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Drug patents under the spotlight

Sharing practical knowledge
about pharmaceutical patents



Médecins Sans Frontières
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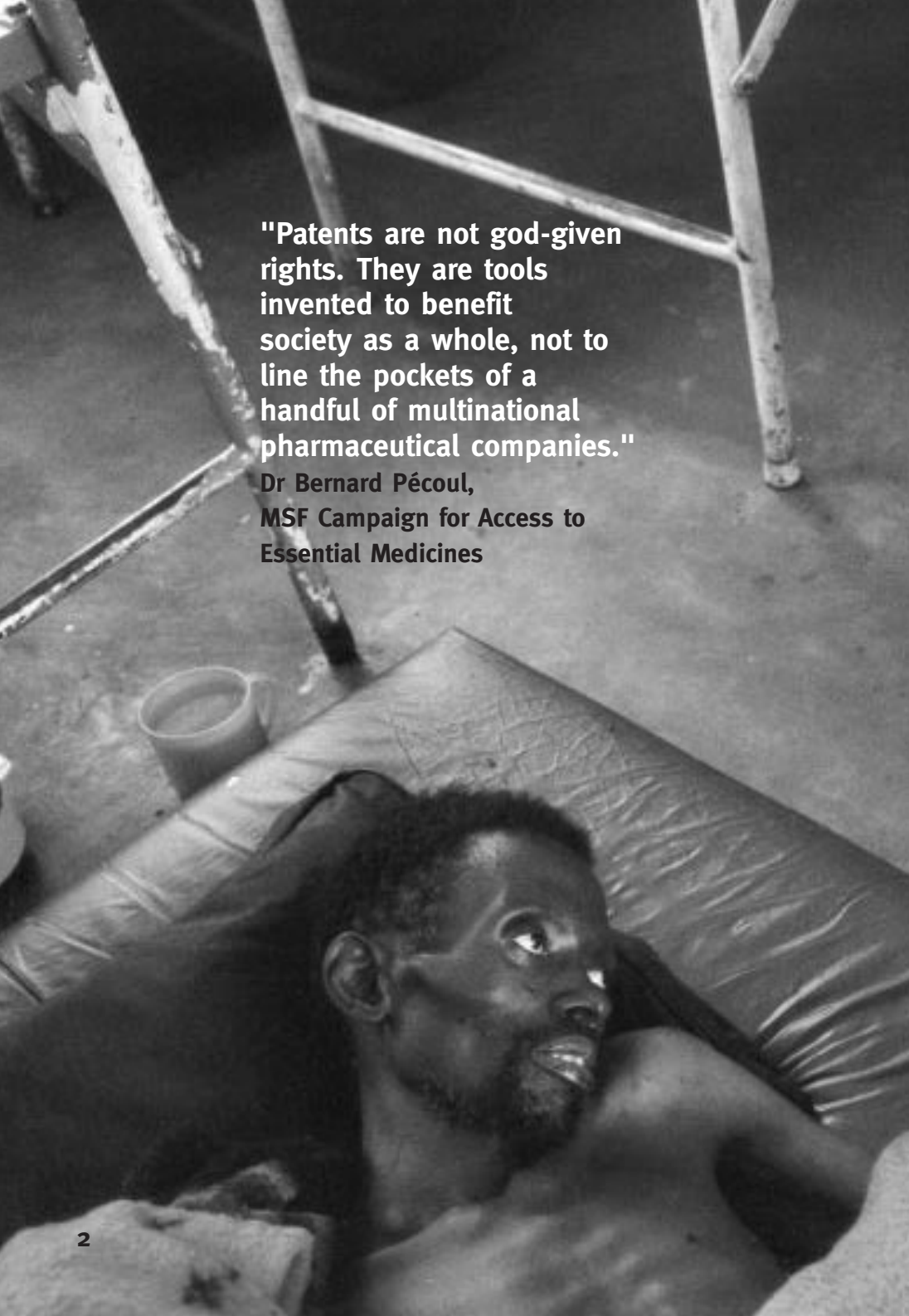
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"Patents are not god-given rights. They are tools invented to benefit society as a whole, not to line the pockets of a handful of multinational pharmaceutical companies."

**Dr Bernard Pécoul,
MSF Campaign for Access to
Essential Medicines**

1 ■ Introduction

Patents have been one of the most hotly debated topics on access to essential medicines since the creation of the World Trade Organization (WTO) and the conclusion of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) in 1994. Patents are by no means the only barrier to access to life-saving medicines, but they can play a significant, or even determinant, role in that they grant the patent holder a monopoly on a drug for a number of years. The patent holder's freedom to set prices has resulted in drugs being unaffordable to the majority of people living in developed countries.

On the other hand, a functioning patent system is also supposed to guarantee that the public at large benefits from any innovation, including medicines. Countries have deployed various strategies to strike a balance between private and public interests in their intellectual property systems, and they have had various degrees of success. Getting the balance just right is particularly important for governments of developing countries as they work to protect public health while making their patent laws TRIPS compliant.

A full and frank re-appraisal of the role that a patent system plays in public health alongside other public policy tools is now taking place. The WTO 2001 Doha Declaration on TRIPS and Public Health has played a powerful role in this process. Another important development has been the publication of the report of the UK Commission on Intellectual Property Rights, "Integrating Intellectual Property Rights and Development Policy" in September 2002^[1], which strongly advocated for patent systems that support the public health policies of developing countries, according to the needs and level of development of each country.

Médecins Sans Frontières (MSF) works in many developing countries around the world. Procurement of medicines is part of the organisation's daily business, which is why we are interested in knowing which medicines are patented in which countries. This information is currently not publicly available in a form that can be easily understood.

Some patent surveys have given only yes or no answers about whether or not a medicine is patented in a given country. But the situation is more complicated than that. For use in its own projects, MSF has had to gather the necessary information for itself. This document has grown out of that process. The table in Annex A shows the patent data we collected regarding 18 pharmaceuticals in 29 countries.

This report hopes to further inform the debate about pharmaceutical patents amongst a wider audience. For those WTO Members that do now provide patent protection for pharmaceutical products, much of the debate surrounding patents and access to essential medicines has so far focused on safeguards in the TRIPS Agreement, such as parallel importation, compulsory licensing and government use^[2], that take effect after a patent has been granted. However, even when fully implemented, the TRIPS Agreement still allows some degree of decision making by WTO Members before a patent has been granted, i.e. about what sort of inventions they will grant patents for. This report focuses on the latter. It draws from MSF's practical experience and is intended to complement much of the work done so far on overcoming patent barriers.

The TRIPS Agreement sets out the minimum standards for patent protection all WTO Members must abide by. Unlike in the days before the TRIPS Agreement, countries that are Members of the WTO can no longer rule out granting patents in particular fields of technology, such as the pharmaceutical sector. But the TRIPS Agreement also requires that patents are granted for inventions which, among other things, are new and inventive. There is no internationally accepted definition of either of these terms and different WTO Members have taken very different approaches, deciding on definitions that best suit their needs. This document will give some concrete examples of the different choices available and the consequences of those choices.

No patent office is perfect. Many patents issued in, for example, the European Patent Office or the United States Patent Office have turned out to be invalid when tested by a court. No patent office is or ever could be in such a position of perfect knowledge that they grant only valid patents. The fact that patents in, for example, OECD countries get revoked now and again shows that there are checks and balances in place to catch cases where a patent should not have been granted.

But when we studied patent systems in developing countries, it quickly became apparent that in many of these countries, very few if any patents have ever been revoked. This cannot be right. The lack of feedback demonstrates that the system isn't functioning properly. Challenging invalid patents is a topic that has received little detailed attention so far. A recent court decision in Thailand gives some hope that this situation may be changing, as will be discussed below.

This report is aimed at a non-expert, non-legal audience, and it aims to offer new approaches to those seeking to overcome patent barriers. We also hope that those with responsibility for deciding which sorts of patents to grant and which not to grant will find some new issues to take into account, so that fewer patent barriers are created in the first place.

MSF is a humanitarian medical aid organisation. We focus on people in need of care. We gathered the information contained in this report as we struggled to find the most appropriate and affordable care for our patients. We grew more familiar with pharmaceutical patents, the TRIPS Agreement and the WTO in the process – not because we wanted to, but because we had to.

Although we are happy to share some of what we have learned, others cannot be complacent. For reasons that we will explain in this report, the information presented can never be regarded as complete. We call on organisations such as the World Health Organization and the World Intellectual Property Organization to use their expertise, resources and mandate to take the work of this report further and produce the public, easily understood and transparent database on pharmaceutical patent status that is so necessary.

We welcome any comments on this report. They should be addressed to access@geneva.msf.org.



2 ■ Four key concepts to understanding drug patents

Some people say that there are “pernicious myths” circulating about patents, pharmaceutical patents in particular, and that a “demystification” needs to take place. We couldn’t agree more. In this chapter we will present some of the issues that most commonly arise on the subject of pharmaceutical patents. The general theme to bear in mind is diversity: different countries have the flexibility to adopt different options in designing their patent systems to best suit their own needs. What works for an OECD country may not work for a least developed country. A patent may be granted for an invention in one country, yet it may be perfectly legally rejected in another. A patent that has been granted in a country may be revoked if it turns out the patent office should not have granted it.

The way a patent is constructed is examined in Annex B with the help of a practical example: a patent for stavudine, a drug used in AIDS combination therapy.

Photo: © Remco Bahle

■ 2.1 The rationale for patents

Patent systems have a long history. They developed as a way to promote innovation, originally either by encouraging the importation of new technologies into a country or by making new inventions. Instead of keeping the invention a secret, countries learned that one effective way of getting inventors to publicly disclose their invention was to offer them limited monopoly rights in exchange for doing so. One way these patent rights were limited was in time, e.g. 7, 14 or 20 years. After this period of time the monopoly rights were lifted and everybody could use the invention freely.

If the invention was not a success, the applicant would abandon the patent application, or stop paying the annual fees to the patent office to keep the patent alive.

So, in theory, the public learned quickly about a new invention when the patent application describing the invention was published, and eventually got free access to use it. In the meantime, the patent holder profited from the patent by selling the new invention at a higher price than would have been the case without a patent since the patent monopoly prevents competition. In an

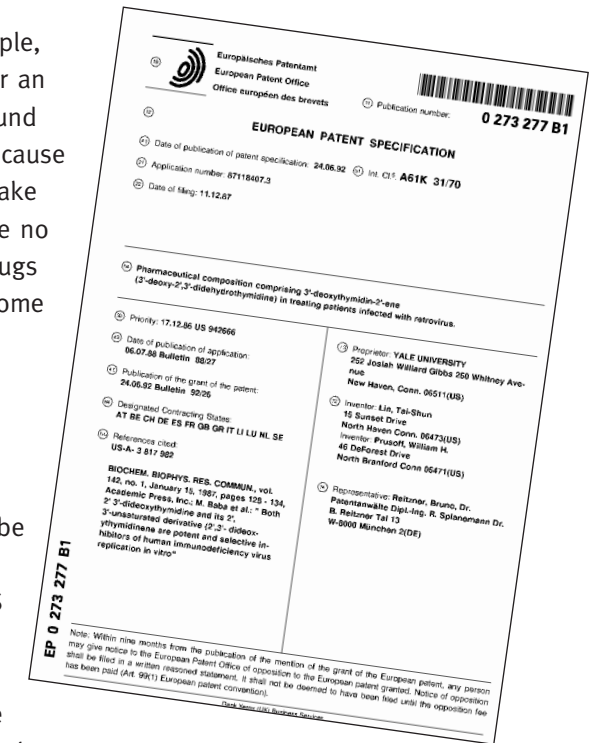
ideal case, both parties benefit from this patent bargain.

Adopting a patent system is supposed to encourage investment of resources in making inventions. Research and development (R&D) for new medicines, and in particular the progress in modern Western medicine, is often given as a good example. In fact, R&D into medicines for some diseases is a good example of exactly the opposite. For neglected diseases such as sleeping sickness, Chagas disease or leishmaniasis, which only affect poor people, a patent holder will never be able to make a profit by charging high prices, so little R&D is conducted on these diseases. The argument for a patent system encouraging R&D for medical needs in their countries falls far short^[3].

Whether or not the patent system delivers the right R&D, the patent monopoly means that a higher price than necessary has to be paid for patented inventions. This is acceptable if this higher price is merely an inconvenience (say, if you can't afford a new patented pen, you can always still use a cheap, old-fashioned pen, or a pencil). However, if the patented invention is essential (say, if it could prevent your untimely death from a disease), then the price is more of a

dilemma. To give a concrete example, the price patent holders charge for an AIDS drug cocktail remains at around US\$10,000 in rich markets. But because generics companies are able to make their own version^[4] where there are no patents to prevent them, these drugs are now available to patients in some developing countries for less than US\$300.

Accordingly, it is crucial that a careful decision is made to distinguish between what should be allowed to be patented and what should not. Before the WTO TRIPS Agreement was signed, states were free to determine what would or would not be patentable within the country. States didn't make one-off, long-term decisions on patents. What they allowed to be patented varied a lot over time depending on the state of development of the country. The scope of patents has not always been expanded; in fact, states have sometimes decided to deny the patentability of inventions that were previously patented, or even abandoned their patent system altogether. The patenting of essential goods such as medicines and foods was for a long time thought to be self-evidently against the public interest. Indeed, when the Uruguay Round of WTO trade negotiations was launched



in 1986, more than 50 countries were not granting patents on pharmaceuticals^[5]. However, the general trend in industrialised countries has been that the “boundaries of the patent system are re-drawn (almost always by widening) as industries which are used to working with patents extend their ambit of operation. In their campaigns for novel patents, they are likely to succeed except where they meet persistent and implacable opposition from some other interest group”^[6].

In rich countries, extensive pharmaceutical patent protection and the high drug prices it entails may not produce immediate health crises since the majority of the population can pay these prices for the new inventions, either privately or through insurance schemes or other public health services – although even this model is looking increasingly stretched in Europe and the United States. In poor countries, where people pay for drugs out of their own pockets and very seldom have health insurance, excessive prices of medicines become a question of life and death.

The pro-pharmaceutical patenting lobby argues time and time again that without patents there will be no new medicines. This is a lazy argument. For example, Africa accounts for some 1% of the world's medicine market. If there were no patent protection at all in Africa, and even if Big Pharma ended up making no sales on the continent, their profits would be only negligibly impacted. Their ability to generate income to perform more R&D – and produce enormous returns for their shareholders – depends overwhelmingly on OECD markets. Patent protection in developing countries is not going to make the difference between Big Pharma developing new medicines or not.

If a developing country chooses to adopt different rules for its patent system than those used, for example, in the United States or Europe, it doesn't mean that system is of a lower standard or quality than the US or European systems. Just giving patent protection to whatever the US or Europe does is not by itself a sign of a quality system. The standard or quality of the system should be judged by how effectively the patent rules that each country has chosen are used to serve the public interest. For example, if a developing country patent law says that patents cannot be granted for new uses, and that a developing country patent office makes sure that it does not grant any patents for new uses, this can be considered a high quality system.



■ 2.2 One pill, many patents

Many people assume that a patented medicine is protected by one particular patent. Unfortunately, it is not as straight-forward as that. Patents do not protect medicines as such, but “inventions”. In the pharmaceutical sector, such an invention may for example relate to a product (e.g. a specific molecule), a process (e.g. the process to manufacture this molecule), a medical indication (e.g. the effect of this molecule on a human body), or a combination of products (e.g. a fixed dose combination of two molecules).

As a consequence, a single medicine can be protected by a large number of separate patents, each relating to a different invention. A company doing basic research for the treatment of a particular disease may discover (or rather, invent) a promising new chemical entity, or molecule, and so a patent application could be filed for this “new” chemical entity (as well as a way of making it). If, as is often the case, the new molecule was actually a whole family of related molecules, it may subsequently be found that a specific sub-group or element of that family is more promising (a so-called selection invention). It may also be that a particularly effective form (e.g. a crystalline form or an optical isomer) is

found, or that it is discovered that this new molecule works particularly effectively in combination with another known molecule. Forms of the active ingredient that appear after a substance has been taken and the body has metabolised it may additionally be found. All these related yet separate inventions may be translated into separate patent applications. Once the best active ingredient(s) have been identified, it may be that the focus of the effort shifts to ways in which they can be delivered, i.e. in what form they should be manufactured. Patent applications on formulations (including e.g. powders, tablets and capsules) may then also be filed. New methods of production may be found. Even years later, scientists may discover that the molecule works against another disease or affliction than the one(s) it was originally patented for, and another patent application (or set of patent applications) can be filed for this “new use” of the now old molecule.

In keeping with the patent bargain, the subject matter of each patent must become available for public use at the end of the patent term, which according to TRIPS Article 33 is now 20 years from the filing date of the patent application. If a later patent application tries to re-monopolize the invention as described in an earlier patent, it should

be rejected^[7]. Clearly there is a significant threat that patent holders will, in effect, be able to extend their 20-year monopoly on the basic molecule by obtaining a series of new patents derived from the basic patent, each new patent based on inventions of the sort listed above and each with their own further 20-year period of monopoly. This process is known as 'ever-greening'^[8] and is by no means a secret in the pharmaceutical industry^[9].

If, for one reason or another, the public always ends up using the version of the medicine which incorporates the latest derivative invention, then the patent holder will, in effect, be able to prolong the monopoly for as long as the patent office keeps granting patents. But there is no international obligation under the TRIPS Agreement, or any other global agreement, to accept and grant patents for all these additional inventions^[10].

■ 2.3 International patents do not exist

There is, as yet, no such thing as an international or global patent^[11]. When a company is said to have patented a medicine worldwide, it really means that they have a whole collection of different patents, one for each country or region of interest to them^[12].

Most people know that patents confer a monopoly on their owner. It is probably less clear how the patent owner's monopoly rights relate to, for example, the TRIPS Agreement.

The TRIPS Agreement is an agreement between WTO Member States. It requires WTO Member States to enact or modify their own patent legislation to regulate the granting and enforcement of patents in accordance with some minimum international rules that it defines. If a WTO Member fails to include such TRIPS rules in their national/regional legislation or includes them in a way which another WTO member does not agree with, then that and/or other WTO Members could file a complaint before the WTO. Private companies or individuals cannot sue a WTO Member at the WTO for failing to have a TRIPS compliant patent law^[13], although it is perhaps true to say that if they can get their government

involved on their behalf, it can amount to much the same thing^[14].

The TRIPS Agreement only provides a general framework with minimum standards for national patent laws. It obliges WTO Members, for example, to grant patents in any field of technology and specifies what minimum exclusive rights a patent should confer. It is then up to the national or regional legislation to implement or complement the general rules contained in the TRIPS Agreement. It is the national or regional rules that make up the basis for the granting and enforcement of patents, not the TRIPS Agreement itself.

At the national level, according to TRIPS Article 28, patents shall confer on their owner the exclusive right to prevent others from "making, using, offering for sale, selling, or importing for these purposes" the invention without the owner's consent. Given that all these rights should be included in the national patent law, if someone makes, uses, offers for sale, sells, or imports for these purposes a patented product, or a product made with a patented process, without the patent owner's permission, then (s)he is likely to be infringing the patent – subject to possible exceptions in accordance with the national law. However, because these rights are only

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CASE STUDY

Patents may hamper the development of new fixed dose combinations

Patents are negative rather than positive rights, they allow a patent holder to stop somebody else from using their invention but they do not actually give permission for the patent holder to use the invention. This has very important consequences for medicines. GlaxoSmithKline (GSK) has patents not only for zidovudine (AZT) and lamivudine (3TC) but also for a fixed dose combination of the two, Combivir® (AZT+3TC). Boehringer Ingelheim (BI) has patents for nevirapine (NVR). The triple combination AZT, 3TC and nevirapine (NVR) is very effective in the fight against HIV/AIDS. Imagine that a single pill could be made containing AZT, 3TC and NVR. This would be much easier for patients to take than individual pills for each. However, where patents exist, either GSK or BI could stop anybody else from manufacturing this pill (since they would infringe both GSK's and BI's patents) but neither GSK nor BI make the pill themselves either (since they would infringe each others' patents). A patent stalemate could prevent anybody from having what would be a vital public health tool. But in fact a single pill containing AZT, 3TC and NVR is produced by the Indian company Cipla, under the name "Duovir-N". This has been possible because the relevant patents are not in force in India. In this sense Cipla has been able to do what Big Pharma is prevented from doing by patents – but this will change when India's patent law becomes TRIPS compliant in 2006. GSK has a triple therapy single pill, "Trizivir", which is limited to containing only those drugs for which they own the patent rights, in this case AZT, 3TC and abacavir.

CASE STUDY

Do imports of generic medicines constitute an infringement in Kenya?

In Kenya, MSF and another local NGO, MEDS, import generic versions of antiretroviral medicines protected by the African Regional Industrial Property Organization (ARIPO) patents. The NGOs are doing this on the basis of section 58(2) of the Kenyan Industrial Property Act 2001, according to which “The rights under the patent shall not extend to acts in respect of articles which have been put on the market in Kenya or in any other country or imported into Kenya”. Regulation 37 of the Industrial Property Regulations 2002 further clarifies that “the limitation on the rights under a patent in section 58(2) of the Act extends to acts in respect of articles that are imported from a country where the articles were legitimately put on the market”.

In accordance with the TRIPS Agreement^[18] and as confirmed by the Doha Declaration on TRIPS and Public Health^[19], Kenya – like any other WTO Member – is allowed to provide for such limitations and exceptions to the rights conferred by patents. Such a limitation/exception is to be regarded as TRIPS-compliant as long as (following another WTO Member contradicting it and filing a WTO complaint thereon) the WTO has not ruled that it is not compliant.

The particular generic versions of medicines were imported from India where they had been legitimately put on the market and therefore fall into the limitation category as provided under section 58(2) and Regulation 37. In addition, the medicines have been duly authorised for use by the Ministry of Health with regard to their quality, safety and efficacy. Should the patent owners disagree with the legitimacy of the importation, it is their responsibility to file an infringement action before the Kenyan Industrial Property Tribunal to claim for damages and/or compensation. Only the Tribunal can assess whether the activities of the NGOs fall under the exception to patent rights.

Thanks to the imported medicines, the local treatment programmes supplied by MEDS are now providing ARVs to up to four times as many patients as before.



▼ The Nyumbani orphanage in Kenya celebrates a donation of 2000 vials of a generic version of the AIDS drug zidovudine from the Brazilian government; the 2001 event was covered by media (Father D’Agostino, the director of the orphanage, interviewed by the press, left) and the Kenyan Minister of State and the Brazilian Ambassador to Kenya participated (second photo from left). As at May 2003, over 30 children living in the orphanage and another 3200 Kenyans living with HIV/AIDS benefit from generic ARVs imported by MSF and MEDS and distributed through local hospitals and treatment programmes, including those run by MSF.

Photos: © MSF



Continued from page 7

private rights, i.e. the state does not police patents for a patent holder^[15], it is up to patent owners to take action before the competent judicial or administrative authorities to stop any infringement. In practice, only after a patent holder has brought a legal action before this competent authority can it be proved that patent infringement has happened^[16]. If a patent holder decides, for one reason or another, not to sue a potential infringer, then the matter will go no further.

Although the state authorities (e.g. the customs authorities) may assist a patent holder, a far more dangerous development from the perspective of access to medicines is the appearance of proposed or actual provisions^[17] to make “deliberate” patent infringement a crime, even if carried out for non-commercial purposes. Instead of the patent holder having to sue, state prosecutors would deal with the matter as a criminal offence. Instead of the patent holder risking looking bad in front of the world (including their shareholders) for suing public health organizations using generic versions of patented medicines, the state would do the job for them. There is absolutely no requirement in the TRIPS Agreement to make any sort of patent infringement a crime. The fight against counterfeiting and piracy (which is required to be

criminalized under the TRIPS Agreement) is a completely different matter than the use of generic versions of patented medicines and patent infringement.

■ 2.4 Existing patents may be invalid

Measures such as compulsory licenses and parallel imports that may be used to overcome patent barriers, and in particular excessive pricing of medicines under patent, have been hotly debated in recent years, and rightly so. However, there has been less debate about whether or not particular pharmaceutical patents are valid. Yet every patent granted is potentially partially or entirely invalid. A patent is deemed to be valid until stated otherwise by a competent administrative or judicial authority, depending on national/regional laws.

The validity of patents is determined according to the conditions of patentability, as laid down in the national and/or regional patent law, and in accordance with general international rules deriving from TRIPS and other agreements that bind Members. TRIPS Article 27.1 states that “patents shall be available for any inventions provided that they are *new*, involve an *inventive step* and are capable of *industrial application*” (italics added).

As a general convention though, the TRIPS Agreement does not define each of these terms, so it is up to WTO Members to determine how the novelty, inventiveness and industrial applicability of a given invention should be understood. This depends on the objectives of the patent law and on previous practice in each Member State, as well as on the country’s own interests. As discussed further below, it is the use that countries make of this freedom that will determine the scope of patentability of pharmaceutical inventions, in conjunction with the possible exclusions of TRIPS Article 27. Whether all or just a selected number of inventions in the pharmaceutical sector are regarded as new, inventive and capable of industrial applications depends on the approach taken in the national law and on the way it is practiced; for instance, in Brazil, the Ministry of Health is involved in evaluating pharmaceutical-related patent applications^[20]. The extent of patentability of pharmaceutical inventions in the developing world will have a major impact on access to medicines in the post-TRIPS implementation era.

In summary, a patent might not be valid even though it has been granted by a patent office. This might be for a variety of reasons: the patent office might have made a mistake in applying the national rules of patentability; the patent office

might not have examined the patent application (see p. 18); the patent office might have made a judgement which turns out to be incorrect; a document might exist which was unknown to the patent office when it granted the patent, and so on. Patent laws should provide mechanisms to challenge granted patents^[21]. If a patent is challenged and found to be invalid by a competent authority, for example a patent office or other administrative body or a court, it should be amended or revoked in whole or in part^[22], depending on what the national law permits. How patents might be challenged is explained on page 18.

It is important that a patent office’s decision to grant a patent taken is not seen as final. These decisions are frequently questioned in industrialised countries, and in the final analysis, it is often a court that settles the matter. Asking these questions, or even bringing an action to revoke a patent, is not necessarily a bad reflection on the patent office or its staff but part of a system of necessary checks and balances intended to protect the public interest.

Unfortunately in many countries that do grant patents, few if any patents have ever been challenged, let alone revoked. Why this might be so is discussed in section 3.5.

3 ■ The patent system should respond to countries' public interest

As pointed out by several experts^[23], developing countries have not always made full use of the options in the TRIPS Agreement to design patent laws that best correspond to their own needs and development objectives. The report of the UK Commission on Intellectual Property Rights^[24] provides a very clear overview of the problem and recommends what might best be done about it.

Many developing countries still have a patent law based on and shaped by that of a former colonial power as part of their legacy. In addition, developing countries often get “technical assistance” in creating, amending or operating their patent systems, for example via collaborative programmes with patent offices in developed countries, or via international organisations such as WIPO. The influence of industrialised country thinking on patents can be either explicit (suggestions for amendment to the patent law^[25]) or implicit (when, for example, a patent office examiner from a developing

MSF volunteers work to increase awareness on HIV/AIDS in a slum in Nairobi, Kenya. ▶



Photo: © Dieter Telemans

country is trained in a cooperation programme with a developed country patent office, they will inevitably be influenced by developed country practices on how to approach patent problems^[26]. Industrialised countries also put pressure on developing countries to make patent laws that favour patent holders such as Big Pharma^[27]. Unfortunately Western patent offices and WIPO do not currently provide technical assistance to implement TRIPS in a pro-public health way^[28], following the Doha Declaration.

Ongoing negotiations within WIPO on a Substantive Patent Law Treaty (SPLT) may have the effect of closing the door to much of the flexibility left to WTO Members on patentability^[29]. These talks aim at harmonizing national/regional patent laws much further than the TRIPS Agreement did, so that a patent could not be granted in one country but rejected in another, as is currently the case. This trend could further hamper access to medicines, as universal patent requirements are very likely to be designed according to standards used in developed countries.

This chapter examines some of the criteria used when the patentability of a product is considered^[30], and discusses some of the practicalities of challenging patents. There is a huge number of



Photo: © Eric Miller

considerations that must be borne in mind when looking at these questions — not least the limited resources available to developing countries.

■ 3.1 The subject matter of a patent must be new

The first fundamental requirement for a valid patent is that the invention is novel. As mentioned earlier, the TRIPS Agreement does not dictate any particular approach to novelty. It is therefore for each WTO Member to determine what is new and what is old.

A typical example of a definition of novelty can be seen in Article 54(1) of the European Patent Convention (EPC)^[31]. It provides that “an invention shall be considered to be new if it does not form part of the state of the art”. The “state of the art” is defined in EPC Art 54(2) to comprise “everything made available to the public by means of written or oral description, by use, or in

◀ South Africa’s dynamic AIDS activist movement has been instrumental in shaping public opinion regarding pharmaceutical patents and other issues around access to essential medicines. A protestor on the stairs of a church on February 14th 2003, when over 10,000 people marched through Cape Town, this time calling on the South African government to introduce a treatment plan for people living with HIV/AIDS.

any other way, before the date of the filing of the European patent application”^[32]. Although this may sound complicated, it is really just the common sense idea that nobody should be allowed to get a patent for something that the public already knew about.

A written description is the most commonly encountered form of disclosure and can include papers published in journals, articles in magazines and patent applications that have been published. An example of oral disclosure might be a researcher describing the invention in a presentation to a conference. Other categories of disclosure include using or demonstrating the product in public, or selling the product^[33].

One important choice still left to WTO Members is whether they define state of the art nationally or internationally. Most countries have chosen to assess it on a global basis rather than just for their own country, thereby allowing their patent examiners to refuse a patent application if the invention has already been revealed to the public in any previous publication or communication worldwide^[34]. On the one hand this gives countries the advantage of considering what the global public rather than the local

public already knew^[35]. On the other hand, exhaustive bibliographic searches are no easy task for IP examiners in developing countries without routine access to international databases. In practice this means that patents might be erroneously granted for inventions that are not novel.

Priority rights are an important concept relating to novelty. In the late 19th century, an earlier era of globalisation, the country-by-country novelty requirement made it difficult for inventors to have their invention protected by patents in several countries. If the invention was made public after a patent application had been filed in one country but not yet in a second country, then when the patent application was eventually filed in the second country, the invention would already be known there and so it could no longer be considered new. Problems like this made it impossible for inventors to obtain patent protection in as many countries as they wanted to. What was needed was a way for each similar patent application filed in a different country to be treated in the same way, as if it was being filed for the first time. This is exactly what the Paris Convention for the Protection of Industrial Property, originally signed in 1883, solved by inventing the “right of priority”.

CASE STUDY

Why patents cannot be filed in Brazil or Thailand to protect existing medicines

The novelty requirement implies that pharmaceutical companies have to file patent applications to protect their inventions at the earliest stage of the development of a medicine, i.e. between basic research and pre-clinical research, without even knowing whether the invention will end up on the market or not.

The novelty requirement helps to explain the availability of generic medicines in some countries, such as Brazil, India or Thailand, as compared to South Africa where many medicines and all ARVs are only available from the patent holder.

The pharmaceutical company Boehringer Ingelheim first applied for a patent protecting the basic molecule of nevirapine, an antiretroviral medicine used to prevent mother-to-child-transmission of HIV/AIDS, in Germany on November 17th 1989. In accordance with the rules of the Paris Convention on the right of priority, the company had until November 17th 1990 to file similar patent applications in any other country. After this date, the novelty of Boehringer Ingelheim's invention was no longer ensured. The company filed a patent application related to nevirapine in South Africa but could not file an application in Brazil or Thailand because the patent laws of these countries did not offer such a possibility at that time. Although both Brazil and Thailand have now revised their patent laws to enable patent protection of pharmaceutical products, the basic molecule of nevirapine cannot be patented any more in these countries because the novelty of the invention has since been destroyed by the publication of the patent application in South Africa and elsewhere, and by the subsequent marketing of the drug.



◀ Thai activists protesting against patent protection of ddI, a key AIDS drug (see p. 20 for more details on the 2001-2002 court case). Bangkok, December 2000.

Photo: © MSF

Under the Paris Convention, the first regular filing of a patent application in a country gives a right of priority to the applicant for the filing of similar patent applications in the vast majority of other countries for a period of 12 months^[36]. The novelty of the invention is thus artificially maintained during those 12 months. The practical consequences of this are important: it is the priority date that a patent office looks at when examining novelty, although the patent term will start running from the filing date. Considerations of novelty are particularly relevant for the class of inventions known as “new uses”, discussed in section 3.3.

■ 3.2 The subject matter of a patent must be inventive

It is not enough for a patentable invention just to be new. In exchange for 20 years of monopoly rights, the inventor should have to give something very valuable to the public. Accordingly, the second fundamental requirement for a valid patent is that the invention involves an inventive step. But working out a technical definition of inventive step is much harder than defining novelty. Whether or not an invention is novel can be determined on the basis

of relatively clear-cut tests; whether or not an invention is obvious is much more a matter of opinion.

An illustrative approach to defining inventive step is that taken by the European Patent Office (EPO) applying the European Patent Convention (EPC). EPC Article 56 provides that “an invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art”^[37].

Who or what is a person skilled in the art, though?^[38] According to common practice, this person is to be viewed as an ordinary researcher in the field. (S)he will be regarded as having all the “standard” knowledge available in the field and having the “standard” capabilities for “routine work and experimentation”^[39] allowing straightforward progress from what is already known. The key thing that a patent application should therefore demonstrate is a step forward which such a person couldn’t have thought of: the invention should require an inventive step which would not have been obvious to him/her.

When considering how to judge the inventive step, a patent examiner has to review the documents (e.g. scientific

or technological literature including other patent documents) which show the state of the art. The examiner then has to decide whether or not the invention described in the patent application is obvious regarding what is demonstrated in the documents. Patent examiners, in other words, have to put themselves in the position of this person skilled in the art to make the necessary judgement. This is one of the reasons why patent examiners should have scientific or technological qualifications. Whether or not an examiner has made the right judgement is the most frequently raised question in disputes about patent validity.

A good indicator to demonstrate an inventive invention is whether it produces some surprising or unexpected effect^[40]. Imagine two drugs, one that

makes people 5cm taller and one that makes them 5cm thinner. If a patient took the two together and got 5cm taller and 5cm thinner, that is just what you might have expected and the combination of the two cannot be said to be an invention. But if a patient took the two together and became completely resistant to malaria instead, this would be a surprising “synergistic” effect and the combination of the two could be a new and separate invention. A practical example of what is claimed to be an unexpected effect is given on stavudine in Annex B.

How surprising (or non-obvious) the invention has to be before a patent is granted in each country should depend on the practice of each patent office, following the rules decided in each country, which can of course vary over

time as well. An invention may be regarded as being obvious in some countries, but it may be regarded as surprising in others. So, setting the level of inventive step required is another important choice open to every WTO member. The current low standard of inventiveness applied in developed countries has resulted in a “proliferation of patents for trivial inventions which may not contribute to the over-riding objective of the patent system which is the advancement of science for public benefit.”^[41]

Each country can decide for itself what sort of rules it designs to test inventiveness, although this may not be easy. An example of four inventions follows on the next page. There are presumably good reasons why each of the patent offices mentioned decided to grant the patents. Perhaps there has been a full and frank debate in each of the countries about what the most suitable inventive step level to choose is. Perhaps there has not. It is known that the African Intellectual Property Organization (OAPI) and the South African patent office do not carry out a full examination of a patent application before a patent is granted (see p. 18), so it can be no surprise that patents are granted there with wide protective scope although the equivalents in e.g. EPO are cut down to size (or rejected,



Photo: © Christian Schweiz

CASE STUDY

How inventive are “combination” and “formulation” inventions?

Combination therapies are a vital tool in the fight against HIV/AIDS and many other diseases. It is well known that if a single medicine is used against an infectious agent, the agent may become resistant to that medicine. One way of reducing this likelihood is to use more than one drug at once since it is less probable that the agent will develop resistance to both attacks simultaneously. Antiretroviral (ARV) treatment is a good example of this, triple therapy now being the recommended approach. The best possible way to deliver these combination therapies is in a single pill to increase compliance and reduce resistance.

A leading example of a fixed dose combination (FDC) medicine combining two known ARVs is Combivir®, the trade name given by GlaxoSmithKline (GSK) to their combination of zidovudine (AZT) and lamivudine (3TC). An example of an FDC combining three known ARVs is Trizivir®, the trade name given by GSK to their combination of AZT, 3TC and abacavir. In this case, GSK also happens to own the patents for the compounds AZT, 3TC and abacavir. If you look at the patent table in Annex A, you will see that GSK has obtained patents widely for both Combivir® and Trizivir®, and has filed for or obtained patents for a particular formulation of these drugs. In order to be able to obtain valid patents to protect each of these inventions, GSK should have demonstrated (or should be able to demonstrate) that the combinations and formulations involved are not obvious.

GSK first filed a patent application back in 1991 to protect the broad “idea” of using AZT and 3TC in combination. The patent application states that using the two drugs together has a surprising effect in that e.g. the emergence of resistance is reduced. Patents were granted quickly in OAPI and South Africa. Later on a patent was granted by EPO but was quickly opposed by Novartis. This opposition was partially successful and the scope of the GSK patent was reduced.

GSK then filed another patent application in 1995 to protect the broad idea of using AZT, 3TC and abacavir in combination. The patent application says that using the three drugs together has a surprising effect in that e.g. the emergence of resistance is reduced. Such patents have been granted in e.g. EPO and ARIPO.

GSK then filed a patent application in 1996 to protect the combination of AZT and 3TC in a tablet formulation (AZT, 3TC and a non-active ingredient, a glidant). A patent for this invention has been granted by OAPI, ARIPO and South Africa but is still under examination by EPO. It is important to follow up what happens in EPO and compare that with the patents already granted elsewhere.

GSK then filed a patent application in 1998 to protect the combination of AZT, 3TC and abacavir in a tablet formulation (this time AZT, 3TC, abacavir and a glidant). None of the patent offices in the table have apparently yet granted any patents for this invention.

see the patent table). Unless the patents are challenged and cut down to size or revoked, people living in the OAPI region and South Africa will very likely frequently be living under broader patents than people in Europe, for example.

■ 3.3 Patentability is a matter of national policy: example of new use inventions

Deciding whether an invention is new or inventive and whether it should be patented requires answering some difficult questions. Of particular importance to the patenting of pharmaceutical inventions are new use inventions.

Imagine that a particular product is already known for a particular purpose (e.g. AZT as a cancer drug since the 1960's). Imagine then that a new use is found for this product (e.g. AZT as an antiretroviral drug in the 1980's). Should a patent be granted for this new use? One way of looking at this might be to say that it is the same old product, but that we now know more about it, and someone has discovered (rather than invented) a new therapeutic use of it. Another way of looking at it might be to say that, in terms of its new function in life, the product is brand new, so it should be seen as novel.

The TRIPS Agreement gives no guidance in the matter as it only requires WTO Members to grant patents for products and processes, thereby leaving Members free to determine their own approach. Most experts agree that “even though the TRIPS text does not specify any exception to new uses for known substances, it can be concluded that TRIPS does not require the grant of such patents”^[42].

There is no accepted international doctrine on the matter. Some countries have decided to grant patents for new uses as product patents, others as process patents, or as a separate patent category. Others have decided to deny the patentability of such new uses for lack of novelty, inventiveness or industrial applicability, or because such a use may amount to a method of medical treatment (which may be excluded from patentability under TRIPS), or because new uses are just discoveries related to a known product and therefore not real inventions^[43].

The research-based pharmaceutical industry has lobbied strongly for this optional protection, arguing that patent protection of new medical indications will provide them incentive to invest resources in investigating potential new uses of known products, which will be less onerous than searching for new

products. In Europe a special novelty exception was created in patent law to allow a first medical use of a known substance to be patented^[44]. To allow a second medical use to be patented was widely seen as impossible twenty years ago in Europe and yet a way was found to allow it to happen. An artificial legal construction was invented, the so-called “Swiss claim”^[45], to justify the practice. Despite strong opposition many countries have decided that they now believe it^[46], within some limits^[47].

In developing countries this question has been even more debated:

“At the time of the TRIPS negotiations, the patent laws of several developed and developing countries excluded from patentability any new uses for known substances. The search for newer and more effective treatment of diseases has to [be] balanced against the well known exclusion of medical methods of treatment and substances already in the public domain. The implementation of TRIPS in the patent laws of developing countries such as the Andean Group expressly excludes second use of known substances. Others like Brazil and Argentina do not have specific exclusions or inclusions to cover this. This means that they could exclude such “second use” inventions as not being novel or inventive enough to

qualify for a patent grant. Korea, on the other hand, explicitly deleted the exclusion of new uses of known chemical substances with effect from 1 July 1987 under its bilateral understanding with the US following action under Section 301”^[48]. Countries of the Andean Community^[49] as well as Kenya^[50] have resisted pressure from multinational companies and industrialised countries and expressly excluded new uses from patentability in order to limit the number of patents granted in the pharmaceutical sector.

The UK CIPR report recommended that “most developing countries, particularly those without research capabilities, should strictly exclude diagnostic, therapeutic and surgical methods from patentability, including new uses of known products”^[51]. However, the example below shows that such a political choice can be difficult to maintain in a world where the global tendency, originating from industrialised countries, is to grant patents for most things, including for second medical use inventions.

CASE STUDY

The right to reject patents for second medical use inventions: The Andean example

According to Article 21 of Decision 486, Common Intellectual Property Regime, of the Andean Community, “products or processes already patented and included in the state of the art ... shall 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”. Despite this exclusion in the common legislation, an unexpected legislative decree was passed in 1997 in Peru, clarifying that patents may be granted for new uses if it complies with the requirements of novelty, inventiveness and industrial applicability. This resulted in the patent office of Peru granting a second medical use patent^[52] to Pfizer in 1999 to protect the anti-impotence drug Viagra®. The generic industry association of Peru complained about this patent to the Secretariat of the Andean Community, which brought the dispute to the Andean Tribunal of Justice. Although powerful forces were involved (14 lawyers to defend Pfizer and the Government of Peru against two for the Secretariat of the Andean Community), the Tribunal ruled that the Government of Peru had violated the regional patent legislation in granting such a patent^[53].

Developing countries have the same sovereign right as developed countries to interpret international agreements with regard to their own needs, when these provisions are unclear or not uniformly accepted. It remains to be seen whether similar efforts can be mounted for less lucrative but more essential drugs.

■ 3.4 The invention should be clearly disclosed to benefit society as a whole

Tests that an invention has to pass before it can be registered as patentable are provided in TRIPS Article 27.1. However, they are not the only tests for a patent application to qualify for grant.

TRIPS Article 29, entitled “conditions on patent applicants”, lists obligations for patent owners, including a mandatory requirement 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”. This means that the patent document must explain at least one way of putting the invention into effect, e.g. making a product or applying a process. If it turns out that the patent applicant has applied for a patent but has left out an essential piece of information so that reading the patent application will not be sufficient to make the invention work, the patent should not be valid. This is based on the patent bargain as explained earlier (see p. 5).

As discussed above regarding inventive step, it is crucial to define what is meant by a person skilled in the art^[54]. Since patents are granted on a national

or regional basis only, the information disclosed in the patent document must be clear and complete enough to a person (or people) in that country or region qualifying as skilled in the art to explain to them how to make the invention work. For sophisticated inventions such as many of those now encountered in the pharmaceutical field, it may be difficult to locate large numbers, or teams, of people who could be considered as skilled in the art, especially in least developed countries.

One of the justifications of the patent bargain is that the information in patent documents is published^[55]. It is true to say that patent documents in Europe or the United States are published for all to see (i.e. anybody, not just European or United States citizens, can read them on the Web). If the relevant people in a developing country can read English (and/or e.g. French or German), that developing country may not gain any new information by publishing patent specifications themselves since they can read the American or European publication of what is essentially the same document. In this case, the patent bargain may not give the extra reward needed to justify granting monopoly rights. This may not be true where the patent document has to be

translated into a different national language, e.g. Mandarin or Thai. However, in Africa, patent documents seem only to be published in English or French and not, for example, in Hausa or Swahili^[56].

Even in countries where there is a strong concentration of scientific and technological know-how, a patent application, or a granted patent, is unlikely to provide all the necessary information for a manufacturer to begin production straight away, for instance in case a compulsory licence had been granted. The patent specification must explain how to make a new chemical entity, for instance, but the method of production may not be suitable for immediate scaling-up. Additionally, should a compulsory licence be granted, the patent holder is by no means obliged to help the compulsory licensee in any way with extra know-how. Moving from patent specification to manufacture may still require considerable effort on the part of a generic manufacturer.

Concerns such as the above explain an optional requirement of TRIPS Article 29.1, i.e. the disclosure of the “best mode for carrying out the invention”. Instead of just requiring an explanation as to at least one way of putting the invention into effect, which is the mandatory minimum requirement, WTO Members have the right to demand that applicants for patents in their country explain the best way known to them at the time of putting the invention into effect. Of course, it will be virtually impossible for a patent office to challenge what the patent applicant says, but having made the demand may prove to be important later on if the patent’s validity is disputed. This is an added TRIPS safeguard intended to ensure that a country is getting the most benefit out of the patent system^[57]. The UK CIPR report recommended that “developing countries should adopt the best mode provision to ensure that the patent applicant does not withhold information that would be useful to third parties”^[58].



■ 3.5 An invalid patent may be revoked

As outlined above, the granting of a patent is far from being a final act: a granted patent may be partly or completely invalid.

When a patent constitutes a barrier to access to essential medicines, it is important to investigate whether the patent is indeed valid (and infringed) before entering into negotiations with the patent holder and/or considering granting a compulsory license or making government use. For reasons both legal and political there may be situations when challenging the validity of a patent has advantages over trying to obtain a compulsory licence. This would not be the case if compulsory licences were routinely issued through simple administrative procedures.

A patent may be invalid for various reasons. On closer inspection, it may fail one or more of the tests that it was supposed to pass when it was granted.

For example, EPC Article 138 includes grounds for revocation on the basis that the invention is not patentable (for example, the invention falls into a category which is excluded from patentability, such as therapeutic or surgical methods, or the invention is

not new or is not inventive), that the patent isn't clear enough about how to carry out the invention, that the patent application or the granted patent has been amended in a way which is not permissible, and that the patent was granted to somebody who was not entitled to it. Some concrete examples include:

- A mistake may have been made during the granting process about whether or not the invention should have been patentable. For instance, GSK claimed to have various patents protecting its antiretroviral medicine Combivir® in Ghana, in order to stop a drug distributor from importing a generic version of this medicine in 2000. Investigations revealed that in fact three of the four GSK patents should not have been granted in the first place, as pharmaceutical inventions were not patentable under the previous Patent Law of Ghana^[59].
- Even if the invention falls into a patentable category the patent office may have made a mistake in judging novelty or inventive step in light of the state of the art that the patent search revealed.
- Documents (or something else) describing the invention dating before the priority date may turn up,

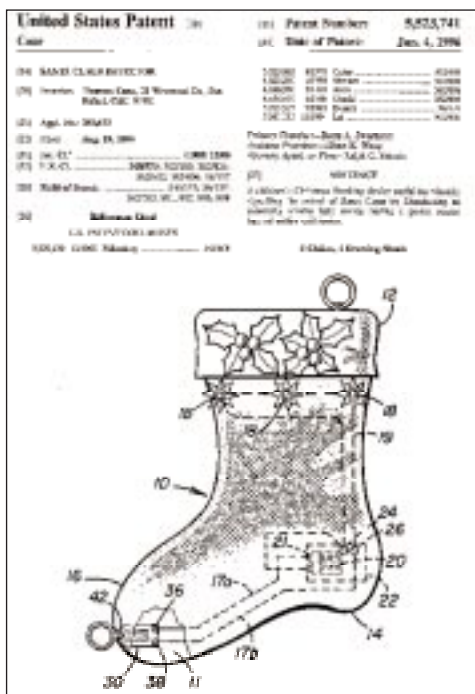
in which case the invention might no longer be novel or inventive. These sorts of things happen frequently in industrialised countries.

- As was mentioned earlier, TRIPS Article 29.1 obliges WTO Members to require that patent applications “disclose the invention in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art”. The fact that such a person, for example working in a generic manufacturing company, can prove that it is not possible to carry out the invention on the basis of the information provided in the patent document could also be a motive for revoking the patent.

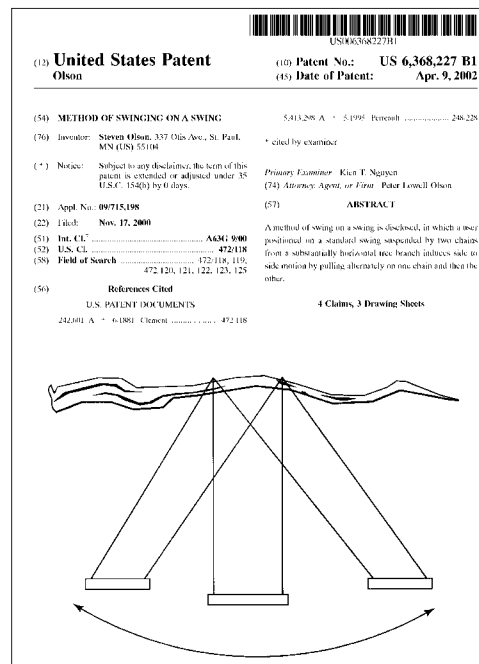
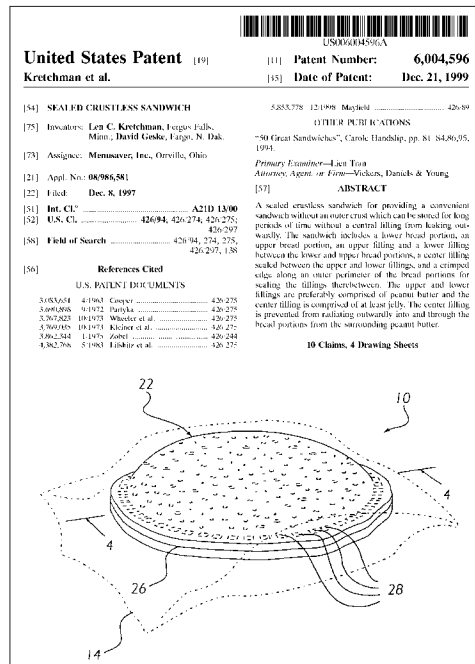
In some cases, challenging the validity of a granted patent may be a good way to test the law of a country on the issue of patentability. An appropriate definition of novelty or inventive step may not have been debated in the country — the patent office may be operating on developed country patent office rules by default, for example if the patent examiners have been trained in developed country patent offices. The country or region might not yet have debated whether they should regard new uses of known substances, for example, as new^[60].

As noted above, a country doesn't necessarily have to examine a patent application before it grants a patent. The TRIPS Agreement does not force countries to apply the patentability tests before a patent is granted. Different countries behave in different ways. Some countries have decided to have a thorough examination of any patent application before a patent is granted. This is the case in the European Patent Office, the United States Patent Office, the Japanese Patent Office and the Chinese Patent Office as well as many others (see p. 18 for some patents that the US office has granted, including a Santa Claus detector). This approach requires a great deal of resources ahead of time in the patent office (at the end of 2001 the European Patent Office had a staff of more than 5,000) but means that fewer invalid patents are likely to be granted.

Then there are patent offices which do not examine each application in depth but merely check that the right papers have been filed and fees paid. This is the case in France, the Netherlands, Nigeria, OAPI and South Africa, for instance. This “registration” approach means much fewer resources need to be invested in patent offices – for instance, there is no need for technically qualified patent examiners.



- ◆ The USPTO has issued patents for such things as a Santa Claus detector (US patent 5523741), a peanut butter sandwich (US patent 6004596) and a method of swinging sideways on a swing (US patent 6368227).



But it also means that patents will be granted which are not valid under the national law. However, this can only be tested in court. Obviously this approach only works well when there is a reasonable chance that a patent actually will be challenged in court. It might be disastrous if a country where there is little likelihood of anyone challenging the patent uses a registration system.

If the patent application is rejected in, for example, EPO, there might be a good case to invalidate the patent in a “registration only” country^[61], to the extent that the law is the same. We discovered cases where a patent had been granted quickly by OAPI, for example, but the corresponding patent in EPO had either been limited compared to the OAPI patent or even refused altogether^[62].

The particular way in which the validity of a patent can be challenged is determined by national law. A revocation process or a process to limit a granted patent may take either an administrative route (e.g. in a patent office) or a judicial route (e.g. in the courts), or both. Article 32 of the TRIPS Agreement requires an opportunity for judicial review of any decision to revoke or forfeit a patent. MSF has indicated in its comments on the WIPO

Patent Agenda that if moves are made to make the granting of patents easier and cheaper, efforts to make the revocation of patents easier and cheaper must be commensurate.

A potentially vital issue is the determination under national law of who is allowed to challenge a patent. If only competitor pharmaceutical companies were allowed the legal standing to challenge a pharmaceutical patent, then many other relevant entities such as individuals and non-governmental organizations (NGOs) would be rendered powerless to challenge. A first instance decision in Thailand (see p. 20) recently considered this question and found that an AIDS treatment NGO and two individuals living with HIV/AIDS did have the right to challenge a patent granted on an HIV drug. Any person should be given the legal standing to challenge a pharmaceutical patent given the life-or-death consequences. Also, a closed group of companies, including generics companies, cannot be relied upon to act in the best interests of public health.

When it is fairly certain that the patent is invalid, a patent can be challenged in a different way, for example, by going ahead and manufacturing or using the product anyway, and waiting for the

patent holder to sue. As noted above, patent rights are private rights. Patent holders have to take action if they wish to protect their rights. If they do, the invalidity of the patent is then raised as a defence. If they don't, for whatever reason, then the matter may go no further^[63].

One of the biggest practical problems in determining whether a patent is likely to be valid or not is the very limited number of people qualified to do so.

Patent law is a complicated field. Although a person skilled in the art is supposed to be able to understand the patent description, it is the claims provided at the end of the patent document (see Annex B) that are judged when deciding if the patent is valid or not. These may only be understood by patent examiners, lawyers and judges. The people involved should have not only a legal background but also a wide-ranging technical understanding so that they

can judge the merits of the invention for themselves. It is not at all unusual for a patent lawyer in the field of pharmaceutical inventions to have a PhD in a science or technology associated with pharmaceuticals as well as being a qualified lawyer. In the developing world, there are still very few practising patent lawyers, and when there is a dispute, existing experts might be hired by pharmaceutical companies rather than by NGOs. Similarly, there are very few

specialised patent judges to hear patent cases.

Before you can challenge its validity, you will have to find the patent, which can be time-consuming and costly. The next step is understanding what it entails.

The case presented on page 20 shows what can be done when committed groups and individuals join forces and share their expertise to challenge an invalid patent.



Photo: © Sebastien Charles

CASE STUDY

Revoking an invalid patent: the case of ddl in Thailand

One important medicine in the fight against HIV/AIDS is didanosine (also known as ddl and sold under the name Videx® by Bristol-Myers Squibb (BMS)), a drug included on the WHO Essential Medicines List. The drug was discovered by the US National Institutes of Health, and the US Government holds the rights to the original ddl invention (see patent table)^[64]. At the time ddl was discovered, Thai law did not permit the patenting of pharmaceutical products, so even if the US government had wanted to obtain a patent in Thailand, it could not have done so. However, in September 1992, Thai law was changed so that pharmaceutical products could be patented.

BMS licensed the rights to ddl from the US Government. Although BMS could no longer obtain patents for ddl itself, since the structure of ddl was publicly known by then, they could still apply at any time for patents for “derivative” inventions relating to ddl (see section 2.2).

On July 7th 1992, BMS filed just such a patent application in Thailand, intended to protect a specific formulation of ddl^[65]. In this patent application, the invention was limited to a specified range of about 5-100mg of ddl per dosage unit.

During the examination of the patent application, the Thai Department of Intellectual Property (DIP) allowed BMS to remove the limitation in the dosage range. In many patent offices it is allowable to amend a patent application, but only so long as certain rules are followed. If the amendment was allowed without following these rules, for example by mistake, and a patent granted, then the patent may be invalid. On January 22nd 1998, the Thai Patent Office granted a patent for this unlimited invention.

The effect of this unlimited patent was apparently to prevent the Thai Government Pharmaceutical Organisation (GPO) from manufacturing any sort of ddl tablet. After a campaign to try to persuade the government to issue a compulsory licence, it was decided to manufacture ddl in a powdered form instead. But the powdered form has an unpleasant taste and side effects that the tablet form does not have, and it is more difficult to take than a tablet.

Accordingly, on May 9th 2001, a case was filed at the Thai Central Intellectual Property and International Trade Court (CIPIT)^[66] by three plaintiffs (the AIDS Access Foundation and two people living with HIV/AIDS against two defendants, BMS and DIP). The plaintiffs demanded, among other things, that BMS amend their patent claim back to the limited dosage range originally asked for.

The three CIPIT judges delivered a comprehensive judgement on October 1st 2002.

The judgment clearly confirmed that these two individuals and the NGO had the right to challenge the BMS patent. The legal reasoning for this finding quotes the 2001 Doha Declaration on TRIPS and Public Health – probably one of the first judgements to refer to the Doha Declaration directly. Since the TRIPS Agreement must be interpreted and implemented so as to promote and support access to medicines for the people as a whole and since those suffering from HIV/AIDS can be injured by a patent blocking access to affordable medicines, the judgement says, they had the right to challenge the patent.

The judgement also found that the amendment that BMS made and the Thai DIP allowed was unlawful. It confirmed that under Thai law the most important factor in determining the scope of patent protection is the wording of the patent claims. The scope of the allowable patent claims depends on the details of the invention described to the public in the patent document. One of the reasons that the amendment was unlawful was that the removal of the dosage limitation of about 5-100mg expanded the scope of protection beyond what was described in the patent document description. The judgement ordered BMS and DIP to amend the patent by putting back the limitation.

This judgement was very important and it will give a lot of support to those fighting for access to essential medicines in Thailand and elsewhere in developing countries.

At the time of writing the judgement was under appeal by BMS and DIP.

4 ■ How to read and use the patent table

The patent table compiled by MSF in Annex A only provides data regarding a selected number of drugs and countries. The drugs chosen are essential medicines^[67] for which patents already constitute a barrier to access or might do so in the coming years. The countries selected are countries where MSF has field projects, or is planning to open them, i.e. in which human resources were made available to obtain patent information.

It should be stressed that the patents mentioned in the table are mostly patents protecting the basic molecule of a given medicine (usually including a manufacturing process) or in the case of old molecules, the target therapeutic use of this medicine, such as the prevention or treatment of HIV/AIDS. We selected these particular patents not only because we couldn't search for all patents protecting a medicine (there may be a significant number in each country), but also because the patent

Thai activists filing a second case at the Thai Central Intellectual Property and International Trade Court in October 2002, after winning the first case (see previous page). This time the activists aim at the withdrawal of the BMS ddI patent in Thailand. ▶

Photo: © MSF



related to the active ingredient of a medicine is generally the first applied for and therefore the first one to expire. This doesn't mean that no additional patent may have been granted later on to protect a different manufacturing process, or an improved formulation with fewer side-effects, or a new combination, and so forth. We would like to insist that the lack or expiry of a patent in a given country as provided in the table doesn't necessarily mean that you can import or manufacture generic versions of the medicine without a risk of being sued by a potential patent holder.

To help people make patent searches in countries that are not mentioned in the table, we have included the main priority date and number of the priority patent application for each medicine, as well as the number of the related international patent application^[68], when it exists, and, for the sake of illustration, the number of the equivalent European patent^[69]. As explained in detail above, the priority date is key in determining the novelty of the invention, which may then give right to a patent. If your country is not included in the document, you could initiate a patent search by providing the priority details (date and number) of the patents related to the drug you are interested in to your patent office. You

can also use the number of the international patent application to ask the patent office whether a patent has been granted in your country.

It is also advisable to first ask the patent office or WIPO from which date patents on medicines have been available in your country: if your country, like Guatemala or Peru, did not allow patenting of pharmaceuticals before a certain date, it is likely that patents with an earlier priority date will not be valid there^[70]. There would then be no need to initiate a patent search on these medicines in the local patent office.

The patent data in the table was obtained from and cross-checked between a variety of sources including local patent offices and a number of free Web sites, based on search by generic name, chemical formula and/or priority dates^[71]. Patent searches can be difficult for many reasons. We came across the following difficulties:

- Because patents protect inventions, a patent document or a patent application only describes the subject matter of the invention (i.e. the chemical formula of a molecule, a manufacturing process, a specific dosage form, a therapeutic use, etc) but seldom refers to the chemical name (INN) or brand name of a

medicine because it may not have been known at the time of the patent application. Patent searches on medicines therefore require technical skills in chemistry to ensure you find out exactly which patents protect which medicines. In developing countries' patent offices, we were sometimes told that no patent protected a medicine but found out later from other sources that a patent had indeed been granted. Other times a patent was found but a thorough chemical analysis revealed that the patent was related to another medicine.

- The legal information we received from ARIPO, OAPI and WIPO was sometimes not consistent: for example, the information we got from ARIPO regarding the term of ARIPO patents conflicted with what WIPO said. Patents granted by ARIPO (numbered AP...) are subject to the national patent legislation of each ARIPO Member State. This explains why the expiry dates of ARIPO patents in Kenya, Malawi, Uganda, Zambia and Zimbabwe are different^[72]. There were also inconsistencies (which later turned out to be mistakes) regarding filing dates in some OAPI patents; the dates are necessary to calculate the estimated expiry date^[73].

- Some countries such as Guatemala, Peru and Thailand are not included in international patent databases. Local patent offices were thus the only available sources to obtain patent data, and double-checking was not possible.
- Some patent offices are not equipped with computers or do not have a local database containing all patent applications and granted patents, which made it very difficult to undertake a precise patent search.
- In Thailand and Ukraine we had to have patent documents translated locally. The translations may not have been 100% reliable given the complexity and technicality of patent documents.
- Requests for patent searches in patent offices are seldom free, and can be very expensive depending on the country.

Due to the above reasons, we insist that the reliability of the data provided in the table cannot be 100% guaranteed.

There have of course been previous "patent surveys" carried out including an earlier version of this report^[74] and a much debated article in the JAMA in



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▲ Activists supporting the South African government against multinational pharmaceutical companies that had sued the government over a law intended to protect public health. The drug companies eventually dropped the case because of public pressure. April 2001.

2001^[75], often used to support a proposition that patents are not a barrier to access to medicines in Africa since “on average” there are said to be few patents (e.g. per country) in Africa. But as scientists and NGOs involved in treating people living with HIV/AIDS pointed out^[76], the actual data presented in the survey did not support the claim: the most popular antiretroviral drug combination in Africa was patented in 37 out of 53 countries at the time. In contrast, many of the

non-patented drugs are impractical for use in resource-poor settings.

The drug patents listed in this report (among others) do exist and cannot be wished away by any averaging process. Every such patent in force is either actually or potentially a barrier to access to an essential medicine. Even if there were only a single patent standing in the way of accessing a safe and effective yet cheap generic medicine, it would still be an obstacle

that needs to be acknowledged and removed.

As explained in this report, a medicine is in any case very unlikely to be protected by a single patent but rather by a set of patents. We lacked time and resources to look for a complete set of patents for each medicine, but we hope that the patent numbers provided in the table will help others further investigate the patent status of essential medicines in their own country.

▼ MSF provides care to adults and children living with HIV/AIDS in Guatemala. The country introduced patent protection for pharmaceuticals in 2001.



Photo: © Juan Carlos Tomasi

5 ■ Conclusions

Each country must be able to design and operate its patent system in its own best national interest, using the flexibilities of the TRIPS Agreement. This principle was re-endorsed by the 2001 Doha Declaration on the TRIPS Agreement and Public Health, which stated that the TRIPS Agreement “does not and should not prevent Members from taking measures to protect public health”.

Patents were designed to ensure that the public benefits from innovations, but it is very clear that people in developing countries are currently not getting their part of the patent bargain. On the contrary: in many countries, patents hamper the public’s access to life-saving medicines – in other words, profits are being put before public health.

This trend may be worsened by WIPO’s ongoing negotiations aiming at developing a ‘Substantive Patent Law Treaty’, a global treaty that is very likely to be based on patent standards used in wealthy countries. This may lead to a system where any new medicine put on the market is patented worldwide.

Industrialised countries are also concluding bilateral agreements with developing and least developed

countries to prevent them from using the Doha Declaration safeguards. Similarly, the US is trying to further limit the freedom of countries to grant compulsory licenses for public health reasons through ongoing negotiations on the Free Trade Area of the Americas (FTAA) Agreement.

As shown in the patent table, not all medicines are patented everywhere. But finding out whether a drug is patented in a particular country currently varies between being difficult and impossible. The World Health Organization (WHO) and WIPO urgently need to set up a user-friendly, public database providing comprehensive and transparent data on pharmaceutical patents of key medicines. This information should be accompanied with clear advice to countries on how to overcome patent barriers to medicines, and with technical assistance in doing so.

Drug patents that need not be granted are being granted in developing countries right now. This is true for example for “new” uses of existing compounds. The TRIPS Agreement defines the minimum intellectual property protection standards Members must adhere to, but there is no reason for countries to expand patent protection beyond that. In fact, patentability requirements in developing

countries should be amended to keep the number of patents granted to an absolute minimum.

Even when a drug is patented, there are ways of overcoming this obstacle.

Patents that have been granted in developing countries may not be valid. Patents are already being challenged in some countries, for instance in Thailand. Countries should put in place appropriate checks and balances to revoke patents if necessary. To assist them, WHO and WIPO should provide data about essential drug patents that have been invalidated.

If patent holders are not willing to ensure equitable drug prices for poor countries or grant licenses voluntarily, governments must act. They can improve access to affordable medicines for their

people by issuing a compulsory license for a patented drug or by making government use of a patent.

However, keeping the number of drug patents to an absolute minimum has advantages over the politically sensitive negotiations that currently precede issuing a compulsory license.

The patent system is a public policy tool: patents are contracts between their owners and society. Countries will come to test the flexibility of the TRIPS Agreement as they implement the Doha Declaration: the next few years will show whether ensuring that TRIPS is interpreted and implemented “in a manner supportive of WTO Members’ right ...to promote access to medicines to all” is feasible in practice. If this turns out not to be the case, the TRIPS agreement will need to be challenged.

"I am revolted when I hear claims that patent rights do not constitute a barrier to treatment here in South Africa. I have seen young women and men die from an AIDS-related brain tumour provoking unbearable headaches. I have seen children covered with scars due to AIDS-related dermatitis, unable to sleep for the pain. I knew that all of them could have been helped with antiretroviral therapy, but the cost of the patented drugs was the only barrier."

Dr Eric Goemaere, MSF, Khayelitsha, South Africa

6 ■ References

- [1] *Integrating Intellectual Property Rights and Development Policy, Report of the Commission on Intellectual Property Rights, London*, September 2002. The full report is available at www.iprcommission.org
- [2] For explanations of these terms, see e.g. www.accessmed-msf.org
- [3] Médecins Sans Frontières and the Drugs for Neglected Diseases Working Group, *Fatal Imbalance – The Crisis in Research and Development for Drugs for Neglected Diseases*, Geneva, September 2002.
- [4] Médecins Sans Frontières, *Untangling the Web of Price Reductions – A pricing guide for the purchase of ARVs in developing countries*, Geneva, December 2002.
- [5] UNCTAD, *The TRIPS Agreement and Developing Countries*, New York and Geneva, 1996.
- [6] Professor W.R.Cornish, *Intellectual Property: Patents, Copyright, Trade Marks and Allied Rights*, Sweet and Maxwell, 4th ed 1999, section 5-70.
- [7] In the UK, see e.g. *Merill Dow Pharmaceuticals Inc v H.N.Norton & Co* 1996 RPC 76.
- [8] For further discussion, see e.g. C.Correa, *Trends in drug patenting: Case studies*, Corregidor, 2001.
- [9] Indeed an advertisement for a conference in 2002 in London (“*Legal Strategies for Maximising Pharmaceutical Patent Life Cycles*”) included a session on “*Extending Patent Life By Patenting Beyond the Basic Compound Claim: Which Patents Are Enforceable?*”. Topics to be discussed include “What are the latest types of patent claims to be filed beyond the basic compound claim? How enforceable are these claims? How do they stand up in court? Claims to formulation, process, product by process, polymorph, metabolite, patenting means of delivery, dosage regime, patenting combination therapies (what support is needed to patent? Is there a need for clinical trials to show benefit?), second medical use claims (new indications, what will the EPO currently let you get away with?)”.
- [10] C.Correa, *Integrating Public Health Concerns into Patent Legislation in Developing Countries*, South Centre, 2nd edition, Geneva, September 2001. TRIPS Art 27.1 states that “Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application...”. TRIPS does not limit how each of the inventions in the list above must be seen i.e. whether they have to be seen as new, inventive or industrially applicable. TRIPS Art 27.3 states that “Members may also exclude from patentability (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals”. Patent applicants have been tireless in trying to find ways round this (optional) prohibition. Note that this exclusion only applies to methods and not to products relating to those methods. Diagnostic kits for HIV testing may be patented as products even though the method of diagnosis itself may not.
- [11] There is such a thing as an international patent application however. A system is administered by WIPO under the Patent Cooperation Treaty (PCT) which allows the filing of international (or “PCT”) patent applications. When a PCT patent application reaches a certain stage in the PCT patent application process however it “splits” up into national/regional patent applications.
- [12] There are four regional patent offices worldwide, that have been established by a treaty amongst the countries of the region, and that grant regional patents (the European Patent Office or EPO, the Eurasian Patent Office or EAPO, the African Regional Industrial Property Organization or ARIPO, and the African Organization of Intellectual Property or OAPI in French). In OAPI, only regional patents valid for all member countries can be granted, whereas in EPO, EAPO or ARIPO countries, patents may be applied and granted either nationally or regionally.
- [13] For example, in South Africa, 42 pharmaceutical companies sued the Government on the motive that the proposed Medicine Act was unconstitutional. This is different from the dispute that arose between the US and Brazil in 2001, where the US was complaining that compulsory licenses provisions of the Brazilian patent law were not compliant with the TRIPS Agreement (although they finally abandoned the case in the course of negotiations).
- [14] A good example of which is the American pharmaceutical industry association PhRMA and its annual reports to the US Trade Representative (the so-called “Special 301” submissions) where it can and often does call on the US government to take action against countries whose patent laws are not thought sufficient for its Members’ needs.
- [15] With the exceptions of customs authorities assisting patent holders at borders (TRIPS Articles 51-60) and potentially criminal procedures (TRIPS Article 61).
- [16] Although action can also be taken if a patent holder has strong fears that a patent infringement is going to take place. TRIPS Article 50.1 provides for such “provisional measures”. If it is too easy to obtain injunctions, major practical problems may arise.
- [17] E.g. article 130 of the Indonesian Patent Law 2001.
- [18] TRIPS Art. 6 and 30.
- [19] Paragraph 5(d).of the *Doha Declaration on the TRIPS Agreement and Public Health* (WT/MIN(01)/DEC/2).
- [20] Ibid 1, p. 119.
- [21] A mechanism can be provided as well which allows opposition to the grant of a patent before it takes place.
- [22] TRIPS Article 32 provides that “An opportunity for judicial review of any decision to revoke or forfeit a patent shall be available”.
- [23] Ibid 1, p. 114, and ibid 10.
- [24] Ibid 1.
- [25] For example *WIPO Nationally Focused Action Plans* (NFAPs).
- [26] It seems that the European Patent Office guidelines for patent examiners are widely used in many patent offices.
- [27] See e.g. the letter from Sir Leon Brittan, Vice-President of the European Commission, to Thabo Mbeki, Vice-President of South Africa, March 23rd 1998 (on file with the *Chicago Journal of International Law*).

[28] See the report from a conference by MSF, the Consumer Project on Technology, Oxfam and HAI in April 2001. <http://www.accessmedmsf.org/upload/reportsandpublications/26420021519443/report.pdf>

[29] Correa, C. and Musungu, S.F. *The WIPO Patent Agenda: The Risks for Developing Countries*, South Centre, Geneva, November 2002.

[30] Ibid 10, p. 47.

[31] This will be used as an example as the TRIPS Agreement provisions on patentability were substantially modelled on those of the EPC. Also, many other patent offices use the *EPO Guidelines for Examination* as a guide in the application of their own law. For the text of the EPC see <http://www.european-patent-office.org/legal/epc/index.html> and for Guidelines as to its application in practice see <http://www.european-patent-office.org/legal/guidelines/index.htm>.

[32] Or before the priority date where available, in accordance with Art 89 EPC.

[33] Where it would be possible to learn how the product works from the sole examination of the product.

[34] It will be assumed for this discussion of novelty and the other sections below that the patent application is being examined by a patent examiner before being granted but this is not always the case and the same considerations apply to e.g. a patent judge testing a patent in court.

[35] Ibid 1, p. 116.

[36] Countries that have not signed the Paris Convention have generally included provisions acknowledging the right of priority in their patent legislation. Article 2.1 TRIPS now obliges WTO Members to comply with “Articles 1 through 12, and Article 19, of the Paris Convention (1967)” (which includes priority issues) whether or not they have signed the Paris Convention.

[37] The “state of the art” is the same general concept as the one applied for novelty, except that it excludes patent applications filed but not published.

[38] See also e.g., “person of ordinary skill”, *ibid* 10, p. 44.

[39] See e.g., *EPO Guidelines*, CIV, 9.6

[40] Although not every country requires an unexpected effect. *Ibid* 10, p. 44.

[41] *Ibid* 1, p. 116.

[42] Watal, J. *Intellectual Property Rights in the WTO and Developing Countries*, Kluwer Law International 2001, p. 104.

[43] *Ibid* 10, pp.20-25.

[44] EPC Art 54(5).

[45] The Swiss claim deals with a situation where a known compound is already known to have a medical use. A medicine may have been made using that compound for the known medical use. Now somebody finds that the medicine can also be used for a different medical use (i.e. a second or subsequent medical use over the one already known). Can they obtain patent protection? The new medical use looks a lot like a method of medical treatment, which is not patentable in Europe. In a remarkable “smoke and mirrors” flourish, the Swiss patent office decided to allow a patent claim for this which was aimed at the process of manufacturing the medicine (even if it was exactly the same process as for manufacturing the medicine for the first medical use) seemingly deciding that it became new just because the medicine is now used for a different purpose than before. Many people have said that pretending this is about a manufacturing process instead of a method of medical treatment is just a way too get round the ban on patenting methods of medical treatment in Europe. Despite these and other objections, Swiss claims are now allowed in Europe and elsewhere.

[46] In the UK, “In the interests of common progress, the Patents Court proceeded to accept the same casuistry [as EPO and the Swiss Patent Office]”, *ibid*. 6, section 5-75.

[47] In the UK it was “not within the “second medical use” exception to claim a medicament so formulated that it would release the drug taxol over three hours instead of 24, thus reducing its side effects”, *ibid*. 6, section 5-76.

[48] *Ibid* 42, p. 105.

[49] The Andean Community includes Bolivia, Colombia, Ecuador, Peru and Venezuela.

[50] *Industrial Property Act, 2001*, section 21(3)(e).

[51] *Ibid* 1, p. 50.

[52] The drug had been patented by Pfizer in Peru for several years to control the symptoms of angina, a heart condition.

[53] For more on this case, see *Patents and Medicines in Peru*, an MSF document available at www.accessmed-msf.org

[54] Note that the TRIPS Agreement uses the term “person skilled in the art” in Art 29 but not Art 27.

[55] An important practical point about the disclosure in the patent application is that it is aimed at telling the public how to carry out the invention. It doesn't have to explain why the invention works (an applicant may not know this), just what has to be done to make it work. When pharmaceutical companies apply for patents they will file their patent applications at a very early stage in the life of the invention. By the time they establish their priority date for an invention they will not know all that there is to know about the invention so obviously they cannot include all the information in the patent application even if they want to. A practice has developed in e.g. the European Patent Office that patent applicants are allowed to file extra material in support of the invention described in the patent application whilst the patent application is being examined. This extra material cannot be used to change what the invention is but can apparently be used to help prove that the invention is indeed inventive. This extra material goes on the public file at EPO but is not officially part of the patent document, so if and when someone looks at the patent document they will not see this extra material. This practice deserves to be scrutinised further vis-à-vis what developing country patent offices allow.

[56] The issue of translating patent documents into all necessary languages causes much political trouble in Europe. Some people believe that all technical people in Europe should be able to read English (or at least one of English, French and German) so there is no need to translate European patent documents into all European languages to get patent protection for all of Europe. Others say that language of publication is a fundamental part of the patent bargain and cannot be ignored and that a translation is little enough to ask for 20 years of monopoly rights.

[57] Another optional requirement in TRIPS Article 29 is that an applicant for a patent may be required to “provide information concerning the applicant’s corresponding foreign applications and grants”. Although this may add to the workload that a patent office in a developing country has to deal with, the office would at least get the benefit of knowing how other patent offices were dealing with the patent application. A potentially important question is whether having to provide “information concerning the applicant’s corresponding foreign...grants” covers only the fact that a patent was granted, or whether there can be a continuing obligation to inform the patent office dealing with an application if the corresponding patents have been opposed or revoked elsewhere.

[58] Ibid 1, p. 117.

[59] *The Wall Street Journal*, December 1, 2000, Glaxo Attempts to Block Access To Generic AIDS Drugs in Ghana, by Mark Schoofs.

[60] Ibid 1, footnote 82 on page 55.

[61] Note that TRIPS Art 29.2 allows WTO Members to “require an applicant for a patent to provide information concerning the applicant’s corresponding foreign applications and grants”. As noted above, it might be argued that information concerning grants includes not only the grant itself but e.g. revocation of the grant. For further discussion on this and other related topics please refer to MSF’s comments on the WIPO Patent Agenda, available at access@geneva.msf.org.

[62] See patent table, Annex A.

[63] Ibid 15.

[64] See <http://www.cptech.org/ip/health/aids/gov-role.html> for more information on the role of the US government in the development of HIV/AIDS drugs.

[65] Although the patent application was filed before the Thai law changed, there were “transitional” provisions in the new law, and since this patent application had not been rejected by the time the law changed, it was treated as a patent application under the new law.

[66] Thailand created a special court to deal with intellectual property disputes. Although probably helpful for those countries that can do this, it is not required by the TRIPS Agreement, see TRIPS Article 41.5, “It is understood that this Part does not create any obligation to put in place a judicial system for the enforcement of intellectual property rights distinct from that for the enforcement of law in general...”.

[67] <http://www.who.int/medicines/organization/par/edl/eml.shtml>.

[68] Although there is no international patent, it is possible to file an international patent application, using the system of the Patent Cooperation Treaty (PCT) managed by WIPO. The applicant can “designate” all the Member Countries of the PCT, in which (s)he wishes to get a patent. The application procedure is centralized though, and it is up to each “designated” patent office to grant or reject the patent application, in conformity with its own national patent law.

[69] Note that only a European patent with a “B” at the end is a granted patent. An “A” indicates publication of a patent application.

[70] Unless some retroactive and/or transitional provisions have been included, as in Thailand or Brazil.

[71] A selection of which include: <http://www.fda.gov/cder/ob/default.htm>
<http://ep.espacenet.com/>
<http://patft.uspto.gov/netahtml/search-bool.html>
http://biotech.about.com/library/patent_expirations

[72] Although this will change in the future: an amendment to the Harare Protocol on patents granted by ARIPO was introduced in 1999 to establish that all ARIPO patents granted after that date would be subject to a 20-year patent term in all ARIPO countries.

[73] These mistakes have been corrected in the patent table.

[74] WHO/UNAIDS, *Patent Situation of HIV/AIDS Related Drugs in 80 Countries*, 2000.
<http://who.int/medicines/library/par/hivrelateddocs/patentshivdrugs.pdf>

[75] Attaran A., Gillespie-White L., *Do patents for antiretroviral drugs constrain access to AIDS treatment in Africa?* JAMA, 2001, vol.286, No.15, pp.1886-1892.

[76] Letters to the Editor, JAMA, 2002, vol. 287, No. 7. pp. 840-842.

■ Annex A

INN(1)	Originator's Trade mark	Patent holder(2) (manufacturer)	Basic patent priority date (number)	International patent application	Representative European corresponding patent	Brazil(3)	Cambodia(4)	China(5)
Amphotericin B liposomal	Fungizone Ambisome	Olin Mathieson (Bristol Myers Squibb) Vestar (Gilead-NeXstar)	28.12.1954 (US478014) 12.11.1987 (US119518)	No No	No EP0317120	No	No	No
						No	No	No
Arthemeter+ Lumefantrine (benflutemol)	Coartem/Riamet(13)	Ciba-Geigy (Novartis)	08.08.1990 (CN106722)	WO92/02217	EP0500823	No	No	08.08.05 (CN1058717)
Azithromycin crystalline dihydrate	Sumamed Zithromax	Pliva (+Pfizer) Pfizer	06.03.1981 (YU592) 09.07.1987 (PCT/US87/01612)	No WO89/00576	GB2094293 EP298650	No	No	No
						No	No	08.07.03 (CN1016785)
Ciprofloxacin tablet formulation(12)	Cipro, Ciproxin	Bayer	03.09.1980 (DE3033157) 21.01.1986 (DE3601566)	No No	EP0049355 EP0230881	No	No	No
						No	No	expired 21.01.02 (CN1084188)
Fluconazole (general) specific	Diflucan	ICI Pfizer	02.06.1980 (GB8017959) 06.06.1981 (GB8117379)	No No	EP0044605 EP0069442	No	No	No
						No	No	No

Footnotes:

- (0) Except when stated differently, this expiry date is 20 years from the filing date, but note that the patent may expire before if the patent holder abandons it (i.e. stops paying the annual fees).
- (1) Patents may be granted to protect the basic molecule of a medicine, but also e.g. to protect the manufacturing process, a specific therapeutic indication, or a specific formulation of the said molecule. Note that a product patent usually covers also a manufacturing process.
- (2) Note that only the first patent holder is named where there are more than one.
- (3) In Brazil, patent protection for pharmaceuticals was only introduced on May 14th 1997. However, between May 15th 1996 and May 15th 1997 it was possible to register a preexisting foreign patent or pending patent application in Brazil in order to obtain pipeline patent protection, i.e., patent protection for medicines which are patent protected abroad but which have not been marketed yet.
- (4) There is no patent law in force in Cambodia. A draft Patent Law was passed by the National Assembly on November 28th 2002. This law is then supposed to go to the Senate for confirmation and is expected to be in force in 2003.
- (5) Chinese Patent Law was amended, with effect on January 1st 1993, to extend patent protection from 15 to 20 years.
- (6) Guatemala only introduced patent protection for pharmaceuticals on November 1st 2000.
- (7) In Malawi and Zambia, patents are granted for an initial term of 16 years from the filing date, with a possible extension.

Expected(o) patent expiry date (patent number) in										
Guatemala(6)	Kenya	Malawi(7)	OAPI(8)	Peru(9)	South Africa	Thailand(10)	Uganda(11)	Ukraine	Zambia(7)	Zimbabwe
No	No	No	No	No	No	No	No	No	No	No
No	No	No	?	No	No	No	No	No	No	No
No	12.06.11 (AP231)	12.06.07 (AP231)	?	No	12.06.11 (ZA9104490)	No	31.01.08 (AP231)	?	12.06.07 (AP231)	12.06.11 (AP231)
No	No	No	No	No	No	No	No	No	No	No
No	15.06.08 (AP44)	15.06.04 (AP44)	abandoned (OA8743)	No	07.07.08 (ZA8804925)	No	27.07.04 (AP44)	?	15.06.04 (AP44)	15.06.08 (AP44)
No	expired 21.08.01 (KE3545)	No	No	No	expired 01.09.01 (ZA8106080)	No	No	No	No	No
No	No	No	No	No	No	No	No	No	No	No
No	expired 14.05.01 (KE3733)	No	No	No	expired 19.05.01 (ZA8103354)	No	No	No	No	No
No	expired 22.04.02 (KE3771)	No	No	No	expired 04.06.02 (ZA8203934)	No	No	expired 01.06.02 (UA8019)	No	No

(8) OAPI patents are effective in the 16 member States of the Organisation Africaine de la Propriété Intellectuelle (Benin, Burkina Faso, Cameroon, Central African Rep., Congo, Ivory Coast, Gabon, Guinea, Guinea Bissau, Equatorial Guinea, Mali, Mauritania, Niger, Senegal, Chad, and Togo).

(9) Patent protection for pharmaceutical products was only introduced on December 11th 1991 in Peru, as in all other members of the Andean Community (Bolivia, Colombia, Ecuador, and Venezuela).

(10) Patent protection for pharmaceutical products has only been available in Thailand since September 30th 1992, including pending applications at this date.

(11) In Uganda, patents are granted for 15 years from the date of grant, and may be extended for 5 additional years if the patent is worked locally.

(12) Note that other patents protect aqueous solutions and flavoured-masqued compositions of ciprofloxacin.

(13) Coartem: name in poor countries / Riamet: name in rich countries.

WO refers to patent applications filed under the system of the Patent Cooperation Treaty (PCT). The PCT allows patent applicants to file a kind of “worldwide” patent application, by designating countries among PCT Member States in which they intend to obtain a patent. However, the applicant must then confirm this wish in each designated country/region and the patent can only be granted by the patent office of the said country/region.

Where ‘?’ appears, the information was not available.

Expected(o) patent expiry date (patent number) in								
INN(1)	Originator's Trade mark	Patent holder(2) (manufacturer)	Basic patent priority date	International patent application	Representative European corresponding patent	Brazil (3)	Cambodia (4)	China (5)
Abacavir (racemic mixture) Abacavir (enantiomer)	Ziagen	Wellcome (GSK) Wellcome (GSK)	27.06.1988 (GB8815265) 22.12.1989 (US455201)	No No	EP0349242 EP0434450	27.06.08 (BR1100288) No	No No	No 21.12.05 (CN1028106)
Didanosine - ddl improved oral formulation	Videx	USA Gov (BMS) BMS	26.08.1985 (US769016) 22.07.1991 (US733547)	WO87/01284 No	EP0216510 EP0524579	No No	No No	No 21.07.07 (CN1042299)
Efavirenz	Stocrin/Sustiva	Merck (MSD, BMS)	07.08.1992 (US926607)	WO94/03440	EP0582455	07.08.12 (BR1100250)	No	06.08.13 (CN1051767)
Indinavir (including sulfate) (related) Indinavir	Crixivan	Merck (MSD) Merck	08.11.1991 (US789508) 07.05.1993 (US059038)	WO93/09096 WO94/26717	EP0541168 EP0696277 (withdrawn)	No No	No No	No under examination (CN1126469)
Lamivudine - 3TC (including enantiomer) enantiomer crystalline form	Epivir Epivir Epivir	IAF Biochem (GSK) IAF Biochem Glaxo	08.02.1989 (US308101) 02.05.1990 (GB9009861) 03.06.1991 (GB911902)	No WO91/17159 WO92/21676	EP0382526 EP0625150 (rejected) EP0517145	No No No	No No No	08.02.05 (CN1033640) 30.04.06 (CN1036196) No
Nelfinavir mesylate	Viracept	Agouron (Roche)	07.10.1993 (US133543)	WO95/09843	EP0722439	07.10.13 (BR1100166)	No	07.10.14 (CN1046269)
Nevirapine Syrup formulation	Viramune Viramune	Boehringer Boehringer	17.11.1989 (US438923) 25.08.1997 (US60/056803)	No ?	EP0429987 ?	No ?	No No	No ?
Ritonavir Combination w/ lopinavir	Norvir Kaletra	Abbott Abbott	29.12.1992 (US998114) 13.12.1995 (US572226)	WO94/14436 WO97/21685	EP0674513 EP0882024	29.12.12 (BR1100661) 13.12.15 (BR1100397)	No No	No under examination (CN1208405)
Saquinavir	Fortovase	Hoffmann-La Roche	11.12.1989 (GB8927913)	No	EP0432695	No	No	10.12.05 (CN1034805)
Stavudine - D4T Pro-drug	Zerit	Yale Univ. (BMS) BMS	17.12.1986 (US942666) 06.05.1988 (US190809)	No No	EP0273277 EP0340778 (withdrawn)	No No	No No	No No
Zidovudine - AZT	Retrovir	Glaxo Wellcome	16.03.1985 (GB8506869)	No	EP0196185	No	No	No
AZT - 3TC combination Tablet formulation	Combivir	Glaxo Wellcome Glaxo Wellcome	16.05.1991 (GB9110624) 31.10.1996 (GB9622681)	WO92/20344 WO98/18477	EP0513917 EP0941100 (expected grant 28.05.03)	No under examination (BR9712614)	No No	15.05.07 (CN1045961) under examination (CN1241142)
AZT + 3TC + abacavir Tablet formulation	Trizivir Trizivir	Glaxo Wellcome Glaxo Wellcome	30.03.1995 (GB9506490) 29.04.1998 (GB9809213)	WO96/30025 WO99/55372	EP0817637 EP1083932 (under examination)	under examination (BR9607851) under examination (BR9910071)	No No	28.03.16 (CN1103593) WO99/55372 ?

Footnotes:

(o) Except when stated differently, this expiry date is 20 years from the filing date, but note that the patent may expire before if the patent holder abandons it (i.e. stops paying the annual fees).

(1) Patents may be granted to protect the basic molecule of a medicine, but also e.g. to protect the manufacturing process, a specific therapeutic indication, or a specific formulation of the said molecule. Note that a product patent usually covers also a manufacturing process.

(2) Note that only the first patent holder is named where there are more than one.

(3) In Brazil, patent protection for pharmaceuticals was only introduced on May 14th 1997. However, between May 15th 1996 and May 15th 1997 it was possible to register a preexisting foreign patent or pending patent application in Brazil in order to obtain pipeline patent protection, i.e., patent protection for medicines which are patent protected abroad but which have not been marketed yet.

(4) There is no patent law in force in Cambodia. A draft Patent Law was passed by the National Assembly on November 28th 2002. This law is then supposed to go to the Senate for confirmation and is expected to be in force in 2003.

(5) Chinese Patent Law was amended, with effect on January 1st 1993, to extend patent protection from 15 to 20 years.

(6) Guatemala only introduced patent protection for pharmaceuticals on November 1st 2000.

Guatemala (6)	Kenya	Malawi (7)	OAPI (8)	Peru (9)	South Africa	Thailand (10)	Uganda (11)	Ukraine	Zambia(7)	Zimbabwe
No	26.06.09 (AP101)	26.06.05 (AP101)	No	No	25.06.09 (ZA8904837)	No	23.10.05 (AP101)	No	26.06.05 (AP101)	26.06.09 (AP101)
No	21.12.10 (AP196)	21.12.06 (AP196)	No	No	20.12.10 (ZA9010365)	No	30.06.07 (AP196)	21.12.10 (UA29382)	21.12.06 (AP196)	21.12.10 (AP196)
No	No	No	No	No	No	No	No	No	No	No
No	No	No	No	No	20.07.12 (ZA9205484)	07.07.12 (7600)	No	No	No	No
No	No	No	No	No	06.08.13 (ZA9305724)	30.07.13 (11367)	No	06.08.13 (UA42699)	No	No
No	No	No	No	No	06.11.12 (ZA9208563)	No	No	03.11.12 (UA45945)	No	No
No	No	WO94/26717?	WO94/26717?	No	05.05.14 (ZA9403104)	under examination (16620)	No	No	No	No
No	08.02.10 (AP136)	08.02.06 (AP136)	08.02.10 (OA 9193)	No	07.02.10 (ZA9000943)	No	05.08.06 (AP136)	No	08.02.06 (AP136)	08.02.10 (AP136)
No	02.05.11 (AP182)	02.05.07 (AP182)	02.05.11* (OA9559)	No	30.04.11 (ZA9103293)	?	30.06.07 (AP182)	No	02.05.07 (AP182)	02.05.11 (AP182)
No	02.06.12 (AP300)	02.06.08 (AP300)	02.06.12* (OA9913)	No	02.06.12 (ZA9204007)	?	20.01.09 (AP300)	02.06.12 (UA41265)	02.06.08 (AP300)	02.06.12 (AP300)
No	07.10.14 (AP600)	07.10.14 (AP600)	07.10.14* (OA10718)	No	07.10.14 (ZA9407815)	No	No	No	No	No
No	16.11.10 (AP179)	16.11.06 (AP179)	16.11.10 (OA9852)	No	18.11.10 (ZA9009246)	No	30.04.07 (AP179)	17.11.09 (UA34420)	16.11.06 (AP179)	16.11.10 (AP179)
Potentially in the mailbox	?	?	?	under examination (718-1998)	?	under examination (41541/opp. filed)	?	11.08.18 (UA44370)	?	?
No	No	No	No	No	No	No	No	?	No	No
Potentially in the mailbox	No	No	No	No	11.12.16 (ZA9610475)	04.12.16 (13302)	No	?	No	No
No	No	18.11.06 (MW9088)	11.12.10 (OA9334)	No	03.12.10 (ZA9009743)	No	No	?	No	13.11.10 (ZW90174)
No	No	No	No	No	22.09.07 (ZA8707171)	No	No	No	No	No
No	No	No	No	No	04.05.09 (ZA8903348)	No	No	No	No	No
No	14.03.06 (AP11)	14.03.02 (AP11)	No	No	13.03.06 (ZA8601933)	No	22.12.02 (AP11)	?	14.03.02 (AP11)	14.03.06 (AP11)
No	No	WO92/20344?	11.05.12*(OA10058)	No	15.05.12 (ZA9203544)	No	No	No	No	No
Potentially in the mailbox	29.10.17 (AP1067)	29.10.13 (AP1067)	29.10.17*(OA11038)	under examination (965-1997)	29.10.17 (ZA9709726)	under examination (37164/opp. filed)	01.05.17 (AP1067)	No	No	29.10.17 (AP1067)
Potentially in the mailbox	28.03.16* (AP652)	28.03.12* (AP652)	WO96/30025 ?	No	27.03.16 (ZA9602477)	under examination (28828)	19.06.13* (AP652)	WO96/30025 ?	No	28.03.16* (AP652)
Potentially in the mailbox	WO99/55372 ?	WO99/55372 ?	WO99/55372 ?	No	WO99/55372 ?	?	WO99/55372 ?	WO99/55372 ?	No	WO99/55372 ?

(7) In Malawi and Zambia, patents are granted for an initial term of 16 years from the filing date, with a possible extension.

(8) OAPI patents are effective in the 16 member States of the Organisation Africaine de la Propriété Intellectuelle (Benin, Burkina Faso, Cameroon, Central African Rep., Congo, Ivory Coast, Gabon, Guinea, Guinea Bissau, Equatorial Guinea, Mali, Mauritania, Niger, Senegal, Chad, and Togo).

(9) Patent protection for pharmaceutical products was only introduced on December 11th 1991 in Peru, as in all other members of the Andean Community (Bolivia, Colombia, Ecuador, and Venezuela).

(10) Patent protection for pharmaceutical products has only been available in Thailand since September 30th 1992, including pending applications at this date.

(11) In Uganda, patents are granted for 15 years from the date of grant, and may be extended for 5 additional years if the patent is worked locally.

WO refers to patent applications filed under the system of the Patent Cooperation Treaty (PCT). The PCT allows patent applicants to file a kind of “worldwide” patent application, by designating countries among PCT Member States in which they intend to obtain a patent. However, the applicant must then confirm this wish in each designated country/region and the patent can only be granted by the patent office of the said country/region.

WO? means that we don’t know if the PCT application has been confirmed at national level.

* There is an error in the published patent document with regard to the filing date (see section 4). The estimated patent expiry date is therefore based on the assumed correct filing date.

Where ‘?’ appears, the information was not available.

■ Annex B

The anatomy of a patent

When somebody applies for a patent they have to explain in their patent document why their invention is “clever” enough to deserve a patent.

According to the theory of the patent bargain, a patent document has to explain how to carry out the invention, so it needs to contain “How To” instructions. Since the monopoly rights give exclusive control over the invention to the patent holder, the document must also carefully define what the invention is. These integral parts of a patent are called the “description” and the “claims” respectively. A “title page” typically provides administrative and procedural details of the patent including such things as the number of the patent and of the application, the date of priority, the date of filing of the application, the date of publication of the application, the date of grant of the patent, the title of the invention, the name of the applicant and of the inventor. Drawings typically accompany the description. A brief summary of the invention, the “abstract” is often also available, although not strictly part of the patent application.

By way of illustration of these concepts, we have reproduced a patent document (starting on the next page). This is a granted European patent (number 0273277) that protects the antiretroviral drug stavudine. Stavudine (also known as d4T) is an important nucleoside reverse transcriptase inhibitor used in antiretroviral combination therapy. Bristol-Myers Squibb (BMS) sells it under the trade name Zerit®. This patent document is conveniently and unusually short.

The title pages (pages 1-2) contain a lot of information, including the following. The title of the invention is in this case “Pharmaceutical composition comprising 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehyrdthymidine) in treating patients infected with retrovirus [sic]”. Although this will not be self-evident to most non-pharmacists, this is stavudine. The owner (proprietor) of the patent is listed as Yale University. The inventors are named as Tai-Shun Lin and William H. Prusoff who worked at Yale University. This European patent claimed priority from an earlier patent application. The concept of priority and the priority year and why these are so important for the international patent system is outlined in section 3.1. In this case, priority is claimed from American patent application 942666, which was filed on December 17th 1986. This European patent was

filed on the December 11th 1987, less than a year later as required to claim priority. The “references cited” entry on the title pages provides a list of the documents that the European Patent Office knew about when they granted this patent. This concept of the “state of the art” is also discussed in section 3.2.

Following the title pages comes the “description” (pages 3-7). The description opens by “setting the scene” for the invention. In this case the invention relates to “pharmaceutical compositions comprising 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehyrdthymidine for treating warm blooded animals infected with retroviruses”. For the avoidance of doubt, “warm blooded animals” includes humans in this context. Crucially, on line 47 of page 34, the inventors tell the reader that “[t]he compound 3'-deoxythymidin-2'-ene is known per se from Carbohydrate Research, Vol. 73, 1979, pages 113 to 124 (Elsevier Scientific Publishing Company, Amsterdam, NL)” and they go on to say “However, no therapeutical use of this compound is described in this document”. This means that the invention in this European patent is not the making of a new chemical entity. This invention is the fact that the inventors have discovered that this compound, the structure of which was

already known back in 1979, has a medical use. The “finding of potent antiretroviral activity” is said to be unexpected. We discuss this on p. 13 .

Pages 4 to 7 of the description outline methods for making and testing the compound. As one of the main purposes of patents is to make technical information available to the public, this disclosure should happen “in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art”^[1].

On page 7, the claims appear. These define the scope of the patent protection. As outlined above, the inventors have discovered that this compound has a medical use in combating retroviruses, so that is what they claim as their “intellectual property”. Claim 1 forbids anybody but the patent owner (Yale University) or anybody they give permission to (e.g. BMS) to make a “pharmaceutical composition for treating warm blooded animals infected with a retrovirus, comprising as an active ingredient an anti-retroviral effective amount of 3'-deoxythymidin-2'-ene, either alone or in admixture with usual additives such as solid, liquid or liquefied gaseous diluents”. If you do it without their permission, in a country where this patent is in effect, you will be infringing

As we have explained above, the TRIPS Agreement does not require WTO Members to grant patents for this sort of invention. Notwithstanding this, if you look at the patent table, you will see that South Africa did grant a patent for this invention^[3]

[2] Claim 8 is a so-called “Swiss claim”, for which see Correa, C.M. *“Integrating Public Health Concerns into Patent Legislation in Developing Countries”*, South Centre, 2nd edition, Geneva, September 2001.

[3] Patent holders have choices in how they exploit their patents. In 2001, MSF South Africa asked Yale, the owner of a key patent on Zerit, to authorise imports to South Africa of generic versions of stavudine for use in providing treatment free of charge to people with HIV/AIDS unable to afford it. A generic manufacturer had offered to produce it 34 times cheaper than BMS. Other NGOs, Yale University students, technicians and researchers joined forces in a petition to support MSF's request. BMS bowed to the pressure and announced that they would allow generic competition, as well as massively reduce the price of the patented drug. For more details on the case, see for example "The high cost of living – Yale shares profits from AIDS drugs" in *Le Monde Diplomatique*, February 2002 (<http://mondediplo.com/2002/02/04stavudine>). For context and further details see the Consumer Project on Technology page on stavudine (<http://www.cptech.org/ip/health/d4/4.html>).

Europäisches Patentamt
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Office européen des brevets

Publication number: **0 273 277 B1**

EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **24.06.92** (51) Int. Cl.⁵: **A61K 31/70**
(21) Application number: **87118407.3**
(22) Date of filing: **11.12.87**

(54) **Pharmaceutical composition comprising 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) in treating patients infected with retrovirus.**

(30) Priority: **17.12.86 US 942666**
(43) Date of publication of application: **06.07.88 Bulletin 88/27**
(45) Publication of the grant of the patent: **24.06.92 Bulletin 92/26**
(94) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE
(56) References cited:
US-A- 3 817 982

BIOCHEM. BIOPHYS. RES. COMMUN., vol. 142, no. 1, January 15, 1987, pages 128 - 134, Academic Press, Inc.; M. Baba et al.: " Both 2' 3'-dideoxythymidine and its 2', 3'-unsaturated derivative (2',3'- dideoxythymidinene are potent and selective inhibitors of human immunodeficiency virus replication in vitro"

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Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

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MOL. PHARMACOL. vol. 32, no. 1, July 1987, pages 162-167, The American Society for Pharmacology and Experimental Therapeutics; J. BALZARINI et al.: "The anti-HTLV-III(anti-HIV) and cytotoxic activity of 2', 3'-didehydro-2',3'- dideoxyribonucleosides: A comparison with their parental 2', 3'-dideoxyribonucleosides"

CANCER LETTERS, vol. 8, 1980, pages 307-315, Elsevier, North- Holland Scientific Publishers Ltd., NL; P. Furmanski et al.: "Inhibition by 2',3'-dideoxythymidine of retro-viral infection of mouse and human cells"

BIOCHEM. BIOPHYS. RES. COMMUN., vol. 140, no. 2, October 30, 1986, pages 735-742, Academic Press Inc.; J. BALZARINI et al.: "Potent and selective anti-HTLV-III/LAV activity of 2',3'-dideoxycytidine the 2', 3'-unsaturated derivative of 2', 3'-dideoxycytidine"

PROC. NATL. ACAD. SCI. USA, vol. 83, March 1986, pages 1911-1915, H. MITSUYA et al.: "Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LAV) by 2', 3'-dideoxy-nucleosides"

CARBOHYDRATE RESEARCH, vol. 73, 1979, pages 113-124, Elsevier Scientific Publishing Company, Amsterdam, NL; T. ADACHI et al.: "Synthesis of uracil and thymine nucleosides of unsaturated 5-(aminoacyl)amino-pentofuranoses".

Description

The present invention relates to pharmaceutical compositions comprising 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) for treating warm blooded animals infected with retroviruses.

- 5 Acquired immunodeficiency syndrome (AIDS) is generally accepted to be a consequence of infection with the retrovirus variously termed human T-lymphotropic virus type III (HTLV-III), lymphadenopathy-associated virus (LAV), AIDS associated retrovirus (ARV), or human immunodeficiency virus (HIV). A number of compounds have demonstrated antiviral activity against this virus which include HPA-23 (D. Dormont, B. Spire, F. Barre-Sinoussi, L. Montagnier and J. C. Chermann, Ann. Inst. Pasteur/Virol., 75, 136E, 10 (1985) and W. Rosenbaum, D. Dormont, B. Spire, E. Vilmer, M. Gentilini, C. Griscelli, L. Montagnier, F. Barre-Sinoussi and J. C. Chermann, Lancet i, 450, (1985)), interferons (D. D. Ho, K. L. Hartshorn, T. R. Rota, C. A. Andrews, J. C. Kaplan, R. T. Schoolkey and M. S. Hirsch, Lancet i, 602, (1985)), ribavirin (J. B. McCormick, J. P. Getchell, S. W. Mitchell and D. R. Hicks, Lancet ii, 1367, (1984)), phosphonoformate (E. G. Sandstrom, J. C. Kaplan, R. E. Byington and M. S. Hirsch, Lancet, i, 1480, (1984) and P. S. Sarin, Y. Taguchi, D. Sun, A. Thornton, R. C. Gallo and B. Oberg, Biochem. Pharmac., 34, 4075, (1985)), ansamycin, 15 (R. Anand, J. L. Moore, A. Srinivasan, V. Kalyanaraman, D. Francis, P. Feorino and J. Curran, Abstracts of the International Conference on Acquired Immune Deficiency Syndrome (AIDS), April 14-17, Atlanta, GA, page 72, (1985)), suramin (H. Mitsuya, M. Popovic, R. Yarchoan, S. Matsushita, R. C. Gallo and S. Broder, Science, 226, 172, (1984); H. Mitsuya, S. Matsushita, M. E. Harper and S. Broder, Cancer Res., 45, 4583s, 20 (1985) and E. DeClercq, Cancer Lett., 8, 9, (1979)), imuthiol (A. Pompidou, D. Zagury, R. C. Gallo, D. Sun, A. Thornton and P. S. Sarin, Lancet, ii, 1423, (1985)), penicillamine (P. Chandra and P. S. Sarin, Drug Res., 36, 184, (1986)), rifabutin (R. Anand, J. Moore, P. Feorino, J. Curran and A. Srinivasan, Lancet, i, 97, (1986)-), AL-721 (P. S. Sarin, R. C. Gallo, D. I. Scheer, F. Crews and A. S. Lippa, New Engl. J. Med., 313, 1289, (1985)), 3'-azido-3'-deoxythymidine (W. Ostertag, T. Cole, T. Crozier, G. Gaedicke, J. Kind, N. Kluge, J. C. Krieg, G. Roselser, G. Sheinheider, B. J. Weimann and S. K. Dube, Proceedings of the 4th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1973, Differentiation and Control of 25 Malignancy of Tumor Cells, Eds. W. Nakahara, T. Ono, T. Sugimura and H. Sugano, page 485, University of Tokyo Press, Tokyo, (1974); W. Ostertag, G. Roseler, C. J. Kreig, T. Cole, T. Crozier, G. Gaedicke, G. Steinheider, N. Kluge and S. K. Dube, Proc. Natn. Acad. Sci. USA, 71, 4980, (1974); S. L. Dube, G. Gaedicke, N. Kluge, B. J. Weimann, H. Melderis, G. Steinheider, T. Crozier, H. Beckmann and W. Ostertag, Proceedings of the 4th International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1973, Differentiation and Control of Malignancy of Tumor Cells, Eds. W. Nakahara, T. Ono, T. Sugimura and H. Sugano, page 99, University of Tokyo Press, Tokyo, (1974); S. K. Dube, I. B. Pragnell, H. Kluge, G. Gaedicke, G. Steinheider and W. Ostertag, Proc. Natn. Acad. Sci. USA, 72, 1863, (1975) and H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. Lehrman Nusinoff, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, Proc. Natn. Acad. Sci. USA, 82, 7096, (1985)), and more recently various 2',3'-dideoxynucleosides (H. Mitsuya and S. Broder, Proc. Natn. Acad. Sci. USA, 83, 1911, (1986)), of which 2',3'-dideoxycytidine (ddCyd) is the most potent. A review of these and other compounds evaluated for their activities against HIV, as well as a discussion of the AIDS problem in general, has been presented (E. DeClercq, J. Med. Chem., 29, 1561, (1986)).

Applicants previously found 2',3'-dideoxycytidin-2'-ene (2',3'-dideoxy-2',3'-didehydrocytidine; D4C) a derivative of 2',3'-dideoxycytidine (ddCyd) to have antiviral activity against HIV (Lin et al, Biochem. Pharmacol, in press). This provided the stimulus to synthesis 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) even though Mitsuya and Broder, supra found 2',3'-dideoxythymidine (3'-deoxythymidine) to be a very poor inhibitor of HTLV-III/LAV. Applicants' finding of potent antiviral activity with 3'-deoxythymidin-2'-ene was, therefore, unexpected based on their report.

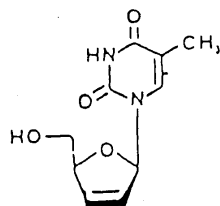
The compound 3'-deoxythymidin-2'-ene is known per se from Carbohydrate Research, Vol. 73, 1979, pages 113 to 124 (Elsevier Scientific Publishing Company, Amsterdam, NL). However, no therapeutical use of this compound is described in this document.

- 50 The antiretroviral activity of the saturated compounds 2'3'-dideoxythymidine and cytidine is known from Biochem.Biophys. Res.Comm., Vol. 140, No. 2, October 30, 1986, esp. page 736. This document also discloses the activity of the unsaturated derivative 2'3'-dideoxycytidine.

The present invention is directed to a pharmaceutical composition for treating warm blooded animals infected with a retrovirus, comprising as an active ingredient an anti-retroviral effective amount of 3'-deoxythymidin-2'-ene, either alone or in admixture with usual additives such as a solid, liquid or liquefied gaseous diluents.

Preferred embodiments are recited in the dependent claims.

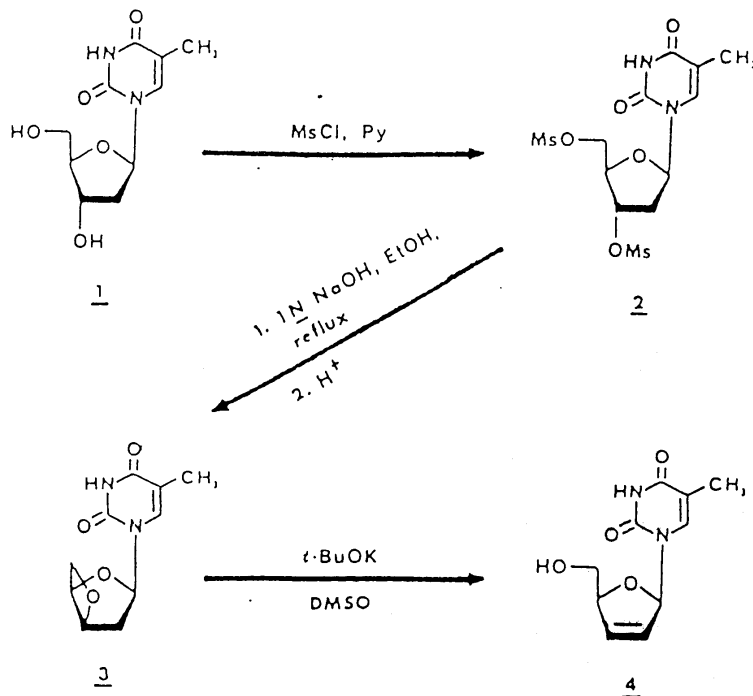
The structure of 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine; D4T) is as follows:



3'-Deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) has antiviral activity against retroviruses, e.g., murine leukemia virus and human immunodeficiency virus, i.e., HIV; HTLV III/LAV virus (the AIDS virus).

Retroviruses are RNA viruses whose genome contains copies of high-molecular weight single-stranded RNA. The virion contains reverse transcriptase. Non-limiting examples of retroviruses include leukemia and sarcoma viruses of animals, foamy viruses of primates and some slow viruses, e.g., visna and maedi of sheep.

A synthesis for the active compound of the present invention is illustrated in the following reaction scheme:



3'-Deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine) (4) can be synthesized basically by the methodology of J. P. Horwitz, J. Chua, M. A. DaRooge, M. Noel and I. L. Klundt, *J. Org. Chem.*, **31**, 205,

(1966) with minor modifications. With reference to the above reaction scheme, treatment of thymidine (1) with methanesulfonyl chloride in pyridine at 0°C gives the corresponding disulfonate 2. Refluxing compound 2 with 1 N NaOH solution in ethanol produces the 3',5'-cyclic ether 3. Treatment of compound 3 with potassium t-butoxide in dry DMSO yields the desired 2'3'-unsaturated derivative 4.

The pharmaceutical composition according to the invention may be present in the form of a sterile and/or physiologically isotonic aqueous solution or in dosage unit form, e.g. in the form of tablets (including lozenges and granules), caplets, dragees, capsules, pills, ampoules or suppositories.

"Medicament" as used herein means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used herein means physically discrete coherent units suitable for medical administration, each containing a daily dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose, or for example, a half, a third or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day, respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g., granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g., starch, sugars, mannitol and silicic acid; (b) binding agents, e.g., carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g., glycerol; (d) disintegrating agents, e.g., agaragar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution, e.g., paraffin; (f) resorption accelerators, e.g., quaternary ammonium compounds; (g) surface active agents, e.g., cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g., kaolin and bentonite; (i) lubricants, e.g., talc, calcium and magnesium stearate and solid polyethyl glycols.

The tablets, dragees, capsules, caplets and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, from polymeric substances or waxes.

The active ingredient can also be made up in microencapsulated form together, with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble diluents, such as polyethylene glycols and fats (e.g., cocoa oil and high esters, [e.g., C₁₄-alcohol with C₁₆-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200, except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers. Specific non-limiting examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for example, ground nut oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g., water, ethyl alcohol, propylene glycol, surface-active agents (e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitane esters) microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain coloring agents and preservatives, as well as perfumes and flavoring additions (e.g., peppermint oil and eucalyptus oil) and sweetening agents (e.g., saccharin and aspartame).

The pharmaceutical compositions according to the invention generally contain from 0.5 to 90% of the active ingredient (3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine)) by weight of the total composition.

In addition to 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine), the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds.

Any diluent in the medicaments of the present invention may be any of those mentioned above in

relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as the sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted by virtue of their shape or packaging for medical administration and may be, for example, any of the following: tablets (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, may include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 2.5 to 250 mg of active ingredient in the case of intravenous administration and 25 to 250 mg of active ingredient in the case of oral administration.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g., a granulate) and then forming the composition into the medicament (e.g. tablets).

It is envisaged that the active compound, namely, 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine), will be administered perorally, parenterally (for example, intramuscularly, intraperitoneally, subcutaneously or intravenously) rectally or locally, preferably orally or parenterally, especially perlingually or intravenously. Preferred pharmaceutical compositions and medicaments are, therefore, those adapted for administration such as oral or parenteral administration. Administration in the method of the invention is preferably oral or parenteral administration.

In general, it has proved advantageous to administer intravenously amounts of from 0.01 mg to 10 mg/kg, preferably 0.05 to 5 mg/kg, of body weight per day and to administer orally 0.05 to 20 mg/kg, preferably 0.5 mg to 5 mg/kg of body weight per day, to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, type of formulation in which the active ingredient is administered, the mode in which the administration is carried out and the point in the progress of the disease or interval at which it is to be administered. Thus, it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered, it may be advisable to divide these into several individual administrations over the course of the day.

The invention will now be described with reference to the following non-limiting examples.

Example 1: Synthesis of 3'-deoxythymidin-2'-ene (3'-deoxy-2',3'-didehydrothymidine)

A solution of the cyclic ether 3 (see the reaction scheme described hereinabove) (8.64 g, 38.4 mmol) in 240 ml of dried DMSO containing 8.70 g (76.4 mmol) of potassium t-butoxide was stirred at room temperature for two hours. The reaction mixture was neutralized to a pH of approximately 7 with ethanolic acetic acid, and the solution was then evaporated to dryness at approximately 50 °C under reduced pressure. The residue was triturated with several portions of hot acetone. The insoluble materials were removed by filtration, and the filtrate was evaporated to dryness. The residue was eluted through a silica gel column (CHCl₃-EtOH, 2:1) to yield 6.5 g (76%) of product: mp 158-160 °C; NMR (Me₂SO-d₆) δ 1.82 (s, 3H, 5-CH₃), 3.53 (m, 2H, 5'-H), 4.80 (m, 1H, 4'-H), 4.96 (t, 1H, 5'-OH, D₂O exchangeable), 5.90 (m, 1H, 3'-H, vinyl), 6.40 (m, 1H, 2'-H, vinyl), 6.82 (m, 1H, 1'-H), 7.67 (s, 1H, 6-H).

Example 2: Biological Assay Procedure for Antiviral Activity Against the Human Immunodeficiency Virus (HIV; HTLV-III/LAV)

Three day-old mitogen stimulated human peripheral blood mononuclear (PBM) cells (10⁶ per ml) were infected with HIV (strain LAV) in the presence and absence of various concentrations of 3-deoxythymidin-2'-ene, 1, 10, 100 μM. Five days after infection, the virus in the supernatant was pelleted and, after disruption, the reverse transcriptase activity was determined.

The methods used for culturing the PBM cells, harvesting the virus and determination of reverse transcriptase activity were those described by J. S. McDougal, S. P. Cort, M. S. Kennedy, C. D. Cabridilla, P. M. Feorino, D. P. Francis, D. Hicks, V. S. Kalyanaramen and L. S. Martin, *J. Immun. Meth.*, **76**, 171, (1985). The virus was added to the cultures at the same time as the drug.

The data obtained indicated that essentially complete inhibition of the replication of the "AIDS" virus

was obtained (>98% inhibition) at all three concentrations.

Example 3: Biological Assay Procedure for Antiviral Activity Against Moloney Murine Leukemia Virus (MuLV) by XC-Assay

The XC assay system is an indirect method for quantitation of murine-leukemia virus (MuLV) originally described by V. Klement, W. P. Rowe, J. W. Hartley and W. E. Pugh, *Proc. Natl. Acad. Sci.*, **63**, 753, (1969) and modified by W. P. Rowe, W. E. Pugh and J. W. Hartley, *Virology*, **42**, 1136, (1970). This test is based on the development of syncytial changes in the XC cell line when it is co-cultivated with mouse fibroblast cells (SC-1 cells) productively infected with MuLV. The XC cell line was derived from a rat tumor induced by the prague strain of Rouse Sarcoma Virus (RSV) (J. Svoboda, P. Chyle, D. Simkovic and J. Hilgert, *Folia Biol.*, **9**, 77, 1963)). This cell line contains the RSV genome, but does not produce infectious virus in the absence of a helper virus.

10E6 SC-1 cells were seeded in Earls Minimum Essential Medium (EMEM)-10% Fetal Bovine Serum (FBS), onto 60 mm petri dishes. The following day, the cells were inoculated with 0.5 ml of a virus dilution containing 25 μg/ml of DEAE-dextran. The dishes were maintained for 1 hour at 37 °C in a humidified 5% CO₂ incubator. The virus inoculum was then removed and replaced with 5 ml of medium containing appropriate concentrations of the test compound (two dishes/concentration). Medium containing 10% FBS was added to the virus control dishes. The medium (with or without the test compound) was changed at 48 hours.

Five days after virus inoculation, the culture fluid was decanted, and the cells were irradiated with a "General Electric" germicidal bulb for 30 seconds (1500-1800 ergs UV-light). Cultures were immediately overlaid with 10E6 SC cells in 5 ml of EMEM-10% FBS/dish. The medium was changed at 2-day intervals. Four days after XC cells addition, cultures were simultaneously fixed and stained with GEIMSATM for 10 to 15 minutes.

Plaques were counted using an inverted microscopy as holes in the cell sheet containing syncytial cells, or as focal masses of multinucleated giant cells. The antiviral activity was highly significant and had an ED₅₀ of 2.5 μM.

Calculation of % Inhibition/Concentration (% Inh./conc.):

$$\% \text{ Inh./conc.} = \left[100 - \frac{\text{average \# of syncytial/conc. of test compound}}{\text{average \# of syncytial in the virus control}} \times 100 \right]$$

ED₅₀: Accumulative % Inhibition using the Reed-Muench Method

Claims

1. A pharmaceutical composition for treating warm blooded animals infected with a retrovirus, comprising as an active ingredient an anti-retroviral effective amount of 3'-deoxythymidin-2'-ene, either alone or in admixture with usual additives such as a solid, liquid or liquefied gaseous diluents.
2. A composition according to claim 1, wherein the retrovirus is Moloney murine leukemia virus.
3. A composition according to claim 1, wherein the retrovirus is HTLV III/LAV.
4. A composition according to anyone of claims 1 to 3, containing 0.5 to 90 % of said active ingredient.
5. A composition according to anyone of claims 1 to 4, in the form of a sterile physiologically isotonic aqueous solution.
6. A composition according to claim 5 containing 0.5 to 90 % of said active ingredient.

7. A composition according to anyone of claims 1 to 6 in the form of a medicament in dosage unit form, such as in the form of a tablet, pill, dragee, capsule, caplet, ampoule or suppository.
8. The use of 3'-deoxythymidin-2'-ene or of a pharmaceutical composition according to anyone of claims 1 to 7 for the preparation of a medicament for the treatment of warm blooded animals infected with a retrovirus.

Revendications

1. Composition pharmaceutique pour le traitement d'animaux à sang chaud infectés par un rétrovirus, comprenant, comme ingrédient actif, une quantité anti-rétrovirale efficace de désoxy-3' thymidinène-2', soit seul, soit en mélange avec des additifs usuels, tels que des diluants solides, liquides ou sous forme de gaz liquéfiés.
2. Composition selon la revendication 1, dans laquelle le rétrovirus est le virus de la leucémie murine de Moloney.
3. Composition selon la revendication 1, dans laquelle le rétrovirus est HTLV III/LAV.
4. Composition selon l'une quelconque des revendications 1 à 3, contenant 0,5 à 90% dudit ingrédient actif.
5. Composition selon l'une quelconque des revendications 1 à 4, sous la forme d'une solution aqueuse physiologiquement isotonique, stérile.
6. Composition selon la revendication 5, contenant 0,5 à 90% dudit ingrédient actif.
7. Composition selon l'une quelconque des revendications 1 à 6, sous la forme d'un médicament se présentant sous la forme d'unités de dosage, telles que sous la forme de pastilles, pilules, dragées, capsules, gélules, ampoules ou suppositoires.
8. Utilisation du désoxy-3' thymidinène-2' ou d'une composition pharmaceutique telle que définie à l'une quelconque des revendications 1 à 7, pour la préparation d'un médicament pour le traitement d'animaux à sang chaud infectés par un rétrovirus.

Patentansprüche

1. Pharmazeutische Zubereitung zur Behandlung von Warmblütlern, die mit einem Retrovirus infiziert sind, enthaltend als aktiven Bestandteil eine anti-retroviral wirksame Menge von 3'-Deoxythymidin-2'-en, entweder allein oder in Gemisch mit den üblichen Zusätzen, z.B. festen, flüssigen oder verflüssigten gasförmigen Verdünnungsmitteln.
2. Zubereitung nach Anspruch 1, worin das Retrovirus Moloney-Maus-Leukämie-Virus darstellt.
3. Zubereitung nach Anspruch 1, worin das Retrovirus HTLV III/LAV darstellt.
4. Zubereitung nach einem der Ansprüche 1 bis 3, enthaltend 0,5 bis 90 % des aktiven Bestandteils.
5. Zubereitung nach einem der Ansprüche 1 bis 4 in Form einer sterilen, physiologisch isotonischen wäßrigen Lösung.
6. Zubereitung nach Anspruch 5, enthaltend 5 bis 90 % des aktiven Bestandteils.
7. Zubereitung nach einem der Ansprüche 1 bis 6 in Form einer Dosiseinheit, z.B. in Form einer Tablette, Pille, eines Dragées, einer Kapsel, Kaplette, Ampulle oder eines Suppositoriums.
8. Verwendung von 3'-Deoxythymidin-2'-en oder einer pharmazeutischen Zubereitung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Medikaments für die Behandlung von Warmblütlern, die mit

einem Retrovirus infiziert sind.

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