



Guidelines for the examination of pharmaceutical patents:

Developing a public health perspective.

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A Working Paper

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About this working paper

This study is made available as a working paper in order to facilitate broader understanding, consultation and inputs. It is intended to be a contribution towards the improvement of transparency and efficiency of patentability examination for pharmaceutical inventions, particularly in developing countries. It proposes a set of general guidelines for the assessment of some of the common modalities of pharmaceutical patent claims, and suggests elements for the development of public health-sensitive guidelines for the evaluation and review of pharmaceutical patents at the national level. It examines the practices of some patent offices and suggests some mechanisms that may be adopted to incorporate public health perspectives in procedures for the granting of pharmaceutical patents.

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Note: This study is currently under a review process. If you would like to provide comments or inputs to this working paper, please send them to dvivas@ictsd.ch.

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FOREWORD

With the creation of the World Trade Organization (WTO) in 1994, the most comprehensive treaty on intellectual property rights to date was established: the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). This Agreement links intellectual property and trade issues for the first time and provides a multilateral mechanism for settling disputes between states. The TRIPS Agreement requires all WTO Members to adopt in their laws minimum universal standards for almost all rights in this field, such as copyrights, patents, and trade marks¹. The Agreement has also substantially limited the freedom that countries enjoyed to design and implement their own intellectual property systems. Under the Agreement all WTO Members are now bound to grant patent protection for at least 20 years to any invention of a pharmaceutical product or process which fulfils the criteria of novelty, inventiveness and usefulness. This obligation did not exist under previous international conventions, as none of these specified minimum standards for intellectual property rights. Prior to the negotiation of the TRIPS Agreement, more than 50 countries did not provide patent protection for pharmaceuticals, many provided only process, and not product, patents and the duration was much less than 20 years in many countries.²

It is now generally acknowledged that the current regime of patent protection, as “globalized” by the TRIPS Agreement, has a significant impact on the pharmaceutical sector. It has also been observed that the standards specified in the TRIPS Agreement are not necessarily appropriate for countries struggling to meet health and development needs. Accordingly, the UK Commission on Intellectual Property Rights (CIPR) in its 2002 report cautioned countries “to ensure that their intellectual property protection regimes do not run counter to their public health policies and that they are consistent with and supportive of such policies”³.

A patent is a title granted by the public authorities conferring a temporary monopoly for the exploitation of an invention upon the person who reveals it, furnishes a sufficiently clear and full description, and claims this monopoly. The criteria for patentability require that a product or manufacturing process fulfils the conditions of novelty, inventiveness and industrial applicability (or utility).

The world has never had at its disposal such a massive treatment arsenal to combat the ailments that afflict humanity. At the same time, many people die because they lack certain drugs and/or vaccines. This is true in the case of emerging diseases, but also of the serious threat posed by the growing resistance to medicines used against deadly common diseases such as AIDS, malaria, tuberculosis, bacterial meningitis and pneumonia.

In order to develop new drugs, mechanisms will have to be put in place that foster innovation and the development of new products, while at the same time ensuring that patients have rapid access to the fruits of such research.

Growing concerns over the way international trade agreements and, particularly, the WTO TRIPS Agreement, can restrict access to medicines led to the adoption of the Doha Ministerial Declaration on the TRIPS Agreement and Public Health. The Declaration marked an important milestone in the debate on intellectual property rights and access to medicines, in affirming that the TRIPS Agreement should be interpreted and implemented in a manner supportive of countries’ right to take measures to protect public health and promote access to medicines. In this regard, the Declaration enshrines the principles that agencies such as WHO have publicly advocated and advanced, namely, the re-affirmation of the right of WTO Members to make full use of the flexibilities of the TRIPS Agreement in order to protect public health and promote access to medicines. An important flexibility in this respect is the right of WTO Members to define the patentability criteria as referred to under the

TRIPS Agreement in accordance with their particular national priorities. This may be an important tool for the promotion of genuinely new and inventive pharmaceutical products.

A common belief is that patents are normally granted to protect new medicines, but while the number of patents annually obtained to protect genuinely new pharmaceutical products is small and declining, thousands of patents are granted for pharmaceuticals. A large number of patents cover minor modifications of older existing drugs.⁴ According to a report of the National Institute for Health Care Management in the United States, in the 12-years period 1989-2000, just 153 (15%) of all new drug approvals were medicines providing a significant clinical improvement⁵.

The cumulative nature of innovations due to low standards of patentability and weaknesses in patent procedures has important repercussions on the patent system, limiting the diffusion of innovations it is intended to promote and reducing access to vital medicines. "Patents on broad scientific principles are generally bad, because in the words of the United States Supreme Court, they may confer power to block off whole areas of scientific development, without compensating benefit to the public⁶."

The guidelines contained in this document are intended to be a contribution to the improvement of transparency and efficiency of the patent system for pharmaceuticals, particularly in developing countries. These countries should pay more attention to the way in which patents are examined and granted to avoid the negative effects resulting from the granting of patents on developments lacking inventiveness.

This working document should be understood in the context of two major issues:

1. The accessibility of medicines to the world's population as a key element of public health policy; and
2. Innovation as an essential prerequisite for the existence of medicines.

In relation to these two issues we should see how to manage the patent system for pharmaceuticals, and more specifically the "strengthened patent system" emerging from the TRIPS and current bilateral trade agreements. Patents are a social contract between the patent owner and the society; this is why it is necessary to explore, identify and implement mechanisms to improve the functioning and transparency of the patent system in the interest of public health.

In order to develop a legal and normative framework for patent protection for pharmaceuticals that ensures a balance between the interests of the patent holders and the users of technology (as required by Articles 7 and 8 of the TRIPS Agreement) several issues should be carefully examined and considered at the national level. These Guidelines are a contribution to this important task.

INTRODUCTION

The pharmaceutical sector is a major user of the patent system. While only a small - and declining - number of new chemical entities are approved annually, thousands of patents are applied for to protect variants of existing products, processes of manufacture or, where admitted, second indications of known pharmaceutical products.

Since patents confer exclusive rights regarding the production, sale and use of the patented subject matter, they can be used to restrain competition and set prices higher than those that would have existed if competitive products were available. This is the very purpose of the patent system, which is generally justified as necessary to encourage investments to develop new products and processes.⁷

Given the substantial effects that patents can have on competition and, hence, prices of medicines, the criteria that are applied to examine and grant pharmaceutical patents are extremely relevant for public health policies, and not only a matter of concern for patent and industrial policy. Policy makers in the health area, as well as patent examiners, should be aware that decisions relating to the grant of a patent (which is generally presumed valid until proven to the contrary) can directly affect the health and lives of the people of the country where the patent is granted and enforced.

The purpose of this document is to provide a set of general guidelines for the assessment of some of the common types of pharmaceutical patent claims. It responds to growing concerns in different circles⁸ about the proliferation of patents that protect minor, and in some cases obvious, variants of existing drugs or processes (such as changes in the drug formulation, salts, esters, ethers, isomers, polymorphs of known molecules, combinations of a known drug with other known drugs) while the number of new chemical entities of pharmaceutical use is small and declining⁹. Although such patents may be weak or, if subject to strict scrutiny, invalid, they can be effectively used in many cases to

prevent generic competition thereby reducing access to medicines.

While recognizing the importance that pharmaceutical follow-on innovation may have in certain cases¹⁰, the present guidelines aim to increase the capacity of patent offices, public health and drug regulatory authorities, as well as of civil society, to evaluate and take the necessary actions, as appropriate under national laws, to protect public health in cases where patent applications or grants cover subject matter that does not deserve the reward of a patent monopoly. This document is ultimately intended to provide support to national patent offices by highlighting the areas in which poor decisions have often been made, including in economically important countries. The complexity and cost of overturning bad decisions generally pose insurmountable barriers to those who are affected. These guidelines aim, hence, at contributing to a sound analysis of pharmaceutical patents based on a rational application of the patentability standards.

First, the document briefly discusses the scope allowed to WTO Member countries by the TRIPS Agreement to determine the standards under which the novelty and inventive step of claimed inventions are assessed. Second, it provides examples of different categories of patent claims for pharmaceutical products¹¹, indicates the practice of some patent offices, and includes recommendations for each category of claims. The proposed recommendations suggest elements for the development of public health-sensitive guidelines for the evaluation and review of pharmaceuticals patents at the national level. Analysis of particular cases and possible exceptions to the general recommendations made herein, should be further undertaken and elaborated in the light of the national applicable law, particularly as regards the concept of 'invention' and patentability criteria. Finally, the document addresses some of the mechanisms that may be adopted to incorporate public health

perspectives into procedures for the granting and review of pharmaceutical patents.

It is acknowledged that the issues dealt with are complex and that any one of them would require a more detailed elaboration, as done in some of the bibliography mentioned in the text. It is outside the remit of this document to undertake such detailed elaboration, since its purpose is only to provide an overview of

problematic areas of patentability and possible ways of generally addressing them¹².

The guidelines, as proposed in this document, do not suggest the application of a new requirement of patentability, but rather to take into account, in applying the ordinary requirements of novelty, inventive step and industrial applicability (or utility), specific considerations relating to innovation in pharmaceuticals.

1 DEFINING PATENTABILITY AND DISCLOSURE STANDARDS

The ordinary meaning of ‘invention’ relates to the output of an intellectual activity in the form of new knowledge of a technical nature. To invent is ‘to create by thought, originate (new method, instrument, etc.)’¹³. It also suggests a distinction between creations and mere discoveries and, more generally, between inventions and other subject matter that is not the outcome of an inventive process¹⁴.

Most patent laws in the world do not define what an invention is. Rather than a gap this has often been regarded as essential to allow a progressive adaptation of patent law to the advancement of science and technology¹⁵. Exceptionally, some patent laws include a definition of ‘invention’. For instance, the Mexican patent law considers as an invention all human creation that permits the transformation of matter or energy that exists in nature, for the benefit of man and to satisfy his concrete needs (Article 15)¹⁶. The law in Chinese Taipei refers to ‘a high-level creation of technical concept(s) by which natural rules are utilized’ (Article 19). These definitions seem to suggest that an invention supposes creating rather than discovering something that was previously undisclosed. In other jurisdictions, however, discoveries that are useful to solve a problem are patentable¹⁷.

In fact, the concept of invention as applied in various countries significantly differs. The TRIPS Agreement, however, does not seem to interfere with such diversity. The wording of Article 27.1 indicates that Members have been left room to interpret in good faith the concept of ‘invention’ within their legal systems¹⁸, subject only to the application of the rules for interpretation set out by the Vienna Convention on the Law of the Treaties¹⁹. Members may require the existence of an invention as a *precondition* for patentability²⁰.

Whatever the definition of invention, the crucial issue is that a patent must contain a non-obvious technical contribution to the state of the art, whereby a technical problem is solved by technical means.

Subject to the same aforementioned interpretation rules, the TRIPS Agreement also allows WTO Member countries to adopt their own definitions of the patentability standards. Article 27.1 prescribes, in effect, that patents “shall be available for any inventions ... provided that they are new, involve an inventive step and are capable of industrial application”, but does not contain any specification about the precise way in which these criteria are to be applied.

The general terms used in Article 27.1 have permitted Member countries to keep different criteria to assess patentability. The definition of such criteria constitutes a key aspect of patent policy, with implications in other areas, such as industrial and public health policies. Obviously, the narrower the novelty standard, the lower the bar to assess inventive step, and the broader the concept of industrial applicability or utility, the greater the number of applications that may be granted in a particular country. A greater number of grants made on the basis of low standards of patentability may lead to unnecessary limitations on competition without any significant trade-off in terms of more innovation to address society’s needs.

Although most countries in the world apply an absolute novelty requirement (that is, disclosure in any form anywhere in the world before the filing date will prevent the granting of a patent) some countries maintain a double standard of novelty depending on whether the disclosure of the invention has taken place within or outside their territory²¹.

In practice, the concept of novelty is narrowly construed by some patent offices, requiring an almost ‘photographic’ disclosure of the invention in a single prior document in order to consider that novelty does not exist. For experienced patent applicants, overcoming novelty barriers may be just a matter of clever design of patent applications.

WTO Members, however, are not constrained to apply a particular concept of novelty, and can adopt a notion that objectively reflects whether

the claimed invention is genuinely new or not. For instance, they may consider non-novel an invention that is not described *expressis verbis* in a document but which may be derived thereof, as well as inventions just selected from a family of already disclosed products (the so called 'selection inventions')²². In addition, novelty may not be normally claimed if a feature was present in a known substance and was inherent thereto, even though that feature was not mentioned in the prior art²³.

Defining 'non-obviousness/inventive step' is one of the most critical aspects of a patent regime, as it determines the level of technical contribution required to obtain a patent and the corresponding limitation on competition. Patent examiners need to consider not only what is disclosed in the prior art but also what a person skilled in the art (such as a person trained and experienced in pharmaceutical formulation) could consider obvious in the light of such prior art. As the TRIPS Agreement does not define this concept either, Member countries are free to determine whether they want a system under which a myriad of incremental innovations²⁴ are patentable²⁵, or one aimed at rewarding more substantive departures from the prior art²⁶. Patent offices and courts can apply more or less lax or stringent criteria to determine non-obviousness/inventive step.

The best policy from the perspective of public health would seem to be the application of a strict standard of inventiveness²⁷ so as to promote genuine innovations and prevent unwarranted limitations to competition and access to existing drugs. This implies that the 'person skilled in the art' should be deemed to have some specialized knowledge and not simply somebody with very general or ordinary knowledge in the relevant technical field²⁸. A person skilled in the art is not just an expert in his technical field but a person who should have some degree of imagination and intuition. He should not only rely on the documents found in the novelty search, but apply his experience and his knowledge. Such an examiner should be particularly strict when examining the inventive step.

Finally, inventions must be susceptible of industrial applicability, since the aim of patent law is to protect technical solutions to a given problem, not abstract knowledge. In some countries, such as the United States, it is sufficient to show that the invention has utility, which obviously allows for a broader scope of patentability than the narrower concept of 'industrial applicability'. Like in the case of novelty and inventive step, the TRIPS Agreement does not define what criteria should be applied to determine industrial applicability or utility. The application of these requirements is problematic in chemistry and biosciences in the absence of concrete experimentation, since these are empirical sciences with low predictive capacity about the specific properties of obtainable substances. Patent claims should contain, as a minimum, a technically viable solution and not merely an unresolved problem or a speculative or intended result.

Another important element in the assessment of patent applications or grants is the disclosure of the invention. In accordance with Article 29.1 of the TRIPS Agreement,

Members shall require that an applicant for a patent shall disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art and may require the applicant to indicate the best mode for carrying out the invention known to the inventor at the filing date or, where priority is claimed, at the priority date of the application.

Lack of sufficient disclosure may be a reason for refusal of an application or invalidation of a patent. This requirement has particular importance in the chemical and pharmaceutical fields to enable the reproduction of the invention during the patent term (for instance, in the case of a compulsory license) or after patent's expiry. A special consideration should be given to cases in which a large number (sometimes millions) of compounds belonging to a group characterized by common elements is claimed²⁹.

Finally, a general rule in patent law is that the patent must cover a single inventive concept, that is, there must be 'unity of invention'. This means that the claimed subject matter should share the same technical features understood as the contributions that each of the claimed inventions, considered as a whole, makes over the prior art³⁰.

In sum, the ways in which national laws conceptualize what an invention is, and how the patentability standards and the requirements regarding disclosure and unity of invention are applied, will certainly be key to determine whether different types of claims relating to pharmaceutical inventions are admissible or not.

2 TYPICAL CLAIMS RELATING TO PHARMACEUTICAL INVENTIONS

A patent claim relating to a pharmaceutical product may relate to an active ingredient as such independently of or jointly with formulations, salts, prodrugs, isomers, etc., or cover any of these subject matters separately. It may also solely cover a manufacturing process or include both a process and a product. In some countries, as noted below, use-related claims are admissible. The following sections include some considerations for the evaluation of different types of claims that are typical in this area.

2.1 Formulations and compositions³¹

The same active ingredient may be presented in different dosage forms, for instance, as tablets, capsules, ointment or aqueous solutions for parenteral administration, which in turn can be formulated using different pharmaceutically acceptable excipients.

A large number of patents claim formulations of new or existing drugs, often including specifications of dose or concentration, either as the principal claim or in subordination to claims over the active ingredients or their uses. 'Composition claims' cover active ingredients and pharmaceutically acceptable carriers or excipients, such as fillers, binders, disintegrants and lubricants.

Patents granted solely on the basis of formulation or composition claims do not protect the active ingredients as such, and different formulations

In undertaking such evaluation it will be important to bear in mind that while the development of new molecules of pharmaceutical use may encompass various levels of inventive steps, pharmaceutical techniques for the preparation of medicines in different forms and dosages are generally well known and part of the pool of knowledge in possession of a 'person skilled in the art'. Hence, there is a narrow range of developments that could be considered genuinely inventive in this field in view of the state of the art.

or compositions comprising the same ingredients may - if they are in the public domain - be commercialized by competing companies. However, such patents may be used to discourage competition through 'strategic' litigation, that is, by alleging infringement and requesting provisional injunctions that block commercialization until a final decision is made.

Formulation or composition claims are deemed acceptable by some patent offices, under certain conditions. This is, for instance, the case of the United Kingdom (see Box 1).

In some cases, a particular claimed formulation is associated with certain effects, such as controlled release in blood of a drug³³. Achieving such effects is generally part of the ordinary skill of a person knowledgeable in the formulation of pharmaceuticals, unless there are exceptional

Box 1: Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office (March 2004), Claims to pharmaceutical compositions, Compositions adapted to a particular use, Paragraph 11431

Known substances may be protected by per se product claims to pharmaceutical compositions containing them, if the composition is in a form which is novel and inventive over any known products. In particular, a claim may be made to a medicament having a form of administration which is novel and distinct from the previous use. For example, an anti-eczema ointment containing X would be regarded as clearly distinct from a tablet containing X for controlling blood pressure³². The ointment is new because X has never been formulated in this form before, and it would be inventive if the previous use of X would not suggest its use in topical form.

circumstances, such as the use in a product of a new excipient that produces a truly unexpected or surprising effect, for instance, a noticeable reduction in side effects or an extraordinary improvement in drug release³⁴, such as a subdermal device that will release insulin for a long period.

In India, the patent office has considered that the Patent Act denies claims to compositions obtained by mere admixture resulting in the aggregation of the properties of the components therefrom. Thus, a novel pharmaceutical composition with a single active ingredient (known or novel) with an inert carrier is not patentable in India as there is no synergy between the components viz. the active compound and the inert carrier (see Box 2). The existence of synergy, however, should not be considered *per se* as demonstrating inventive step, if the composition is obvious to a person skilled in the art.

As a general rule, formulation techniques and the range of compounds that may be used for developing pharmaceutically viable products in different forms are well known to a person skilled in the art. For instance, it is not inventive to use particular stabilizing agents (such as pH regulators) or some compounds to improve bio-availability, as these are well known. In some cases, certain salts are preferred for the preparation of particular formulations, such as tablets, while other salts may be preferred for the formulation of liquid pharmaceutical preparations. In most cases, it is likely that the claimed inventions in this field lack inventive step.

Similarly, claims relating to pharmacokinetic parameters, micronisation of a known product or particles distribution within a given diameter or weight should not generally be deemed admissible. As mentioned above, the existence or not of inventive step is not to be determined exclusively on the basis of documentation in the prior art, but taking into account the average knowledge of a person trained and experienced in pharmaceutical formulation.

Finally, it should be noted that processes to prepare formulations or compositions are generally well known and routinely applied. Hence, claims over such processes would rarely be inventive. Likewise, simple experiments/trials are not sufficient to support patentability.

Recommendation: New formulations and compositions, as well as processes for their preparation, should generally be deemed obvious in the light of the prior art, particularly when a single active ingredient is claimed in association with known or unspecified carriers or excipients. Exceptionally, claims of this type could be patentable if a truly unexpected or surprising effect is obtained, for instance, when a really difficult problem or a long standing need, such as a noticeable reduction in side effects, is solved in a non-obvious way, or when the solution found leads to a tremendous advantage compared to the state of the art.

Box 2: Draft Manual of Patent Practice and Procedure. Patent Office, India - 2005. Annexure - 1. 6.0 Pharmaceutical Compositions

- 6.1 The pharmaceutical compositions other than mere admixtures resulting in the aggregation of properties of the ingredients, but having synergistic effect may normally be patentable.
- 6.2 The known pharmaceutical compositions in different new dosages and different form such as capsules, tablets, syrups, suspensions etc, are not patentable under sections 2(1)(j) , 3(d) and 3(e) of the Act
- 6.3 New use of known substance or its new use in a pharmaceutical composition is not normally patentable.
- 6.4 Any method of using pharmaceutical composition is not patentable.

2.2 Combinations³⁵

Claims are sometimes directed to combinations of previously known active ingredients³⁶. In some cases, the specific covered compounds and quantities are indicated³⁷, while in others they generally refer to a category of therapeutic compounds, such as antacids. If claims on combinations are accepted subsequent to a patent on the relevant active ingredient/s, the patent owner may be able to indirectly extend the term of protection granted under the basic patent.

In some countries, combinations claims are rejected unless the combination generates a new and non-obvious synergy or distinct effect. If a synergistic effect is to be relied on to allow patentability, it must be possessed by everything covered by the claims³⁸, appropriately described and proven in the patent specification (for instance, on the basis of biological tests) and be the manifestation of an inventive step. A new synergy need not be considered, as such, as inventive, since it may be obvious for a person skilled in the art. Moreover, the synergy

between two or more drugs may be deemed a 'discovery' rather than an 'invention', since the synergy takes place in the body and is found through clinical trials.

It is also to be noted that, in some cases, combination claims may in practical terms be equivalent to claims over medical treatments (the patentability of which is excluded in most countries), to the extent that they only provide a method of administering a combination of existing drugs. Also, combining drugs to avoid resistance is normal practice in pharmaceutical development and should generally be seen as evident to a person with average skills in the field.

Recommendation: Combinations of known active ingredients should be deemed non-inventive. If, however, a new and non-obvious synergistic effect is considered a basis for patentability, it should be properly demonstrated by biological tests and appropriately disclosed in the patent specifications.

2.3 Dosage/dose³⁹

Some patent applications claim inventions consisting of the dosage for administration to patients of an existing product, including pediatric dosages. Although drafted as product claims, these claims have the same effect as claims over methods for medical treatment⁴⁰, as the subject matter is not a product or process but the way in which a product is therapeutically used.

Some countries admit patents on dosages under certain circumstances. For instance, the UK Guidelines allows for the patenting of a dosage where there is a *new* medical indication and the dosage is substantially different from that for the known use (see Box 3). The UK approach is only valid, however, where second indication patents are permitted⁴¹. When the only

contribution made by the applicant is a new dosage for the same use of a drug, the subject matter would not be patentable. The same would apply if the dosage refers to a new use⁴², to the extent that a new use is not patentable.

Moreover, changes in dosages would rarely be of an inventive nature and may be considered as not meeting the industrial applicability standard, since the invention would only have effects on the body and not technical effects.

Recommendation: New doses of known products for the same or a different indication do not constitute inventions, particularly (but not only) in countries where methods of medical treatment are not patentable as such.

Box 3: Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office (March 2004), Claims to pharmaceutical compositions, Claims to unit dosage forms, Paragraph 120

It may be possible in cases where the required dosage for a new medical use is **markedly** different from that for the known use, to allow a claim to a unit dosage form containing the known active ingredient in such an amount that the unit dosage form is novel and not obvious to have been made up in that amount for the prior art use. Thus if the new medical use requires a dose of, for example, ten times (or one tenth) that for the prior art use, then a claim to a unit dosage form might be judged to be novel and inventive and allowable. In assessing the inventiveness of such claims it should be remembered that dosages required are usually related to body weight so that children's doses are smaller than those for adults.

2.4 Salts, ethers and esters⁴³

Frequently, pharmaceutical patents protect new salts of known active ingredients. Salts are normally formed to increase stability or solubility of the drug. It is common knowledge in the pharmaceutical field that salts result in different solubility and, therefore, in different bioavailability. If an active ingredient is an acid or base, then any chemistry student knows how to make a salt, and can make predictions about its likely physicochemical properties. Patents on salts are one of the main avenues for the 'evergreening'⁴⁴ of pharmaceutical patents.

There may be exceptional cases in which new salts present unexpected advantages in properties as compared to what is in the prior art. Such advantages should be supported by information about the results of appropriate tests incorporated into the patent specifications.

The processes for forming salts are also normally obvious to a person trained in the field. There

may be very exceptional cases where forming a salt (for instance, with optimal crystalline characteristics) of complex molecules require special skills and may be eventually patentable as a process. However, the complexity of a process does not provide sufficient ground for claiming inventive step.

Similarly, ethers⁴⁵ as well as esters of known alcohols, although fundamentally different to salts⁴⁶, are generally subject to the same objection of obviousness⁴⁷.

The Indian patent office has issued draft guidelines specifically providing criteria for the examination of applications relating to hydrates, salts and other derivatives (see Box 4). The amendment introduced to the Indian Patent Act in 2005, moreover, incorporated a specific provision with regard to claims regarding salts, esters and other 'forms' of existing products

Box 4: Draft Manual of Patent Practice and Procedure. Patent Office, India - 2005. Annexure - 1.

5.6. HYDRATES AND OTHER SUBSTANCES ETC:

Hydrates, acid addition salts and other derivatives, which are routinely prepared *prima facie*, lack inventive step. However where there is a problem, like stability, absorption etc., and there is a long standing problem in preparing the derivatives, patentability of such process may be considered.

The clear objective of the amendment to the Indian Patent Act is to limit the proliferation of patents around existing pharmaceutical products. It provides in section 3(d) that the following shall not be treated as an invention within the meaning of the Act:

the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation.—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy⁴⁸.

2.5 Polymorphs⁴⁹

Some therapeutically active ingredients present polymorphic forms, that is, they may exist in different physical forms (as amorphous solid and/or in different crystalline forms), which may have different properties more or less pharmaceutically significant (such as solubility and therefore bioavailability). Polymorphism is a natural property: polymorphs are not 'created' or 'invented'; they are discovered normally as part of routine experimentation related to drug formulation. They result from the conditions under which a compound is obtained⁵⁰. Any compound that presents polymorphism will naturally tend to its more stable form⁵¹, even without any human intervention.

The significance of different polymorphs is almost entirely in their relative rate of dissolution (in theory the extent of dissolution can be affected too but this is rarely of practical significance). Occasionally there is an effect on long-term stability if the most stable polymorph

Any special claims made by an applicant regarding, for instance, a faster therapeutic response of a new salt, should be supported by clinical data that demonstrate this effect. The more special claims that are made, the more data should be required to examine the viability of the application. It is critical that the new data be properly assessed. Health regulatory authorities have the appropriate expertise in these matters; hence, an articulated cooperation with patent offices in examining these applications might, as discussed below, facilitate the task of the patent offices and improve the quality of their decisions.

Recommendation: New salts, ethers, esters and other forms of existing pharmaceutical products can generally be obtained with ordinary skills and are not inventive. This may not apply, exceptionally, when tests, appropriately conducted and described in the specifications, demonstrate unexpected advantages in properties as compared to what was in the prior art.

had not been selected for development in the first place. The practical effect of changing the polymorph is, consequently, on the dissolution rate of the finished product and, potentially, an effect on bioavailability, or a change in the long term stability profile. There could also be in some cases manufacturing advantages in choosing a particular polymorph. However, there is no question of an effect on safety or efficacy, since the active ingredient is the same.

Independent patent applications on polymorphs have become increasingly frequent and controversial, as patents thereon can be used to obstruct or delay the entry of generic competition. Polymorphs can be deemed within the prior art - and therefore non-patentable - if they are inevitably obtainable following the process of the basic patent on the active ingredient. Moreover, the possibility of discovering different crystals is obvious when polymorphism is found.

A well-known example of a dispute on a polymorph patent related to cimetidine. The patent holder applied for a patent on a polymorph of cimetidine approximately five years after the patent on the active ingredient was granted. That polymorph patent, however, was cancelled in the UK and other countries on the grounds that the polymorph was inevitably obtained by applying the process already claimed in the original patent⁵². Another example is the case of ranitidine (see example 22 in the annex). The patentee obtained in the United States a patent for a polymorph expiring in 2002 as opposed to 1995 for the main patent⁵³.

Polymorph claims are accepted in many countries. For instance, the EPO regularly grants patents on newly identified polymorphic forms, in line with the practice of the German Patent Office and the Federal Patent Court. According to the “Kristallformen” case, products of the same chemical formula are not identical if they differ in some reliable parameter⁵⁴. Patents over polymorphs have been rejected, however, in other jurisdictions⁵⁵. The Indian draft guidelines for patent examination, for instance, provide specific criteria for assessing claims of such forms (see Box 5).

Solvates, including hydrates, were originally considered as “pseudo-polymorphs”⁵⁶. Neverthe-

less, according to the International Conference of Harmonization (ICH) of 1999, they are to be deemed ‘polymorphs’⁵⁷. Hydrates/solvates will rarely be inventive, as they are obvious to produce in most situations. Hence, claims relating to changes in the content of water in known molecules (deriving in mono-hydrates, bi-hydrates, etc.) should generally be considered non-inventive and not patentable.

It should also be noted that for most solvates and polymorphs, like for new salt forms, only data on quality and, where required, bioequivalence are needed, that is, no more data than for the approval of a generic product. This is the reason why in many jurisdictions these variants of a substance are deemed to be the ‘same’ substance for health regulatory purposes⁵⁸.

Recommendation: Polymorphism is an intrinsic property of matter in its solid state. Polymorphs are not created, but found. Patent offices should be aware of the possible unjustified extension of the term of protection arising from the successive patenting of the active ingredient and its polymorphs, including hydrates/solvates. Processes to obtain polymorphs may be patentable in some cases if they are novel and meet the inventive step standard.

Box 5: Draft Manual of Patent Practice and Procedure. Patent Office, India - 2005. Annexure - 1.

5.3 POLYMORPHS

5.3.1 Some compounds present in polymorphic forms, i.e., they crystallize in diverse forms. Such forms can be deemed within the prior art and therefore not patentable. However, process patent may be allowed for the new polymorph, if the polymorph is prepared by a novel process involving inventive step.

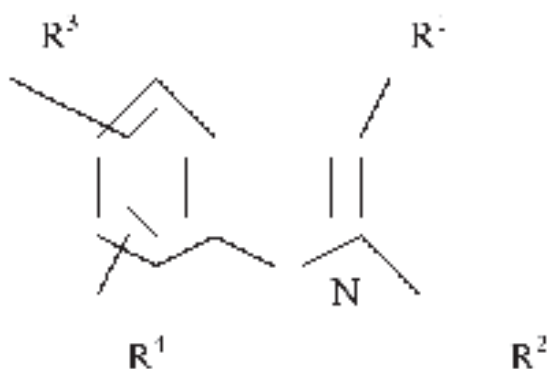
5.3.2. Some therapeutically active ingredients present polymorphic forms, that is, they may crystallize in diverse forms, which may have different properties that are more or less significant in terms of their therapeutic use. Such forms can be deemed within the prior art - **and therefore nonpatentable**- if they were inevitably obtained following the process of the basic patent on the active ingredient or were covered by a previous product patent.

2.6 Markush claims

Often broad (“generic”) patent claims are drafted covering a family of a large number (sometimes thousands or millions) of possible compounds. The so-called ‘Markush claims’ refer to a chemical structure with multiple functionally equivalent chemical entities allowed in one or more parts of the compound. Markush claims may include a vast number (sometimes millions) of possible compounds. They may be used to obtain a wide patent coverage including a large number of compounds whose properties have not been tested, but only theoretically inferred from the equivalence with other compounds within the claim. Hence, the acceptance of Markush claims generate rights over an extremely broad set of compounds without prior testing or experimentation.

An example of a Markush claim is the following:

Claim 1: The compounds of the general formula:



Wherein, R¹ is selected from phenyl, pyridyl, thiazolyl, thioalkyl, alkoxy and methyl; R²-R⁴ are methyl, tolyl or phenyl... the compounds are used as a pharmaceutical for increasing the oxygen-intaking capability of blood.

Explanation: In the general formula, indolyl is the main structure unit common to all the Markush compounds, and all the compounds have the same use. Therefore, this Markush claim possesses unity of invention⁵⁹.

Patent examination guidelines of several countries include detailed instructions to deal with this type of claims (see Boxes 6 and 7).

In addition to the ordinary issues relating to the patentability requirements, the consideration of Markush claims raises issues of disclosure and enablement, since the patent applicant has effectively obtained only a few of the possible elements of the group. Given that a search of prior art for millions of compounds is virtually impossible, the search of the patent office and the corresponding patent grant should be limited to what has been actually assessed and supported by the examples provided in the specification.

Recommendation: Claims covering a large range of compounds should not be allowed. Patent offices should require patent applicants to provide sufficient information, such as fusion point, Infrared Absorption Spectrum (IR) or Nuclear Magnetic Resonance (NMR), obtained through true testing and experimentation to enable the reproduction by the disclosed method of each embodiment of the invention for which protection is sought. Claims of limited scope could be granted if evidence is provided at least that, with the substitution of any member within the same family class, the same disclosed result would be obtained. The coverage of the patent should be limited to what is actually enabled by the disclosure in the specification.

Box 6: Manual of Patent Examining Procedure (MPEP), Eighth Edition, August 2001 - Latest Revision October 2005 - 800 Restriction in Applications Filed Under 35 U.S.C. 111; Double Patenting, 803.02 Markush Claims [R-3]⁶⁰

If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction.

Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

This subsection deals with Markush-type generic claims which include a plurality of alternatively usable substances or members. In most cases, a recitation by enumeration is used because there is no appropriate or true generic language. A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s). In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.

As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

*Box 7: Guidelines for examination in the European Patent Office,***Part C, Chapter III (Claims), (7) Unity of invention, (7.4a) Markush grouping⁶¹**

Where a single claim defines (chemical or non-chemical) alternatives, i.e. a so-called "Markush grouping", unity of invention should be considered to be present if the alternatives are of a similar nature (see III, 3.7).

When the Markush grouping is for alternatives of chemical compounds, they should be regarded as being of a similar nature where:

- (i) all alternatives have a common property or activity, and
- (ii) a common structure is present, i.e. a significant structural element is shared by all of the alternatives, or all alternatives belong to a recognised class of chemical compounds in the art to which the invention pertains.

A "significant structural element is shared by all of the alternatives" where the compounds share a common chemical structure which occupies a large portion of their structures, or, in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together. The alternatives belong to a "recognised class of chemical compounds" if there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention, i.e. that each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

2.7 Selection patents⁶²

A "selection patent" is a patent under which a single element or a small segment within a large known group is "selected" and independently claimed based on a particular feature not mentioned in the large group. A "selection invention" may be applied for, for instance, when a range of products characterized as having *n*-carbon atoms has been patented, and later on a patent on a specific range (e.g. C₁-C₄) is claimed.

If a large group of elements is patented, the patent owner may use the selection patent to extend the term of protection for the selected subset beyond the expiration of the original patent⁶³. While accepted in some jurisdictions when the selected elements possess a surprising advantage, selection patents have been denied when the supposed advantage is a property shared by all or nearly all the large group.

Although differences exist in the treatment of these claims by patent offices, including between

the EPO and some national patent offices in Europe, the admission of selection patents is subject to limitations in most jurisdictions (see the EPO and UK Guidelines in Boxes 8, 9, and 10).

In Germany, the Bundesgerichtshof has held that even in a relatively large generic group of compounds, disclosure of the group is, to the skilled chemist, fully equivalent to a disclosure of each compound within the group⁶⁶. Selection inventions in the normal sense of the word may, hence, be regarded as unpatentable in Germany.

If a previous patent contains, for instance, a Markush-type claim with a large number of possible compounds without a detailed disclosure, and the compounds claimed in a subsequent patent are not found by simple experiments and show an unexpected advantage, far enough away from the completely disclosed compounds in the previous patent, an issue of inventive step will

essentially arise in considering the patentability of the selection.

Recommendation: As a general rule, selection patents should not be granted if the selected components have already

been disclosed or claimed and, hence, lack novelty⁶⁷. If unexpected advantages of existing products were deemed patentable under the applicable law, the patentability of a selection could be considered when an inventive step is present⁶⁸.

Box 8: Guidelines for examination in the European Patent Office, Part C, Chapter IV - Annex (Examples relating to the requirement of inventive step indicators), (3.1) Obvious and consequently non-inventive selection among a number of known possibilities.

3.1 Obvious and consequently non-inventive selection among a number of known possibilities:

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

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

(a) are not described as having, nor shown to possess, any advantageous properties not possessed by the prior art examples; or

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

Box 9: Examination Guidelines for Patent Applications relating to Biotechnological Inventions in the UK Patent Office (May 2005), Inventive step - Paragraphs 24⁶⁴, Section 3 of the Manual of Patent Practice, paragraph 3.27⁶⁵

A "selection" invention should meet the criteria laid down in I G Farbenindustrie AG's Patent, 47 RPC 289 at pages 322-3, namely,

- (1) the selection must be based on some substantial advantage gained or some substantial disadvantage avoided,
- (2) substantially all the selected members must possess the advantage in question, and
- (3) the selection must be in respect of a quality of special character which can fairly be said to be peculiar to the selected group; this is not necessarily nullified if it transpires that some other members of the class from which the selection is made have this quality, but the claim may be invalid if it is found that the quality is common to many other members in addition to those selected.

Box 10: Guidelines for examination in the European Patent Office, Part C, Chapter IV, (9.) Inventive step, (9.12) Dependent claims; claims in different categories

...[I]f a claim to a product is new and non-obvious there is no need to investigate the novelty and non-obviousness of any claims for a process which inevitably results in the manufacture of that product or of any claims for a use of that product. In particular, analogy processes, i.e. processes which themselves would otherwise not involve an inventive step, are nevertheless patentable insofar as they provide a novel and inventive product (see T 119/82, OJ 5/1984, 217). It should, however, be noted that in cases where the product, process and use claims have different effective dates, a separate examination as to novelty and inventive step may still be necessary in view of intermediate documents.

2.8 Analogy processes

Products and processes are two distinct categories of eligible subject matter for the purposes of patent protection. The patentability of each of them must be evaluated according to their own properties and characteristics. However, manufacturing processes (often called 'analogy processes') that are not by themselves novel or inventive but which are used for the preparation of new or inventive but unpatented compounds are deemed patentable in some jurisdictions under a legal fiction (see box on EPO guidelines). The doctrine of analogy processes expands the possibility of appropriation of knowledge in the public domain⁶⁹.

In the United States, the patent office has held "analogy process" claims to be unpatentable unless they were inventive in themselves⁷⁰, but legislation carved out an exception for biotechnology. A statutory amendment to the U.S. law in 1993 determined that a biotechnological process claim would be non-obvious if it involved new and non-obvious starting materials or produced a new and non-obvious result⁷¹. While this solution was only targeted to biotechnology, it has been extended

2.9 Enantiomers⁷⁵

Enantiomers (or optical isomers⁷⁶) behave in relation to one another as an image does to its mirror image. In organic chemistry, enantiomers spontaneously occur, for example, in compounds that comprise a carbon atom with four different substituents⁷⁷. This property has been exploited in the patent field by often claiming, first,

by case law to other fields of technology⁷².

An example of a patent probably granted on the basis of an implicit application of the concept of analogy process is patent AR 242.562 on the process for obtaining amlodipine besylate. The claimed and described process is a simple chemical reaction: the production of a salt from an acid with a base. This reaction is described by the simple formula: acid + base = salt + water, which can be found in elementary chemistry textbooks⁷³.

The application of the doctrine of analogy processes may lead to the protection of non-patentable pharmaceuticals⁷⁴, as the TRIPS Agreement (Article 28.1(b)) requires the extension of patent protection to the products directly obtained with a patented process.

Recommendation: Non-novel or obvious pharmaceutical processes, regardless of whether the starting materials, intermediaries or the end product are novel or inventive, should be considered not patentable as such.

the "racemic" mixture of both enantiomers, and later claiming rights over the most active enantiomer⁷⁸, thus evergreening the originally obtained protection⁷⁹.

It is routine to test whether one or the other enantiomer in isolation is more active than the

racemic mixture of both, as it is expected that one optical isomer will typically have much higher activity than the other, so that superior activity for at least one of the isomers as compared to the racemate is to be expected⁸⁰. When the chemical formula of a compound with enantiomers is disclosed, the novelty of the latter is also lost as the formula necessarily reveals the existence of the enantiomers⁸¹.

Some patent offices, such as EPO, have considered that enantiomers of known racemates may be deemed novel, but that its patentability is a matter of inventive step. A single enantiomer (of an active ingredient that was previously registered with the health authority as a racemate) may be registered in

its own right if it is of adequate quality, safety and efficacy⁸². But this does not equate to a patentable invention, since the enantiomers were present in the racemate⁸³ and the latter's pharmacological/therapeutic activity was based almost entirely (if not entirely) on the active enantiomer. The draft guidelines for patent examination of India provide some criteria for the evaluation of claims of this kind (see Box 11).

Recommendation: Single enantiomers should generally not be deemed patentable when the racemic mixture was known. However, processes for the obtention of enantiomers, if novel and inventive, may be patentable.

Box 11: Draft Manual of Patent Practice and Procedure. Patent Office, India - 2005. Annexure - 1.

5.0 Patentability of various forms of chemical substances:

5.1 Isomers

5.1.1. Isomers are different compounds that have the same molecular formula which may be broadly divided into two kinds namely structural isomers or positional isomers and stereo isomers.

5.1.2. Structural Isomers or positional isomers may be structurally similar or dissimilar compounds. The simplest examples are butane and isobutane and ethanol and dimethyl ether. In the former case the compounds are having structural and functional similarity. In the second set of compounds, although they have the same molecular formula but are structurally and functionally different. Such isomers even having close structural similarity may be considered to be novel over the prior art. But when such chemical compounds have close structural similarity, similar functional similarities and if it is found that the enabling methods are available, a case of obviousness may be made.

5.1.3. Isomers having the same empirical formula but having structural differences may be considered novel and may not normally offend "obviousness" as they are structurally different.

An example is that cyclohexylstyrene is not considered prima facie obvious over prior art isohexyl styrene.

5.1.4. Stereo Isomers are prima facie obvious. Once a racemic compound is known, its enantiomers are obvious because a person skilled in the art knows that a compound having a chiral center exists in two optically active forms. Hence product patent may not be granted for the enantiomers. When a new compound is claimed for the first time in its optically active pure form, product patent may be granted. In a case (S)-enantiomer of a compound, capable of producing antidiabetic effects was claimed. The cited prior art disclosed the racemate of the same compound which was claimed for the same purpose and was not allowed.

2.10 Active metabolites and prodrugs⁸⁴

In some cases, pharmaceutical compounds generate an active metabolite, which is the product of the compound's metabolism in the body⁸⁵. Metabolites are derivatives from the active ingredients that are produced in the body, and cannot be deemed as 'created' or 'invented'. However, active metabolites can have different safety and efficacy profiles to those of the parent molecule⁸⁶.

On the other hand, when metabolized in the body, inactive compounds (called "prodrugs") can produce a therapeutically active ingredient⁸⁷. In some cases, patent claims cover a drug and its prodrug/s⁸⁸. In situations where the active ingredient is not patented, a patent over a prodrug as such may extend control by

the patentee over the market of the active ingredient that is metabolized. A prodrug may be regarded as the original drug 'in disguise'⁸⁹.

In the case of terfenadine, which had been sold for many years in the United Kingdom as an antihistamine drug, the patent holder obtained a further patent on the active metabolite fexofenadine and attempted to block competition in the market of terfenadine, after the patent for the latter had expired. This was deemed to be an unacceptable attempt to extend patent protection⁹⁰.

Specific guidelines to deal with metabolites and prodrugs have been developed by some patent offices (see Box 12).

Box 12: Draft Manual of Patent Practice and Procedure. Patent Office, India - 2005. Annexure - 1.

5.4 METABOLITES: Metabolites are the compounds that are formed inside a living body during metabolic reaction. The types of metabolites are-

- (i) Active metabolites formed from inactive precursors (e.g Dopa & Cyclophosphamide)
- (ii) Active metabolites formed from precursors that show mechanism of action that is different from that of parent compound (e.g Buspirone & 1-pyrimidyl piperzine Fenflouromine & norfenfleuromine)
- (iii) Active metabolites which contribute to the duration of action of the parent compound (e.g. Hexamethylmelamine & Clobazam)
- (iv) Active metabolites that show antagonistic effect on the activity of the parent compound (e.g Trezodone & m-chlorophenyl pierzine, Aspirin & salicylate)

5.4.1 A metabolite is **unpatentable** since giving the drug to a patient naturally and inevitably results in formation of that metabolite.

5.5 PRODRUGS :

5.5.1 Prodrugs are inactive compounds that can produce an active ingredient when metabolized in the body. Hence prodrugs and metabolites are interlinked. When metabolized in the body, inactive compounds(pro-drug) can produce a therapeutically active ingredient,. It must be determined whether the patent on the compound covers the prodrug and the extent to which claims relating to certain compounds should also be allowed to include their prodrugs. The inventive aspects of prodrug may be decided based on the merits of the case.

5.5.2 However, if there is a marked improvement over the primary drug, prodrugs may be patentable.

One possible way of dealing with patents over prodrugs - which may be novel and inventive in some cases - is to allow them when the patentability standards are met, provided that the active ingredient is properly disclaimed (that is, excluded from the patent claims).

Recommendation:

- a) Active metabolites of drugs should generally not be deemed patentable separately from the active ingredient from which they are derived.
- b) Patents over prodrugs, if granted,

should disclaim the active ingredient as such, if previously disclosed or otherwise non-patentable. Like other subject matter claimed in a patent, a prodrug should be sufficiently supported by the information provided in the specifications. In addition, evidence may be required that the prodrug is inactive or less active than the compound to be released, that the generation of the active compound ensures an effective level of the drug and that it minimizes the direct metabolism of the prodrug as well as the gradual inactivity of the drug.

2.11 Method of treatment⁹¹

Some patents claim methods of treatment, including prophylaxis, cure, relief of pain, diagnosis or surgical methods. These claims do not cover a product per se, but the way in which it is used in order to obtain certain effects. National patent policies considerably differ on this subject and, in some cases, adopt a very expansive approach (see Japan Guidelines below in Box 13).

In many cases, a method of treatment claim is not apparent at first sight since reference may be made, for instance, to compositions which are not characterized by their chemical structure or intrinsic characteristics but by their dosage or form of administration. It is important, hence, to carefully examine the claims in order to identify and appropriately deal with cases in which under the appearance

of product claims it is a method of treatment that is actually disclosed.

The TRIPS Agreement (Article 27.2) explicitly allows Members to exclude therapeutic, diagnostic and surgical methods from patent protection, and many countries do follow this approach. If such exclusion has been provided for, claims describing such methods or claims that are equivalent thereto should be refused.

Even in the absence of a specific exclusion from patentability, such methods should be deemed not patentable in countries where the standard of industrial applicability applies, since they only produce effects on the body and have no industrial application⁹². The same would apply to the case of cosmetic methods.

Box 13: Examination Guidelines for Patent and Utility Model in Japan. Part VII: Examination guidelines for inventions in specific fields, Chapter 3 Medicinal Inventions, (2.1) Industrial Applicability⁹⁴

As a medicinal invention means "an invention of a product.", it does not come under the category of "methods for treatment of the human body by surgery or therapy and Diagnostic methods practiced on the human body" despite the fact that the application possibly involves the administration of a dosage to a human body or the spreading on the human body, and it is considered to be an "industrially applicable invention." It should be noted that a medicinal invention defined by combination of two or more medicines, or defined by a mode of medical treatment such as a dosing interval, a given dose, or the like is handled in the same way because it is also "an invention of a product" (Refer to the Examination Guidelines Part II, Chapter 1, 2.1 "Industrial Applicability")

Box 14: Guidelines for examination in the European Patent Office, Part C, Chapter IV (Patentability). (4.) Industrial application, (4.2) Surgery, therapy and diagnostic methods⁹⁵

"Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods." Hence, patents may be obtained for surgical, therapeutic or diagnostic instruments or apparatuses for use in such methods. The manufacture of prostheses or artificial limbs could be patentable. For instance, a method of manufacturing insoles in order to correct the posture or a method of manufacturing an artificial limb should be patentable. In both cases, taking the imprint of the footplate or a moulding of the stump on which an artificial limb is fitted is clearly not of a surgical nature and does not require the presence of a medically qualified person. Furthermore, the insoles as well as the artificial limb are manufactured outside the body. However, a method of manufacturing an endoprosthesis outside the body, but requiring a surgical step to be carried out for taking measurements, would be excluded from patentability under Art. 52(4) EPC (see T 1005/98, not published in OJ).

Art. 52(4)

Patents may also be obtained for new products for use in these methods of treatment or diagnosis, particularly substances or compositions. However, in the case of a known substance or composition, this may only be patented for use in these methods if the known substance or composition was not previously disclosed for use in surgery, therapy or diagnostic methods practised on the human or animal body ("first medical use"). The same substance or composition cannot subsequently be patented for any other use of that kind. A claim to a known substance or composition for the first use in surgical, therapeutic and/or diagnostic methods should be in a form such as: "Substance or composition X" followed by the indication of the use, for instance "... for use as a medicament", "... as an antibacterial agent " or "... for curing disease Y". In contrast to what is stated in general in III, 4.8, these types of claims will be regarded as restricted to the substance or composition when presented or packaged for the use. Art. 54(5) thus provides for an exception from the general principle that product claims can only be obtained for (absolutely) novel products. However, this does not mean that product claims for the first medical use need not fulfil all other requirements of patentability, especially that of inventive step (see T 128/82, OJ 4/1984, 164).

In cases where aspects of a therapeutic method are undistinguishable from a non-therapeutic method (for instance a method for cleaning teeth), the EPO jurisprudence has tended to consider it of therapeutic and, hence, non-patentable nature⁹³.

Recommendation: Methods of treatment, including for prevention, diagnosis or prophylaxis should be deemed non-patentable where industrial applicability is required as a condition for patentability (including in cases where the patentability of such methods is not expressly excluded).

2.12 Use claims, including second indications

Patenting of the medical use of a product, including first and second indications⁹⁶ of a known medicinal product has become common practice in the pharmaceutical field. According to a literal interpretation of the TRIPS Agreement⁹⁷, which only obliges to grant patents over products and processes, Members should be under no obligation to grant use claims, including second indications.

The European Patent Office (EPO) jurisprudence has distinguished between a claim to a composition *adapted* for a given use, as opposed to one *suitable* for such a use (see the following Box 15).

The EPO Guidelines also refer to the case of "pack" or "kit of parts" claims, which are usually used where the invention comprises the administration of two or more different drug compositions at particular time intervals, or merely simultaneously or sequentially. A claim of this form was considered by the EPO Board of Appeal in T 09/81[56]. It was held in this case that the combination was novel and inventive, but needed to be "purpose limited" - i.e. in the first medical use format - to distinguish it from a medical kit, collection or package containing the two agents together for their known independent uses.

As illustrated in the boxes below, the European Patent Convention and the law of some

countries allow for the patenting of the first pharmaceutical indication of a known product. Second indications are accepted under European jurisprudence and in other countries when framed in accordance with the so called 'Swiss' claims⁹⁹. However, the patenting of a new use of a known product including, in particular, second indications, expands the scope of protection inconsistently with the novelty requirement¹⁰⁰.

In addition to the lack of novelty, there are other possible objections to the patentability of second indications:

- there is no industrial applicability, since what is new is an identified effect on the body, not the product as such or its method of manufacture;
- a patent covering the second medical indication of a known product is substantially equivalent to a patent over a method of therapeutic treatment.

Admitting the patentability of second indications extends the protection of pharmaceuticals to cases where no new product has been developed. Many countries reject claims over such indications (see illustrative legislation in the Boxes 16, 17, and 18).

Recommendation: Claims relating to the use, including the second indication, of a known pharmaceutical product can be refused, inter alia, on grounds of lack of novelty and industrial applicability.

Box 15: Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office (March 2004), Claims to Pharmaceutical Compositions, Compositions adapted to a particular use, Paragraph 114.

A claim to a formulation "adapted for only topical, to the exclusion of oral and injectable administration" was accepted by the EPO in T 289/84 ⁹⁸. In this case, the Board of Appeal held that there was a difference in meaning between a claim to composition adapted for topical use, as opposed to one suitable for such a use. Both eye drops and injectable formulations typically consist of sterile aqueous solutions, so either might be "suitable" for the other use. However, an eye-drop formulation was not "adapted" for use as an injectable solution or vice versa - injectable solutions had to both be sterile and pyrogen-free, whereas eye-drops do not need to be pyrogen-free but have a very narrow range of acceptable pH. However, a claim to a composition "adapted to" a specific use should be objected to on clarity grounds as being defined by its intended result, unless it would be clear to the person skilled in the art as to what is meant.

Box 16: Examination Guidelines for Patent Applications relating to Medical Inventions in the UK Patent Office (March 2004). First medical use, Section 2(6), Paragraph 64

Section 2(6) protects the **first** medical use only. Even if the claim defines a substance "for use in" the treatment of a specific disease, the claim will not be novel if that substance has been used in the treatment of any other disease previously. ... First medical use claims are normally used in cases where the substance is known. However, first (and second) medical use claims are acceptable for new compounds, for example, as a fall-back in the event of a prior disclosure of the compound coming to light after grant.

Therapy, Guidelines for determining whether a method is "treatment by therapy", Paragraph 18.

The intention underlying [Article 52(4)] is to ensure that nobody who wants to use methods specified in this Article as part of the medical treatment of humans or animals should be prevented from this by patents. T 24/91 THOMPSON/Cornea OJEPO 1995, 512

Second Medical Use, Swiss-type claims, Paragraph 79.

"... [I]t is legitimate in principle to allow claims directed to the use of a substance ... for the manufacture of a medicament for a specified new and inventive therapeutic application, even in a case where the process of manufacture as such does not differ from known processes using the same active ingredient." G 05/83 EISAI/Second medical use OJEPO 1985, 64

Second Medical Use, Second medical use - forms of claim, Paragraph 80.

The use of X in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of Y

The use of X in the preparation of an anti-Y agent in ready-to-use drug form for treating or preventing Y

The use of X in the manufacture of an anti-Y agent in a package together with instructions for its use in the treatment of Y

Second Medical Use, Second medical use - forms of claim, Paragraph 81.

Unacceptable second medical use claims

Substance X for use in the treatment of medical condition Y.

The use of substance X in the treatment of disease Y.

Package containing as an active pharmaceutical agent substance X together with instructions for treating condition Y.

Box 17: Guidelines for examination in the European Patent Office, Part C, chapter IV (Patentability), (4.) Industrial application, (4.2) Surgery, therapy and diagnostic methods

Art. 54(5)

A claim in the form "Use of substance or composition X for the treatment of disease Y ..." will be regarded as relating to a method for treatment explicitly excluded from patentability by Art. 52(4) and therefore will not be accepted.

Art. 82

If an application discloses for the first time a number of distinct surgical, therapeutic or diagnostic uses for a known substance or composition, normally in the one application independent claims each directed to the substance or composition for one of the various uses may be allowed; i.e. an a priori objection of lack of unity of invention should not, as a general rule, be raised (see III, 7.6).

A claim in the form "Use of a substance or composition X for the manufacture of a medicament for therapeutic application Z" is allowable for either a first or "subsequent" (second or further) such application ("second medical use"-type of claim or "Swiss-type" claim), if this application is new and inventive (cf. G 5/83, OJ 3/1985, 64). The same applies to claims in the form "Method for manufacturing a medicament intended for therapeutic application Z, characterised in that the substance X is used" or the substantive equivalents therefrom (see T 958/94, OJ 6/1997, 241). In cases where an applicant simultaneously discloses more than one "subsequent" therapeutic use, claims of the above type directed to these different uses are allowable in the one application, but only if they form a single general inventive concept (Art. 82). Regarding use or method claims of the above type, it should also be noted that a mere pharmaceutical effect does not necessarily imply a therapeutical application. For instance, the selective occupation of a specific receptor by a given substance cannot be considered in itself as a therapeutic application; indeed, the discovery that a substance selectively binds a receptor, even if representing an important piece of scientific knowledge, still needs to find an application in the form of a defined, real treatment of a pathological condition in order to make a technical contribution to the art and to be considered as an invention eligible for patent protection (see T 241/95, OJ 2/2001, 103). See also III, 4.14, for the functional definition of a pathological condition.

Box 18: Decision 486, Common Regime on Industrial Property, Andean Community of Nations

Products or processes already patented and included in the state of the art within the meaning of Article 16 of this Decision may not be the subject of new patents on the sole ground of having been put to a use different from that originally contemplated by the initial patent (Article 21).

Indian Patent Act (as amended in 2005)

The following shall not be treated as an invention within the meaning of the Act: "...the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant" (Section 3(d)).

3 MECHANISMS TO ENHANCE THE EXAMINATION OF PHARMACEUTICAL PATENTS FROM A PUBLIC HEALTH PERSPECTIVE

There are several measures that countries can implement in order to incorporate a public health perspective into patent examination

3.1 Pre- and post-grant opposition

Patents are granted, even in countries where substantive examination takes place, without the State's guarantee about the utility of the invention or the validity of the patent. However, challenging the validity of a granted patent before judicial courts is costly, and obtaining a decision may take years. This gives a major advantage to title holders, since third parties - especially small and medium enterprises in developing countries or the public that may be affected by a wrongly granted patent - will be reluctant or unable to bear the cost and take the risk of litigation¹⁰². Wrongly granted patents that unduly block competition and prejudice consumers may, hence, remain in force for the full period of the grant.

To address this problem and enhance the examination of patents, many patent laws provide for the possibility of filing observations or an opposition to the granting of a patent application. Such a presentation can be made after the publication of the application (or a summary thereof) within a specified term or, if allowed by the applicable law, at any time before the approval of the application. Of course, the longer the period, the greater the opportunities for the patent office to receive observations from third parties, as the existence or relevance of some patent applications may not be immediately recognized. The admissible observations generally relate to non-compliance with any of the patentability requirements, but may also include insufficiency of disclosure and other reasons.

Pre-grant opposition mechanisms help examiners to improve the analysis they undertake, as third parties can bring to their attention precedents that may not have been identified, and lead to the granting of more solid patents

procedures. Such measures include pre- and post-grant opposition and the adoption of special examination criteria and procedures¹⁰¹.

while avoiding the creation of rights over developments that are not really inventive. As noted by the US Federal Trade Commission, the circumstances in which patents are granted "suggest that an overly strong presumption of a patent's validity is inappropriate" and that "it does not seem sensible to treat an issued patent as though it had met some higher standard of patentability"¹⁰³.

Filing a pre-grant opposition or observations requires capacity to monitor published patent applications and the skills necessary to make the search and analysis of precedents that may be opposed. This requires enhancing the technical knowledge of domestic pharmaceutical companies, ministries of health and civil society to deal with the intricacies of patent law and claims' drafting and interpretation.

A key issue is also the extent to which the information contained in the publication about a patent application is sufficient for interested parties to identify those situations in which an opposition should be submitted. In many cases, the published abstracts and other data about a patent application do not properly characterize a claimed pharmaceutical invention. For instance, the majority of abstracts relating to pharmaceutical inventions do not include the International Nonproprietary Name (INN) that identifies the relevant compounds, but rather report the chemical formula, chemical names or other names that do not allow an easy identification of the patent as related to the compound¹⁰⁴.

Pre-grant procedures should be implemented in a manner that does not obstruct *bona fide* patent applications. In some countries, the person who files a pre-grant opposition or

observations can participate in some way in the ensuing procedures (*inter-partes* procedures). In others, they must be considered by the examiner, but the person who submitted them does not become party (*ex-parte* procedures).

In some countries post-grant reexamination mechanisms before the administration exist. In the USA, for instance, the validity of a patent may be challenged, based on prior art precedents. These procedures, however, have been rarely used in the USA¹⁰⁵ and may take a long time (and generate significant expenses, particularly lawyers' fees). Post-grant procedures are also available, *inter alia*, at the EPO¹⁰⁶. The use of these procedures is particularly intense in areas of high patenting activity and the likelihood of opposition increases with patent value¹⁰⁷.

3.2 Examination rules and procedures

Countries may adopt different types of measures to increase the quality of patents granted in the pharmaceutical and other sectors. Despite the fact that the TRIPS Agreement bans discrimination between fields of technology (Article 27.1), a justified differentiation is viable¹⁰⁸. This is particularly so in the area of public health, as indicated by the Doha Declaration on the TRIPS Agreement and Public Health¹⁰⁹. The singling out of public health and, in particular, pharmaceuticals as an issue that needs special attention in the implementation of the TRIPS Agreement, constitutes a clear recognition that public health-related patents and other forms of intellectual property rights can be treated differently if necessary to protect public health.

Special rules for the examination and grant of pharmaceutical patents may be established in national laws and regulations, as well as in guidelines of patent offices. Such rules may

The availability of post-grant administrative procedures is also important to enhance the quality of patents granted, as these procedures may generally be completed at a lower cost and in a shorter time than court procedures.

In sum, it is advisable that national laws provide for mechanisms of pre- and/or post-grant opposition. The effectiveness of such mechanisms may be significantly enhanced if the published patent applications or their summaries include all relevant data for the identification of the subject matter of the application. In particular, patent offices should require that all patent applications (and their summaries) related to pharmaceuticals include the INN, where available.

include the definition of specific criteria for the approval of patent applications, as adopted by the amendment to the Indian law of 2005.

In addition to prescribing criteria to be applied by the patent offices, it would be desirable to develop a close cooperation between, on the one hand, the ministries of health and health regulatory authorities and, on the other, the patent offices, for the examination of pharmaceutical patent applications. Moreover, the intervention of authorities competent in the area of public health can be envisaged. For instance, in Brazil, a provisional measure by the President (December 14, 1999) subsequently converted into Federal Law 10.196 of February 14, 2001, introduced into the Industrial Property Code a requirement of "prior consent" by the National Sanitary Supervision Agency (ANVISA) for the granting of pharmaceutical patents. A similar requirement has been established in Paraguay.

CONCLUSIONS

Whether subject to the TRIPS Agreement or not, countries can determine their own criteria to assess patent applications consistently with their public health policies. Patent regimes are generally part of national technological and industrial strategies, but is also crucial to design them consistently with public health strategies. It is important, in particular, that the scope of patentability be congruent with public health policies, and that governments be aware that unduly expanding what can be patented may distort competition and reduce access to medicines. Patents over minor developments may be effectively used to discourage or block competition, as generic producers, purchasing agencies and consumers, especially in developing countries, generally lack the substantial technical and financial resources needed to challenge wrongly granted patents or defend against infringement claims.

The analysis and criteria presented in this document intend to provide general guidance to patent offices and other bodies that participate in the examination of pharmaceutical patents, in a way that is consistent with patent law and, at the same time, congruent with public health objectives, in particular with the right of access to medicines by all. They should be further refined and adjusted to national legislation, as appropriate.

As discussed above, it is unlikely that the following classes of product patent applications be admissible:

- A new salt, ester, ether or polymorph, including hydrates and solvates, of an existing chemical entity.
- A single enantiomer of an existing chemical entity.
- A new combination of two or more active ingredients that are already available as single entities.
- A new dosage form that allows a new route of administration (e.g. an injection when an oral tablet already exists).
- A controlled release dosage form when a non-controlled release dosage form already exists.
- A new route of administration of an existing dosage form (e.g. intravenous administration of an injection when subcutaneous administration is already approved).
- A change in formulation.

In order to be able to implement these guidelines, or otherwise preserve the capacity to determine the criteria for the examination of pharmaceutical patents, countries should not adhere to international instruments¹¹⁰ that may erode the flexibilities currently allowed by the TRIPS Agreement for that purpose, such as the capacity to define the concept of invention and the criteria to apply the standards of patentability, notably with regard to the level of inventive step.

An indispensable requirement for dealing with patent applications with a public health perspective, is obviously to adequately train and retain qualified examiners. Training provided by patent offices of developed countries may increase examiners' technical skills, but also induce standards of evaluation that may lead to an undue expansion in the scope of patentability of pharmaceuticals.

Finally, patent examiners should be aware that the decisions they take, although apparently technical in nature, may have very practical implications for the health and life of people, as wrongly granted patents can be used to unduly restrict competition and limit access to needed medicines.

ENDNOTES

- 1 See Velasquez and Boulet (1999). For a detailed legal analysis of the minimum standards under the TRIPS Agreement, see UNCTAD-ICTSD Project on Intellectual Property Rights and Sustainable Development, "Resource Book on TRIPS and Development", Cambridge University Press, 2005 (available at <http://www.iprsonline.org/unctadictsd/ResourceBookIndex.htm>).
- 2 See UNCTAD-ICTSD Project on Intellectual Property Rights and Sustainable Development, "Intellectual Property Rights: Implications for Development"; Policy Discussion Paper, Geneva (2003).
- 3 Commission on Intellectual Property Rights (2002).
- 4 See Correa (2004).
- 5 National Institute for Health Care Management (2002).
- 6 See Barton (2004).
- 7 On the functions of the patent system, see Commission on Intellectual Property Rights, Innovation and Public Health, *Public Health, Innovation and Intellectual Property Rights*, World Health Organization (available at www.who.int) 2006 (hereinafter 'CIPIH').
- 8 See, e.g. Federal Trade Commission (FTC) (2003) ; Jaffe and Lerner (2004); Correa, (2001a).
- 9 The number of new molecular entities (NMEs) approved by the US Food and Drug Administration drastically declined since the mid-1990s (from 53 in 1996 to a minimum of 17 in 2002). See *CDER, NDAs approved in calendar years 1990-2004 by therapeutic potential and chemical type*. United States Food and Drug Administration, 22 March 2005 (<http://www.fda.gov/cder/rdmt/pstable.htm>, accessed 14 November 2005).
- 10 CIPIH, p. 17. However, patents may, in some circumstances, deter follow on innovation, specially when outputs of up-stream science are patented. See, e.g. Commission on Intellectual Property Rights (2002); Sampath (2005), p.29.
- 11 The examples include the abstract and one or more claims as an illustration. There has been no intention to judge the validity of the patents mentioned (or any of their claims) in particular jurisdictions. The examples have been selected with the assistance of Lic. Romina Gomez (Faculty of Exact and Natural Sciences, University of Buenos Aires).
- 12 This document does not address issues relating to the patentability of pharmaceutically relevant biotechnological inventions, such as those relating to human proteins or genes.
- 13 The *Concise Oxford Dictionary*, 1989, p. 527.
- 14 Many patent laws make such a distinction. For instance, Article 52 (2) of the European Patent Convention stipulates that '[T]he following in particular shall not be regarded as inventions within the meaning of paragraph 1: (a) discoveries, scientific theories and mathematical methods; (b) aesthetic creations; (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; (d) presentations of information'.
- 15 See, e.g. Burnier (1981), p. 22.
- 16 The same concept is contained in the Argentine patent law (Article 4(a)).
- 17 The European Patent Convention, for instance, is interpreted to only exclude from patentability discoveries *as such*. See, e.g. Cook (2002), p. 179.
- 18 See Straus (1996), p. 187.
- 19 See Articles 31 and 32 of the Convention. The method of interpretation codified by this Convention has been extensively used in GATT/WTO jurisprudence, including with regard to the TRIPS Agreement. See, e.g. Frankel (2006).

- 20 As suggested by decision in the UK and by the European Patent Office. See, e.g. Bently and Sherman (2001), p. 370-371.
- 21 According to US law, for example, "[A] person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States ..." (35 U.S.C section 102). In responding to a question about the novelty standard applied under this Section, the US held that in the TRIPS Agreement there was 'no prescription as to how WTO Members define what inventions are to be considered "new" within their domestic systems' and, hence, that its legislation was 'perfectly consistent with the provisions of the TRIPS Agreement' (document IP/Q3/USA/1, May 1, 1998).
- 22 See below.
- 23 See e.g, the decision by the Opposition Division of the European Patent Office of 20-1-05 revoking EP-B-1049467 (relating to compositions of 'Celecoxib'); see also *in re Benner*, 174 F.2d 938, 942 (C.C.P.A. 1949) ("[N]o provision has been made in the patent statutes for granting a patent upon an old product based solely upon discovery of a new use for such product."); *in re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349-50 (Fed. Cir. 2002) (inventor's recognition of substances that render broccoli and cauliflower particularly healthy does not permit patent on identifying broccoli seeds or preparing broccoli as a food product); *ABBOTT LABORATORIES and CENTRAL GLASS COMPANY, LTD. v. BAXTER PHARMACEUTICAL PRODUCTS, INC. and BAXTER HEALTHCARE CORP*, United States Court of Appeals for the Federal Circuit, November 9, 2006.
- 24 'Incremental innovations' (as opposed to 'major' innovations) are modifications, such as improvements or adaptations of existing products and processes. Irrespective of their practical usefulness, such improvements may be obvious to develop for a person having ordinary skills in the art.
- 25 Scherer noted almost two decades ago: 'As the bleary-eyed reviewer of some 15,000 patent abstracts in connection with research... I was struck by how narrowly incremental (adaptive?) most "inventions" are' (Scherer, 1987, p 124).
- 26 In an early US court decision Justice Bradley stated that "[I]t was never the object of [the patent] laws to grant a monopoly for every trifling device, every shadow of a shade, of an idea, which would naturally and spontaneously occur to any skilled mechanic or operator in the ordinary progress or manufactures" (*Atlantic Works v. Brady*, 107 U.S. (17 Otto) 192, 1883). Fifty years later Justice Douglas stated that a new device, to be patentable, "must reveal the flash of creative genius" (*Cuno Engineering Corp.*, 314 U.S. 84, 51 U.S.P.Q. 1, 1941) (quoted in Chisum, Donald and Jacobs, Michael (1992)) . The US policy on the matter has significantly changed, however, since these statements were made, as the patent office and courts applied a less rigorous concept of non-obviousness. See, e.g., Federal Trade Commission (FTC) (2003); Jaffe and Lerner (2004).
- 27 See, e.g. World Bank (2001), p. 147, recommending that developing countries generally apply strict criteria for the granting of patents.
- 28 Finding a solution to a problem should not be deemed as a basis for patentability, unless the solution is non-obvious. On the problem-solution approach applied by the European Patent Office, see Cook, op. cit. p. 208-210.
- 29 This paper does not deal with issues relating to the breadth of patent claims, except in relation to the so-called 'Markush claims'. Such issues also deserve a careful and systematic analysis. See, e.g. Merges (1996), p. 120-144.
- 30 See Bently and Sherman (2001), p. 370-371.
- 31 See examples 1 to 10 in the Annex.
- 32 This example refers to a case where there is a new indication for a known product with a different therapeutic effect.
- 33 For example, a prolonged release (PR) dosage form,

- 34 Most regulatory authorities would not allow such a product to be registered unless there were demonstrated benefits to the patient such as reduced incidence of adverse effects or prolonged efficacy leading to reduced frequency of dosing. In some cases, however, prolonged release dosage forms may add an undesirable variability.
- 35 See examples 11 to 13 in the Annex.
- 36 For instance, CIPLA, the Indian pharmaceutical firm, filed a PCT application for the combination of three antiretrovirals: efavirenz (EFV), zidovudine (AZT) and lamivudine (3TC) and their analogues. Another example is the application filed by GlaxoSmithKline for the tablet formulation of the combination of zidovudine (AZT) and lamivudine (3TC), also known under the brandname 'Combivir'.
- 37 For instance, claims on the combination of aspirin 325 mg + carisoprodol 200 mg + codeine phosphate 16 mg were granted in the USA, with expiry date 13/08/2002.
- 38 See Glaxo Group Ltd's Patent [2004]RPC 43. Report of Patent, Design and Trade Mark Cases (RPC). The RPC is published by Sweet & Maxwell on behalf of the Patent Office (UK).
- 39 See example 14 to 16 in the Annex.
- 40 A method of medical treatment (or therapeutic method) is a set of steps, that may include the administration of a medicine, applied to the human (or animal) body to treat or cure a disease.
- 41 See an analysis of this issue below.
- 42 It is possible for an active ingredient to have different indications at different doses. For example clonidine is used to treat hypertension in a regimen of 150-300 micrograms twice daily, but at 25 micrograms twice daily for migraine prophylaxis.
- 43 See examples 17 to 19 in the Annex.
- 44 'Evergreening' is a patenting strategy consisting of acquiring patents on minor, often trivial, modifications of existing pharmaceutical products or processes in order to indirectly extend the period of patent protection over previously patented compounds.
- 45 See Wegner (1994), p. 283.
- 46 Salt forms can affect stability, dissolution rate and manufacturing properties (eg powder flow in a hopper). Esters and ethers are generally more lipid soluble than are salts, thus altering tissue penetrability and sometimes rate of release (for example steroids have quite different topical potencies when administered as esters). In some cases, the use of esters may confer an advantage in terms of safety and efficacy.
- 47 See, e.g. *Ex parte Kortzen*, 71 USPQ 173 (1946) quoted in Wegner (1994), p. 283, who also quotes a later case where an ester of a known alcohol was deemed patentable because the motivation to esterify it could not be presumed to necessarily exist.
- 48 Some comments on this provision seem pertinent here. In accordance with this provision, if not significantly different in properties with regard to efficacy, salts, esters and ethers are considered to be the *same* substance and, hence, no separate patent could be granted. Establishing such differences with regard to efficacy (which is not a *technical* effect, but the result of the use of the substance in the body) would not be sufficient, however, to obtain a patent, since in any case the novelty, inventive step and utility requirements should be met. In other words, an increased efficacy would only prove that the substance is different, and not that it is patentable. An important issue is how a difference in efficacy is to be determined, since at the time of filing a patent application the results of clinical tests are generally not yet available. In the USA, for instance, the Court of Appeals for the Federal Circuit reversed *in re Brana* (51 F.3d 1560, Fed. Cir. 1995) a decision of the US Patent and Trademark Office (USPTO) holding that a compound was useful enough to be granted a patent, even without the approval of the FDA at that stage (the USPTO had rejected the patent application as it had not yet been approved by the FDA for Phase II clinical trials). In a more recent case, the Court held that where there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects" the applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement (Novak, 306 F.2d at 928; Rasmusson and Reynolds v. Smithkline Beecham, June 27, 2005).

- 49 See examples 20 to 23 in the Annex.
- 50 The usual process for finding new polymorphs is to recrystallise the active pharmaceutical ingredient from different solvents, or under different recrystallisation conditions such as temperature or rate of stirring.
- 51 Many polymorphs are metastable, that is they have short-term stability, which reduces their utility from a manufacturing and storage perspective. An ordinary skilled chemist that develops a new substance for pharmaceutical use, will normally seek to identify the most stable polymorph. On some technical aspects relating to polymorphism, see Dunitz (1995) p. 193-200; Bernstein (1999), p. 3440-3461.
- 52 See, e.g. Cook, Doyle and Jabbari (1991), p. 89; Hansen and Hirsch (1997), p. 113.
- 53 See, e.g. Cook, Doyle and Jabbari (1991), p. 90; Grubb (1999), p. 205.
- 54 See Hansen and Hirsch (1997), p. 112.
- 55 See, for instance, the decision by the Superintendencia de Industria y Comercio of Colombia regarding crystalline forms of atorvastatine (Tribunal de Justicia de la Comunidad Andina, Proceso N° 151-IP-2005. Interpretación prejudicial de las disposiciones previstas en los artículos 1, 4 y 7 de la Decisión 344 de la Comisión del Acuerdo de Cartagena, así como en los artículos 45 y 48 y en la Disposición Transitoria Primera de la Decisión 486 de la Comisión de la Comunidad Andina, con fundamento en la solicitud formulada por el Consejo de Estado de la República de Colombia, Sala de lo Contencioso Administrativo, Sección Primera. Expediente: N° 2003-00255).
- 56 Substances that can be described as polymorphs of each other have the same chemical composition, whereas a solvate and a non-solvate do not. Indeed different solvates have different chemical compositions.
- 57 "Polymorphic forms: Some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified" (*Specifications: Test Procedures & Acceptance. Criteria for New Drug Substances and New Drug Products: Chemical substances Q6A, ICH 1999*).
- 58 As quoted above, the recent reform of the Indian Patent Act provides that polymorphs, inter alia, 'shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy' (Section 3 (d)).
- 59 Chinese Guidelines, Chapter 10. Several Provisions for the Examination of Applications for Patent for Invention in the Field of Chemistry.
- 60 <http://www.uspto.gov/web/offices/pac/mpep/index.htm>.
- 61 http://www.european-patent-office.org/legal/gui_lines/e/index.htm.
- 62 See example 24 in the Annex.
- 63 However, a selection patent may be applied for by a third party, and not necessarily by the owner of the original patent. This may raise issues of patent-dependency and eventually trigger the application of compulsory licenses. See Article 31(l) of the TRIPS Agreement.
- 64 <http://www.patent.gov.uk/patent/reference/biotechguide/index.htm>.
- 65 <http://www.patent.gov.uk/patent/reference/mpp/ss1-6.pdf>.
- 66 'A compound, in the sense of Patent Law, is every chemical entity that can be reliably differentiated from another chemical entity, through the provision of sufficient, suitable parameters. Fundamentally, compounds having the same chemical composition are identical. This does not apply for special forms of compounds having the same chemical composition, if these forms could not be produced, despite their chemical composition being known' (Grubb (1999), p. 197-199).

- 67 When a prior claim or document in the prior art includes a range, for instance, in the form of C₁-C₄ or 50° to 75° of temperature, all the comprised possibilities (e.g. C₂ and C₃; 60° of temperature) should be deemed disclosed and, hence, not patentable as a 'selection'.
- 68 The patentability of a selection will proceed in this case if an exception to the strict principles of novelty were allowed under the applicable law. See, e.g. Cook, *op. cit.*, p. 291.
- 69 A different situation arises when a compound has to be produced by a large number of consecutive steps (chemical reactions). It may be inventive to produce this compound by another much more efficient route (comprising less steps), even if this individual chemical reactions as such were known for other compounds.
- 70 See, e.g. Grubb (1999), p. 206.
- 71 See, e.g. Dratler, §2.03[3].
- 72 See, e.g. Grubb (1999), p. 207.
- 73 The validity of this patent has been challenged before Argentine courts (decision still pending).
- 74 This situation may arise, in particular, in countries that did not grant patent protection for pharmaceutical products before the TRIPS Agreement obliged the granting of patents in all fields of technology (Article 27.1).
- 75 See examples 25 and 26 in the Annex.
- 76 Enantiomers are "stereoisomers whose mirror images cannot be superimposed. Enantiomers have identical physical and chemical properties except that they rotate the plane of polarized light in opposite directions and behave differently in a chiral environment". 'Stereoisomers' are compounds made up of the same atoms bonded in the same sequence but having different orientations in space. [...]" See http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/stereo_e.pdf.
- 77 During the synthesis of asymmetric molecules equal amounts of enantiomeric pairs will always form, except when one of the starting materials or reagents is itself a single enantiomer. In other words, unequal amounts of enantiomers will form only if the chemist deliberately selects starting materials or reagents that are single enantiomers.
- 78 See, e.g. Hansen and Hirsch (1997), p. 113. It is estimated that over a quarter of known pharmaceuticals present this property. See, e.g. Cook, Doyle and Jabbari (1991), p. 84.
- 79 Although the patent on an isolated enantiomer would not normally be deemed infringed by the commercialization of the racemic mixture, promotion of the enantiomer as more advantageous than the latter may massively drive prescribing doctors towards the new product.
- 80 See, e.g. Grubb (1999), p. 199-200; Hansen and Hirsch (1997), p. 113-118. For instance, esomeprazole is the *S*-enantiomer of omeprazole. Improved efficacy of this single enantiomer over the racemic mixture of omeprazole has been claimed (see, e.g. <http://en.wikipedia.org/wiki/Esomeprazole>). Another example is citalopram and escitalopram.
- 81 An enantiomer might have in some cases useful properties that are not the same as those of the racemate, which useful properties could not have been predicted but were masked in the racemate by the other enantiomer. It will depend on the applicable national law whether the identification of such properties could provide the basis for obtaining a patent or whether it would be considered a non-patentable discovery or anticipated in the prior art.
- 82 For instance, it might be found that one enantiomer is leading to adverse reactions, so using its mirror image alone confers an advantage in terms of safety. It's often the case that the two enantiomers in a pair have a different safety and efficacy profile. (e.g. 3-hydroxy-tyrosine and levodopa. D-dopa is highly toxic). Article 10(2)(b) of the 2001/83/EC Directive (as amended by Directive 2004/27/EC) provides that for abridged applications by generic companies, different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active ingredient, are considered to be essentially similar drugs unless they differ significantly in properties with regard to safety and/or efficacy.

- 83 This applies to the individual isomers (cis and trans) that are components of the existing mixture.
- 84 See examples 27 to 34 in the Annex.
- 85 An example is nelfinavir and its active metabolite M8.
- 86 When an active metabolite of an existing product is registered with the health authority in its own right, it is possible that a full set of new safety and efficacy data will be required, similar to that which was generated for the parent compound. There are cases where an active metabolite has been registered for a different indication to that of the parent drug (for example, the primary indication for temazepam, an active metabolite of diazepam, is as a hypnotic whereas the primary indication for diazepam itself is anxiety).
- 87 Some examples are the following: enalapril is converted by esterase to the active enalaprilat; valaciclovir is converted by esterase to the active aciclovir; levodopa is converted by DOPA decarboxylase to the active dopamine; fosamprenavir calcium is a pro-drug of the protease inhibitor and antiretroviral drug amprenavir.
- 88 In some cases, the prodrug might have benefits in terms of being more readily administered than the active compound.
- 89 In the UK, for instance, it was held that sales of hetacillin, an acetone adduct of ampicillin which was immediately hydrolyzed in the body to ampicillin, infringed the ampicillin patent, because it was "ampicillin in disguise" (Grubb (1999), p. 211).
- 90 See, e.g. Grubb (1999), p. 212-213. The decision however, did not invalidate the patent to the active metabolite when produced other than by metabolism. Another conflict arose with regard to a Bristol Myers patent over the monohydrate form of cephalosporin, which is metabolized in the body from a semi-hydrate form developed by Zenith. See, e.g., Soto Vázquez, Cárdenas y Espinosa, Parra Cervantes y Cassaigne Hernández (2001), p. 54.
- 91 See examples 35 to 40 in the Annex.
- 92 The medical profession is not an industry, as stated in a landmark decision by the German Federal Supreme Court in *Operation for baldness* (38 BGHZ 313, 1968 GRUR 142). See, e.g. Thomas (2003), p. 850.
- 93 See Thomas (2003), p. 870.
- 94 http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/Guidelines/PartVII-3.pdf.
- 95 http://www.european-patent-office.org/legal/gui_lines/e/c_iv_4_2.htm.
- 96 A well known example of a 'second indication' patent relates to sildenafil citrate. Another example is zidovudine, developed as an anticancer drug and then covered by patent as a HIV drug.
- 97 As required by the Vienna Convention on the Law of the Treaties.
- 98 EPO Board of Appeal, 10 November 1986, Case number: T 0289/84 - 3.3.1, Application number: EP80104029.
- 99 The formulation of these claims, deemed to have been first introduced by the Swiss patent office, is of the type 'use of x for the manufacture of product y to treat disease z'. See examples 41 and 42 in the Annex.
- 100 However, this formula suffers from "the logical objection that it lacks novelty, since it claims the use of the compound for preparation of a medicament, and normally the medicament itself will be the same as that already used for the first pharmaceutical indication" (Grubb (1999), p. 221).
- 101 Other measures may include reducing the legal standard for proving a patent invalid in court. For instance, in the United States currently such standard is "clear and convincing evidence", which is much tougher than a "preponderance of the evidence" standard. See e.g. FTC (2003); Pamela Samuelson, Legally Speaking: Why Reform the U.S. Patent System?, 47 *Communications of the ACM*, June 2004, available at <http://www.sims.berkeley.edu/~pam/papers/cacm%20patent%20reform.pdf>. Patent

quality may also be enhanced by establishing an obligation on the applicant to inform about the grant or refusal of corresponding foreign patent applications (as allowed by Article 29.2 of the TRIPS Agreement), and by prescribing ways of describing prior art in the patent specifications. Peer review mechanisms can also be used. For instance, under The Community Patent Review project (<http://dotank.nyls.edu/communitypatent>) it is proposed to establish a system for researchers to be informed whenever patent applications in their areas of expertise are published. They could then voluntarily use an electronic bulletin-board to post any prior publications that might be relevant. This project has been under consideration of the US Patent and Trademark Office and is backed by some large US firms, such as IBM (see Editorial, *Nature*, 441, 256, 18 May 2006).

- 102 Moreover, if a patent is invalidated as a result of a legal challenge, the decision would benefit all competitors in a given field, thus giving incentives to potential challengers to reach an agreement with the title-holder rather than bearing alone the costs of litigation.
- 103 FTC (2003), p. 8. Orrin Hatch and Patrick Leahy, chairmen of the U.S. Senate's intellectual-property panel, introduced in August 2006 the 'Patent Reform Act of 2006' that, in order to stave off excessive litigation, proposes an enhanced "postgrant opposition" system that would allow outsiders to dispute the validity of a patent before a board of administrative judges within the Patent Office.
- 104 An INN is generally not available when a patent for the compound is first filed. It is assigned later in the development process.
- 105 FTC, op. cit, p. 27. There are currently initiatives in the USA to introduce changes to the patent law, *inter alia*, in order to make the post-grant procedures more effective. See, e.g. <http://www.law.com/jsp/article.jsp?id=1124109330603>. See also Bill S.3818 submitted by Senators Hatch and Leahy.
- 106 In the case of India, in accordance with the amended Patents Act, unlike as under the Patents Act, 1970, patents can be opposed even before grant, but full-scale proceedings for opposition can start only after the patent is granted.
- 107 See Harhoff and Reitzig (2002).
- 108 In a WTO case between the EC and Canada, it was held that: "Article 27 prohibits only discrimination as the place of invention, the field of technology, and whether products are imported or produced locally. Article 27 does not prohibit *bona fide* exceptions to deal with problems that may exist only in certain product areas. Moreover, to the extent the prohibition of discrimination does limit the ability to target certain products in dealing with certain of the important national policies referred to in Articles 7 and 8.1, that fact may well constitute a deliberate limitation rather than frustration of purpose" (WT/DS114/R, 17 March 2000, para 7.92).
- 109 WT/MIN(01)/DEC/W/2, 14 November 2001, available at www.wto.org.
- 110 With regard to initiatives for the harmonization of substantive patent law, see Carlos Correa (2005).

ANNEX

- **EXAMPLE 1**

Oral administration forms of a medicament containing pantoprazole

Patent number: HK1005851

Publication date: 1999-01-29

The invention relates to oral presentation forms for pantoprazole, which consist of a core, an intermediate layer and an outer layer which is resistant to gastric juice.

Claims

1. An orally administrable medicament in pellet or tablet form which is resistant to gastric juice, and in which each pellet or tablet consists of a core in which active compound or its physiologically-tolerated salt is in admixture with binder, filler and, optionally, a member selected from the group consisting of another tablet auxiliary and a basic physiologically-tolerated inorganic compound, an inert water-soluble intermediate layer surrounding the core and an outer layer which is resistant to gastric juice, wherein the active compound is pantoprazole, the binder is polyvinylpyrrolidone and/or hydroxypropylmethylcellulose and, optionally, the filler is mannitol.

- **EXAMPLE 2**

Oral pharmaceutical multiple unit tableted dosage form

Patent number: WO 96/01623

Publication date: 1996-01-25

A new pharmaceutical multiple unit tableted dosage form containing omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, a method for the manufacture of such a formulation, and the use of such a formulation in medicine.

Claims

1. An oral pharmaceutical multiple unit tableted dosage form comprising tablet excipients and individually enteric coating layered units of a core material containing active substance in the form of omeprazole or one of its single enantiomers or an alkaline salt of omeprazole or one of its single enantiomers, optionally mixed with alkaline compounds, covered with one or more layer(s), of which at least one is an enteric coating layer, whereby the enteric coating layer has mechanical properties such that the compression of the individual units mixed with the tablet excipients into the multiple unit tableted dosage form does not significantly affect the acid resistance of the individually enteric coating layered units.
2. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units is in coherence with the requirements on enteric coated articles defined in the United States Pharmacopeia.
3. A tableted dosage form according to claim 1, wherein the acid resistance of the individually enteric coating layered units does not decrease more than 10 % during the compression of the individual units into the multiple unit tableted dosage form.

4. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units comprises a plasticized enteric coating layer material.
5. A tableted dosage form according to claim 1, wherein the enteric coating layer covering the individual units has a thickness of at least 10µm.
6. A tableted dosage form according to claim 1, wherein the individually enteric coating layered units are further covered with an over-coating layer comprising pharmaceutically acceptable excipients.
7. A tableted dosage form according to claim 1, wherein the active substance is a magnesium salt of omeprazole having a degree of crystallinity which is higher than 70 % as determined by X-ray powder diffraction.

• **EXAMPLE 3**

Didanosine granula composition and its preparation method

Patent number: CN1565422 (WO0003696)

Publication date: 2005-01-19

The invention discloses an AIDS drug didanosine granula composition and its preparation method, the particle composition comprises a therapeutically effective dosage of inosine, acid preparation, filler and binder.

Claims

1. An enteric coated pharmaceutical composition comprising a core in the form of a tablet and having an enteric coating surrounding said core, said core comprising an acid labile medicament, a binder or filler, a disintegrant, and a lubricant, said enteric coating comprising a methacrylic acid copolymer, and a plasticizer, and imparting protection to said core so that said core is afforded protection in a low pH environment of 3 or less while capable of releasing medicament at a pH of 4.5 or higher.

• **EXAMPLE 4**

Extended release formulation containing venlafaxine

Patent number: EP0797991

Publication date: 1997-10-01

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets.

Claims

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropylmethylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose.

- **EXAMPLE 5**

Antibiotic preparations

Patent number: GB1479655

Publication date: 1977-07-13

A powder which may be dispersed in water to yield an orally administerable pharmaceutical composition comprises (a) particles of particle size 5 to 500Å comprising a water-soluble acid addition salt of an in vivo hydrolysable ester of a penicillin or cephalosporin which has an amino-group in the acetylamino side chain which particles are at least 50% coated with a pharmaceutically acceptable water-insoluble coating agent and (b) a water-soluble salt of a weak organic acid, the weight ratio (a):(b) being from 5:1 to 1:5. The salt (b) may be included within the penicillin, or cephalosporin particles. The antibiotic may be ampicillin phthalidyl ester hydrochloride or ampicillin pivaloyloxy-methyl ester hydrochloride. The weak acid salt may be disodium citrate or trisodium citrate. The coating agent may be ethyl cellulose, poly(dimethylaminoethylmethacrylate) or poly-(vinyl acetal diethylaminoacetate). Other ingredients specified include monmorillonite clay, preservative, flavouring and caster sugar.

Claims

1. A powder which may be reconstituted into an orally administrable pharmaceutical composition in suspension or solution form by the addition of water which powder contains (a) fine particules of a water-soluble acid addition salt of an in vivo hydrolysable ester of a penicillin or cephalosporin which has an amino group in the acylamino side chain and which fine particles are substantially or wholly coated by a pharmaceutically acceptable water-insoluble coating agent, (b) a water-soluble salt of a weak organic acid and (c) conventional carriers; the weight ratio of penicillin or cephalosporin derivative to water-soluble salt of a weak organic acid being from 5:1 to 1:5.

- **EXAMPLE 6**

Celecoxib compositions

Patent number: WO0032189

Publication date: 2000-06-08

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 1000 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 1000 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 0.5 h after administration;
 - (b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

- (c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;
 (d) a terminal half-life (T_{1/2}) not less than about 10 h; and
 (e) a maximum concentration (C_{max}) not less than about 200 ng/ml.
2. A composition of Claim 1 wherein the time course of blood serum concentration of celecoxib is characterized by a T_{1/2}, not greater than about 3 h, preferably not greater than about 2 h, and more preferably not greater than about 1.7 h, after administration.
 3. A composition of Claim 1 wherein the C_{max} is not less than about 200 ng/ml, preferably not less than about 400 ng/ml.
 4. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having relative bioavailability not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution containing an equivalent amount of celecoxib.
 5. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a distribution of celecoxib particle sizes such that Duo if the particles is less than 200 pLm, preferably less than 100 urn, more preferably less than 40 nm, and most preferably less than 25 um, in the longest dimension of said particles.

• **EXAMPLE 7**

Oral pediatric Trimethobenzamide formulations and methods

Patent number: WO03072021A2

Publication date: 2003-09-04

Oral pediatric trimethobenzamide compositions and methods for treating and controlling nausea and/or vomiting are disclosed in warm blooded animals, especially humans including children. The oral pediatric trimethobenzamide compositions and methods of the present invention are believed to be at least as effective as a 200 mg intramuscular I.M. trimethobenzamide HCl injectable formulation when administered at a dose of about 100 mg. In addition, an oral pediatric composition containing about 120 mg of trimethobenzamide HCl is believed to be uniquely approximately bioequivalent to a 200 mg intramuscular I.M. trimethobenzamide HCl injectable formulation when administered at a dose of about 100 mg.

Claims

1. An oral pediatric trimethobenzamide composition for treating and controlling nausea and/or vomiting in a child comprising trimethobenzamide and a suitable pharmaceutical excipient, wherein said oral pediatric trimethobenzamide composition is at least about as effective as a 200 mg intramuscular (I.M.) trimethobenzamide HCl injectable formulation when administered in a dose of about 100 mg to treat and control nausea and/or vomiting.
2. An oral pediatric trimethobenzamide composition of [claim 1](#), wherein said trimethobenzamide is present in an amount greater than 120 mg.

- **EXAMPLE 8**

Taxol for use in cancer therapy

Patent number: EP0584001

Publication date: 1994-02-23

The invention concerns products containing taxol for use in cancer therapy. According to this invention, the products contain an anti-neoplastically effective amount of taxol and sufficient medications to prevent severe anaphylactic-like reactions and are formulated and packaged for separate or sequential or simultaneous use in cancer therapy with a patient over a period of about 24 hours or less. These products find application in the treatment of all types of cancers, treatable by taxol.

Claims

1. Products containing an anti-neoplastically effective amount of taxol and sufficient medications to prevent severe anaphylactic-like reactions formulated and packaged for separate or sequential or simultaneous use in cancer therapy with a patient over a period of about 24 hours or less.

- **EXAMPLE 9**

Pharmaceutical composition

Patent number: WO2004010993

Publication date: 2004-02-05

The instant invention provides a pharmaceutical composition comprised of a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor, one or more anti-oxidants, microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate and lactose. The composition need not contain ascorbic acid in order to obtain desirable stability.

Claims

1. A pharmaceutical composition comprised of from 1% to 20% by weight of ezetimibe; from 1% to 80% by weight of simvastatin; and from 0.01% to 2% by weight of BHA.
2. The composition of claim 1 comprised of from 1.25% to 10% of ezetimibe, and from 1% to 20% of simvastatin.
3. The composition of claim 2 comprised of from 5% to 10% of simvastatin.
4. The composition of claim 1 comprised of 0.01% to 0.05% of BHA
5. The composition of claim 4 comprised of about 0.02% of BHA
6. The composition of claim 1 further comprised of 0.2% or less by weight of propyl gallate.
7. The composition of claim 6 comprised of from 0.001% to 0.05% by weight of propyl gallate.

- **EXAMPLE 10**

Modified release ibuprofen dosage form

Patent number: WO2006039692

Publication date: 2006-04-13

The present invention is a solid dosage form for oral administration of ibuprofen comprising a modified release formulation of ibuprofen which provides an immediate burst effect and thereafter a sustained release of sufficient ibuprofen to maintain blood levels at least 6.4 g/ml over an extended period of at least 8 hours following administration of a single dose. The dosage form releases ibuprofen at a rate sufficient to initially deliver a effective amount of ibuprofen within about 2.0 hours following administration. The dosage form then subsequently delivers the remaining amount of ibuprofen at a relatively constant rate sufficient to maintain a level of ibuprofen over a predetermined delivery period of for at least 8 hours.

Claims

1. A solid dosage form for modified oral administration of ibuprofen comprising: a hydrophilic polymer; 300 to 800 mg of ibuprofen in the solid dosage form uniformly dispersed in said polymer; a dissolution additive dispersed in said hydrophilic polymer in an amount in the range of 10% to 35% by weight of the ibuprofen, said dissolution additive comprising an alkali metal salt, an amino acid having a neutral to alkaline side chain, croscarmellose or a salt thereof, or a combination of any two of such dissolution additives; and an inert formulation additive dispersed in said hydrophilic polymer in an amount in the range of 15% to 75% by weight of the ibuprofen, said formulation additive comprising microcrystalline cellulose, silica, magnesium stearate, stearic acid, lactose, pre-gelatinized starch, dicalcium phosphate or a combination of any of them, wherein at least 20% of the ibuprofen is released within 2 hours following oral administration or exposure to an agitated aqueous medium of a single dosage unit, then thereafter releases ibuprofen at a relatively constant rate over a period of at least 8 hours, and wherein at least 70% of the ibuprofen is released over a period of not more than 14 hours following such administration or exposure.
2. The solid dosage form of claim 1, wherein ibuprofen is present in each dosage form in an amount of about 300 mg, 400 mg or 600 mg.

• **EXAMPLE 11**

Novel combination

Patent number: US 20050065176

Publication date: 2005-03-24

Combinations comprising

- a) an activator of soluble guanylate cyclase and
- b) an inhibitor of angiotensin converting enzyme (ACE) are useful for treating hypertension.

Claims

1. The use of a combination of an activator of soluble guanylate cyclase and an inhibitor of angiotensin converting enzyme (ACE) for the preparation of a medicament for the palliative, curative or prophylactic treatment of a cardiovascular or metabolic disorder.
11. A pharmaceutical composition comprising an activator of soluble guanylate cyclase and an inhibitor of angiotensin converting enzyme (ACE).
12. A pharmaceutical combination for simultaneous, separate or sequential administration for treating hypertension, comprising an activator of soluble guanylate cyclase and an inhibitor of angiotensin converting enzyme (ACE).

- **EXAMPLE 12**

Pharmaceutical composition containing a statin and aspirin

Patent number: EP1071403 B1

Publication date: 2005-07-27

A pharmaceutical composition is provided which is useful for cholesterol lowering and reducing the risk of a myocardial infarction, which includes a statin, such as pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin or fluvastatin, in combination with aspirin, in a manner to minimize interaction of aspirin with the statin and minimize side effects of aspirin. A method for lowering cholesterol and reducing risk of a myocardial infarction employing such composition is also provided.

Claims

1. A pharmaceutical composition comprising a statin cholesterol lowering agent and aspirin in a formulation to reduce statin:aspirin interaction wherein the statin and aspirin are formulated together in a bilayered tablet, the aspirin being present in a first layer, and the statin being present in a second layer.
 2. The pharmaceutical composition as defined in claim 1 wherein the layer containing the statin also includes one or more buffering agents.
 3. The pharmaceutical composition as defined in claim 1 wherein the tablet includes a core and a coating layer surrounding said core and wherein one of the statin and aspirin is present in the core and the other is present in the coating layer surrounding the core.
-

- **EXAMPLE 13**

Composition comprising a tramadol compound and acetaminophen and its use

Patent number: EP0566709 B1

Publication date: 1998-12-08

This invention relates to a composition comprising a tramadol material and acetaminophen, and its use. As used herein tramadol refers to various forms of tramadol. The compositions are pharmacologically useful in treating pain and tussive conditions. The compositions are also subject to less opioid side-effects such as abuse liability, tolerance, constipation and respiratory depression. Furthermore, where the components of the compositions are within certain ratios the pharmacological effects of the compositions are superadditive (synergistic).

Claims

1. A pharmaceutical composition comprising a tramadol compound and acetaminophen.
 2. The pharmaceutical composition of claim 1 wherein the the tramadol compound and acetaminophen are in a ratio that is sufficient to provide a synergistic pharmacological effect.
-

- **EXAMPLE 14**

Composition comprising 5-[4-[2-(n-methyl-n-2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione

Patent number: WO9855122

Publication date: 1998-12-10

A pharmaceutical composition comprising Compound (I), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor, the use of such a composition in medicine, processes for the preparation of such a composition and intermediate composition useful in such a process.

Claims

1. A pharmaceutical composition comprising 5-[4-[2-(N-methyl-N (pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'), characterised in that the composition comprises 2 to 12 mg of Compound (I) in a pharmaceutically acceptable form and optionally a pharmaceutically acceptable carrier therefor.
2. A composition according to claim 1, which comprises 2 to 4 mg of Compound (I) in a pharmaceutically acceptable form.
3. A composition according to claim 1, which comprises 4 to 8 mg of Compound (I) in a pharmaceutically acceptable form.
4. A composition according to claim 1, which comprises 8 to 12 mg of Compound (I) in a pharmaceutically acceptable form.
5. A composition according to claim 1, which comprises 2 mg of Compound (I) in a pharmaceutically acceptable form.
6. A composition according to claim 1, which comprises 4 mg of Compound (I) in a pharmaceutically acceptable form.
7. A composition according to claim 1, which comprises 8 mg of Compound (I) in a pharmaceutically acceptable form.

• **EXAMPLE 15**

High dose ibandronate formulation

Patent number: US2004121007

Publication date: 2004-06-24

The invention relates to a high dose oral formulation of bisphosphonates and to a process for the preparation of such formulations.

Claims

1. A pharmaceutical composition containing as active substance up to about 250 mg of bisphosphonates or a pharmaceutically acceptable salt thereof for oral application.
4. A pharmaceutical composition according to claim 1 comprising the equivalent of 150 mg bisphosphonates or a pharmaceutically acceptable salt thereof as active substance.
5. A pharmaceutical composition according to claim 1 comprising the equivalent of 100 mg bisphosphonates or a pharmaceutically acceptable salt thereof as active substance.
6. A pharmaceutical composition according to claim 1, wherein the active substance is ibandronic acid or a pharmaceutically acceptable salt thereof.

- **EXAMPLE 16**

Dosage forms and method for ameliorating male erectile dysfunction

Patent number: WO9528930

Publication date: 1995-11-02

Psychogenic impotence or erectile dysfunction can be identified in psychogenic male patients and can be ameliorated, without substantial undesirable side effects, by sublingual administration of apomorphine dosage forms that contain about 2.5 to about 10 milligrams of apomorphine and dissolve within a time period of about 2 to about 5 minutes.

Claims

1. A method of ameliorating erectile dysfunction in a psychogenic male patient which comprises administering to said patient apomorphine or a pharmaceutically acceptable acid addition salt thereof sublingually prior to sexual activity, and in an amount sufficient to induce an erection adequate for vaginal penetration but less than the amount that induces nausea.
 2. The method in accordance with claim 1 wherein the amount of apomorphine administered is in the range of about 2.5 milligrams to about 10 milligrams.
 3. The method in accordance with claim 1 wherein the amount of apomorphine administered is in the range of about 25 to about 60 micrograms per kilogram of body weight.
 4. The method in accordance with claim 1 wherein apomorphine is administered as the hydrochloride salt.
-

- **EXAMPLE 17**

Salts of amlodipine

Patent number: GB19860008335

Publication date: 1993-04-30

Improved pharmaceutical salts of amlodipine, particularly the besylate salt, and pharmaceutical compositions thereof. These salts find utility as anti-ischaemic and anti-hypertensive agents.

Claims

1. The besylate salt of amlodipine.
-

- **EXAMPLE 18**

Paroxetine methanesulfonate

Patent number: GB2336364

Publication date: 1999-10-20

Paroxetine methanesulfonate is a novel compound having pharmaceutical activity. It may be obtained as a 1:1 solvate with acetonitrile and it can be converted to paroxetine hydrochloride.

Claims

1. Paroxetine methanesulfonate.

• **EXAMPLE 19**

Bisulfate salt of HIV protease inhibitor (atazanavir)

Patent number: US6087383

Publication date: 2000-07-11

The present invention provides the crystalline bisulfate salt of the formula which is found to have unexpectedly high solubility/dissolution rate and oral bioavailability relative to the free base form of this azapeptide HIV protease inhibitor compound.

Claims

1. The bisulfate salt having the formula
 2. A pharmaceutical dosage form comprising the bisulfate salt of claim 1 and a pharmaceutically acceptable carrier.
-

• **EXAMPLE 20**

Intermediates and process for preparing olanzapine

Patent number: EP0831098

Publication date: 1998-03-25

The present invention provides a process for preparing olanzapine and intermediates therefor.

Claims

1. A compound which is an olanzapine dihydrate.
 2. A compound of Claim 1 wherein the dihydrate is an intermediate for preparing Form II olanzapine.
 3. A compound of Claim 1 wherein the dihydrate is crystalline Dihydrate B olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings (d) as set forth in Table 2 [omitted]:
-

• **EXAMPLE 21**

Crystalline polymorphic form of irinotecan hydrochloride

Patent number: WO03074527

Publication date: 2003-09-12

This invention relates to a novel crystalline polymorphic form of irinotecan hydrochloride. A process for preparing this novel polymorphic form, pharmaceutical compositions comprising it as an active ingredient and the use of the same and its pharmaceutical compositions as a therapeutic agent is also within the scope of the present invention.

Claims

1. Polymorphic form of crystalline irinotecan hydrochloride of formula:
EMI21.1 characterized by providing an X-ray powder diffraction pattern comprising 20 angle values of about 9.15 ; about 10.00 ; about 11.80 ; about 12.20 ; about 13.00 and about 13.40.

- **EXAMPLE 22**

Ranitidine

Patent number: US4521431

Publication date: 1985-06-04

A novel crystal form of ranitidine (N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethenediamine) hydrochloride, designated Form 2, and having favorable filtration and drying characteristics, is characterized by its infra-red spectrum and/or by its x-ray powder diffraction patterns.

Claims

Form 2 ranitidine hydrochloride characterised by an infra-red spectrum as a mull in mineral oil showing the following main peaks [*table omitted*]

- **EXAMPLE 23**

Cephadroxil monohydrate

Patent Number: US4504657

Publication date: 1985-03-12

A novel crystalline monohydrate of 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-cephem-4-carboxylic acid is prepared and found to be a stable useful form of the cephalosporin antibiotic especially advantageous for pharmaceutical formulations.

Claims

1. Crystalline 7-[D- α -amino- α -(p-hydroxyphenyl)acetamido]-3-methyl-3-cephem-4-carboxylic acid monohydrate exhibiting essentially the following x-ray diffraction properties:

<tb>Line Spacing d(A)

<tb> Relative Intensity

<tb>1 8.84 100

<tb>2 7.88 40

<tb>3 7.27 42

- **EXAMPLE 24**

Heterocyclic compounds

Patent number: GB2078719

Publication date: 1982-01-13

Fungicidal compounds of the formula [] wherein R1 is an optionally substituted-alkyl, -cycloalkyl, -aryl or -aralkyl group, Y1 and Y2 are =CH- or =N-; and salts, metal complexes, ethers and esters thereof.

Claims

1. A compound selected from the group consisting of compounds having the formula: III [*omitted*]

wherein R¹ is selected from the group consisting of: phenyl or benzyl substituted with one or more of the following: halogen, alkyl or haloalkyl each containing from 1 to 5 carbon atoms, alkoxy or haloalkoxy each containing from 1 to 4 carbon atoms, nitro, cyano, hydroxy, alkylthio containing from 1 to 40 carbon atoms, vinyl, phenyl or phenoxy; and wherein the alkyl moiety of the benzyl is unsubstituted, or substituted with alkyl containing from 1 to 4 carbon atoms, phenyl or chlorophenyl, Y¹ and Y² are =CH or .=N; and salts, metal complexes, methyl, ethyl, propyl, butyl, phenyl, benzyl, p-chlorobenzyl, allyl and propargyl ethers and acetate, pivaloate, benzoate, tosylate and mesylate esters thereof.

• **EXAMPLE 25**

Substantially pure enantiomers of 2-azabicyclo(2,2,1)hept-5-en-3-one

Patent number: US5498625

Publication date: 1996-03-12

Lactams of 1-amino-3-carboxylic acid cyclic compounds are produced in enantiomeric form, together with an enantiomer of the corresponding ring-opened amino-acid or ester, by reaction of the racemic lactam with a novel lactamase. The products are useful in the synthesis of chiral carbocyclic nucleotides. The enantiomer is preferably 2-azabicyclo(2,2,1)hept-5-en-3-one. It is desirable to isolate the enantiomer comprising predominantly the (+) enantiomer and a residual amount of the (-) enantiomer, wherein the (+) enantiomer is present in an enantiomeric excess of at least about 88% over the (-) enantiomer or the enantiomer comprising predominantly the (-) enantiomer and a residual amount of the (+) enantiomer, wherein the (-) enantiomer is present in an enantiomeric excess of at least about 98% over the (+) enantiomer.

Claims

1. 2-Azabicyclo(2,2,1)hept-5-en-3-one, comprising predominantly the (+) enantiomer and a residual amount of the (-) enantiomer, wherein the (+) enantiomer is present in an enantiomeric excess of at least about 88% over the (-) enantiomer
2. The 2-azabicyclo-[2,2,1]hept-5-en-3-one of claim 1, formed by a process comprising the steps of reacting a racemate of 2-azabicyclo(2,2,1)hept-5-en-3-one with an enzyme having lactamase activity or a microorganism having lactamase activity which stereoselectively cleaves the (-) enantiomer thereby forming the (-) enantiomer of 4-amino-cyclopent-2-ene-1-carboxylic acid or an ester thereof, and then isolating the 2-azabicyclo(2,2,1)hept-5-en-3-one having an enantiomeric excess of the (+) enantiomer.

• **EXAMPLE 26**

New enantiomers and their isolation

Patent number: EP0347066B1

Publication date: 1995-03-15

The novel (+) enantiomer of 1-(3-dimethylaminopropyl)-1-(4 min -fluorophenyl)-1,3-

dihydroisobenzofuran-5-carbonitrile as well as acid addition salts thereof are described as valuable antidepressants, geriatrics or in the treatment of obesity and alcoholism. Novel intermediates and a method for the preparation of the (+) enantiomer as well as the racemic mixture are described.

Claims

1. (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile having the general formula and non-toxic acid addition salts thereof.
6. A method for the preparation of a compound as defined in claim 1, which comprises, converting(-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxy methyl)benzonitrile or a monoester thereof in a stereoselective way to (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof

- **EXAMPLE 27**

Terfenadine

Patent number US 6509353

Publication date: 2003-01-21

Methods and pharmaceutical compositions employing a terfenadine metabolite and a leukotriene inhibitor for the treatment or prevention of inflammation or allergic disorders, such as asthma, or symptoms thereof. Also included are methods and compositions employing a terfenadine metabolite, a leukotriene inhibitor, and a decongestant for the treatment or prevention of inflammation or allergic disorders, such as asthma, or symptoms thereof.

Claims

1. A method for treating or preventing a condition responsive to leukotriene inhibition in a human which comprises administering to a human in need of such treatment or prevention a therapeutically effective amount of terfenadine metabolite, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a leukotriene inhibitor, or a pharmaceutically acceptable salt thereof.

- **EXAMPLE 28**

1-phenyl-2-dimethylaminomethyl cyclohexane compounds used for the therapy of depressive symptoms, pain, and incontinence

Patent number: WO2004009067

Publication date: 2004-01-29

The invention relates to metabolites of [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine as free bases and/or in the form of physiologically acceptable salts, corresponding medicaments, the use of [2-(3-methoxyphenyl)-cyclohexylmethyl]-dimethylamine and the metabolites thereof for producing a medicament used for treating depressions, and methods for treating depressions.

Claims

1. Use of :

-3-(2-dimethylaminomethyl-ciclohexyl) - phenol(1R,2R)-3-(2-dimethylaminomethyl-cycloexyl)-phenol [...]

optionally in the form of their racemates, their pure stereoisomers, in particular enantiomers or

diastereomers, or in the form of mixtures of the stereoisomers, in particular the enantiomers or diastereomers, in any desired mixture ratio; in the form shown or in the form of their acids or their bases or in the form of their salts, in particular the physiologically acceptable salts, or in the form of their solvates, in particular the hydrates; for the preparation of a medicament for treatment of depressions.

• **EXAMPLE 29**

N3 Alkylated Benzimidazole derivatives as MEK inhibitors

Patent number: WO03077855

Publication date: 2003-09-25

Disclosed are compounds of the formula (I) and pharmaceutically acceptable salts and prodrugs thereof, wherein W, t, R<1>, R<2>, R<7>, R<9>, R<10>, R<11> and R<12> are as defined in the specification. Such compounds are MEK inhibitors and useful in the treatment of hyperproliferative diseases, such as cancer and inflammation, in mammals. Also disclosed is a method of using such compounds in the treatment of hyperproliferative diseases in mammals, and pharmaceutical compositions containing such compounds.

Claims

1. A compound of the formula [*Formula omitted*]

and pharmaceutically accepted salts, prodrugs and solvates thereof, wherein: R1, R2, R9 and R10 are independently selected from hydrogen, halogen, cyano, nitro, trifluoromethyl, difluoromethoxy, trifluoromethoxy, azido, -[...].

• **EXAMPLE 30**

Prodrugs of carbonic anhydrase inhibitors

Patent number: US5095026

Publication date: 1992-03-10

Prodrugs are prepared of the carbonic anhydrase inhibitors 2-benzothiazolesulfonamide, hydroxymethazolamide, and dichlorphenamide. The prodrugs link a water soluble compound to the pharmacologically active carbonic anhydrase inhibitor through an enzymatically or hydrolytically degradable bond.

Claims

1. Prodrugs of 2-benzothiazolesulfonamide carbonic anhydrase inhibitors (CAI) having the formula:

wherein Z is a water soluble carrier, and A is a moiety which when attached to said 2-benzothiazolesulfonamide will still retain CAI activity and which can also form an enzymatically cleavable bond with Z .

2. The prodrugs of claim 1 wherein the water soluble carrier Z is selected from the group consisting of monosaccharides and 6-carboxylic acid derivatives of monosaccharides.

- **EXAMPLE 31**

Controlled release pharmaceutical composition containing midodrine and/or desglymidodrine

Patent number: WO0174334A1

Publication date: 2001-10-11

Novel controlled release pharmaceutical compositions for oral use containing midodrine and/or its active metabolite desglymidodrine. The novel compositions are designed to release midodrine and/or desglymidodrine after oral intake in a manner which enables absorption to take place in the gastrointestinal tract so that a relatively fast peak plasma concentration of the active metabolite desglymidodrine is obtained followed by a prolonged and relatively constant plasma concentration of desglymidodrine. Also disclosed is a method for treating orthostatic hypotension and/or urinary incontinence, the method comprising administration to a patient in need thereof of an effective amount of midodrine and/or desglymidodrine in a composition according to the invention.

Claims

1. A controlled release pharmaceutical composition for oral use comprising midodrine (ST 1085) or a pharmaceutically acceptable salt thereof and/or its active metabolite desglymidodrine (ST 1059) or a pharmaceutically acceptable salt thereof, the composition being adapted to release midodrine and/or desglymidodrine in such a manner that a relatively fast peak plasma concentration of desglymidodrine is obtained and that a therapeutically effective plasma concentration of desglymidodrine is maintained for at least about 9 hours such as, e.g. at least about 10 hours, at least about 11 hours, at least about 12 hours, at least about 13 hours, or at least about 14 hours.

- **EXAMPLE 32**

Pharmaceutically active morpholinol

Patent number: US6274579

Publication date: 2001-08-14

New active isomer of bupropion morpholinol metabolite.

Claims

1. (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or pharmaceutically acceptable salts and solvates thereof.
2. Pharmaceutical compositions comprising a compound according to claim 1 or pharmaceutically acceptable salts and solvates thereof together with one or more pharmaceutically acceptable carriers, diluents or excipients.

• **EXAMPLE 33**

Antihistaminic 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines

[Loratadine] Patent number: US4282233

Publication date: 1981-08-04

11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines and their 5,6-dihydro derivatives are disclosed. The compounds are useful as antihistamines with little or no sedative effects.

Claims

1. A compound of the formula wherein the dotted line represents an optional double bond; X is hydrogen or halo; and wherein Y is --COOR or SO₂ R; with the proviso that when Y is --COOR, R is C₁ to C₁₂ alkyl, substituted C₁ to C₁₂ alkyl, phenyl, substituted phenyl, C₇ to C₁₂ phenylalkyl, C₇ to C₁₂ phenylalkyl wherein the phenyl moiety is substituted or R is -2,-3, or -4 piperidyl or N-substituted piperidyl wherein the substituents on said substituted C₁ to C₁₂ alkyl are selected from amino or substituted amino and the substituents on said substituted amino are selected from C₁ to C₆ alkyl, the substituents on said substituted phenyl and on said substituted phenyl moiety of the C₇ to C₁₂ phenylalkyl are selected from C₁ to C₆ alkyl and halo, and the substituent on said N-substituted piperidyl is C₁ to C₄ alkyl; and with the proviso that when Y is SO₂ R, R is C₁ to C₁₂ alkyl, phenyl, substituted phenyl, C₇ to C₁₂ phenylalkyl, C₇ to C₁₂ phenylalkyl wherein the phenyl moiety is substituted, wherein the substituents on said substituted phenyl and said substituted phenyl moiety of the C₇ to C₁₂ phenylalkyl are selected from C₁ to C₆ alkyl and halo.
7. 11-(N-carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine [The active metabolite of loratadine is descarboethoxyloratadine (DCL)]

• **EXAMPLE 34**

Antihistaminic 8-(halo)-substituted 6,11-dihydro-11-(4-piperidylidene)-5H-

benzo[5,6]cyclohepta[1,2-b]pyridines

Patent number: US4659716

Publication date: 1987-04-21

Disclosed are 7- and/or 8-(halo or trifluoromethyl)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines and the pharmaceutically acceptable salts thereof, which possess antihistaminic properties with substantially no sedative properties. Methods for preparing and using the compounds and salts are described.

Claims

1. A compound of the formula or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.

- **EXAMPLE 35**

Methods of treating HIV infection

Patent number: WO2005058237

Publication date: 2005-06-30

The invention includes methods of treating HIV infection in a patient where the method includes administration of an antibody to TNF-alpha and an antibody to interferon-gamma to the patient and administering antiretroviral therapy to a patient. The invention further includes methods of treating HIV infection in a patient where the method comprises administration of an antibody to TNF-alpha and an antibody to alpha interferon to the patient and administering antiretroviral therapy to a patient. The invention further includes a method of treating HIV infection in a patient where the method includes administering an antibody to alpha interferon and antiretroviral therapy to a patient. The invention further includes a method of treating an HIV infection in a patient where the method comprises administering a chimeric TNF-alpha receptor and antiretroviral therapy to a patient.

Claims

1. A method of treating an HIV infection in a treatment experienced patient, the method comprising administering an effective amount of a chimeric tumor necrosis factor alpha receptor.
2. The method of claim 1, wherein the chimeric tumor necrosis factor alpha receptor is administered by the route selected from the group consisting of intramuscularly, intravenously, intradermally, cutaneously, subcutaneously, ionophoretically, topically, locally, orally, rectally and inhalation.
3. The method of claim 1, wherein the chimeric tumor necrosis factor alpha receptor is selected from the group consisting of a chimeric tumor necrosis factor alpha receptor comprising a 55 kDa tumor necrosis factor alpha receptor and a chimeric tumor necrosis factor alpha receptor comprising a 75 kDa tumor necrosis factor alpha receptor.
4. The method of claim 1, wherein the treatment experienced patient is further administered an effective amount of an antiretroviral therapy.

- **EXAMPLE 36**

Intraoral dosing method of administering trifluorobenzodiazepines, propoxyphene, and nefazodone

Patent number: US5504086

Publication date: 1996-04-02

A method of therapeutically administering certain BZ1 specific trifluorobenzodiazepines in order to maximize the BZ1 effects and minimize the BZ2 effects on the human central nervous system in order to maximize the anti-anxiety, anticonvulsant and hypnotic effects and minimize the ataxic and incoordination effects of the drug. Also, a method of sublingual administration of trifluorobenzodiazepines and certain other compounds, such as propoxyphene and nefazodone, in order to decrease unwanted metabolites.

Claims

1. A method for administering nefazodone compound to the human central nervous system wherein a therapeutically effective amount of said compound is sublingually or buccally administered to a human, the improvement comprising the steps of: a. selecting a lipid soluble compound comprising 2-(3-(4-(3-chlorophenyl)-1-piperazinyl)propyl)-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3H-1,2,4-triazol-3-one hydrochloride that has one or more unwanted or aversive metabolites comprising m-chlorophenylpiperazine that are increased by portal vein entry to the liver; b. placing said compound in a suitable sublingual or buccal formulation; c. sublingually or buccally administering a therapeutically effective amount of said sublingual or buccal formulation so as to bypass the portal vein entry to the liver and thereby to decrease the formation of the unwanted metabolites; d. increasing the ratio of nefazodone to the unwanted metabolite m-chlorophenylpiperazine made available to the central nervous system; and e. utilizing this sublingual or buccal method over a period of one or more doses to achieve sustained high levels of the nefazodone relative to the unwanted metabolite m-chlorophenylpiperazine.

• EXAMPLE 37

Method for inhibiting bone resorption

Patent number: EP0998292B1

Publication date: 2001-11-21

Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

Claims

1. Use of alendronic acid or a pharmaceutically acceptable salt thereof, or a mixture thereof, for the manufacture of a medicament for inhibiting bone resorption in a human wherein said medicament is adapted for oral administration, in a unit dosage form which comprises from about 8.75 mg to 140 mg of alendronic acid or a pharmaceutically acceptable salt thereof, on an alendronic acid active weight basis, according to a continuous schedule having a periodicity from about once every 3 days to about once every 16 days.

• EXAMPLE 38

Ibandronic acid for the promotion of the osseointegration of endoprostheses

Patent number: EP1135140B1

Publication date: 2005-08-31

The invention relates to use of ibandronic acid (1-hydroxy-3-(N-methyl-N-pentyl)aminopropyl-1,1-diphosphonic acid) or physiologically compatible salts or esters thereof for improving the osseointegration of cement-free anchored endoprostheses. Ibandronate or salts thereof is applied for a short time immediately after insertion of an endoprosthesis, with the surprising result that secondary stability of the implant is obtained in only 5 weeks or less after the operation.

Claims

1. Use of ibandronic acid or physiologically compatible salts or esters thereof for the manufacture of medicaments for improving the osseointegration of cement-free anchored endoprostheses by short term application directly after the operation and for a period of two to four weeks.
2. Use according to claim 1 **characterized in that** ibandronate is in a form for application at a dosage of 1 to 100 µg/kg body weight.
3. Use according to claim 1 or 2, **characterized in that** ibandronate in solution form is in a form for parental application with a content of active substance of 0.01 to 20 mg.

- **EXAMPLE 39**

Terfenadine metabolites and their optically pure isomers for treating allergic disorders

Patent number: WO9403170A1

Publication date: 1994-02-17

A pharmaceutical composition comprising a compound of formula (I): wherein Z is COOH, COOCH₃ or CH₂OH, or a pharmaceutically acceptable salt thereof, for use in an anti-histaminic treatment which does not induce any significant cardiac arrhythmia, comprising administering a therapeutically effective amount of a compound of formula (I) to a human patient.

Claims

1. A pharmaceutical composition comprising a compound of formula I wherein Z is COOH, COOCH₃ or CH₂OH, or a pharmaceutically acceptable salt thereof, for use in an anti-histaminic treatment which does not induce any significant cardiac arrhythmia, comprising administering a therapeutically effective amount of a compound of formula I to a human patient.

- **EXAMPLE 40**

Methods for the treatment of mental disorders

Patent number: WO0113905A2

Publication date : 2001-03-01

The anti-allergic medication comprising loratadine or a metabolite of loratadine

Claims

1. A method for treating a patient suffering from a mental disorder, comprising administering an effective amount of an anti-allergic medication to said patient to diminish the symptoms of said mental disorder.
2. The method of Claim 1, wherein said mental disorder is selected from the group consisting of depression, alcoholism, weight management disorders, social disorder, impotence/sexual dysfunction, panic and obsessive/compulsive disorder.
3. The method of Claim 2, wherein said anti-allergic medication is loratadine or a metabolite of loratadine.
9. The method of Claim 5, wherein said metabolite of loratadine is desloratadine

• **EXAMPLE 41**

Treating premenstrual or late luteal phase syndrome

Patent number: EP0386117

Publication date: 1990-09-12

Abstract (as contained in application WO8903692)

Compositions useful in the treatment of disturbances of appetite, disturbances of mood, or both, associated with premenstrual syndrome, as well as methods of use therefor. The compositions include serotonergic drugs, such as d-fenfluramine and fluoxetine.

Claims

1. Use of one or more serotonin-mediated neurotransmission enhancing drugs for the manufacture of a medicament for treating disturbances of mood, disturbances of appetite, or both, associated with premenstrual syndrome in women.

6. Use of a drug selected from the group consisting of a monoamine oxidase inhibitor, lithium and tryptophan and a drug selected from the group consisting of d-fenfluramine, d,l-fenfluramine, chlorimipramine, cyanimipramine, fluoxetine, paroxetine, fluvoxamine, citalopram, femoxetine, cianopramine, ORG 6582, RU 25591 and LM 5008, IS-4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-naphthylamine, DU 24565, indalpine, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone, amitriptyline imipramine, trimipramine, doxepin, protriptyline, nortriptyline and dibenzoxazepine; b. tryptophan and a drug selected from the group consisting of: metergoline, methysergide, cyproheptadine, deprenyl, isocarboazide, phenelzine, tranlycypromine, furazolidone, procarbazine, moclobemide and brofaromine; c. a drug selected from the group consisting of fluoxetine, paroxetine, cyanimipramine, fluvoxamine, citalopram, femoxetine, cianopramine, ORG 6582, RU 25591, LM 5008, IS-4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-naphthylamine, DU 24565, indapline, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone, amitriptyline, imipramine, trimipramine, doxepin, protriptyline, nortriptyline, dibenzoxazepine, and a drug selected from the group consisting of metergoline, methysergide, and cyproheptadine; or d. d-fenfluramine, d,l-fenfluramine or chlorimipramine and a drug selected from the group consisting of fluoxetine, fluvoxamine, citalopram, femoxetine, paroxetine, cianopramine, ORG 6582, RU 25591, LM 5008, IS-4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-l-naphthylamine, DU 24565, indalpine, CGP 6085/A, WY 25093, alaprociate, zimelidine, trazodone cyanimipramine, amitriptyline, imipramine, trimipramine, doxepin, protriptyline, and dibenzoxazepine; all for the manufacture of a medicament for treating disturbances of mood, disturbances of appetite, or both, associated with premenstrual syndrome, in a woman having premenstrual syndrome.

• **EXAMPLE 42**

Use of carbazole compounds for the treatment of congestive heart failure

Patent number: EP0808162

Publication date: 1997-11-26

Abstract (as contained in application WO9624348)

A method of treatment using a compound of formula (I), wherein R1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl; R2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl; R3 is hydrogen or lower alkyl of up to 6 carbon atoms; R4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R4 together with R5 can represent -CH₂-O-; X is a valency bond, -CH₂, oxygen or sulfur; Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl; R5 and R6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or R5 and R6 together represent methylenedioxy; or a pharmaceutically acceptable salt thereof, preferably carvedilol, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides for decreasing mortality resulting from congestive heart failure (CHF) in mammals, particularly humans.

Claims

10. The use of carvedilol for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals according to the following regimen:
 - (a) administering a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7-28 days, given once or twice daily,
 - (b) administering thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7-28 days, given once or twice daily, and
 - (c) administering finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.
12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schemes comprising three dose regimens, the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7-28 days.

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