, wherein the compound is substantially free of a 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl) phenylsulfonyl]-4-methyl-piperazine compound, or a pharmacologically acceptable salt, hydrate or solvate thereof.
3. A medicament comprising a compound of formula (1A) or a pharmacologically acceptable salt, hydrate or solvate thereof.

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68. See, e.g., Arvind K. Bansal, Lokesh Kumar, Aeshna Amin, 'Salt Selection in Drug Development', *Pharmaceutical Technology*, Vol. 3, Issue 32, 2 March 2008, available at <http://www.pharmtech.com/node/230746?rel=canonical>; Harry G. Brittain, 'Developing an Appropriate Salt Form for an Active Pharmaceutical Ingredient', *The Review of American Pharmaceutical Business and Technology*, 1 December 2009, available at www.americanpharmaceuticalreview.com/Featured-Articles/117788-Developing-an-Appropriate-Salt-Form-for-an-Active-Pharmaceutical-Ingredient/
69. Often, generic references to "all pharmaceutically acceptable salts" are included in patent applications claiming other subject matter, such as a new active ingredient, enantiomer, prodrug, etc.
70. *Pfizer Inc. v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.*, United States Court of Appeals, Federal Circuit, 359 F.3d 1361, 27 February 2004. The patent on besylate of amlodipine was later invalidated. See Box 6.
71. The patent claimed certain dihydropyridine compounds and their acid addition salts, including the compound having the common name amlodipine and its salts.
72. See, e.g., Arvind K. Bansal, Lokesh Kumar, Aeshna Amin, 'Salt Selection in Drug Development', *Pharmaceutical Technology*, Vol. 3, Issue 32, March 2, 2008, available at www.pharmtech.com/node/230746?rel=canonical.



Moreover, as noted in the Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*: 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 person skilled in the art. Thus, when the solution is from a limited set of alternatives which is obvious to try, even the demonstration of surprising effects etc. do not provide any answer to the obviousness.⁷³

A salt will not meet the inventive step requirement even when a pharmacologically acceptable anion selected from a list of salt-forming candidates has been seldom used for approved drugs. For instance, if the most commonly used anion is hydrochloride, but besylate is chosen because of advantageous properties, this does not mean that the person skilled in the art would have been unable to carry out experiments and choose a substitute to the known alternative from the prior art.⁷⁴ Thus, a patent on the besylate salt of amlodipine was revoked in Canada and the United States on grounds of lack of inventive step (see Box 6).

Box 6. Revocation of patents on a besylate salt

On 11 July 2009, the Canadian Federal Court invalidated patent number 1,321,393 claiming amlodipine besylate (Pfizer's 'NORVASC'), as being obvious. The patent claimed that the besylate salt showed a "unique combination of good solubility, good stability, non-hygroscopicity and good processability which makes it outstandingly suitable for the preparation of pharmaceutical formulations of amlodipine."

The Court found that salt screening, a "well-known" process, was used to find the patented salt. It noted that "[a]ll of this is routine for a person skilled in the art at the time" and that a skilled person "would be motivated to test sulphonic acid salts in general and would have every reason to test the besylate salt as this had already been shown to offer advantages over other salts in terms of stability."

A patent on the same salt was invalidated in the United States by the US Court of Appeals for the Federal Circuit.⁷⁵ The Court found that "a reasonable fact-finder could only conclude that Apotex has shown by clear and convincing evidence that the skilled artisan would indeed have been so motivated to combine the prior art to produce the besylate salt of amlodipine" and concluded that "[t]he record also satisfies us that . . . a reasonable fact-finder could only conclude that the skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine."

The Court also stated that "the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing," and that Pfizer's experimentation with amlodipine besylate was "not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success." It added that "the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt."

There is abundant case law illustrating courts' analyses of patents covering salts. For instance, on 27 July 2013, India's Intellectual Property Appellate Board revoked patent IN 221171 of 20 June 2008 covering the salt/crystalline form of ditosylate, a cancer drug.⁷⁶ The revocation was based on lack of inventive step (and inconsistency with section 3(d) of the Patent Act). The patent would have expired more than two years after the compound patent in 2022. Another case is presented in Box 7.

73. Para. 8.6.

74. See *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*, 2014, para. 8.1, example 3.

75. *Pfizer, Inc. v. Apotex, Inc.*, 2006-1261, 22 March 2007 (emphasis added).

76. See www.pharmamedtechbi.com/~media/Supporting%20Documents/Pharmasia%20News/2013/August/GSK%20Fresenius%20IPAB%20Order%201%20%20Aug%201%202013.pdf



Box 7. Revocation of tenofovir patent in China⁷⁷

The Patent Review Board of China’s State Intellectual Property Office rejected Gilead Sciences’ claims regarding their Viread patent covering the compounds of the fumarate of Bis (POC) PMPA, which is an active ingredient in treating HIV, AIDS and Hepatitis B, known by the trade name Viread.

The Board declared all claims invalid. Claim 1 was found to lack inventive step over the combined teachings of two prior art documents. Part of claim 1 was directed at the fumarate of Bis (POC) PMPA, which according to the description, has unexpected physical and chemical properties when compared to its free base. Some of the Bis (POC) PMPA properties were disclosed in one piece of prior art. Another disclosed a number of acids, including fumeric acid, for forming salts of a compound similar to the Bis (POC) PMPA. The Board concluded that those skilled in the art would be motivated to improve the stability of the free base by trying different salts based on the common understanding that salts of the free base usually retain their pharmacological activity.

The Board also concluded that experimental data comparing only the chemical stability of citrate and fumerate are not sufficient to show that fumarate is considerably better than all other salts.

Source: Lexology, www.lexology.com/library/detail.aspx?g=8fa9fa74-8bce-4f11-b77a-43a677bf66fb

Recommendations

The preparation of salts, with advantageous properties over the drug in its free base/acid form, is part of the common knowledge of a person skilled in the art. Patent applications on particular salts will normally face an objection of lack of inventive step. Generic references to pharmaceutically acceptable salts in patent applications covering a compound should not be allowed either, as they would fail the sufficiency of disclosure requirement.

6. Ethers and esters

Ethers, such as e-series glycol ethers, and esters⁷⁸ are sometimes used in pharmaceutical products (see Box 8). The use of esters may improve the safety or efficacy of a drug. Esters and ethers are generally more lipid soluble than salts, thereby altering tissue penetrability and sometimes the rate of release, as with steroids. However, they would not generally enhance the therapeutic efficacy of a drug.

Generic formulas for ethers and esters are of the type R1-O-R2 and R1-C-O- R2, respectively, where R1 and R2 are independent alkyl groups.

The preparation of ethers and esters of a compound is part of the common knowledge of a person skilled in pharmaceuticals. It is generally obvious to predict the claimed advantages that an ether or ester will provide compared

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77. Patent applications on tenfovir Disoproxil fumarate were rejected in other countries, such as India and Brazil, where pre-grant oppositions were filed (see, e.g., <http://spicyip.com/2009/09/patent-office-rejected-tenofovir.html>).
78. Ethers are two simple hydrocarbon chains that are separated by an oxygen. Esters are similar except they have a double-bonded oxygen on the carbon adjacent to the oxygen separating the two hydrocarbon groups.
See: www.sussext.k12.de.us/science/Chemical%20Substances/Ethers%20and%20Esters.htm



Box 8. Examples of patents covering ethers and esters

Example 1: Chalcones and esters thereof with antiproliferative activity in uterus, ovary and breast tumors.

Publication number: US5808137 (A) / Publication date: 15 September 1998.

Abstract: The present invention relates to the use of some natural or synthetic chalcones and the esters thereof with straight or branched aliphatic acids, saturated and unsaturated, containing up to 22 carbon atoms in the therapy and prevention of uterus, ovary and breast tumors, as well as the formulations containing them. Chalcones such as isocordoin, cordoin, 2-hydroxyderricin, 2', 4'-dihydroxychalcone, 4, 2', 4'-trihydroxychalcone have a marked affinity to the estrogen receptors of type II and an antiproliferative activity on uterus, ovary and breast tumor cell lines. These molecules proved to be useful both in therapy and in the prevention of such tumors.

Claims:

1. An ester of isocordoin, cordoin, 4-hydroxyderricin, 2-hydroxyderricin, 3-hydroxyderricin, 2', 4'-dihydroxychalcone or 4, 2', 4'-trihydroxychalcone with palmitic or ximeninic acid.
2. The cordoin or isocordoin esters according to claim 1.
3. A complex of one of the esters of claim 1 with a phospholipid.

Example 2: Diphenyl ether compounds useful in therapy.

Publication number: WO0172687 (A1) / Publication date: 4 October 2001.

Abstract: A compound of general formula (I), or pharmaceutically acceptable salts, solvates or polymorphs thereof; wherein R₃ is independently CF₃, OCF₃, C₁-C₄ alkylthio or C₁-C₄ alkoxy; n is 1, 2 or 3; and the other variables are as defined in the claims. These compounds inhibit monoamine re-uptake and in particular exhibit activity as selective serotonin re-uptake inhibitors. They are useful in disorders such as depression, attention deficit hyperactivity disorder, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse disorders and sexual dysfunction, including premature ejaculation.

Claims:

1. A compound of general formula (I), or pharmaceutically acceptable salts, solvates. or polymorphs thereof; EM1143.1 wherein ; R₁ and R', which may be the same or different, are hydrogen, C₁-C₆ alkyl, (CH₂)_m(C₃-C₆ cycloalkyl) wherein m = 0, 1, 2 or 3, or R' and R₂ together with the nitrogen to which they are attached form an azetidine ring ; each R₃ is independently CF₃, OCF₃, (C₁-4 alkylthio or C₁-C₄alkoxy ; n is 1, 2 or 3; and R₄ and R₅, which may be the same or different, are: A-X, wherein A =-CH=CH=- or -(CH₂)_p- where p is 0, 1 or 2; X is hydrogen, F, Cl, Br, I, CNR₆R₇, SO₂NR₆R₇, SO₂NHC(=O)R₆, OH, C₁-4alkoxy, NR₈SO₂R₉, NO₂, NR₆R'', CN, CO₂R', CHO, SR', S (O) R₉ or SO₂R₁₀; R₆, R₇ R₈ and R₁₀ which may be the same or different, are hydrogen or C₁-6alkyl optionally substituted independently by one or more R'₂; R₉ is C₁-6 alkyl optionally substituted independently by one or more R'₂; R'' is hydrogen, Cl. alkyl optionally substituted independently by one or more R, C (O) R, CO₂R₉, C (O) NHR' or SO₂NR₆R₇; R₁₂ is F, OH, CO₂H, C₃-6cycloalkyl, NH₂, CONH₂, C₁-6alkoxy, C₁-6alkoxycarbonyl or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O optionally substituted independently by one or more R'₃ ; or R₆ and together with the nitrogen to which they are attached, form a 4-, 5- or 6-membered heterocyclic ring optionally substituted independently by one or more R'₃; or a 5- or 6-membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, S and O, optionally substituted independently by one or more R'₃ ; wherein R'₃ is hydroxy, C₁-C₄alkoxy, F, C₁-C₆alkyl, haloalkyl, haloalkoxy, -NH₂, -NH (C₁-C₆alkyl) or -N(C₁-C₆alkyl)-₂; wherein when R' and R₂ are methyl, R₄ and R₅ are hydrogen, and n is 1, R₃ is not a-SMe group para to the ether linkage linking rings A and B.

to the free base or free acid compound. A skilled person would be able to anticipate the characteristics that may be achieved and how the compound will perform.

The considerations applicable to salts are generally also applicable to ethers and esters.



Recommendations

The preparation of ethers or esters to achieve advantageous properties over the drug in its free base or acid form is part of the common knowledge of a person skilled in the art. Patent applications on particular ethers and esters will normally lack inventive step. Generic references to ethers or esters in patent applications covering an active ingredient or other subject matter should not be allowed.

7. Compositions

A large number of patent applications claim ‘compositions’ (or ‘formulations’) of known drugs (see Box 9).

The formulation of active ingredients using pharmaceutically acceptable carriers or excipients – such as fillers or diluents, binders, stabilizing agents (such as pH regulators), disintegrants, and lubricants – is a mature technological field and falls within the competence of a person normally skilled in pharmaceutical formulation. The techniques for the preparation of compositions to ensure the delayed (e.g. using one or more enteric coating layers) or rapid release of an active ingredient are also well known. It is obvious for a person working in formulation to seek the most appropriate form for administering a drug. Similarly, the micronization of a drug (for instance, when it is poorly soluble) is a well-known method to improve drug delivery that only entails changes in the physical form.⁷⁹

If granted, patents over formulations may obstruct the functioning of the generic market for the respective active ingredient, even if off-patent, particularly when a given composition is the most suitable for administration of a medicine. The blocking effect of a composition patent was demonstrated by the Canadian Federal Court’s decision in *AstraZeneca Canada Inc. et al. v. Apotex Inc.*, 2015 FC 322, issued on 16 March 2015.⁸⁰ At issue was Canadian patent number 1,292,693, a formulation patent of omeprazole (first patented in 1978)⁸¹ covering “an oral pharmaceutical preparation composition comprising. . .an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of material selected from among tablet excipients and polymeric film forming compounds.” As a result of the Court’s decision, the generic firm Apotex was prevented from commercializing the product.

While a particular composition may have some advantageous effects (e.g. increased bioavailability, more stability during storage, inhibiting gastric acid secretion), this does not mean that its preparation results from an inventive activity. As noted, formulation techniques and the compounds that may be used are part of the common knowledge of a person skilled in the art. While some compositions may meet the novelty requirement, they would normally fail to satisfy the inventive step requirement when what is commonly known to a person trained in pharmaceutical formulation is considered, rather than only documents directly referring to the particular drug.

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79. See, e.g. Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, para. 8.10, example 6.

80. See www.nortonrosefulbright.com/knowledge/publications/127093/pharma-in-brief-federal-court-declares-omeprazole-formulation-patent-valid-and-infringed.

81. See Carlos Correa, Trends in Drug Patenting. Case Studies, Buenos Aires, 2001; available at <http://apps.who.int/medicinedocs/en/d/Js4915e/2.5.html>.



Box 9. Examples of patents on compositions

Example 1: New oral pharmaceutical formulation containing magnesium salt of omeprazole.

Publication number: CA 2193681(A1) / Publication date: 25 January 1996.

Abstract: A new oral pharmaceutical formulation containing a novel physical form of a magnesium salt of omeprazole coated with one or more enteric coating layers, a method for the manufacture of such a formulation, the use of such a formulation in medicine and a blister package containing the new formulation.

Claims: An oral enteric coated formulation containing a core material of an active substance coated with one or more enteric coating layers characterized in that the core material as active substance contains a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 percent as determined by X-ray powder diffraction and on the core material enteric coating layer(s), whereby the thickness of the enteric coating does not essentially influence the release of omeprazole into aqueous solutions at pH values predominantly present in the small intestine.

Example 2: Sustained release pharmaceutical composition comprising venlafaxine.

Publication number: WO2006010605(A2) / Publication date: 2 February 2006.

Abstract: A method for the preparation of a pharmaceutical composition containing venlafaxine or a pharmaceutically acceptable salt thereof comprising the steps of (1) preparing a dispersion of venlafaxine or a venlafaxine salt in a solvent wherein venlafaxine or the venlafaxine salts has a solubility of less than 25 g/l at room temperature; (2) converting the dispersion of step (1) into particulate form; (3) coating the particles obtained in step (2) with a layer of a sustained release polymer, as well as pharmaceutical compositions obtainable by this process.

Claims: 24. A pharmaceutical composition obtainable by the process of any one of claims 1 to 2.

Example 3: Pharmaceutical formulations and methods for modified release of statin drugs.

Publication number: WO2004021972(A2) / Publication date: 18 March 2004.

Abstract: The present invention is directed to compositions and methods of their use in treating, preventing and/or managing one or more cardiovascular diseases using at least one poorly water-soluble statin, such as, for example, simvastatin and/or lovastatin. One method of the invention involves delaying release of the poorly water-soluble statin for a time sufficient to avoid metabolism of the statin at or near the gastrointestinal tract wall by the cytochrome P450 3A metabolic system, and releasing said statin in the ileum, colon or both, with subsequent uptake into the hepatic portal vein and distribution to hepatocytes, wherein HMG-CoA reductase activity may be inhibited with minimal adverse drug interactions.

Claims: 32. Pharmaceutical formulation for oral administration comprising a therapeutically effective amount of at least one poorly water-soluble statin; means for preventing the release of the at least one poorly water-soluble statin in the stomach, duodenum, and jejunum; and means for optimizing the uptake of the at least one poorly water-soluble statin in the ileum, colon or both.

Example 4: Celecoxib compositions.

Publication number: WO0032189 / Publication date: 8 June 2000.

Abstract: Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1,000 mg in intimate mixture with one or more pharmaceutically acceptable excipients. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

Claims: 1. Pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1,000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib characterized by at least one of: (a) a time to reach 100 ng/ml not greater than about 0.5h after administration; (b) a time to reach maximum concentration (Tmax) not greater than about 3h after administration.



Sometimes claims refer to pharmacokinetic parameters (such as Tmax, Cmax, under the plasma drug concentration-time curve- AUC), as shown in Box 9, example 4. This type of claim is objectionable to the extent that it describes the alleged biological effects of the composition in the body; that is, what the claimed invention does and not what it actually is. This type of claim may, in fact, mask a method-of-treatment claim under the appearance of a product claim.

Recommendations

The preparation of pharmaceutical compositions (formulations) requires the use of techniques and compounds commonly known to a person skilled in that field. Patent applications on compositions will normally confront an objection of lack of inventive step. Generic claims over compositions associated with new active ingredients, prodrugs, etc. with unspecified carriers or excipients will also be objectionable.

8. Doses

Some patent applications claim independently, or as part of a broader claim, the dose for administering a particular drug. Patents over doses constitute another form of evergreening, potentially blocking the marketing of generic versions when, for instance, the prescribed dose of a drug is included in the range covered by the patent. Thus, a report by the US Government Accountability Office noted:

The practice commonly known as producing line extensions – deriving new products from existing compounds by making small changes to existing products, such as changing a drug’s dosage. . . According to analysts, these changes are typically made to blockbuster drugs shortly before their patents expire. Some analysts also concluded that this practice redirects resources that otherwise could be applied to developing new and innovative drugs.⁸²

Examples of claims related to doses are presented in Box 10. Often, claims of this type are drafted with the appearance of a claim covering composition. For instance, the patent application presented as example 3 in Box 9 includes the following claim 34:

The formulation according to claim 32, wherein the formulation achieves a therapeutic effect with a daily dose ranging from about 0.1 to about 200 mg of said at least one statin.

Dose-based claims are subject to objections of lack of industrial applicability. While they may be drafted in a manner that suggests a product claim, in reality they cover a *method of medical treatment* that, by definition, produces effects in the body and is deprived of industrial applicability. The examiner is bound to establish the true nature and scope of a claim, independent of how it has been drafted.

In addition to the lack of industrial applicability, in countries where methods of treatment are excluded from patentability, a dose-based claimed would be unacceptable.

In countries where considerations around industrial applicability would not arise, claims relating to doses must be examined under the novelty and inventive step criteria. In Australia, for instance, Astra Zeneca asserted against generic producers patent AU200023051 relating to the use of a ‘low dose’ (doses of 5mg or 10mg) of rosuvastatin

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82. Government Accountability Office, *New Drug Development. Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, Washington D.C., 2006, p. 34.



to treat hypercholesterolemia. The patent was declared invalid on grounds of novelty and inventive step, among other reasons.⁸³

Box 10. Examples of claims relating to doses

Example 1: Combination of atovaquone with proguanil for the treatment of protozoal infections.

Publication number: US6166046 (A) / Publication date: 26 December 2000.

Abstract: The invention relates to combinations of atovaquone and proguanil, their use in the treatment and prophylaxis of parasitic infections such as protozoal parasitic infections, e.g. malaria and toxoplasmosis, and infections caused by *P. carinii* and their use in the manufacture of medicaments for the treatment and/or prophylaxis of such infections. The combinations can conveniently be administered in a single pharmaceutical formulation. Preferably, atovaquone and proguanil are administered in a potentiating ratio so that they act in synergy.

Claims:

- 5. A unit dose formulation comprising 50 mg to 3 mg each of 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone and 1-(4-chlorophenyl)-5-isopropylbiguanide hydrochloride in a ratio in the range of 1:1 to 3:1.
- 6. A unit dose formulation according to claim 5 comprising 500 mg of 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone and 200 mg of 1-(4-chlorophenyl)-5-isopropylbiguanide hydrochloride.

Example 2: Aminopterin dosage forms and methods for inflammatory disorders.

Publication number: US2006205729(A1) / Publication date: 14 September 2006.

Abstract: Embodiments of the present invention provide dosage forms and methods for treating a patient with an inflammatory disorder with a therapeutically effective amount of aminopterin, or a pharmaceutically acceptable salt thereof, that achieve efficacy without concomitant toxicity. Within certain embodiments, the present invention provides a method for treating an inflammatory disorder in a patient with uninterrupted doses of aminopterin.

Claims:

A pharmaceutical composition comprising a therapeutically effective amount of aminopterin, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition contains between about 0.01 and about 0.5 mg aminopterin.

Recommendations

Claims over the dose of a drug fail to comply with the industrial applicability requirement. They should be treated as a method of medical treatment, in spite of their appearance, for instance, as a composition (or combination) claim.

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83. See www.nortonrosefulbright.com/knowledge/publications/76233/federal-court-delivers-significant-judgment-allowing-launch-of-generic-crestor-rosuvastatin.



9. Combinations

Often two (or more) known drugs are combined in a single product, and patent protection over the combination is claimed (see Box 11).

Many patent laws specifically exclude from patentability the juxtaposition or combination of known products, unless a new or synergistic effect may be found, such as when one of the drugs enhances or magnifies the therapeutic effects of the other. A typical example is the combination of certain doses of codeine with acetaminophen or ibuprofen to enhance pain relief. In the absence of such synergistic effects, a patent application on a combination of drugs will be rejected by many patent offices, or a patent will be revoked by courts. For instance, in *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories Ltd.*, the US Court of Appeals confirmed in 2013 a district court decision that held invalid patent number 6,677,358 with regard to a combination of repaglinide with metformin. The District Court had found that:

it was obvious to try combination therapy using metformin and repaglinide to treat Type II diabetes. . . It was apparently well known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy. . . Combination therapy using insulin sensitizers and insulin secretagogues was common at the time, and metformin was the most widely used insulin sensitizer as of the '358 patent's filing date.

Box 11. Examples of claims relating to combination of drugs

Example 1: Pharmaceutical combinations for the treatment of stroke and traumatic brain injury.

Publication number: US2002045656 (A1) / Publication date: 18 April 2002.

Abstract: This invention relates to methods of treating traumatic brain injury or hypoxic or ischemic stroke, comprising administering to a patient in need of such treatment an NR2B subtype selective N-methyl-D-aspartate (NMDA) receptor antagonist in combination with either: (a) a neutrophil inhibitory factor (NIF), (b) a sodium channel antagonist; (c) a nitric oxide synthase (NOS) inhibitor; (d) a glycine site antagonist; (e) a potassium channel opener; (f) an AMPA/ kainate receptor antagonist; (g) a calcium channel antagonist; (h) a GABA-A receptor modulator (e.g. a GABA-A receptor agonist); or (i) an anti-inflammatory agent.

Claims: 2. A pharmaceutical composition for treating traumatic brain injury or hypoxic or ischemic stroke in a mammal, comprising: (a) a neutrophil inhibiting factor (NIF) or a pharmaceutically acceptable salt thereof; (b) an NR2B subtype selective NMDA receptor antagonizing compound or a pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active agents (a) and (b) are present in such composition in amounts that render the combination of the two agents effective in treating such disorder.

Example 2: Combination of atovaquone with proguanil for the treatment of protozoal infections.

Publication number: US6166046 (A) / Publication date: 26 December 2000.

Abstract: The invention relates to combinations of atovaquone and proguanil, their use in the treatment and prophylaxis of parasitic infections such as protozoal parasitic infections, e.g. malaria and toxoplasmosis, and infections caused by *P. carinii* and their use in the manufacture of medicaments for the treatment and/or prophylaxis of such infections. The combinations can conveniently be administered in a single pharmaceutical formulation. Preferably, atovaquone and proguanil are administered in a potentiating ratio so that they act in synergy.

Claims:

1. A combinations of 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone and 1-(4-chlorophenyl)-5-isopropylbiguanide hydrochloride wherein the 2-[4-(4-chlorophenyl) cyclohexyl]-3-hydroxy-1,4-naphthoquinone and the 1-(4-chlorophenyl)-5-isopropylbiguanide hydrochloride are present in a ratio in the range of 1:1 to 3:1.



As noted by the Indian *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*:

Quite often, the claims of combination of pharmaceutical products escape the question of novelty and are dealt [with] under the inventive step. . [but] sometimes it may happen that the combination has already fallen in the public domain and hence, should be dealt [with] under novelty also.⁸⁴

A novelty objection may be articulated, for instance, when the medical profession already used drugs in combination to attain a certain therapeutic result before a patent application was filed. In fact, most claimed combinations have already been tested in medical practice by administering the components independently.⁸⁵

A claim over a combination of drugs may also be disallowed on the grounds that in practical terms, they are equivalent to claims on a medical treatment,⁸⁶ whose patentability is excluded by lack of industrial applicability, or in some cases, by a specific exclusion.

Recommendations

Combinations of known drugs may be considered a method of treatment and hence be deemed non-patentable because they lack industrial applicability or are excluded from protection under national law. In some cases, combination claims do not meet the novelty standard, such as when the combination was previously known and practised by the medical profession. In addition, such a combination will not satisfy the inventive step standard, unless a synergistic effect, justified by appropriate clinical tests, can be demonstrated. However, synergistic effects that may be reasonably expected from the combination of two or more drugs of known therapeutic classes do not meet the inventive step standard.

10. Prodrugs

Many medicines are commercialized as prodrugs. A prodrug is a precursor of a drug, which undergoes a chemical conversion by metabolic processes in the body before becoming therapeutically active. Some prodrugs are activated inside the cells (Type I) while others become active extracellularly (Type II). One example is tenofovir disoproxil fumarate, a prodrug of tenofovir, an antiretroviral of the class known as nucleotide analogue reverse transcriptase inhibitors (nRTIs). Another example is sulfasalazine, a prodrug that is broken down by bacteria into 5-aminosalicylic acid (5ASA) and sulfapyridine to become therapeutically active.

Prodrugs are often claimed independently from the active drug (see Box 12) when a patent on the active drug has expired or is about to. In some cases, patent applications contain generic references to 'all prodrugs' of a given compound. The active moiety of the drug and prodrug is the same, hence the latter will generally lack inventive step. A prodrug may be regarded as the original drug 'in disguise' as noted by a British court in the case of hetacillin, an acetone adduct of ampicillin that is immediately hydrolyzed in the body to ampicillin.⁸⁷

84. Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals, para. 7.7.

85. See, e.g., Joint Resolution 118/2012, 546/2012 and 107/2012 (Ministry of Industry, Ministry of Health and National Industrial Property Institute), Adoption of Guidelines for the Examination of Patent Applications of Chemical and Pharmaceutical Inventions, 2012, para. (4)(x) (unofficial translation).

86. Ibid.

87. See Carlos Correa, Guidelines for the examination of pharmaceutical patents: developing a public health perspective, Working Paper, WHO, ICTSD and UNCTAD, Geneva, 2006, available at: <http://www.ictsd.org/themes/innovation-and-ip/research/guidelines-for-the-examination-of-pharmaceutical-patents>.



In examining patent claims relating to prodrugs, consideration should be given to the extent to which the prodrug is inactive (or much less active than the corresponding original active drug) and, once metabolized, provides the required level of the active drug. A prodrug may have advantages compared to the basic drug (e.g. better stability and bioavailability, fewer side effects, better pharmacokinetic profile, increased concentration of the drug at the site of action, and longer duration of action).⁸⁸ However, a prodrug may also present disadvantages, such as poor aqueous stability and incomplete or slow *in vivo* conversion. A key consideration under patent law is whether the development of a new prodrug is the outcome of an inventive activity or of routine research and experimentation.

Box 12. Examples of claims over prodrugs

Example 1: Benzimidazolidinone derivatives as muscarinic agents.

Publication number: US 2008/0070948 A1 / Publication date: 27 November 2007.

Abstract: Benzimidazolidinone derivative compounds, which increase acetylcholine signalling, or effect in the brain, and highly selective muscarinic agonists, particularly for the M₁ and/or M₄ receptor subtypes, pharmaceutical compositions comprising the same, as well as methods of treating psychosis using these compounds are disclosed.

Claims: 1. A compound of Formula I or a pharmaceutically acceptable salt or prodrug thereof, wherein X is selected from the group consisting of CH, O, N and S Z is selected from the group consisting of CH and NY is selected from the group consisting of =O, =NH and =S or tautomers thereof.

Example 2: Transdermally deliverable opioid prodrugs, abuse-resistant compositions and method of using opioid prodrugs.

Publication number: US 2008/0076789 A1 / Publication date: 24 September 2007.

Abstract: Described herein are opioid prodrugs, methods of making opioid prodrugs, formulations comprising opioid prodrugs, and methods of using opioid prodrugs. One embodiment described herein relates to the transdermal administration of a buprenorphine prodrug in an abuse-resistant formulation for treating and preventing diseases and/or disorders.

Claims: 1. A compound having the formula I: wherein R₁ is selected from the group consisting of oxygenated alkyl carbonate, alkyl carbonate and oxygenated ester.

Example 3: Polysacchocride prodrug of 5-fluorouracil (5-FU) with enhanced target specificity for galectin-3 expressing cancers.

Publication number: US 2008/0004237 A1 / Publication date: 17 September 2007.

Abstract: This application discloses embodiments of a novel prodrug and its method of synthesis. The prodrug comprises a galactose-containing polysaccharide covalently linked to 5-fluorouracil (5-FU). The galactose residues that are part of the backbone of the galactose-containing polysaccharide mediate the binding between the prodrug and the lectin galectin-3, which is expressed in various cancers. The galactose-containing polysaccharide is isolated from various plant material and covalently bonded to 5-FU. Various formulations (parenteral or other local or systemic forms) can be used to administer this 5-FU-releasing prodrug to target galectin-3 expressing cancers.

Claims: 1. A prodrug suitable for targeted delivery of a therapeutic compound to a tumor expressing galectin-3, comprising, a) a polysaccharide bound by galectin-3; b) a parent therapeutic compound, and c) a covalent bond connecting a) to b).

Recommendations

Examiners should, as the first step in examining claims over prodrugs, determine whether the patent on the basic drug covers the prodrug. If this is the case, the new application will not be admissible. A claim on a prodrug will generally fail to meet the inventive step standard unless evidence is provided that it overcomes pharmaceutical or pharmacokinetically based problems of the parent drug in a non-evident manner. Generic claims over specified prodrugs should not be allowed.

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88. A typical example is enalapril, an ethyl ester prodrug of enalaprilat, which greatly enhances the absorption in the gastrointestinal tract of the active ingredient.



11. Metabolites

An active metabolite is the compound that remains after a drug is metabolized by the body. Enzymes in the liver are responsible for chemically changing drug components into metabolites, which contain the same functional group as its parent drug. An active metabolite retains most, if not all, of the properties of its parent drug, until its carbon structure blends into larger structures or is reduced to smaller structures.⁸⁹

Active metabolites may be identified, synthesized and commercialized as a product different from the parent drug. Often, patent applications on specific active metabolites are filed (see Box 13). In some cases, however, generic references to ‘all metabolites’ are included in patents claiming an active ingredient.

Box 13. Example of claim over active metabolites

Example: Stable and active metabolites of 1,25-dihydroxy-16-ene-cholecalciferol.

Publication number: US 5,401,733 / Publication date: 28 March 1995.

Abstract: The invention relates to the compounds 1, 25-dihydroxy-16-ene-24-oxo-cholecalciferol and 1,24,25-trihydroxy-16-ene-cholecalciferol which stimulate differentiation of HL-60 cells, rendering them useful as an agent for the treatment of neoplastic diseases such as leukemia, and also decrease proliferation of human keratinocytes, rendering them useful as agents for the treatment of hyperproliferative disorders of the skin, such as psoriasis.

Claims: 1. 1,25-dihydroxy-16-ene-24-oxo-cholecalciferol.

Active metabolites cannot be deemed an invention because they are naturally produced through the metabolism. Although there may be advantages in administering an active metabolite compared to the parent drug, any advantages do not stem from an inventive activity. Isolating and characterizing a metabolite can be done using knowledge common to a person skilled in the pharmaceutical field. Moreover, an active metabolite may be deemed deprived of novelty, based on the concept of inherency.

For instance, in *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373 (Fed. Cir. 2003), the US Court of Appeals for the Federal Circuit examined the validity of a patent over descarboethoxyloratadine (DCL), the active metabolite of loratadine, a compound used to suppress allergic reactions. The Court found the patent invalid because the alleged invention was anticipated by the patent on loratadine, meaning its novelty was lost. The Court stated that when a feature is inherently implied in the piece of prior art, the claimed invention is anticipated. In the United Kingdom, claims on metabolites may also face objections of lack of novelty even if a prior patent does not disclose how to manufacture the pure metabolite. In *Merrell Dow Pharmaceuticals Inc. v. HN Norton & Co. Ltd* [1996] R.P.C. 76 (HL), the House of Lords found that to the extent that the prior patent described that administering terfenadine will produce chemical reactions in the patient’s body and that antihistamine effects will be achieved, this was sufficient to allow any person to produce the claimed compound through metabolism.

Recommendations

Claims on metabolites are not admissible. They can be rejected on the grounds of absence of an invention or lack of novelty/inventive step.

89. See, e.g., Edward D. Harris, Biochemical Facts behind the Definition and Properties of Metabolites, available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3942b1_08_Harris%20Paper.pdf



12. New medical use

Claims over a new medical use of a known medicine (often called 'second use claims') account for a good part of the proliferation of pharmaceutical patents (see Box 14). When a patent is about to expire or has expired, pharmaceutical companies may attempt to extend their monopoly by applying for patents for one or more new therapeutic uses of an active ingredient. If granted, such patents may be used to prevent generic competition and to justify high prices for drugs that are actually off-patent. For instance, AZT (Zidovudine), a drug effective in both the treatment of AIDS and the reduction of mother-to-child transmission, was first developed as a cancer treatment in 1964 in the United States, by the National Cancer Institute in Detroit. Eleven years later, its antiretroviral activity was recognized in studies also conducted at the National Cancer Institute. Burroughs Wellcome laboratories carried out subsequent clinical trials and first patented the antiretroviral use of AZT in 1985, which became the first breakthrough in AIDS therapy. Prices for AZT were significantly higher in countries where patent protection was obtained than in those where generic competition was possible.⁹⁰

Box 14. New medical uses

Example 1: Use of cimetidine for the control of retrovirus infections.

Publication number: US5541212 (A) / Publication date: 30 July 1996.

Abstract: The invention relates to histamine H₂-receptor antagonists such as cimetidine and related compounds such as ranitidine and famotidine that can be used for controlling human immunodeficiency virus (HIV) infection. The preferred agent is cimetidine. The invention comprises a method in vitro as well as in vivo for controlling, i.e., prevention and/or treatment of HIV infection, associated with the development of acquired immune deficiency syndrome (AIDS), at pharmacological doses of these drugs commonly used for the treatment of gastrointestinal ulcers. The method is based on inhibiting HIV in vitro or on the administration to a host that has been exposed to HIV prior to diagnosis or has been diagnosed as having an HIV infection, of an amount of a H₂ antagonist that is sufficient to exert an anti-HIV effect for a sufficient period of time.

Claims:

1. A method for the suppression of the in vivo replication of HIV that comprises administering to a patient infected with HIV who has not exhibited clinical symptoms of an HIV infection an amount of cimetidine sufficient to exert an anti-HIV effect for a sufficient period of time to prevent the emergence of clinical symptoms of HIV infection.
2. A method as defined in claim 1 wherein said method comprises administering 200 mg/day to 2,000 mg/day of cimetidine.
3. A method for the suppression of the in vivo replication of HIV that comprises administering to a host that is infected with HIV but is asymptomatic, an effective amount of cimetidine in combination with an anti-viral treatment for a sufficient period of time to suppress the in vivo replication of HIV.
4. A method for the suppression of the in vivo replication of HIV as defined in claim 3 which comprises administering to a host that is infected with HIV but is asymptomatic, an effective amount of an H₂ antagonist in combination with an anti-viral drug selected from the group consisting of 3'-azidothymidine, 2', 3'-dideoxyinosine and 2', 3'-dideoxycytidine.

Example 2: Thiazolidine derivatives for the treatment of hypertension.

Publication number: US6110951 (A) / Publication date: 24 September 2007.

Abstract: This invention relates to a second medical use of thiazolidine compounds having anti-diabetic properties. These compounds are also of use for the control of essential hypertension.

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90. See, e.g., Dipika Jain and Rachel Stephens, *The Struggle for Access to Treatment for HIV/AIDS in India*, Human Rights Law Network, 2008, p.18.



/ box 14 continued

Claims:

1. A method for controlling essential hypertension and its related cardiovascular syndrome in a mammalian host in need thereof by administration of an effective amount of a 5-aryl substituted thiazolidine derivative of formula I STR47 where: R1 is an aromatic carbocyclic or an aromatic heterocyclic; X is a lower alkylene or a bond, or --HC.dbd.CH--, Y is oxo or imino; Z is oxo or imino; or pharmaceutically acceptable salts thereof with the proviso that R1 is not of the formula. STR48 where n is 1-4, and where R31 is a hydrogen or a lower alkyl of 1-4 carbons and the cyclohexane ring may be optionally substituted at any available methylene with a single oxo or hydroxy; and, when Z and Y are both oxo, R1 cannot be an oxyalkylamine substituted phenyl wherein the amine is a secondary or tertiary amine.
2. A method of claim 1 wherein the thiazolidine derivative is a thiazolidine-dione having both Y and Z are oxo.
3. A method of claim 1 wherein the thiazolidine derivative is further selected from compounds where R1 is a substituted benzyl and X is a lower alkylene radical.

Example 3: New medical use of the meldonium.

Publication number: WO2006022536 (A1) / 2 March 2006.

Abstract: Second medical use of Meldonium is disclosed for treating of skin and subcutaneous tissue lesions and treatment of skin irritation as well as topical compositions containing Meldonium. Topical pharmaceutical compositions of Meldonium were shown to substantially improve the healing of wounds, prevent skin irritation of allergic and other origin. Thus said compositions are useful for treating and prevention of skin and subcutaneous tissue lesions and skin irritation of various origins.

Claims:

1. Use the Meldonium for manufacture of topical acting medicaments for treating and/or preventing tissue lesions of skin and subcutaneous tissue.
2. Use the Meldonium for manufacture of topical acting medicaments for treating and/or preventing topical skin irritation.

‘Second use’ claims have been accepted in some jurisdictions. In Europe, for instance, on the basis of a fiction of novelty and industrial applicability, they were allowed if drafted as “use of a substance or composition X for the manufacture of a medicament for therapeutic application Z.” This so-called Swiss-type claim gives the appearance of a claim to an invention with a technical character, which is actually absent ⁹¹ (see example 3 in Box 14).

While some countries followed the EPO approach, others explicitly exclude the patentability of new uses of known medicines.⁹² In India, for instance, the Intellectual Property Appellate Board rejected an application that claimed the use of known fumaric acid derivatives for a second medical indication. The examiner stated that the claims were not allowable under section 2(1)(j) of the Indian Patent Act in that they related neither to product nor process, and the compounds of the invention were admittedly known. To overcome the objections, the claims were amended to product claims, but the issue of lack of novelty remained. The Controller refused the application on the grounds of lack of novelty, a decision later upheld by the Intellectual Property Appellate Board.⁹³

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91. The Swiss claim format became unnecessary after an amendment to the European Patent Convention entered into force in 2007. The EPO held that “[W]here the subject matter of a claim is rendered novel only by a new therapeutic use of a medicament, such claim may no longer have the format of a so-called Swiss-type claim as instituted by decision G 5/83.” Decision G 0002/08 (Dosage regime/Abbott Respiratory) of 19 February 2010, available at <https://www.epo.org/law-practice/case-law-appeals/recent/go80002ex1.html>

92. See, e.g., article 21 of Decision 486, Common Regime on Industrial Property, Andean Community of Nations; section 3(d) of the Indian Patent Act (as amended in 2005).

93. *Revised Draft Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals*, para. 6.2.



Knowing that an existing compound can also be used to treat other diseases or symptoms is not an invention, as the pharmacological effect is intrinsic to the compound. The new use is simply discovered through clinical trials or observation during the marketing period. Patentability of a use claim can be denied based on the grounds that it is a discovery rather than an invention.

A claim on the new use of a medicine is equivalent to a claim on a method of medical treatment. The only contribution made in such a claim is information for the physician about the way to use a drug to achieve a new therapeutic effect. The effects take place in the body. There is no technical effect, since the claim does not cover the product and process of manufacture, but merely a given form of use. It does not matter how a claim relating to a new use of a drug is drafted;⁹⁴ it does not change its essence as a claim on method of treatment.

The denial of patentability of new use claims is fully compatible with the TRIPS Agreement, which only requires the grant of patents with regard to products and processes, and does not define 'invention'. Furthermore, the TRIPS Agreement specifically allows WTO members to exclude from patentability, *inter alia*, methods of medical treatment (article 27.3(a)).

In some cases, the potential new medical uses of a known drug are claimed in patent applications but not sufficiently supported by medical evidence. For instance, the Canadian Federal Court revoked a patent in which Eli Lilly claimed that it had discovered that olanzapine had a "marked superiority in the treatment of schizophrenia"⁹⁵ compared with other compounds of the larger group it had previously patented. The Court found that Eli Lilly had claimed the second monopoly on the basis of studies that failed to establish any particular treatment advantage of olanzapine over the already-patented class to which it belonged.⁹⁶ Moreover, it was found that Eli Lilly had filed

at least 29 other Canadian patent applications relating to olanzapine, purporting to have invented at least 16 distinct new and surprising uses for the compound, ranging from sexual dysfunction to autism. The majority of these other patent applications contained no reference to actual research conducted, or contained an ambiguous reference to clinical studies that may or may not have been conducted before the filing of the corresponding patent applications.⁹⁷

Recommendations

Claims relating to the new use of a known drug can be rejected on various grounds:

- (a) it is the discovery of a property.
- (b) there is no invention, given the absence of a technical character.
- (c) there is no novelty, as the compound and its process of manufacture are known.
- (d) absence of industrial applicability, since the effects take place in the body.
- (e) exclusion of methods of medical treatment, when such exclusion is provided for in a national patent law.

.....

94. As noted above, in some cases claims on new use have the appearance of a composition or combination claim.

95. See Government of Canada, Statement of Defence, In the Matter of an Arbitration Under Chapter Eleven of the North American Free Trade Agreement and The UNCITRAL Arbitration Rules (1976) Between: Eli Lilly and Company and the Government of Canada. 30 June 2014, para. 3.

96. *Ibid.*

97. *Ibid.*, para. 67.



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