The role of intellectual property in local production in developing countries

Opportunities and challenges

Intelectual Property and Trade

R&D Innovation

Technology Transfer

Improving Access

Financing

Monitoring and Reporting

World Health Organization

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The role of intellectual property in local production in developing countries: opportunities and challenges.

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Contents

Abbreviations

AIDS	acquired immunodeficiency syndrome
ARIPO	Africa Regional Intellectual Property Organisation
HIV	human immunodeficiency virus
HPV	human papillomavirus
ICTSD	International Centre for Trade and Sustainable Development
I-MAK	Initiative for Medicines, Access & Knowledge
LDC	least developed country
OAPI	Organisation Africaine de la Propriété Intellectuelle
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
UNCTAD	United Nations Conference on Trade and Development
UNDP	United Nations Development Programme
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

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Background

This paper forms part of Phase 2 of a project undertaken by the World Health Organization and supported by the European Commission on improving access to medical products in developing countries through building capacity for local production and related technology transfer.

Phase 1 of the project reviewed the main trends and barriers to local production of pharmaceuticals, vaccines and diagnostics. The evidence gathered in Phase 1 suggests that developing countries that have developed a viable and successful manufacturing industry adopted a long-term vision and followed it up with perseverance. It was identified that a mutually supportive, complementary and coherent combination of policies is required to ensure long-term sustainability. Alignment between medical regulation, industrial and investment policies, science, technology and innovation policies, intellectual property policies, health insurance policies, procurement policies and technology transfer policies appears to be particularly important *(1)*.

Phase 2 of the project seeks to continue to develop the policy framework identified in Phase 1 by conducting a deeper analysis of the areas identified in order to develop policy coherence. One of the policy areas where further analysis is required is the role played by intellectual property rights in local production and access to medical products in developing countries – in particular, how indirect government support can be provided by the development of policies to support incremental innovation and production and suitable intellectual property rights regimes.

Executive summary

Intellectual property plays an important role both for the researching pharmaceutical industry, which relies heavily on intellectual property to protect its products, and for generic companies, which produce copies of existing medicines once patent protection expires. Beyond patent protection, trademarks are another form of intellectual property rights used to identify and market pharmaceutical products. Trade secrets and protection of clinical test data are other important elements of this industry. Consequently, how a national intellectual property system is set up is important when considering options for local production of pharmaceuticals in developing countries.

Using practical examples and patent landscapes, this report attempts to set out the various strategies and options available to facilitate local production. The report describes the options available to countries with a generic industry to design an intellectual property system that is favourable for local production and potentially for public health. The report highlights the importance of transparent and fair patent administration systems using the example of access to patent information. The report exemplifies how this can also support the use of certain pre-grant flexibilities to increase the space for local generic companies and facilitate local production. In this context, the questions of whether and how to examine patents are essential. Where countries decide to provide for substantive examination, they need to pay particular attention to what standards need to be followed to ensure implementation of pre-grant flexibilities in practice. Favourable interpretation of various provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) to support local industry is important: simply writing flexibilities into legislation will not achieve their intended impact without a good understanding by local producers of patent laws and patent systems. Competent intellectual property professionals and a transparent, fair and efficient court system also need to be in place to allow such policies to flourish.

The existence of a patent does not mean local production is not possible. This report provides practical examples showing multiple ways that allowed for local production through cooperation and/or the use of TRIPS flexibilities. Collaboration by patent holders has increased over the past years. Licensing has become common in the area of HIV/AIDS, and we have also seen cooperation in the area of hepatitis C. In this context, implementing pre- and post-grant flexibilities and using them strengthens the negotiating position of local companies when they endeavour to enter into licensing and technology transfer deals.

This report provides patent information on a number of medicines to show that it is a simplification to describe a medicine as "under patent". Patents are granted for national or regional jurisdictions, and the complete landscape often reveals countries where patents have not been filed or granted and thus where local production could take place if the technical problems associated with the production of affordable good-quality medicines can be overcome.

Local production depends on many conditions; the intellectual property environment is only one of these conditions and in itself will not be decisive. The mere absence of a patent in a country will not lead to local production of a medicine or ensure access to that medicine. The intellectual property system can, however, be used and designed to

favour local pharmaceutical innovation and manufacturing. Local production does not necessarily lead to improved access and health outcomes, which require good-quality essential medicines to be produced and marketed at affordable prices.

1. Introduction

A key feature for pharmaceutical production is intellectual property. This applies for both the researching pharmaceutical industry, which relies heavily on intellectual property protection to recoup its investment and defend its market position, and generic companies, which enter the market once patent protection expires or with the authorization of the patent holder. Beyond patent protection, trademarks are another form of intellectual property rights used to identify and market pharmaceutical products. Trade secrets and protection of clinical test data are other important elements of this industry. Consequently, the set-up of a national intellectual property system is important when considering options for local production of pharmaceuticals.

The level of protection of intellectual property rights appropriate to meet the needs of the society and of the local pharmaceutical industry depends on the character of the local industry, its technological capacities and its business model. In developing the appropriate intellectual property rights regime to promote local pharmaceutical production, attention needs to be paid to the country's level of economic and technological development and its industrial policy objectives. For example, local producers in developing countries may seek to file patents on incremental improvements of existing medicines or manufacturing processes, depending on their level of technological capability and commercial needs.

The appropriate level of protection of intellectual property may differ between industry branches. For example, in the same country, the local generic pharmaceutical industry may be interested in a flexible patent system that allows for early entry of generic products, while the local textile industry may be interested in stronger design protection to prevent competing companies from copying its original designs. Therefore, consideration needs to be given to an environment that balances the long-term interests of society with the interests of (local) producers in different sectors for commercial needs. As such, there is no single approach to how a country's national intellectual property rights laws should draw the line between exclusive rights on the one hand and the promotion of competition on the other hand. An analysis has to be carried out to assess what the appropriate policy should look like. Box 1 provides an overview of how local companies are concerned with intellectual property policies.

Box 1 How are local generic companies in developing countries concerned with intellectual property?

Local generic companies in developing countries:

- need to know whether they infringe any patents when producing a specific medicine;
- need to monitor the patent situation in potential countries of export;
- may want to file patent oppositions against certain applications on products of interest;
- may want to file patents on improvements of a medicine or production process in countries of interest;
- usually file for a trademark to protect their company name and logo and their products to distinguish them from their competitors and earn a premium on branded generics;
- may enter into licence agreements or transfer of technology arrangements with originator companies.

Most countries do not start from scratch when developing their national intellectual property systems. The situation depends on which international World Intellectual Property Organization (WIPO) treaties the country adheres to, whether the country is a member of the World Trade Organization (WTO), and any obligations arising from other regional or bilateral agreements that include intellectual property protection. This study focuses on countries that are WTO members and that have a local generic industry with some capacity for innovation. The study highlights the features of the patent system relevant to pharmaceutical companies situated in developing countries and discusses how companies and governments of developing countries can use the system in an optimal manner to facilitate local production and improve access.

The objective of this report is to:

- provide guidance to policy-makers on designing an intellectual property system that is conducive for local production and public health;
- show how and where local production can take place despite existing intellectual property regimes;
- illustrate that even if a medicine is patented in certain countries and regions, the complete landscape of the patents could reveal that local production of the same medicine is possible in countries where the patents were not filed or granted.

This report is part of a wider World Health Organization (WHO) and European Union project on local production, which covers the different aspects and challenges of local production and the conditions under which local production may increase access to essential medicines and thus benefit public health outcomes. Intellectual property considerations are only one aspect of this connection. Availability of a skilled workforce, technical knowledge, infrastructure and government incentives are dealt with in separate studies. Given the complexity of the current international standards for good manufacturing practices, the patented knowledge and consequently the knowledge disclosed in a patent are only a fraction of the technical understanding required to set up a production process for a given product. This is even truer for the increasing number of biological drugs. Thus, even in the absence of patent protection, a major challenge for generic companies remains to understand and absorb the patent information and apply it in such a way that it results in affordable good-quality medicines and enhancement of business – that is, where transfer of know-how and technology plays a decisive role, in particular for countries and companies that do not have generic industries that are as well developed as those in China and India.

2. Designing a national system conducive to local pharmaceutical industry

For WTO members, except least developed countries (LDCs), the key consideration is how to implement the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) when crafting national legislation. The TRIPS Agreement sets minimum standards for the protection of intellectual property, but countries retain considerable policy space that allows them to adapt intellectual property systems in general to their local needs. This policy space is often summarized as "TRIPS flexibilities" *(2,3)*, but in reality it is beyond the well-known flexibilities and includes "exceptions" and interpretations of various TRIPS provisions to suit the national situations. Although the use of this policy space in crafting legislation can be used to facilitate local production of pharmaceuticals, it is not enough. To be of benefit in practice to the industry and the public, intellectual property administration infrastructure and procedures also need to be functional, coherent, transparent and fair. It is beyond the scope of this study to describe all the necessary features of a functioning intellectual property system. Instead, the study uses the example of patent information where the need for a functioning system is particularly striking.

2.1 Access to patent information

The patent system requires the disclosure of inventions to the public and makes published patents and patent applications an important source of technical and legal information *(2)*. The importance of easy access to reliable patent information is essential for a number of reasons. By having access to patent information, local producers can determine their business strategies; this could include determining whether relevant patents have been filed or granted that eventually could block them from manufacturing and coming to market with a generic version of a product, for input into research and development processes, and to identify potential needs for licensing from the patent holder.

Access to patent information is critical to allow local producers or other parties to file pre-grant and post-grant oppositions, as shown in Box 2, or observations during the patent examination process where the patent law provides for such an option. During the examination process, patent applicants seek to overcome prior art, which is any evidence that the invention is already known by filing amendments to the scope of the claims in an application *(4)*. Such amendments should be published electronically, to ensure that third parties when filing oppositions or observations address the claims as subsequently amended during examination.

Box 2 New medicines to treat hepatitis C

New treatments for hepatitis C exemplify the importance of access to reliable patent information within the context of access to medicines. Given the high prevalence of hepatitis C and the high cure rates associated with new treatments, an increasing number of countries are looking into procuring these treatments at affordable prices. For ministries of health and procurement agencies to be properly informed regarding from where they can legally procure these products, they need to know the patent status. Generic companies use this information to assess whether they can produce copies in countries where patents have not been filed or granted and to identify potential export markets. Generic companies and nongovernmental organizations may file patent oppositions if they consider that a patent application does not fulfil the necessary conditions, as for example in the case of sofosbuvir in India and at the European Patent Office.

In October 2014 WHO published an analysis of the patent situation of seven new hepatitis treatments to aid achieving affordable access to medicines *(5)*.

Without the required patent information, health authorities cannot determine whether relevant patents have been filed in their country and whether it is necessary to seek the consent of the patent owner to manufacture or import a generic version of the product. For example, during the H5N1 crisis, some countries considered issuing compulsory licences, until the company that holds the market authorization for oseltamivir announced there were no patents that would prevent local production of generic versions in these countries *(6)*. Finding and interpreting patent information is not an easy task, but there is an increasing number of sources for patent data that are more accessible for health practitioners, as shown in Box 3.

Box 3 Accessing and finding patent information for medicines

Sources for patent information on specific medicines

- The Medicines Patent Pool database for antiretroviral medicines provides patent information for human immunodeficiency virus (HIV) medicines in low- and middle-income countries *(7)*.
- The UNITAID patent landscape reports provide patent information on specific medicines for HIV, acquired immunodeficiency syndrome (AIDS), hepatitis C, tuberculosis and malaria *(8)*.
- The "Orange Book" lists the patents of new medicines authorized by the Food and Drug Administration for the market in the United States of America *(9)*.
- The WHO hepatitis landscapes provide patent information for hepatitis treatments *(5)*.
- The WIPO patent landscape reports provide patent information for specific technologies *(10)*.
- The Initiative for Medicines, Access & Knowledge (I-MAK) patent landscape reports provide analysis and data on patents related to specific medicines *(11)*.

Manuals on retrieving patent information

- The United Nations Development Programme (UNDP) explains how to search for patents in developing countries using publicly available sources *(12)*.
- WHO provides a starting point for health authorities, procurement bodies and others to identify whether patents relating to a pharmaceutical product exist in the country of interest *(13)*.
- General guidance on using patent information
- WIPO provides a guide to searching for technology information using patent documents (14).

2.2 Making policy choices to favour local production of pharmaceuticals in developing countries

Policy options available to WTO members within the TRIPS Agreement have the capacity to offer strategic opportunities. The policy options that help stimulate local pharmaceutical production have been well documented *(2,15,16)*; less well documented are how these TRIPS flexibilities play out in practice and their opportunities and challenges. This section takes a closer look at the practical aspects of using the available flexibilities by providing examples from the patent landscapes discussed in Section 4 and the annexes and case studies of experiences of developing countries to date.

Flexibilities available under the TRIPS Agreement can be separated into pre-grant and post-grant flexibilities. Pre-grant flexibilities apply before the grant of a patent and thus normally concern the granting process. They can contribute to preventing the issuing of patents for products or variations of products that do not merit a patent for lack of innovative or novel content. Post-grant flexibilities include the exception of post-grant oppositions or revocation mechanisms, and different exceptions for acts that would otherwise amount to infringement of patent rights. Both pre-grant and post-grant flexibilities allow policy-makers to shape intellectual property systems to suit their respective needs.

Pre-grant flexibilities include *(2)*:

- to further define on a national level the patentability criteria and what is constituted as patentable subject matter;
- exclusions from patentability;
- observation or pre-grant opposition mechanisms that permit any third party to file evidence as to why a pending patent application does not meet patentability or patentable subject matter criteria;
- a well-designed disclosure requirement that can support access to relevant knowledge, for example by requiring the patent applicant to disclose the best method in line with Article 29 of the TRIPS Agreement.

Post-grant flexibilities include *(2)*:

- post-grant opposition, revocation or invalidation mechanisms that permit third parties to challenge a patent after its grant;
- the ability of researchers and pharmaceutical companies to carry out experimentation on patented substances without the patentee's authorization and risk of infringement;
- the regulatory review exception (also known as the Bolar exception), which allows local producers to use the patented substance and, for example, to produce a first batch of a patented medicine in order to obtain marketing approval;
- compulsory licences, including government use, whereby a government for the purpose of public interest can authorize itself or third parties to use the subject matter of a patent without the consent of the patentee; such licences can be issued for any grounds determined in national laws, including to rectify behaviour that impedes competition among market players (anticompetitive behaviour), to rectify abuse by the patentee

of its exclusive rights, to address national emergencies and for noncommercial use for government needs;[1]

- the Paragraph 6 System under the Doha Declaration, which creates a framework for compulsory licences in order to enable manufacturing of medical products exclusively for export to countries with insufficient or no manufacturing capacities in the pharmaceutical sector;
- the use of competition law in order to ensure that intellectual property rights holders do not abuse their rights, such as by not allowing reasonable access to a patented product or unreasonable pricing of a product;
- allowing for parallel importation of products first marketed abroad on a regional or international level.

In addition, the TRIPS Agreement lets members decide how to protect clinical trial data (also referred to as test data protection) against disclosure and unfair commercial use, which is important with respect to the approval of generic versions of originator products *(2)*. It also provides for specific transition periods for LDCs that can delay the introduction of substantive provisions of the TRIPS Agreement, including the granting of pharmaceutical patents and the protection of clinical test data until 2021. The LDC group in 2015 also filed for the extension of the specific transition period for pharmaceutical patents *(17)*.

2.3 Patentability standards and opposition procedures

The refusal of a patent as a result of not meeting a country's legal requirement of patentability can pave the way for local production. Strict patent standards alongside opposition procedures can therefore facilitate local production. An illustration of how pre-grant flexibilities can work in practice and pave the way for local production and access is presented in Box 4.

Box 4 Case study: imatinib (India)

In coming into full compliance with its TRIPS obligations, India installed a number of pre-grant flexibilities. Through using the full transitional period available under Article 65 of the TRIPS Agreement, India delayed the introduction of patent protection for pharmaceutical products until 2005. Consequently, the base patent covering imatinib as a chemical compound could not be filed in India before 1995. In countries that did not use the transitional period, such as Brazil, China and South Africa, the patent was granted (see Annex 3). During this transitional period, between 1995 and 2005 a number of local Indian manufacturers started manufacturing and selling generic versions of the drug at much lower prices. India in addition "grandfathered" those who had taken up production of medicines during this period, allowing them to continue to do so after 2005, even if patents were filed in the meantime through the so called "letterbox system" (Article 70.8 of the TRIPS Agreement).

Later Novartis filed another patent on the beta-crystalline form of imatinib (imatinib mesylate; see Annex 3). This form related to the product produced by Novartis to treat chronic myeloid leukaemia and gastrointestinal stromal tumours.

1 Countries are free to determine the grounds for compulsory licences, which can, for example, include unaffordable prices or limited availability.

The patent application for the beta-crystalline form of imatinib mesylate claimed to have improved bioavailability over the form described in the earlier patent for the base compound. Under India's patent law, new forms of known substances would not be considered inventions unless they showed an enhancement of efficacy.[2] Several generic companies and a non-profit-making organization filed pre-grant patent oppositions, making use of another pre-grant flexibility. The pre-grant opposition mechanism as set up in India allows any person to file an opposition before the grant of the application, thereby allowing noncommercial actors to also file oppositions. Moreover, it allows the opponents to respond throughout the proceedings to the patent applicant's evidence and be heard in the matter.

The key arguments raised in the oppositions were that the invention claimed for the beta-crystalline form of imatinib mesylate in the patent application was not novel and lacked an inventive step in light of the disclosures made in the earlier patent for the base compound imatinib. It was also argued that the beta-crystalline form did not meet the enhanced efficacy standards now required under Section 3d and therefore should not be considered an invention. After taking into consideration the oppositions, India's patent office refused the patent application in 2006 on all grounds, including Section 3d. Novartis filed subsequent appeals, but in 2013 the Supreme Court of India upheld the decision to refuse the patent.

This case study shows how using various pre-grant flexibilities can allow local production when secondary patents for incremental-type inventions would otherwise pose a barrier.

Other examples demonstrating how enforcement of patent standards and non-patentability criteria alongside pre-grant patent opposition can remove potential patent barriers include decisions by the Indian Patent Controller relating to the HIV drugs nevirapine hemihydrate and tenofovir disoproxil fumarate. In both cases, the patents were rejected for lacking an inventive step and for not being patentable under Section 3d *(18)*.

India's introduction of more stringent patentability standards and pre-grant oppositions has influenced other countries with local production capacity, such as Argentina *(19)*, Brazil *(20)*, the Philippines *(21)* and South Africa *(22)*, to revise the patentability requirements with respect to pharmaceuticals.

Alternative options or additional instruments can also be used. In Brazil[3] and Egypt,[4] for example, the ministries of health play an active role in the patent examination process for pharmaceutical patents, combining the expertise of patent and health experts to allow a more thorough examination of patent applications to determine whether they meet the requirements of novelty and inventive step.

Moving towards stricter interpretation of patentability criteria to preserve space for further innovation is not a move unique to developing countries. Switzerland in 2007 revised its patent law and introduced stricter standards towards the patentability of genes. The

2 "The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. Explanation—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy" (Section 3(d)).

3 Brazilian Law No. 10 196 of 14 February 2001 determines that any patent application relating to pharmaceuticals needs consent by the Agência Nacional de Vigilância Sanitária.

4 Under Article 17 of Egyptian Law No. 82 of 2002 pertaining to the protection of intellectual property rights, the Egyptian Ministry of Health can oppose the publication and granting of patents with health implications.

revised law (Article 1b of the Swiss Federal Act on Patents for Inventions (Patents Act) of 25 June 1954) excludes from patentability naturally occurring gene sequences and partial sequences of a gene. Sequences derived from a naturally occurring sequence are patentable only if their function is specifically indicated.

Australia in 2012 adopted the Intellectual Property Laws Amendment (Raising the Bar) Act 2012, which among other things raised the standards for patentability and disclosure.

Introducing flexibilities does not necessarily have to happen through legislative changes. For patent examination, the way national guidelines for examination are drafted is key to ensuring thorough implementation of patentability criteria. An example of this approach is the adoption by Argentina in 2012 of guidelines that had the objective of limiting the proliferation of patent applications on marginal improvements or changes of existing pharmaceutical substances *(19)*. ICTSD, WHO and UNCTAD published draft guidelines to contribute to the improvement of examination of pharmaceutical inventions, particularly in developing countries. Various other guidelines have been published that provide useful guidance to countries in this respect (see Box 5).

Box 5 Patentability guidelines

To support the examiners' work and to ensure all patentability criteria are met, many patent authorities have established search and examination guidelines that describe in detail the application of patent law to particular circumstances. To aid this process, WIPO has published links to the guidelines produced by a range of patent offices *(23)* and has published Patent Cooperation Treatment international search and preliminary examination guidelines *(24)*. ICTSD, WHO and UNCTAD have published draft guidelines for the examination of pharmaceutical patents *(25)*.

For local pharmaceutical producers, the way patents are examined and standards are applied for examination can make a difference. Stringent patentability standards for marginal changes of existing pharmaceutical products limit the granting of secondary patents.[5] This can preserve space for local industry or – from a public health perspective – for importing generic versions. For example, for atazanavir, only the secondary patent for the formulation was applied for and granted in Egypt and Indonesia (see Annex 1); this secondary patent is a barrier for local producers in these countries unless they are able to work around the patent by developing an alternative salt form of the active ingredient for formulation purposes.

Implementing a policy of more stringent patentability criteria can be a double-edged sword for developing countries: As the technological capability of local producers develops, they may also wish to seek patent protection on their own incremental inventions. Many of the secondary patents at the European Patent Office, for example on imatinib, are filed by

5 Secondary patents are follow-on patents filed after the main patent, which usually covers the key active ingredient or protein sequence. Secondary patents typically cover formulations, methods of administration and second or new uses of existing compounds. Industry refers to such patents as "incremental innovation" and they are part of lifecycle management strategies, allowing patients to switch from the existing version of a medicine to a slightly improved version. Public health advocates have coined the term "evergreening" for such practice, as some of these patents are aimed at delaying generic entry *(26)*.

generic companies,[6] showing that, where possible, they adopt similar patent strategies to originator companies and try to protect investment in any further improvements or changes. Typically, generic companies, when moving to invest in research and development, will start with incremental innovation, meaning improvements and further development of existing medicines. (For a more detailed discussion, see UNCTAD *(15)*, pages 57–63.) If these are not patentable, then the incentive for investing in these improvements is lost to a certain extent.

It is difficult to define the line between what is commonly called "evergreening" and deciding which incremental innovations or variations of an existing compound do or do not merit a patent. (For further details, see WTO, WIPO and WHO *(2)*, pages 130–132.) When trying to make this distinction, it is important to recognize that from a public health perspective, improved efficacy of a medicine is not the only possible improvement. For example, creating a new version with considerably fewer side-effects, moving to a simpler form of dosing (such as from injection to oral) or producing a more heat-stable form that can be stored in a fridge rather than a freezer can make a huge difference to treatment, particularly in developing countries. Separating cases where such improvements are genuine innovations from those where no inventive step is involved needs careful assessment. The draft guidelines for the examination of pharmaceutical patents provide some useful guidance in this respect *(25)*.

2.4 Ensuring appropriate patent examination

Enforcing strict patentability standards requires a thorough patent examination that ensures patents are granted only in accordance with the standards required by a country's law. This aspect of patent administration is important, because incorrectly granted patents can prevent legitimate local production from taking place, thereby unnecessarily impacting access to essential medicines. Ensuring a thorough examination is not straightforward.

If countries want to use the policy space provided by the TRIPS Agreement and to ensure a strict examination, they have to develop certain examination capacities on their own. Currently, such expertise does not exist in many developing countries. In principle, every country could train its own examiners and implement its own examination practices to reflect national laws. This requires considerable investment in infrastructure and hiring and training of qualified technical examiners in the relevant fields of technology, who may not be available in every country or who may opt for better-paid jobs in the private sector. Where standards are comparable, it also leads to duplication of efforts, as examinations of the same patents are carried out again and again. These are the main reasons for the creation of regional patent organizations, such as the European Patent Office, the Eurasian Patent Organization, the African Regional Intellectual Property Organization (ARIPO) and the Organisation Africaine de la Propriété Intellectuelle (OAPI).

One option for reducing the financial burden of examination of patents is to rely on or take into account search and examination reports of the patent offices of other developed or developing countries. This includes the preliminary examination reports prepared by national patent offices that are recognized as international search authorities under the WIPO Patent Cooperation Treaty. Adhering to standards of foreign patent offices, however,

6 Search results from esp@cenet for keyword "imatinib" in October 2013: Chinese applicants – 57; Indian applicants – 32; Novartis – 17.

bears the risk of importing their patent standards, which mirror their national patent legislation and consequently reflect their national policy. Relying on foreign examination thus means the importation of a certain standard that may not be adapted to local needs; in particular, it may reflect the interests and capacities of the researching pharmaceutical industry despite the importing country not having such an industry. If a country wants to implement the post-grant flexibilities linked to the patent granting process as described above, it has to develop examination procedures that reflect the peculiarities of the national law and implement the policy decisions, for example with respect to the patentability of first or second medical indications or excluded subject matter. This does not exclude taking into account foreign examination results or cooperating with other patent offices, but requires adaptation of the results to the local environment. Simply taking over patent standards bears risk for the local industry, as shown in Box 6.

In this context, there may be options for more south–south cooperation between patent offices and their examiners that have similar approaches towards patentability of pharmaceutical products and processes. This could be particularly productive with developing countries that have invested more in their patent office infrastructure and have patent laws that have incorporated some of the flexibilities available in the TRIPS Agreement.

Countries also need to engage more in the regional intellectual property organizations they are partner to, such as ARIPO and OAPI. Although members of, for example, the East African Community and the West Africa Health Organisation have adopted policies on TRIPS flexibilities, these have not been translated into amendments of the relevant regional agreements and practices and thus have only limited impact.

Box 6 New trend of validation of European patents

Following an agreement signed between the Moroccan Patent Office and the European Patent Office with effect from 1 March 2015, applicants that file patents at the European Patent Office have the possibility to validate European patent applications and patents in Morocco, where, after validation, they will confer essentially the same protection as patents granted by the European Patent Office for member states. The applicant requests the validation when filing a European or international patent application against payment of a validation fee *(27)*. Although this is convenient for applicants, it means that in the future Morocco is likely to receive many more patent applications, including in the area of pharmaceuticals, consequently reducing the freedom to operate of local pharmaceutical manufacturers and the possibility of importing generic products.

In October 2013 the State Agency on Intellectual Property of the Republic of Moldova and the European Patent Office signed a similar validation agreement, which, when finally approved, will allow European patent applications and patents to take legal effect in the Republic of Moldova without additional examination *(28)*.

2.5 Limiting divisional patent applications

When setting up patent administration systems and implementing rules, countries should seek to curb the use of divisional patents by patent applicants, as this can have a serious impact on local production of pharmaceuticals.

Under certain conditions, a filed patent application can be divided into different and independent applications. This can be important to enforce the principle of "unity of invention", meaning that each patent application should claim only one invention or group of inventions that form a single general inventive concept. If the examiner considers an application to contain more than one invention or a group of inventions that do not form a single inventive concept, the examiner will require the applicant to split the parent application into one or more divisional applications *(29)*.[7]

More problematic in practice are the numerous cases where the applicant on their own initiative files divisional applications when the parent application is facing refusal or has been opposed. This practice, in particular when divisional applications are divided again, can be used to delay the final decision on the merits in the hope that a different examiner will not raise an objection. By using divisional applications systematically, patent applications stay pending, despite the fact that the parent application may have been rejected. This creates uncertainty for potential competitors *(30,31)*. This practice places an additional burden on patent offices and competing companies or third parties seeking to oppose or file observations because they have to use resources to keep monitoring the publication of patents to identify divisional patent applications and re-file their opposition or observations *(29)*.

India has attempted to combat this practice by including in its patent office examination guidelines that all divisional applications shall be examined referring back to the main application, meaning that the examiner, when examining a divisional application, must take into account the decision on the main patent *(32)*. This practice ensures that parent applications that were refused during examination do not slip through the system as divisional applications. It also saves potential opponents from having to keep re-filing patent oppositions.

Australia has restricted the practice of divisional applications through its Raising the Bar Act. Australia achieved this by limiting the timeframe available to make a divisional application, which ensures divisional applications cannot be filed late or converted in opposition proceedings. In addition, the commissioner must consent to withdrawal of an opposed application and can therefore refuse withdrawal of an opposed application where the applicant filed a divisional application claiming a substantially similar or the same invention. This limits the applicant's ability to avoid a decision with respect to an invention claimed in one opposed application by withdrawing and pursuing a divisional application instead *(33)*.

The European Patent Office has introduced an additional fee as part of the filing fee for divisional applications. The filing of divisional applications in respect of earlier divisional applications (second-generation divisional applications) is subject to an additional fee. This fee is progressive and increases with each subsequent generation of divisional applications *(34)*.

7 See Article 4G(1) of the Paris Convention, which allows the applicant to file divisional applications in cases where the examination reveals that an application contains more than one invention, and Article 4G(2), which allows the applicant, on their own initiative, to file a divisional application and recognizes the right of each contracting state to determine the conditions under which such division shall be authorized.

2.6 Post-grant flexibilities: the example of compulsory licences

Compulsory licensing is a well-established feature of international, regional and national patent legislation *(35,36,37)*. The Doha Declaration has restated the right of countries to use the TRIPS flexibilities, including compulsory licensing. This instrument is not limited to health emergencies or infectious diseases; unaffordable prices and unavailability of medicines are among the legitimate reasons for the use of compulsory licences. Thus, depending on the national legislation and on the situation within a country regarding access to and affordability of essential health products, a government may consider issuing a compulsory licence and allow the importation or local manufacturing of a medical product. Such licensing has to be in compliance with the requirements of the TRIPS Agreement and national legislation, which should include payment of a royalty (adequate remuneration, taking into account the economic value of the licence) to the patent owner and requires previous negotiations with the patent owner, unless it is for government use or for a health emergency.[8] There are a number of examples for local production under compulsory licence *(18)*, but two main challenges exist:

Given the confrontational approach of production under a compulsory licence, a country needs to be able to set up good-quality production without any technical assistance from the patent holder. The patent discloses only the patented invention rather than the technical know-how needed to produce the medicine. Thus, if a country wishes to pursue this option, the ability of local manufacturers to overcome these technical barriers is required.

The TRIPS Agreement requires that the products produced under a compulsory licence are "predominantly for the supply of the domestic market" (Article 31f). This limits the export of medical products produced under compulsory licences. Depending on the size of the domestic market, building up sustainable and competitive local production might be challenging.

For these reasons, local production under compulsory licences is often not the most cost-effective solution *(37,38)*. The threat of issuing a compulsory licence, however, can be an effective tool in negotiations with the patent holder and can lead to collaboration, as in the case described in Box 7.

8 When a non-voluntary patent licence is issued to remedy an anticompetitive practice, this may be taken into account when determining the amount of remuneration, which could be negligible depending on the circumstances (WTO TRIPS Agreement, Article 31(k)).

Box 7 Case study: collaboration on raltegravir in India

The Indian generic company Cipla applied for a compulsory licence to manufacture the patented drug raltegravir on the basis that it was unaffordable for patients in need. India's provision on compulsory licensing states specifically that there is ground for making an application for the grant of a compulsory licence on a granted patent where the patented invention is not available to the public at a reasonably affordable price *(39)*. Subsequently, Merck and Cipla entered into a co-marketing agreement that allows Cipla to sell the Merck product in India under its own brand name at a lower price *(40)*.

Although this agreement did not lead to local production, it shows that using the threat of a compulsory licence can lead to cooperation. What might be in the interest of companies, however, does not necessarily improve access to medicines. In this case, the price at which Cipla will market raltegravir remains to be seen. In general, open competition leads to lower prices than co-marketing agreements with a limited number of companies.

As the case studies in Boxes 4 and 7 show, the use of pre-grant and post-grant flexibilities can be used to create space to overcome patent barriers in order to help facilitate local production. Although many other factors play an important part, such as whether local producers have the required technical know-how to manufacture a particular product without the need for technology transfer, the availability of trained workforce, infrastructure, local market conditions and disease burden are important factors for local production; creating a national intellectual property system conducive to local production can be a contribution to fostering local production in the pharmaceutical area.

3. Enabling local production through agreements

Although crafting legislation and ensuring a functioning intellectual property administration is in the competence of governments, the daily management of existing intellectual property is done by the intellectual property holders. The simple fact that there is a patent does not necessarily hinder local production; the decisive question is how the patent holder manages the patent. In cases where patents have been granted, various options are available that may allow local production to take place. These options include:

- negotiation of an exclusive or nonexclusive voluntary licence agreement between the originator company and the local producer or government body;
- non-assert declarations or non-assertion covenants and immunity from suit agreements where the patent holder will not assert their rights;
- a joint-venture agreement between the patent holder and a local producer, which includes some form of technology transfer;
- a joint venture with a third party that has technology that will allow the local producer to work around a patent and manufacture a competing product.

Other relevant agreements that are regularly used to protect or share different forms of intellectual property include agreements for confidentiality, for the transfer of biological material, for development (in which the licensee is responsible for further development), for co-development (in which two parties collaborate on continued development) and for distribution of proprietary products (for example, see Box 7). It is beyond the scope of this study to describe the various options, challenges and opportunities linked with these agreements. Guidance on the different agreements and tips for the negotiations and model texts are available *(41)*.

The case studies in Boxes 8 and 9 illustrate how some of the above options can be used to manage patented inventions and some of the issues that can arise when managing intellectual property rights.

Box 8 Case study: atazanavir (Brazil)

In November 2011 Bristol-Myers Squibb and the Brazilian public laboratory Farmanguinhos entered into a licensing agreement to develop the ability to manufacture locally and sell the antiretroviral medicine atazanavir. As shown in Annex 1, the base compound patent covering atazanavir was granted in Brazil, as was a separate process patent. The patent application for the end formulation, the bisulfate salt, was refused, however.

The terms of the agreement provided for technology transfer, including training. In exchange, the agreement requires the Brazilian Government to purchase the drug from Bristol-Myers Squibb until the end of the agreement. The agreement with Bristol-Myers Squibb has been criticized because:

it prevents Farmanguinhos from manufacturing fixed-dose combinations of atazanavir with ritonavir, which is required as a booster to the former to enhance treatment compliance;

it is restricted to Brazil only;

Brazil will purchase the product from Bristol-Myers Squibb until the end of 2017, which is when the patent on the base compound expires anyway *(42)*.

This case study illustrates the fine balance between seeking to develop local production capability and obtaining technology transfer, while trying to achieve affordable access to essential medicines.

In 2013 Bristol-Myers Squibb also entered into a licence agreement with the Medicines Patent Pool that enables generic producers to apply for a sub-licence allowing Bristol-Myers Squibb to manufacture and market atazanavir in 110 countries and countries where the patent was not granted *(43)*.

There are numerous other examples of licensing agreements between originator companies and local producers, in particular in the area of HIV but more recently also in the area of hepatitis C (for example, see WHO *(38)*). As most of these agreements are not available publicly, it is difficult to judge the extent to which they contain transfer of technology or restrictions for the licensees. The agreements negotiated by the Medicines Patent Pool in the area of HIV are a notable exception and in general aim to achieve better health outcomes instead of focusing on the business considerations of the licensing partners. Licences negotiated via the Medicines Patent Pool "provide licensees with the highest level of flexibility and broadest geographic scope" *(44)*. If not under the Medicines Patent Pool, negotiating agreements can be challenging for generic companies. Essentially, local producers and governments need to look at the options available and consider the best practices before signing such agreements *(45)*. Although licensing terms offer some options, they are also designed to manage the competition and divide the market, which often draws the focus to business interests rather than public health needs.

Box 9 The Medicines Patent Pool

The Medicines Patent Pool was established in 2010 with the support of UNITAID to enhance access to affordable good-quality HIV medicines in developing countries through the voluntary licensing of patents on antiretroviral medicines. Since its establishment, the Medicines Patent Pool has negotiated licences on 12 antiretroviral medicines and has issued sub-licences to 10 generic manufacturers, including many of the leading suppliers of antiretroviral medicines in the developing world. The licences negotiated by the Medicines Patent Pool contain a number of public health-friendly provisions that contribute to opening up the market for patent antiretroviral medicines, promoting generic competition and enabling the development of formulations needed in developing countries, such as formulations for children.

Medicines Patent Pool licences are issued on a nonexclusive basis to qualified manufacturers with the willingness and capacity to manufacture antiretroviral medicines in line with international quality requirements. Although most of the licences from the Medicines Patent Pool are available for sub-licensing to local manufacturers based anywhere in the world, some are limited to manufacturers based in certain countries, such as China and India.

In some cases where patents have been granted, there are ways to achieve local production and more affordable access without having to enter into an agreement with the originator company or patent holder. The case study in Box 10 demonstrates a different way of managing intellectual property rights through working around a patent and obtaining technology transfer from a third party.

Box 10 Case study: pegylated interferon alfa-2a (Egypt)

Pegylated interferon alfa-2a is used as a treatment for hepatitis C in combination with ribavirin. As pegylated interferon is a biological product (rather than a product made from small chemical molecules), there are no generic equivalents but only biosimilar versions. F. Hoffmann-La Roche, the originator of pegylated interferon alfa-2a, has applied for patents in several countries, including Egypt. F. Hoffmann-La Roche was granted a patent for its product in Egypt (see Annex 5). The patent covers a physiologically active pegylated interferon alfa conjugate in which the average molecular weight of the PEG units is between 26 000 and 66 000 daltons. In 2002–2003, when the product was first registered in Egypt, F. Hoffmann-La Roche charged 1400 Egyptian pounds (approximately US $ 200) per ampoule *(46)*.

In 2004 a local producer, Minapharm Pharmaceutical, registered its own version of pegylated interferon alfa-2a. The product is not biosimilar but uses a different molecular weight outside the claims of the granted patent and derived from *Hansenula polymorpha (47,48)*. Minapharm Pharmaceutical's development of a product that did not infringe the existing patent was helped by a joint venture project with a German scientific research office, which provided the required technology transfer of the *H. polymorpha* expression system *(49)*.

Minapharm Pharmaceutical introduced its product at 370 Egyptian pounds (approximately US $ 51) per ampoule. Following market introduction, F. Hoffmann-La Roche reduced the price of its product to 250 Egyptian pounds (approximately US $ 35) per ampoule after negotiations with the Egyptian Ministry of Health.

To identify opportunities for local production of patented products, it can be worthwhile to study the patent policy of the pharmaceutical companies holding the relevant patents. Several major researching companies have committed to either not filing or not enforcing their patents in LDCs, with some companies also including low-income and lower-middle-income countries (see Table 1). Although it is important to note that LDCs have no obligation to grant patents under the TRIPS Agreement until 2021, these policies can still be useful for LDCs that do grant pharmaceutical patents, for example Ethiopia and the LDC members of OAPI. For example, Merck and Novartis commit to not filing or enforcing patents in countries classified as LDCs under the United Nations system; thus, even if a patent is granted in one of these countries, this should not constitute a barrier. F. Hoffmann-La Roche extents this policy beyond LDCs and includes all low-income countries under the World Bank system. Novartis recently expanded its policy: although it will file patents in LDCs, it commits not to enforce these patents and offers nonexclusive licences to qualified generic companies in and outside LDCs for the production and supply of any of their patented products exclusively to LDCs *(50)*.

Table 1 shows the different areas where companies have committed not to file or enforce patents based on the Access to Medicine Index 2014 *(44)*.

Table 1 Patent filing and enforcement policies of major pharmaceutical companies

No specific commitment	Subset of products		All patented products	
	Subset of countries	LDCs	LDCs and a subset of LICs	LDCs, LICs, some LMICs
Astellas	AbbVie	Eisai	AstraZeneca	F. Hoffmann-La Roche
Gilead	Bristol-Myers Squibb	Novo Nordisk Novartis	Bayer	Merck KGaA
Pfizer	Johnson & Johnson	Merck	Eli Lilly	
Takeda		Sanofi[a]		

LDC, least developed country; LIC, low-income country; LMIC, lower-middle-income country.

[a] All countries low on the United Nations Development Programme Human Development Index.

Despite the existence of granted patents, local producers may still be able to enter the field by using alternative technologies, by entering into joint ventures or licence agreements, or by other arrangements. A major advantage of such cooperation is that it is often linked with transfer of technology that is not necessarily disclosed in patent documents. Licence agreements will always be a compromise, for example when it comes to the question over which countries are included in the territory.

4. Patent landscapes

The objective of the patent landscapes included in the annexes was to:

- identify the most relevant patents with respect to the medicines;
- identify the countries in which these patents have been filed and granted.

There are often numerous patents relating to a single medicine. These patents cover different aspects and innovations around the same product. Not all patents are equally relevant, however, as many patents cover variations or production processes but do not prevent another company producing the medicine, for example by using a different process.

The patent landscapes provide an analysis of the patent situation focusing on those patents most relevant to local producers. The landscapes do not constitute a freedom-to-operate analysis, and a full legal assessment of the patent situation in a given country is required to determine whether producing the respective medicine would constitute a patent infringement. The landscapes do, however, provide a first indication of whether the patent situation might allow for local production to take place in the countries included in this analysis.

4.1 Scope

It is beyond the scope of this study to include patent information for all WHO Member States. A selection was made that includes developing countries from all WHO regions, with a focus on the African region in line with the focus of the overall project. The patent numbers provided enable readers to follow up the relevant patent applications in all other national and regional jurisdictions using publicly available databases such as Esp@cenet, WIPO Patentscope and national databases. The data can easily be used to assess the patent situation in countries not included in the annexes.

The countries or regions of focus of the patent landscapes are Brazil, China, the European Patent Office, Egypt, Ethiopia, Ghana (ARIPO[9]), India, Indonesia, Jordan, Kenya (ARIPO), Morocco, Nigeria, South Africa, the United Republic of Tanzania (ARIPO), Uganda (ARIPO), the United States of America and patents filed via the regional systems provided by the European Patent Convention[10] and OAPI.[11]

4.2 Products

Following discussions with the advisory group of the overall project, it was decided to include products addressing both communicable and noncommunicable diseases. It was also decided not to limit the products to those already included in the WHO Model

9 ARIPO is the regional patent system covering Botswana, Gambia, Ghana, Kenya, Lesotho, Liberia, Malawi, Mozambique, Namibia, Rwanda, Sao Tome and Principe, Sierra Leone, Somalia, Sudan, Swaziland, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe.

10 Countries covered by the European Patent Convention and the European Patent Office are Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Monaco, the Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovenia, Sweden, Switzerland, Spain, The former Yugoslav Republic of Macedonia, Turkey and the United Kingdom of Great Britain and Northern Ireland.

11 Countries covered by OAPI are Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Guinea, Guinea-Bissau, Mali, Mauritania, Niger, Senegal and Togo.

List of Essential Medicines *(51)* but to include chemical medicines, biological products and vaccines. To identify the respective products not listed in the Model List of Essential Medicines, consultations were held with the relevant WHO departments. The inclusion of any of these products in this study does not imply they are endorsed or recommended by WHO in general or in preference to other products of a similar nature that are not mentioned.

- Atazanavir is a protease inhibitor antiviral medicine indicated for treatment of HIV infection. It is included in the 19th edition of the WHO Model List of Essential Medicines.
- The human papillomavirus (HPV) vaccine Gardasil is a quadrivalent recombinant vaccine for the prevention of cervical cancer and genital warts caused by HPV types 6, 11, 16 and 18. HPV vaccination is included in the WHO Model List of Essential Medicines based on WHO immunization policy recommendations.
- Imatinib is an antineoplastic medicine for the treatment of some cancers and tumours. It is included in the WHO Model List of Essential Medicines to treat chronic myeloid leukaemia and gastrointestinal stromal tumours.
- Pegylated interferon alfa-2a is an antiviral medicine indicated for treatment of chronic hepatitis C. It is included in the WHO Model List of Essential Medicines.
- Raltegravir is an HIV integrase strand transfer inhibitor antiviral medicine indicated in combination with other antiretroviral agents for the treatment of HIV infection. It is not included in the WHO Model List of Essential Medicines.
- Sitagliptin is an antidiabetic drug indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It is not included in the WHO Model List of Essential Medicines.

4.3 Methodology

The patent landscapes and analysis were produced by I-MAK.

The methodology used for the landscapes included identifying American patents via the United States Food and Drug Administration's Orange Book and their related Patent Cooperation Treaty or European applications. Once the relevant American, Patent Cooperation Treaty and European patents were identified, the patent families for filings in other countries available from Esp@cenet, WIPO Patentscope and Thomson Innovation were checked. Additional sources used were the Medicines Patent Pool antiretroviral database, the WIPO patent landscape report on atazanavir *(52)* and an earlier study on patents for the HPV vaccine *(53)*.

The patent information provided in the landscapes reflects the patent status up to and including 12 June 2015. The draft patent landscapes were shared with the companies that hold the market authorizations for comments. F. Hoffmann-La Roche and Novartis shared relevant patent information and filled in the gaps in the landscapes on pegylated interferon and imatinib, respectively.

4.4 Limitations

Every effort has been made to obtain comprehensive and accurate information, including on the legal status of the patents. In many countries, however, patent information is not readily available or is not updated on a regular basis. Thus, patent information in many

countries is difficult to retrieve, as reflected by the gaps in the annexes. N/A indicates that no information could be retrieved for the relevant patents; this can mean either that the information in the databases is not up to date or not complete, or that the patents were not filed in these jurisdictions. Certainty can be achieved only by checking the information with the local patent office The patent numbers provided in this report allow retrieval of information through national patent offices or national patent registries. A WIPO webpage provides links to all national online patent search tools to search national patent registries *(54)*.

The landscapes do not contain all patents related to the respective medical product. As this study endeavours to identify the most relevant patents, it does not include all patents and applications filed by the sponsor and other entities. More patent applications may have been published after the searches were conducted and thus may not be included in this study.

This study is not a freedom-to-operate analysis. The information provides useful guidance but reflects the situation at a particular point in time. WHO does not accept any responsibility for the completeness of the data. Before taking any investment or other legally relevant decision, readers are advised to consult a local patent expert to provide a full assessment of the patent situation in a given country.

4.5 Further resources

Box 3 contains links to further resources for accessing and finding patent information for medicines.

Material on the relationship between public health and intellectual property can be found in the joint WTO, WIPO and WHO document *(2)*.

These publications and other relevant publications on issues related to public health and intellectual property can be found on the WHO website *(55)*.

5. Conclusions

Intellectual property plays an important role both for the researching pharmaceutical industry, which relies heavily on intellectual property to protect its products, and for generic companies, which produce copies of existing medicines once patent protection expires. Beyond patent protection, trademarks are another form of intellectual property rights used to identify and market pharmaceutical products. Trade secrets and protection of clinical test data are other important elements of this industry. Consequently, the set-up of a national intellectual property system is important when considering options for local production of pharmaceuticals in developing countries.

Using practical examples and patent landscapes, this report attempts to set out the various strategies and options available to facilitate local production. The report describes the options available to countries with a generic industry to design an intellectual property system that is favourable for local production and potentially for public health. The report highlights the importance of transparent and fair patent administration systems using the example of access to patent information. The report exemplifies how this can also support the use of certain pre-grant flexibilities to increase the space for local generic companies and facilitate local production. In this context, the questions of whether and how to examine patents are essential. Where countries decide to provide for substantive examination, they need to pay particular attention to what standards need to be followed to ensure implementation of pre-grant flexibilities in practice. Favourable interpretation of various provisions of the TRIPS Agreement to support local industry is important: simply writing flexibilities into legislation will not achieve their intended impact without a good understanding by local producers of patent laws and patent systems. Competent intellectual property professionals and a transparent, fair and efficient court system also need to be in place to allow such policies to flourish.

The existence of a patent does not mean local production is not possible. The decisive question is how the patent will be managed by the patent holder. This report has attempted to show this using some practical examples of multiple ways to cooperate and allow for local production to varying degrees. This depends a lot on the willingness of the patent holder, but collaboration has increased over the past years, sometimes blurring the line of distinction between originator and generic companies. Licensing has become common in the area of HIV/AIDS, and we have also seen cooperation in the area of hepatitis C. In this context, implementing pre- and post-grant flexibilities can strengthen the negotiating position of local companies when they endeavour to enter into licensing and technology transfer deals.

This report provides patent information on a number of medicines to show that it is a simplification to describe a medicine as "under patent". Patents are granted for national or regional jurisdictions, and the complete landscape often reveals countries where patents have not been filed or granted and thus where local production could take place if the technical problems associated with the production of affordable good-quality medicines can be overcome.

Local production depends on many conditions; the intellectual property environment is only one of these conditions and in itself will not be decisive. The mere absence of a patent in a country will not lead to local production of a medicine or ensure access to that

medicine. The intellectual property system can, however, be used and designed to favour local pharmaceutical innovation and manufacturing. Local production can potentially lead to improved access and health outcomes when good-quality essential medicines are produced and marketed at affordable prices.

Annex 1 Atazanavir: analysis of patent landscape

The patent search identified 12 patents that would be particularly relevant for a local producer to take into consideration. If granted, the various patents identified give a period of protection around atazanavir for up to 35 years from the date of the primary base compound patent (1996–2031) subject to the filing of additional patents covering further innovations around atazanavir.

The key or main blocking patents that cover the current marketed product for atazanavir are patent number 1 (the primary patent), which covers the base compound or active ingredient, and patent number 2 (1 of 11 secondary patents), which covers the formulation. Subject to any patent term extensions, these patents are expected to expire around April 2017 and January 2018, respectively.

In Brazil patent number 1 has been granted and thus in principle blocks local production until around April 2017, unless a licence or other agreement is entered into with the patent holder. As patent number 2 has been refused in Brazil, local producers could potentially manufacture atazanavir using the formulation identified in patent number 2, but only after patent number 1 has expired. Local producers would have to ensure they use a different process to that claimed in patent number 4, which is granted and is expected to expire around July 2021. Local producers would also have to monitor the status of patent numbers 3 and 7. Patent number 3, which is currently refused but under appeal, also covers a process and, if granted, is expected to expire in July 2021. Patent number 7 covering a process for the formulation is currently pending and would expire around May 2025 if granted.

In China patent numbers 1–4 and 7 have been granted. Local producers would have to wait until at least around January 2018 until they could produce generic versions. If local producers are unable to work around the processes covered by patent numbers 3, 4 and 7, however, then they could be further delayed until around May 2025. Other patents for local producers to monitor are patent numbers 11 and 12, which cover different tablet formulations.

In Egypt and Indonesia there is potentially only one patent, patent number 2, which expires in January 2018, that would be an obstacle to local producers.

In India currently only patent numbers 3 and 4 for processes have been granted. Therefore, provided local producers can work around these process patents, they are free to produce the product. It must be observed, however, that despite the initial parent application having been refused, there are pending divisional applications for patent number 1. If granted, this patent would prevent local producers from making atazanavir without a licence or other agreement with the patent holder. Notably, there are pending applications for secondary patents, patent numbers 7–11, that could pose an issue if granted.

In South Africa patent numbers 1,2 and 7 have been granted. Patents 1 and 2 block local production until they expire, while patent number 7 would have to be worked around.

Notably, there appear to be no patents that would block production of atazanavir in Ethiopia, Ghana, Jordan, Morocco, Nigeria, OAPI countries, Uganda or the United Republic of Tanzania.

Bristol-Myers Squibb entered into a licence agreement with the Medicines Patent Pool in 2013. Under this agreement, generic producers can apply for sub-licences that allow then to produce and market generic atazanavir in 110 countries and in countries where the patents were not filed or granted. Further information, including the full licence agreement, is available on the Medicines.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6
	Antivirally Active Heterocyclic Azahexane Derivatives (This patent covers various heterocyclic azahexane derivatives that can be employed as retroviral aspartate proteases, including the base compound atazanavir, their salts and use alone or in combination with other antivirally active compounds)	**Bisulfate Salt of HIV Protease Inhibitor** (This patent covers the crystalline bisulfate of atazanavir and its pharmaceutical dosage form as used in the marketed product)	**A Process for the Preparation of α' Chloroketones** (This patent covers a process useful in the synthesis of intermediates for atazanavir)	**Stereoselective Reduction of Substituted Oxo-Butanes** (This patent covers a process useful in the synthesis of intermediates for atazanavir)	**Use of Atazanavir in HIV Therapy** (This patent covers a method for reducing elevated plasma LDL and/or tryglyceride levels in a HIV infected patient undergoing HIV protease therapy which comprises administering an effective amount of atazanavir in combination with an HIV inhibiting amount of at least one HIV protease inhibitor)	**A Method of Treating HIV Infection in AtazanavirResistant Patients Using a Combination of Atazanavir and Another Protease Inhibitor** (This patent covers a method of treating HIV, where the HIV strain has become resistant to atazanavir, and atazanavir is administered with at least one other protease inhibitor)
Applicant/Patent Holder	Novartis AG	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company
International Patent Publication No. or U.S/European Patent No.	WO 1997/40029	WO 1999/36404	WO 2002/014256	WO 2002/14528	WO 2003/020206	WO 2005/058248
Expected Expiry (if granted and not subject to patent term extensions)	14 April 2017	20 January 2018	20 July 2021	20 July 2021	21 August 2022	14 December 2024
PATENT STATUS						
Brazil	Granted Patent No. PI9701877	App No. PI9814736 Refused	App No. PI0112820 Refused-under appeal	Granted Patent No. PI0113236	App No. PI0211544 Lapsed	No patent
China	Granted Patent No. 1082508	Granted Patent No. 1116282	Granted Patent No. 1264792	Granted Patent No. 100335643	Granted Patent No. 1245988 Lapsed due to non-payment of annual renewal fee	No patent
Egypt	No patent	Granted Patent No.23936	No patent	No patent	NA	No patent
European Patent Office (EP)	Granted Patent No. 0900210	Granted Patent No. 1056722	Granted Patent No. 1309535	Granted Patent No. 1309714	Granted Patent No. 1420799 Lapsed due to non-payment of annual renewal fee	Pub No. EP1696918 Withdrawn
Ethiopia	No patent	No patent	No patent	No patent	N/A	No patent
Ghana (ARIPO)	No patent	No patent	No patent	No patent	No patent	No patent

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5	Patent 6
	Antivirally Active Heterocyclic Azahexane Derivatives (This patent covers various heterocyclic azahexane derivatives that can be employed as retroviral aspartate proteases, including the base compound atazanavir, their salts and use alone or in combination with other antivirally active compounds)	**Bisulfate Salt of HIV Protease Inhibitor** (This patent covers the crystalline bisulfate of atazanavir and its pharmaceutical dosage form as used in the marketed product)	**A Process for the Preparation of α' Chloroketones** (This patent covers a process useful in the synthesis of intermediates for atazanavir)	**Stereoselective Reduction of Substituted Oxo-Butanes** (This patent covers a process useful in the synthesis of intermediates for atazanavir)	**Use of Atazanavir in HIV Therapy** (This patent covers a method for reducing elevated plasma LDL and/or tryglyceride levels in a HIV infected patient undergoing HIV protease therapy which comprises administering an effective amount of atazanavir in combination with an HIV inhibiting amount of at least one HIV protease inhibitor)	**A Method of Treating HIV Infection in AtazanavirResistant Patients Using a Combination of Atazanavir and Another Protease Inhibitor** (This patent covers a method of treating HIV, where the HIV strain has become resistant to atazanavir, and atazanavir is administered with at least one other protease inhibitor)
India	App No. 805/MAS/1997 (Pre-grant opposition – Application Abandoned) App No. 310/CHE/2007 (Divisional-pending) App No. 3234/CHE/2008 (Divisional-pending) App No. 3235/CHE/2008 (Divisional-pending)	App No. 6425/ DELNP/2006 (Pre-grant opposition – Refused) App No. 2933/ DELNP/2009 Divisional (Pre-grant opposition – Application refused)	Granted Patent No. 210496	Granted Patent No. 206217	No patent	No patent
Indonesia	No patent	Granted Patent No. ID0009860	No patent	No patent	N/A	No patent
Jordan	No patent	No patent	No patent	No patent	N/A	No patent
Kenya (ARIPO)	No patent	No patent	No patent	No patent	No patent	No patent
Morocco	No patent	No patent	No patent	No patent	N/A	No patent
Nigeria	No patent	No patent	No patent	No patent	N/A	No patent
OAPI	No patent	No patent	No patent	No patent	N/A	No patent
South Africa	Granted Patent No. 9703387	Granted Patent No. 990056	No patent	No patent	App No. 200401412 Lapsed	No patent
Tanzania (ARIPO)	No patent	No patent	No patent	No patent	No patent	No patent
Uganda (ARIPO)	No patent	No patent	No patent	No patent	No patent	No patent
USA	Granted Patent No. 5849911 Granted Patent No. 6110946 Granted Patent No. 6300519 Granted Patent No. 6166004	Granted Patent No.6087383	Granted Patent No. 6399793	Granted Patent No. 7083973 Pending Patent No.2002/0042124	Pub No. 2003/0045501 Abandoned	Pub No. 2005/0148523 Abandoned

	Patent 7	Patent 8	Patent 9	Patent 10	Patent 11	Patent 12
	Process for preparing Atazanavir Bisulfate and Novel Form (This patent covers a process for preparing atazanavir bisulfate in the form of Form A crystals).	**Tableted Compositions Containing Atazanavir** (This patent covers a composition comprising atazanavir bisulfate and a plurality of granules to form a compressed tablet)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising raltegravir and granules containing atazanavir sulfate and an intragranular lubricant)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising abacavir sulfate and granules containing atazanavir sulfate and an intragranular lubricant)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising ritonavir and granules containing atazanavir sulfate and an intragranular lubricant)	**Atazanavir Sulfate Formulations with Improved pH Effect** (A compressed tablet comprising atazanavir sulfate and an acidifying agent)
Applicant/Patent Holder	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company
International Patent Publication No. or Corresponding U.S/ European Patent No.	WO 2005/108349	WO 2009/002821	WO 2009/002823	WO 2009/002826	WO 2009/002829	WO 2011/127244
Expected Expiry (if granted and not subject to patent term extensions)	3 May 2025	20 June 2028	20 June 2028	20 June 2028	20 June 2028	7 April 2031
PATENT STATUS						
Brazil	App No. PI0509595 Pending	No patent	No patent	No patent	No patent	N/A (Application may not have yet entered national phase)
China	Granted Patent No. 1980666 Granted Patent No. 101565398	Pub No. 101778624 Withdrawn	Pub No. 101801348 Withdrawn	Pub No. 101778625 Withdrawn	Pub No. 101795674 Pending	Pub No. 102917695 Pending
Egypt	N/A	No patent	No patent	No patent	No patent	N/A
European Patent Office (EPO)	1755596 Pending 2669273 (Divisional of 1755596-Pending)	Granted Patent No. 2170292	Granted Patent No.2178511	Granted Patent No. 2178512	Granted Patent No. 2178513	Pub no. 2555757
Ethiopia	No patent	No patent	No patent	No patent	No patent	N/A
Ghana (ARIPO)	No patent	No patent	No patent	No patent	No patent	N/A

	Patent 7	Patent 8	Patent 9	Patent 10	Patent 11	Patent 12
	Process for preparing Atazanavir Bisulfate and Novel Form (This patent covers a process for preparing atazanavir bisulfate in the form of Form A crystals).	**Tableted Compositions Containing Atazanavir** (This patent covers a composition comprising atazanavir bisulfate and a plurality of granules to form a compressed tablet)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising raltergravir and granules containing atazanavir sulfate and an intragranular lubricant)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising abacavir sulfate and granules containing atazanavir sulfate and an intragranular lubricant)	**Tableted Compositions Containing Atazanavir** (This patent covers a compressed tablet comprising ritonavir and granules containing atazanavir sulfate and an intragranular lubricant)	**Atazanavir Sulfate Formulations with Improved pH Effect** (A compressed tablet comprising atazanavir sulfate and an acidifying agent)
India	App No. 6425/DELNP/2006 (Pre-grant opposition – Refused) App No. 2933/DELNP/2009 Divisional (Pre-grant opposition – Application refused)	App No. 8328/ DELNP/2009 Pending	App No. 8524/ DELNP/2009 Pending	App No. 8330/ DELNP/2009 Pending	App No. 8332/DELNP/2009 Pending	App No. 9097/CHENP/2012 Pending
Indonesia	No patent	No patent	No patent	No patent	No patent	N/A
Jordan	No patent	No patent	No patent	No patent	No patent	N/A
Kenya (ARIPO)	No patent	No patent	No patent	No patent	No patent	N/A
Morocco	No patent	No patent	No patent	No patent	No patent	N/A
Nigeria	No patent	No patent	No patent	No patent	No patent	N/A
OAPI	No patent	No patent	No patent	No patent	No patent	N/A
South Africa	Granted Patent No. 200609084	No patent	No patent	No patent	No patent	No patent
Tanzania (ARIPO)	No patent	No patent	No patent	No patent	No patent	N/A
Uganda (ARIPO)	No patent	No patent	No patent	No patent	No patent	N/A
USA	Granted Patent No. 7838678 Granted Patent No. 8513428 Granted Patent No. 7829720	Pub no. 2013/0266648 Pending	Pub No. 2010/178339 Abandoned	Pub No. 2010/178340 Abandoned	Pub No. 2010/183716 Abandoned	Pub No. 2013/203759 Pending Pub No. 2015/080399 Pending

* N/A – information not available
* No patent – no patent filed

Annex 2 Raltegravir: analysis of patent landscape

The patent search identified four key patents that would be particularly relevant for a local producer to take into consideration.

The primary patent, patent number 1, covers the base compound and active ingredient. This patent is expected to expire around October 2022. The secondary patents, patent numbers 2–4, cover the salt form of raltegravir and various compositions for the marketed end-product. These patents are all expected to expire around December 2025.

In Brazil patent numbers 1, 3 and 4 are still pending.

In China all four key patents have been granted. As a result, unless such patents were to be invalidated or a licence agreement signed with the patent holder, local producers are blocked from coming to market until at least December 2025.

In India patent number 1 has been granted and therefore blocks any generic production. The application for patent number 2 has been abandoned, and applications for patent numbers 3 and 4 are pending. Notably, patent number 4, covering the key formulation patent, has been opposed under India's pre-grant opposition system.

In Indonesia patent numbers 1 and 4 have been granted and would block local production. Information for patent numbers 2 and 3 was not available. Accordingly, local producers would have to conduct additional searches to establish whether these patents have been filed in Indonesia.

In South Africa the primary patent, patent number 1, and patent numbers 3 and 4 have been granted and therefore block local production.

In Egypt, Ethiopia, Ghana, Jordan, Kenya, Morocco, Nigeria, OAPI countries, Uganda and the United Republic of Tanzania, patent number 1 has not filed. In Egypt patent numbers 2–4 do not appear to have been filed and so there is potential for local production. For the other countries in this list, either the data were not available or only patent number 4 had not been applied for or granted (in Ghana, Kenya, Nigeria, OAPI countries, Uganda and the United Republic of Tanzania). Additional checks would be needed to assess any risks for these countries; this would not be necessary for countries classified as LDCs under the United Nations system (such as Ethiopia, Uganda and the United Republic of Tanzania), as Merck commits not to file or enforce patents in these countries. Patent number 4 has been granted in Morocco and so would likely block production there, even though the primary patent, patent number 1, has not been filed there.

In 2015 Merck entered into a licence agreement with the Medicines Patent Pool signed for raltegravir for paediatric use that allows generic producers to apply for a sub-licence. Further information, including the full licence.

	Patent 1	Patent 2	Patent 3	Patent 4
	N-Substituted HydroxypyrimidinoneCarboxamide Inhibitors of HIV Integrase (This patent covers N-Substituted hydroxypyrimidinonecarboxamides, including the base compound raltegravir, their pharmaceutically acceptable salts, synthesis and use as inhibitors of the HIV integrase enzyme)	**Pharmaceutical Composition Containing An Anti-Nucleating Agent** (This patent covers a pharmaceutical composition for oral administration as a solid dose comprising an effective amount of a drug compound in the form of a salt, including the potassium salt of raltegravir)	**Pharmaceutical Formulation Containing A Release Rate Controlling Composition** (This patent covers a pharmaceutical formulation for oral administration as a solid dose comprising an effective amount of a base salt of a compound, including the potassium salt of raltergavir, and a release rate controlling composition comprising a solubilizing agent and optionally a water soluble filler)	**Potassium Salt of an HIV Integrase Inhibitor** (This patent covers potassium salts and their crystalline forms of an HIV integrase inhibitor, including raltegravir, and pharmaceutical compositions)
Applicant/Patent Holder	Istituto Di Recerche Di BiologiaMolecolare P. Angeletti SPA	Merck & Co. Inc	Merck & Co. Inc	Merck & Co. Inc Istituto Di Recerche Di BiologiaMolecolare P. Angeletti SPA
*International Patent Publication No.or U.S/European Patent No.	WO 2003/035077	WO 2006/060681	WO 2006/060711	WO 2006/060712 WO 2006/060730
Expected Expiry (if granted and not subject to patent term extensions)	21 October 2022	2 December 2025	2 December 2025	2 December 2025
PATENT STATUS				
Brazil	App No. PI0213522 Pending	No patent	App No. PI0518781 Pending	App No. PI0518760 Pending
China	Granted Patent No. 1700918	Granted Patent No. 101068533	Granted Patent No. 101068550	Granted Patent No. 101068793
Egypt	No patent	No patent	No patent	App No. 2007534
European Patent Office (EPO)	Granted Patent No. 1441735	Pub No. 1819323 Pending	Granted Patent No. 1904067 Pub No. 2586444	Granted Patent No. 1819700 Granted Patent No. 1819683
Ethiopia	No patent	N/A	N/A	N/A
Ghana (ARIPO)	No patent	N/A	N/A	No patent
India	Granted Patent No. 212400	App No. 4029/DELNP/2007 Abandoned	App No. 4028/DELNP/2007 Pending	App No. 4187/DELNP/2007 Pending – Pre grant opposition filed
Indonesia	Granted Patent No. 36866	N/A	N/A	Granted Patent No. 31730
Jordan	No patent	N/A	N/A	N/A
Kenya (ARIPO)	No patent	N/A	N/A	No patent
Morocco	No patent	N/A	N/A	Granted Patent No. MA29120
Nigeria	No patent	N/A	N/A	N/A
OAPI	No patent	N/A	N/A	N/A
South Africa	Granted Patent No. 200402796	No patent	Granted Patent No. 200703866	Granted Patent No. 200704130
Tanzania (ARIPO)	No patent	N/A	N/A	No patent
Uganda (ARIPO)	No patent	N/A	N/A	No patent
USA	Granted Patent No. 7169780 Granted Patent No. 7217713 Granted Patent No. 7435734 Granted Patent No. 7754731	Granted Patent No. 8771733	Granted Patent No. 8852632	Granted Patent No. 7754731

* N/A – information not available
* No patent – no patent file

Annex 3 Imatinib: analysis of patent landscape[12]

The patent search identified three patents. Patent numbers 1 and 2 would be particularly relevant for a local producer to take into consideration.

The primary patent, patent number 1, covers the base compound and active ingredient. This patent is expected to have expired around September 2014. Therefore, provided a country does not grant patent term extensions, patent number 1 should not be a hindrance to local producers. The key secondary patent, patent number 2, covers the crystalline form of imatinib and is used for formulating the marketed end-product (imatinib mesylate). This patent is expected to expire around July 2018.

In Brazil patent number 1 has expired and is therefore no longer an obstacle to local producers. Notably, patent numbers 2 and 3 have been refused but are under appeal. Technically, local producers could commence production, but they would have to monitor the status of patent number 2 in particular to ensure it does not get granted.

In China all three patents have been granted. Even though patent number 1 has expired, patent number 2 and possibly patent number 3 would block local producers. The situation is similar for Indonesia and South Africa. The situation may vary to a certain extent, depending on whether claims were amended. This will require a more detailed analysis of the granted patents.

In Egypt none of the three patents identified appears to have been filed and so local production is potentially possible.

In India patent number 1 was never filed, as India used the flexibility permitted under the TRIPS Agreement, namely the transitional period within which not to grant pharmaceutical product patents. Patent number 2 was refused and patent number 3 has not been filed. Accordingly, local production for imatinib is actually taking place in India as there are no patent barriers.

No patents were filed in Egypt, Ethiopia, Ghana, Jordan, Kenya, Morocco, Nigeria, OAPI countries, Uganda or the United Republic of Tanzania.

12 Novartis kindly reviewed the patent data on imatinib and filled in gaps in the data.

	Patent 1	Patent 2	Patent 3
	Further Pyrimidine Derivatives and their Preparation (This patent family covers a N-(flouroalkoxyphenyl)-2-pyrimidine amine derivative, including the base compound imatinib and a pharmaceutically acceptable salt, a method of use for the chemotherapy of tumors and a process for preparing the compounds).	**Crystal Modification of a N-Phenyl-2-Pyrimidineamine Derivative Processes for its Manufacture and its Use** (This patent family covers the beta crystalline form of the methanesulfonic acid addition salt of imatinib (imatinibmesylate), its pharmaceutical composition, use for the treatment of a tumor disease and process for preparing the beta crystalline form).	**Treatment of Gastrointestinal Stromal Tumors** (This patent family covers the use of imatinibmesylatefor treatment of gastrointestinal stromal tumors – GIST)
Applicant/Patent Holder	Ciba-Geigy Assigned to Novartis AG	Novartis AG	Novartis AG, et al.
*International Patent Publication No. orU.S/European Patent No.	US 5,521,184 / EP 0 564 409	WO1999/03854	WO2002/34727
Expected Expiry (if granted and not subject to patent term extensions)	25 March 2013	16 July 2018	26 October 2021
PATENT STATUS			
Brazil	Granted Patent No. PP1100739 (expired)	App No. PI9810920 Refused – Under Appeal	App No. PI0114870 Refused –Under Appeal
China	Granted Patent No. 1043531 (expired)	Granted Patent No. 1134430	Granted Patent No. 1276754
Egypt	No patent	No patent	No patent
European Patent Office (EPO)	Granted Patent No. 0564409 (expired – SPCs are in force in some EU countries)	Granted Patent No. 0998473	Granted Patent No. 1332137
Ethiopia	No patent	No patent	No patent
Ghana (ARIPO)	No patent	No patent	No patent
India	No patent	App No. 1602/MAS/1998 Refused following Pre-Grant Oppositions and Appeals up to the Supreme Court	No patent
Indonesia	Granted Patent No. ID0005127 (expired)	Granted Patent No. ID0028432	Granted Patent No. ID0019531
Jordan	No patent	No patent	No patent
Kenya (ARIPO)	No patent	No patent	No patent
Morocco	No patent	No patent	No patent
Nigeria	No patent	No patent	No patent
OAPI	No patent	No patent	No patent
South Africa	Granted Patent No.9302397 (expired)	Granted Patent No. 9806362	Granted Patent No. 200302155
Tanzania (ARIPO)	No patent	No patent	No patent
Uganda (ARIPO)	No patent	No patent	No patent
USA	Granted Patent No. 5521184 (expired)	Granted Patent No. 6894051 Granted Patent No. 7151106 Granted Patent No. RE43932	Granted Patent No. 6958335

*No patent – no patent filed

Annex 4 Sitagliptin: analysis of patent landscape

The patent search identified five key patents that would be particularly relevant for a local producer to take into consideration.

The main patents that could affect local production are patent numbers 1 and 3. Patent number 1 covers the base compound/active ingredient and, if granted, is expected to expire around July 2022. Patent number 3 relates to the salt of the base compound and is the main patent covering the marketed formulation. This patent is expected to expire around June 2024 if granted. Patent number 3 could be problematic as it covers intermediate compounds and a process for making the active ingredient and would need to be worked around. Patent 4 covers a crystalline form and could be an issue, as sometimes base compound forms can seed into the crystalline/polymorphic form, given the polymorphic forms are inherent in the base. Patent number 5 is most likely a defensive secondary patent against alternative formulations that competitors may seek to adopt.

In Brazil patent number 1 has been granted and would block local producers. Patent number 3 is still pending.

In China patent numbers 1, 3 and 4 are granted. Therefore, local production is blocked until these patents expire, a licence of some form is entered into, or the patents are invalidated.

In Egypt patent numbers 1 and 3 appear to have been filed, but their status is not available. Further checks would be needed to establish the current position of these applications. If granted, they would block any local production.

In India a local producer has initially come to market, despite patent number 1 being granted. This was achieved partly by challenging the patent application for patent number 3 to remove that as a barrier, but the case is still pending before the courts, which have issued an interim injunction against further sales *(56)*.

In Indonesia applications were filed for patent numbers 1 and 3, but their status is not available. Further checks would be necessary to establish the status and determine whether these patents are an issue for local producers.

In Jordan patent numbers 1 and 3 have been granted and so local producers would be prevented from production.

In Morocco and South Africa patent number 1 has been granted and so local producers would be blocked from production. Patent number 2 has been granted in South Africa; the legal status for Morocco was not available and would need to be checked.

Patent information for the other countries of interest was not available and so further checks would be necessary. This would not be necessary for countries classified as LDCs under the United Nations system (such as Ethiopia, Uganda and the United Republic of Tanzania) as Merck commits not to file and enforce patents in these countries.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
	Beta-Amino Tetrahydroimidazo (1, 2-A) Pyrazines and Tetrahydrotrioazolo (4, 3-A) Pyrazines as Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes (This patent covers beta-amino tetrahydrotriazolo [4,3-a] pyrazine compounds, including sitagliptin, a pharmaceutically acceptable hydrate salt thereof, pharmaceutical composition and a method of treatment of type 2 diabetes).	**Process and Intermediates for the Preparation of Beta-Amino Acid Amide Dipeptidyl Peptidase –IV Inhibitors** (This patent covers an improved process for the preparation of beta-amino acid amide dipeptidyl peptidase –IV and certain useful intermediates compounds.	**Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor** (This patent covers a monobasic dihydrogenphosphate salt of sitagliptin and crystalline hydrates thereof, in particular crystalline monohydrate, a process for preparing the salt and a method for the treatment of type 2 diabetes).	**Novel Crystalline Forms of a Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor** (This patent covers crystalline solvates and anhydrates of the dihydrogenphosphate salt of sitagliptin, a pharmaceutical composition comprising the same and a method of treating type 2 diabetes).	**Novel Crystalline Salts of a Dipeptidyl Peptidase Inhibitor** (This patent covers crystalline hydrochloric acid, benzenesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and tartric acid salts of sitagliptin).
Applicant/Patent Holder	Merck & Co, Inc	Merck & Co Inc	Merck & Co Inc	Merck & Co Inc	Merck & Co Inc
International Patent Publication No. or U.S/European Patent No.	WO2003/004498	WO2004/087650	WO2005/003135	WO2005/020920	WO2005/072530
Expected Expiry (if granted and not subject to patent term extensions)	5 July 2022	23 March 2024	18 June 2024	27 August 2024	12 January 2025
PATENT STATUS					
Brazil	Granted Patent No. PI0210866	PCT application does not appear to have entered national phase	App No. PI0411726 Pending	No patent	No patent
China	Granted Patent No. 1290848 Pub No. 1861077 Withdrawn	PCT application does not appear to have entered national phase	Granted Patent No. 1832949	Granted Patent No. 100457108	No patent
Egypt	App No. 746/2002 Legal status not available	PCT application does not appear to have entered national phase	App No. PCT828/2005 Legal status not available	N/A	N/A
European Patent Office (EPO)	Granted Patent No. 1412357 Granted Patent No. 1625847 Pub No. 2226324 Pending	PCT application does not appear to have entered national phase	Granted Patent No. 1654263	Pub No. 1662876 Withdrawn	Pub No. 1708571 Withdrawn
Ethiopia	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
Ghana (ARIPO)	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
India	Granted Patent No. 209816	PCT application does not appear to have entered national phase	App No. 5948/DELNP/2005 Abandoned – Pre-grant opposition filed	App No. 1130/DELNP/2006 Abandoned	No patent
Indonesia	App No. W-0200402626 Legal status not available	PCT application does not appear to have entered national phase	App No. W-00200503444 Legal status not available	N/A	N/A

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
	Beta-Amino Tetrahydroimidazo (1, 2-A) Pyrazines and Tetrahydrotrioazolo (4, 3-A) Pyrazines as Dipeptidyl Peptidase Inhibitors for the Treatment or Prevention of Diabetes (This patent covers beta-amino tetrahydrotriazolo [4,3-a] pyrazine compounds, including sitagliptin, a pharmaceutically acceptable hydrate salt thereof, pharmaceutical composition and a method of treatment of type 2 diabetes).	**Process and Intermediates for the Preparation of Beta-Amino Acid Amide Dipeptidyl Peptidase –IV Inhibitors** (This patent covers an improved process for the preparation of beta-amino acid amide dipeptidyl peptidase –IV and certain useful intermediates compounds.	**Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor** (This patent covers a monobasic dihydrogenphosphate salt of sitagliptin and crystalline hydrates thereof, in particular crystalline monohydrate, a process for preparing the salt and a method for the treatment of type 2 diabetes).	**Novel Crystalline Forms of a Phosphoric Acid Salt of a Dipeptidyl Peptidase-IV Inhibitor** (This patent covers crystalline solvates and anhydrates of the dihydrogenphosphate salt of sitagliptin, a pharmaceutical composition comprising the same and a method of treating type 2 diabetes).	**Novel Crystalline Salts of a Dipeptidyl Peptidase Inhibitor** (This patent covers crystalline hydrochloric acid, benzenesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid and tartric acid salts of sitagliptin).
Jordan	Granted Patent No. 2230	PCT application does not appear to have entered national phase	Granted Patent No. 2625	N/A	N/A
Kenya (ARIPO)	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
Morocco	Granted Patent No. 27053	PCT application does not appear to have entered national phase	App No. PV28675 Legal status not available	N/A	N/A
Nigeria	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
OAPI	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
South Africa	Granted Patent No. 200309294	PCT application does not appear to have entered national phase	Granted Patent No. 200509933	No patent	No patent
Tanzania (ARIPO)	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
Uganda (ARIPO)	N/A	PCT application does not appear to have entered national phase	N/A	N/A	N/A
USA	Granted Patent No. 6699871 Granted Patent No. 7125873 Granted Patent No. 8168637 Pub No. 2006270679 Abandoned Pub No. 2013217695 Pending	PCT application does not appear to have entered national phase	Granted Patent No. 7326708	Pub No. 2006287528 Abandoned	Pub No. 2008227786 Abandoned

* N/A – information not available
* No patent – No patent filed

Annex 5 Pegylated interferon alfa-2a: analysis of patent landscape[13]

The patent search identified seven key patents that local producers would need to take into consideration if they were intending to develop a biosimilar version of pegylated interferon alfa-2a. Patent numbers 4 and 5 are the most important patents to be avoided. These patents, if granted, are expected to expire around March 2016 and May 2017, respectively.

In Brazil patent number 5 has been granted, and patent number 4 is pending. Therefore, local producers would be blocked from developing a biosimilar product, given that patent number 5 has been granted. Local producers could still develop an alternative product, however, provided they could stay outside the claims of patent number 5. Additionally, to avoid the risk of infringing patent number 4 should it be granted, local producers would have to develop a different formulation.

In China patent numbers 4, 5 and 6 have been granted and would therefore block local producers from developing a biosimilar version.

In India patent number 5 has been revoked following a post-grant opposition. Patent numbers 4 and 6 have been granted, however, and would have to be worked around, licensed or invalidated to produce a biosimilar version.

In South Africa patent numbers 1–6 have been granted and therefore would be a block to any local producers considering manufacturing a biosimilar product.

No patents were filed in Ghana, Kenya, OAPI countries, Uganda or the United Republic of Tanzania. F. Hoffmann-La Roche commits to not file or enforce patents in countries classified as LDCs under the United Nations system or low-income countries under the World Bank system; thus even if a patent is granted in one of those countries, this should not constitute a barrier.

13 F. Hoffmann-La Roche kindly reviewed the patent data on pegylated interferon and filled in gaps in the data.

	Patent 1	Patent 2	Patent 3	Patent 4
	Improved interferon polymer conjugates (This patent covers a process for preparing a long-acting α-IFN containing composition, comprising contacting α-IFN with a substantially non-antigenic polymer in the presence of a surfactant under conditions which are sufficient to effect conjugation of the protein and polymer).	**Interferon-polymer conjugates and process for preparing the same** (This patent covers a process for preparing IF-polymer conjugates by reacting an IFN with a bis-activated substantially non-antigenic polymer in a molar ratio of substantially non-antigenic polymer to IFN of from about 0.125:1 to about 1:1 under conditions sufficient to effect covalent conjugation of said IFN and said polymer and form a reaction mixture containing mono-IFN polymer conjugates and bis-IFN conjugates).	**Improved interferon polymer conjugates** (This patent covers a pharmaceutical composition comprising a mixture of α-IFN polymer conjugate positional isomers, wherein one of the said positional isomers comprises an α-IFN covalently conjugated to a substantially non-antigenic polymer at a histidine residue on said α-IFN).	**Interferon Solution** (This patent covers an aqueous IFN solution containing an IFN-α, IFN-α-2a or PEG-IFN α2A with a non-ionic detergent, a buffer for adjusting pH 4.4–5.5, benzyl alcohol and an isotonizing agent).
Applicant/Patent Holder	EnzonInc	EnzonInc	EnzonInc	F. Hoffman-La Roche Ltd.
*International Patent Publication No. or European/ U.S Patent No.	WO1995/13090	WO1997/18832	WO1999/32139	EP0736303
Expected Expiry (if granted and not subject to patent term extensions)	10 November 2014	31 October 2016	16 December 2018	30 March 2016
PATENT STATUS				
Brazil	No patent	No patent	No patent	App No. PI9601276 Pending
China	No patent	No patent	No patent	Granted Patent No. 1141808
Egypt	No patent	No patent	No patent	Not filed
European Patent Office (EPO)	Granted Patent No. 0730470	Granted Patent No. 0862455	Granted Patent No. 1039922	Granted Patent No. 0736303
Ethiopia	Not filed	Not filed	Not filed	Not filed
Ghana (ARIPO)	Not filed	Not filed	Not filed	Not filed
India	No patent	No patent	No patent	Granted Patent No.234072
Indonesia	Not filed	Not filed	Not filed	Not filed
Jordan	Not filed	Not filed	Not filed	Not filed
Kenya (ARIPO)	Not filed	Not filed	Not filed	Not filed
Morocco	Not filed	Not filed	Not filed	Not filed
Nigeria	Not filed	Not filed	Not filed	Not filed
OAPI	Not filed	Not filed	Not filed	Not filed
South Africa	Granted Patent No. 9811590	Granted Patent No. 9609557	Granted Patent No. 9811590	Granted Patent No. 9602553
Tanzania (ARIPO)	Not filed	Not filed	Not filed	Not filed
Uganda (ARIPO)	Not filed	Not filed	Not filed	Not filed
USA	Granted Patent No. 5711944 Granted Patent No. 5951974	Granted Patent No. 5738846	Granted Patent No. 6042822	Granted Patent No. 5762923

N/A – information not available

Annex 6 Gardasil human papillomavirus vaccine: analysis of patent landscape

The patent search identified nine key patents that local producers would need to take into consideration if they were intending to developing a biosimilar version of the HPV vaccine.

Given that patent numbers 1 and 2 should now have expired if they were granted in a country, the key patents for local producers to consider are patent numbers 6–9. If granted, patent numbers 6–8 would be expected to expire in 2024, and patent number 9 would expire in 2028.

In Brazil patent numbers 6–8 are currently pending. In China these patents have been granted. In India patent numbers 6 and 8 have been granted and patent number 9 is pending. In South Africa patent numbers 6–8 have been granted. In Indonesia an application was filed for patent number 6, but further checks are required to determine the current status.

Patent information for the other countries of interest for this study was not available. Merck commits to not file or enforce patents in countries classified as LDCs under the United Nations system; thus even if a patent is granted in one of these countries, this should not constitute a barrier.

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
	Papilloma Virus Vaccine (This patent covers a method for production of papilloma virus like particles (VLPs) including constructing one or more recombinant DNA molecules which encode papilloma virus L1 protein or a combination of papilloma virus L1 protein and papilloma virus L2 protein).	**Production of Human Papillomavirus Capsid Protein and Virus-Like Particles** (This patent covers a method of expressing the capsid protein sequence of papillomavirus in a cell, comprising transfecting a cell with a recombinant expression vector containing a papillomavirus capsid protein coding sequence. The HPV is selected from a group consisting of HPV-6, 11, 16, 18, 33, 35, 5 and 8).	**DNA Encoding Human Papilloma Virus Type 18** (This patent covers and isolated and purified DNA molecule, which encodes HPV type 18 or a functional derivative thereof).	**Oral Immunization with Papillomavirus-Like Particles** (This patent covers a method of vaccinating a mammal for papillomavirus comprising administering papillomavirus VLPs orally to a mammal in an amount sufficient to induce an immune response to the papillomavirus. The HPV types includes HPV Types 16 and 11).	**Optimized Expression of HPV 31 L1 in Yeast** (This patent covers a human papillomavirus vaccine formulation comprising HPV VLPs which are absorbed on an aluminium adjuvant; a salt; a buffer which provides for a PH range of the vaccine solution of from about pH 6.0 to 6.5 and a non-ionic surfactant).
Applicant/Patent Holder	The University of Queensland and CLS Limited	University of Rochester	Merck & Co Inc	University of Rochester	Merck & Co Inc
*International Patent Publication No.	WO1993/002184	WO1994/020137	WO1996/029413	WO1999/061052	WO2000/045841
Expected Expiry (if granted and not subject to patent term extensions)	20 July 2012	8 March 2014	18 March 2016	27 May 2019	19 March 2024
PATENT STATUS					
Brazil	App No. PI1100183 Refused	No patent	No patent	No patent	No patent
China	No patent	No patent	Granted Patent No. 1100876	No patent	No patent
Egypt	No patent	No patent	No patent	No patent	No patent
European Patent Office (EPO)	Granted Patent No. 0595935	Granted Patent No. 1618888 Granted Patent No. 0688227	Granted Patent No. 0817851	Pub No. 1079858 Withdrawn	Granted Patent No. 1150712
Ethiopia	N/A	N/A	N/A	N/A	N/A
Ghana (ARIPO)	N/A	N/A	N/A	N/A	N/A
India	No patent	No patent	No patent		No patent
Indonesia	N/A	N/A	N/A	N/A	N/A
Jordan	N/	N/A	N/A	N/A	N/A
Kenya (ARIPO)	N/A	N/A	N/A	N/A	N/A
Morocco	N/A	N/A	N/A	N/A	N/A
Nigeria	N/A	N/A	N/A	N/A	N/A
OAPI	N/A	N/A	N/A	N/A	N/A
South Africa	No patent	No patent	Granted Patent No. 9602245	No patent	No patent

	Patent 1	Patent 2	Patent 3	Patent 4	Patent 5
	Papilloma Virus Vaccine (This patent covers a method for production of papilloma virus like particles (VLPs) including constructing one or more recombinant DNA molecules which encode papilloma virus L1 protein or a combination of papilloma virus L1 protein and papilloma virus L2 protein).	**Production of Human Papillomavirus Capsid Protein and Virus-Like Particles** (This patent covers a method of expressing the capsid protein sequence of papillomavirus in a cell, comprising transfecting a cell with a recombinant expression vector containing a papillomavirus capsid protein coding sequence. The HPV is selected from a group consisting of HPV-6, 11, 16, 18, 33, 35, 5 and 8).	**DNA Encoding Human Papilloma Virus Type 18** (This patent covers and isolated and purified DNA molecule, which encodes HPV type 18 or a functional derivative thereof).	**Oral Immunization with Papillomavirus-Like Particles** (This patent covers a method of vaccinating a mammal for papillomavirus comprising administering papillomavirus VLPs orally to a mammal in an amount sufficient to induce an immune response to the papillomavirus. The HPV types includes HPV Types 16 and 11).	**Optimized Expression of HPV 31 L1 in Yeast** (This patent covers a human papillomavirus vaccine formulation comprising HPV VLPs which are absorbed on an aluminium adjuvant; a salt; a buffer which provides for a PH range of the vaccine solution of from about pH 6.0 to 6.5 and a non-ionic surfactant).
Tanzania (ARIPO)	N/A	N/A	N/A	N/A	N/A
Uganda (ARIPO)	N/A	N/A	N/A	N/A	N/A
USA	Granted Patent No. 7476389	Granted Patent No. 8062642	Granted Patent No. 5840306 Granted Patent No. 6908615	Granted Patent No. 6153201	Granted Patent No. 6251678

	Patent 6	Patent 7	Patent 8	Patent 9
	Optimized Expression of HPV 31 L1 in Yeast (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV31 L1 protein and a vaccine comprising VLPs comprised of recombinant L1 protein + L2 proteins of HPV31).	**Optimized Expression of HPV 45 L1 in Yeast** (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV45 L1 protein and a vaccine comprising VLPs comprised of recombinant L1 protein + L2 proteins of HPV45).	**Optimized Expression of HPV 58 L1 in Yeast** (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV58 L1 protein).	**Papillomavirus Vaccine Compositions** (This patent covers a pharmaceutical composition comprising VLPs of at least one HPV, an aluminum adjuvant, an ISCOM-type adjuvant and a pharmaceutically acceptable carrier wherein the said VLPs are comprised of recombinant L1 protein or recombinant L1 + L2 proteins of HPV and wherein the said VLPs are absorbed to the said aluminum adjuvant).
Applicant/Patent Holder	Merck & Co Inc	Merck & Co Inc	Merck & Co Inc	Merck & Co Inc
*International Patent Publication No.	WO2004/084831	WO2005/032586	WO2005/047315	WO2008/112125
Expected Expiry (if granted and not subject to patent term extensions)	19 March 2024	24 September 2024	10 November 2024	6 March 2028
PATENT STATUS				
Brazil	App No. PI0408639 Pending	App No. PI0408639 Pending	App No. PI0416393 Pending	No patent
China	Granted Patent No. 100506999	Granted Patent No. 1859923	Granted Patent No. 1942583	Pub No. 101622008 Pending
Egypt	N/A	N/A	N/A	N/A

	Patent 6	Patent 7	Patent 8	Patent 9
	Optimized Expression of HPV 31 L1 in Yeast (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV31 L1 protein and a vaccine comprising VLPs comprised of recombinant L1 protein + L2 proteins of HPV31).	**Optimized Expression of HPV 45 L1 in Yeast** (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV45 L1 protein and a vaccine comprising VLPs comprised of recombinant L1 protein + L2 proteins of HPV45).	**Optimized Expression of HPV 58 L1 in Yeast** (This patent covers a nucleic acid molecule comprising a sequence of nucleotides that encodes an HPV58 L1 protein).	**Papillomavirus Vaccine Compositions** (This patent covers a pharmaceutical composition comprising VLPs of at least one HPV, an aluminum adjuvant, an ISCOM-type adjuvant and a pharmaceutically acceptable carrier wherein the said VLPs are comprised of recombinant L1 protein or recombinant L1 + L2 proteins of HPV and wherein the said VLPs are absorbed to the said aluminum adjuvant).
European Patent Office (EPO)	Granted Patent No. 1608767	Granted Patent No. 1673106	Granted Patent No. 1687329	Granted Patent No. 2129394
Ethiopia	N/A	N/A	N/A	N/A
Ghana (ARIPO)	N/A	N/A	N/A	N/A
India	Granted Patent No. 237941	No patent	Granted Patent No. 2930/DELNP/2006	App No. 5570/DELNP/2009 Pending
Indonesia	App No. W00200502537 Legal status not available	N/A	N/A	N/A
Jordan	N/A	N/A	N/A	N/A
Kenya (ARIPO)	N/A	N/A	N/A	N/A
Morocco	N/A	N/A	N/A	N/A
Nigeria	N/A	N/A	N/A	N/A
OAPI	N/A	N/A	N/A	N/A
South Africa	Granted Patent No. 200507178	Granted Patent No. 200601961	Granted Patent No. 200603106	No patent
Tanzania (ARIPO)	N/A	N/A	N/A	N/A
Uganda (ARIPO)	N/A	N/A	N/A	N/A
USA	Granted Patent No. 7276243 Granted Patent No. 7482428	Granted Patent No. 7250170 Granted Patent No. 7482015	Granted Patent No. 7498036 Granted Patent No. 7976848	Granted Patent No. 7709010 Pub No. 201089744 Abandoned Pub No. 2012177684 Abandoned

* N/A – information not available
* No patent – no patent filed

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