



**Hepatitis C and Tuberculosis
Long-Acting Medicines:
Analysis of Patenting Trends and
Implications for Access**
Activist Reference Tool 2021

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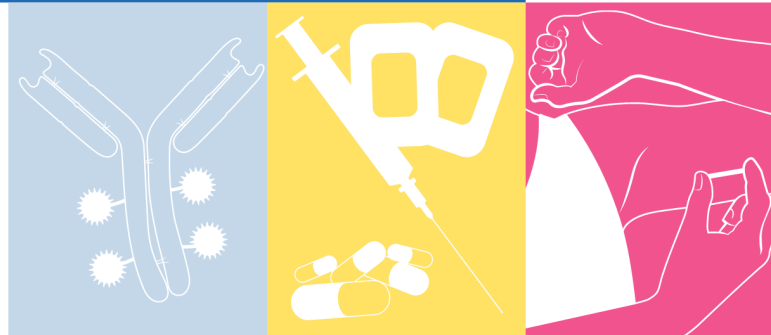
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Consultants

Long-acting technologies (LAT)

- **Long-acting technologies (LAT or sustained release, controlled release, extended release, protracted drug release, prolonged drug release):** terms used interchangeably to describe any technology that can prolong a patient's exposure to a medication
- **Long-acting formulations:** designed to deliver exposure to therapeutic concentrations of active pharmaceutical ingredients (API) over a protracted period of time
- Different routes of administration: oral, parenteral
- Perspective of potential benefits for public health
 - Improve people's acceptability and adherence to medicines
 - Reduce clinical intervention

Illustrated Glossary for Long-Acting Technologies



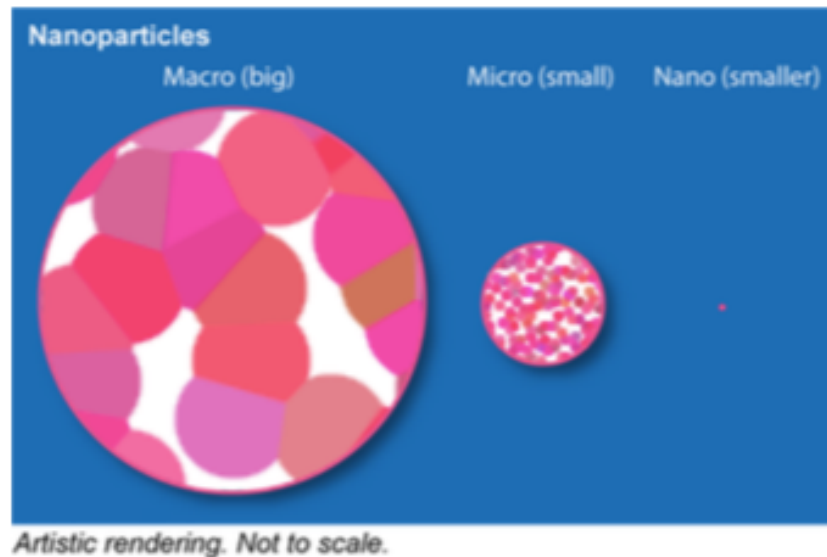
<https://www.treatmentactiongroup.org/publication/illustrated-glossary-for-long-acting-technologies/>

Background

- Long-acting injectables
 - injection of solutions
 - particle suspensions
- Different devices and platforms
 - nanoparticles suspensions
 - injectable monoliths
 - in situ-forming depots/implants
 - microneedle delivery
- Longevity project: technology platform of **solid drug nanoparticle (SDN)**, useful for long-acting formulations and other medical applications

Nanoparticles

A nanoparticle is a particle of material that is smaller than 1 micrometer ($1\ \mu\text{m} = 1000\ \text{nm}$). Nanoparticles may be formed from different types of material including metals and ceramics. When they are made from active pharmaceutical ingredients, they may contain many thousands of molecules and are bigger than dissolved molecules. Because many active pharmaceutical ingredients do not dissolve well in water or body fluids, reducing the particle size down to the nanometer scale helps medicines deliver benefits to patients.



Why looking at patent issues?

- **Evergreening strategy:** filing several patent applications related to the same Active Pharmaceutical ingredient (API)
 - Primary patent: covers the API (and its synthesis process)
 - Secondary patents: may cover other aspects of the medicine, such as salts, polymorphs, methods of treatment, combinations, uses, prodrugs and pharmaceutical compositions
- **Access:**
 - How patents will affect the development of LAF?
 - How patents will affect the availability and prices of LAF when they are approved for use?

Type of claim	Definition
Compositions (or 'formulations')	A large number of patent applications claim 'compositions' (or 'formulations') of known drugs. The formulation of active ingredients using pharmaceutically acceptable carriers or excipients – such as fillers or diluents, binders, stabilizing agents (such as pH regulators), disintegrants, and lubricants – is a mature technological field and falls within the competence of a person normally skilled in pharmaceutical formulation.
Doses	Some patent applications claim independently, or as part of a broader claim, the dose for administering a particular drug
Method of treatment*	Some patent applications involve methods of therapeutic treatment, including prophylaxis, healing, diagnostic or surgical methods. Such claims do not involve a product per se, but how it is used to obtain certain effects (p.30).
New medical use	Claims over a new medical use of a known medicine (often called 'second use claims') account for a good part of the proliferation of pharmaceutical patents.
Salts	Salts are generally sought when the drug is not sufficiently soluble or stable, or when it is difficult to purify, handle or process during manufacturing. Different salts may lead to different solubility, bioavailability and efficacy, and to different organoleptic characteristics or other properties.
Prodrugs	Many medicines are commercialized as prodrugs. A prodrug is a precursor of a drug, which undergoes a chemical conversion by metabolic processes in the body before becoming therapeutically active. Some prodrugs are activated inside the cells (Type I) while others become active extracellularly (Type II).
Combinations	Often two (or more) known drugs are combined in a single product, and patent protection over the combination is claimed.
Polymorphs	Most drugs exhibit structural polymorphism, which appears in the solid state of a chemical compound. Polymorphism is the ability of the chemical molecules or ions to exist with different internal crystal structures. Such a person will generally seek to obtain the most thermodynamically stable polymorph of the drug to assure a reproducible bioavailability over the drug's shelf life, including under a variety of storage conditions.
Enantiomers	Enantiomers are chiral molecules, meaning they are mirror images of one another (see figure 2). They have identical physical characteristics (energy, solubility in typical achiral solvents, boiling and melting points, NMR and IR spectra, etc.) except for their ability to rotate plane-polarized light (optical activity). A racemic mixture contains an equal amount of each enantiomer.

Source: ICTSD/UNCTAD/WHO (2007) and UNDP (2016) ; Silva (2008)

Why companies file several patent applications around the same medicine?

To extend the monopoly on the technology for more than 20 years (based on the first patent)

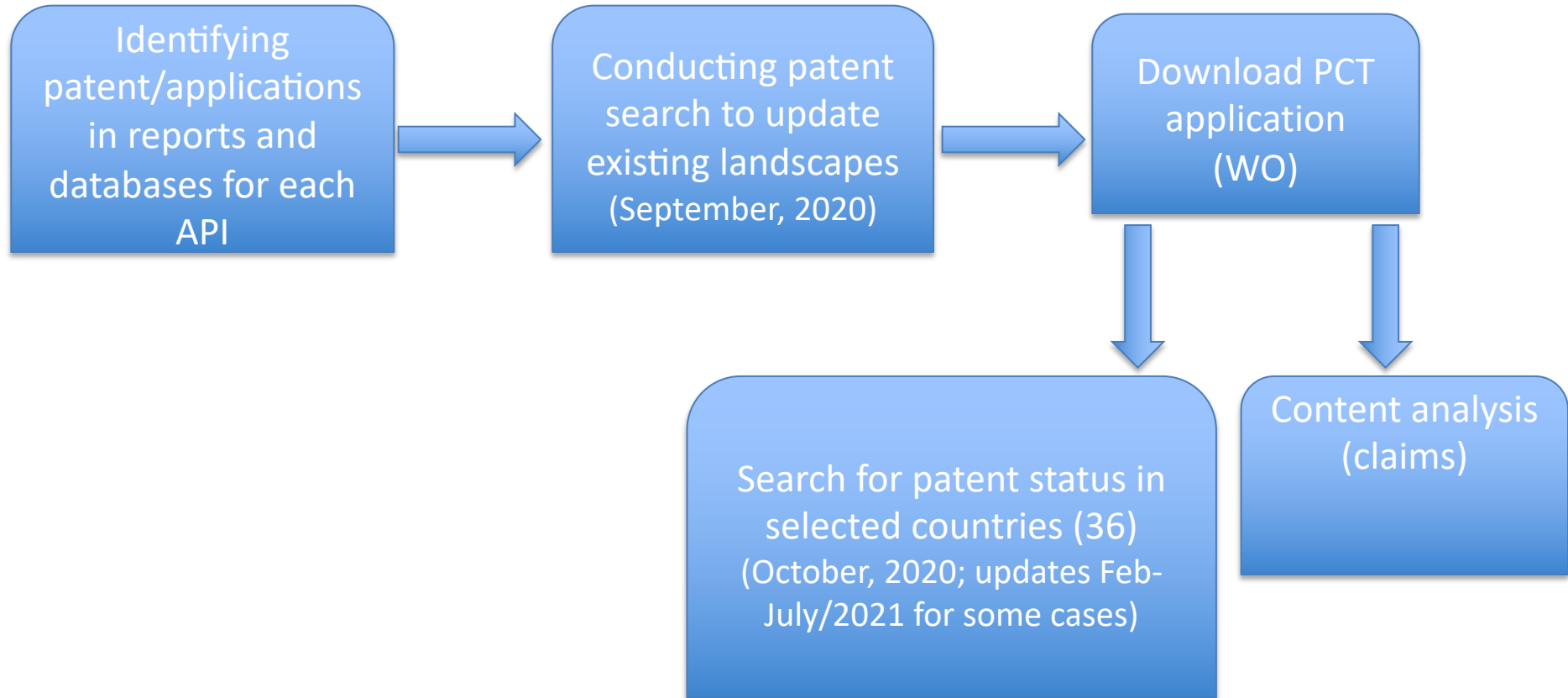
To obtain a monopoly on a technology in a certain country even if there is no protection on the first patent

Objective

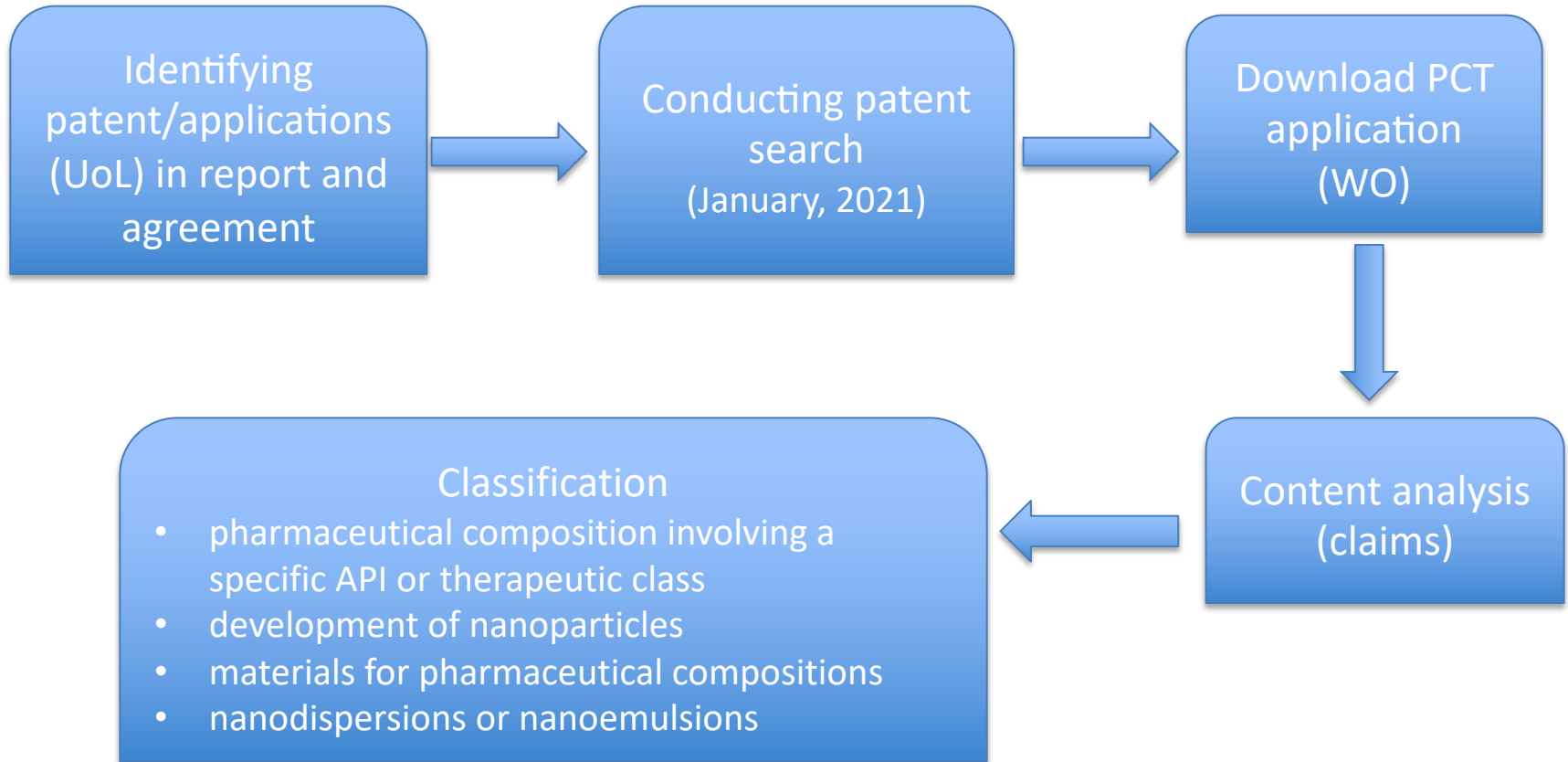
To investigate if there are potential patent barriers for the development and delivery of LAFs for selected hepatitis C and tuberculosis medicines

- To analyze patenting trends for selected hepatitis C (*glecaprevir* and *pibrentasvir*) and tuberculosis medicines (*rifapentine* and *isoniazid*, *bedaquiline*, *delamanid*)
- To develop a preliminary and non-exhaustive patent landscape on the technology used to make the drugs into long-acting formulations under the LONGEVITY Project and its subsidiary Tandem Nano Ltd.

Methodology (Part 1)



Methodology (Part 2)



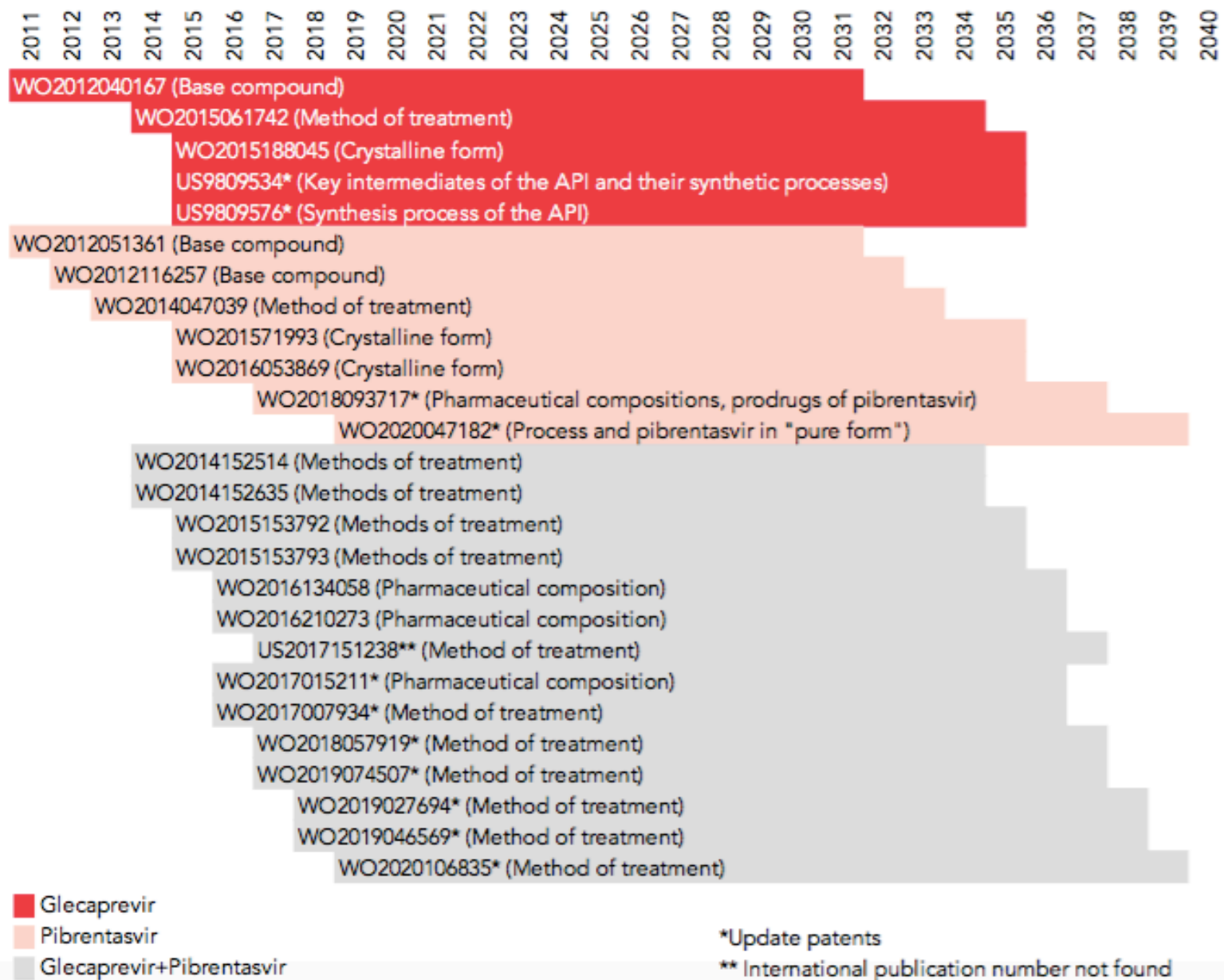
Main findings

- Patenting trends
- Estimate of patent terms
- Access challenges

Glecaprevir and Pibrentasvir

- A total of 26 patents and/or patent applications (by the Originator company) were identified for both glecaprevir and pibrentasvir
 - 5 for glecaprevir
 - 7 for pibrentasvir
 - 14 for the combination of glecaprevir + pibrentasvir (and others)
- After the API patent applications, between 2013 and 2019, there was **an average of 3.3 patent applications filed per year**
- Secondary patents: majority on **methods of treatment, aiming to protect medical indications** for the combination of glecaprevir + pibrentasvir, currently under investigation **in clinical trials**
- No patent application filed by AbbVie on long-acting formulations G/P was found
- GSK patent applications on long-acting formulations for specific compound
 - Claims on combinations with other API, such as glecaprevir and pibrentasvir

Timeline of Potential Patent Protection Related to Glecaprevir, Pibrentasvir and Their Combination



Source: The authors. Estimates based on 20 years patent term counted from the international filing date. Scenario based on patents filed or granted in selected countries.

Approaches to address patent barriers

- November 2018: Medicines Patent Pool signed a royalty-free license agreement with AbbVie for glecaprevir/pibrentasvir covering 96 countries and territories
- 2018/2019: patent oppositions filed by civil society organization for the API patent applications (glecaprevir and pibrentasvir) in India

Main Conclusions

In relation to potential barriers to the development of and access to long-acting formulations

- No patent application filed by AbbVie on long-acting pharmaceutical composition was found. However, patents (whenever filed and granted in a specific country) related to the base compound for both glecaprevir and pibrentasvir are expected to expire at least in 2031 and it is likely to be a barrier for the development of, production of, and access to long-acting formulations.
- GSK has at least three patents/applications involving the long-acting pharmaceutical composition of HCV medicines. They target a specific compound (GSK2878175) developed by the company in which either glecaprevir and pibrentasvir are one of multiple options to be in combination in this specific pharmaceutical composition. Where compound GSK2878175 is included in the development of long-acting formulations, those patents can be considered relevant.
- Considering the prodrug strategy can be adopted for the development of LA solution-based injections, it is important to monitor the patent landscape regarding patents covering prodrugs of the API. However, the one patent covering prodrugs of pibrentasvir (WO 2018/093717) does not seem to be a barrier as it was only identified in the US, and was later withdrawn.
- Most patents/applications related to method of treatments are linked to specific dosage and therapeutic regimens involving existing oral pharmaceutical form, therefore they are unlikely to block the availability of long-acting pharmaceutical composition.

In relation to what was found in the pipeline

- Updating the patent landscape allowed the authors to identify newer medical indications for the combination of glecaprevir + pibrentasvir (i.e., short treatment of acute HCV infection, in combination with sofosbuvir for re-treatment cases) as well as the adoption of approaches such as prodrugs of pibrentasvir.

Isoniazid + Rifapentine (3HP)

Patent	International publication number (publication date) Title *	Brief analysis
Patent 1	WO 2015/011161 (A1) (29/01/2015) Antituberculosis stable pharmaceutical composition in the form of a coated tablet comprising granules of isoniazid and granules of rifapentine and its process of preparation	Adult composition Process
Patent 2	WO 2015/011162 (A1) (29/01/2015) Antituberculosis stable pharmaceutical composition in the form of dispersible tablet comprising granules of rifapentine and its process of preparation	Pediatric composition Process
Patent 3	WO 2014/037121 (A1) (13/03/2014) Use of rifapentine in the treatment of tuberculosis in patients infected with the Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) and treated with antiretroviral combination	Use of rifapentine for active tuberculosis disease or tuberculosis infection in patients with HIV/AIDS and on antiretroviral treatment. Doses of rifapentine varying from 300 to 900 mg; administration once a week over 12 weeks. ARV treatment described is an efavirenz-based combination (i.e., efavirenz, emtricitabine, and tenofovir disoproxil fumarate). Pharmaceutical composition involving rifapentine and isoniazid for patients with HIV/AIDS on ARV treatment (efavirenz-based combination). Pharmaceutical kit involving (a) pharmaceutical composition of rifapentine+isoniazid and (b) galenic formulation of efavirenz, emtricitabine, and tenofovir.

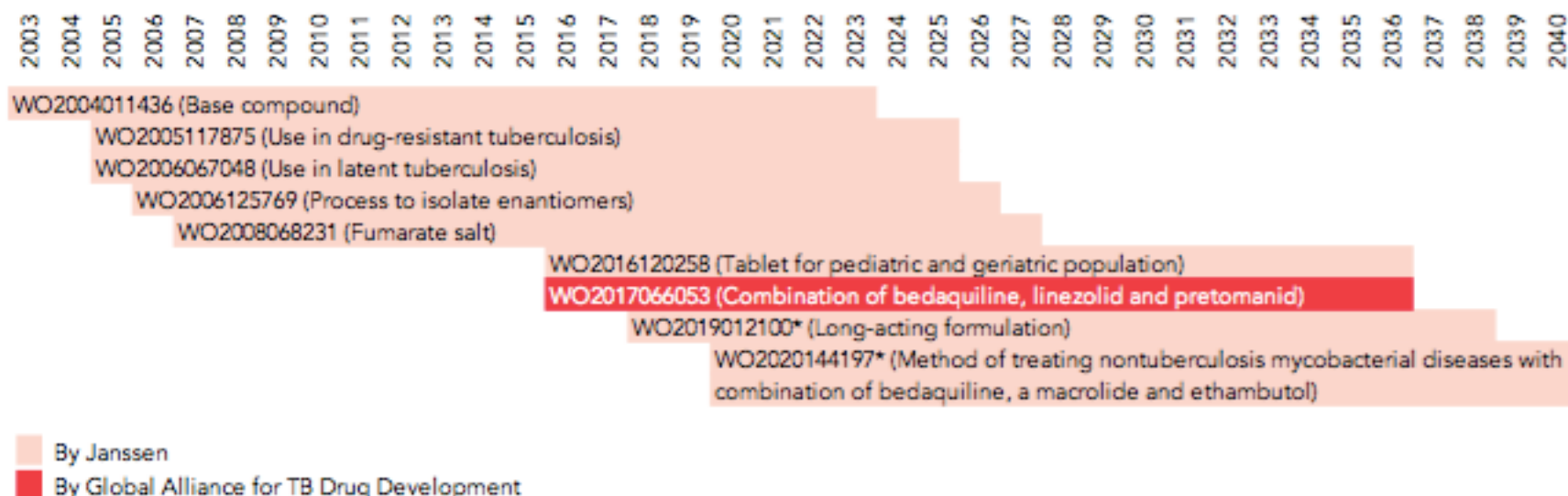
Access issues

- 2020: TAG published a report *Access Roadmap and Patent Landscape on Isoniazid/Rifapentine (3HP)* which covered two patent applications (WO 2015/011161 and WO 2015/011162) filed by Sanofi
- August 2020: TAG and OTMeds (Observatoire de la transparence dans les politiques du médicaments) requested Sanofi to reverse its efforts to patent two combinations of rifapentine and isoniazid.
 - Sanofi’s response indicated they have begun the process of withdrawing those two patent/applications in countries and have committed “not to reinstate any of the patent/ applications, and not to initiate any action against any party who would like to manufacture the specific formulations of the combinations once covered by Sanofi’s two patent families, before the abandonments become effective under the relevant national patent regulations.”
- Findings indicate there are not patent barriers for the development of long-acting formulation on isoniazid + rifapentine in relation to Sanofi

Bedaquiline

- 9 patent/applications identified
- Patenting trends
 - to protect the API, a process to isolate its isomer forms and the production of its fumarate salt form
 - To protect pharmaceutical compositions available in the market or in development, **including long-acting formulations** and combinations of bedaquiline with other compounds
 - To protect indications of bedaquiline, approved and under investigation

Timeline of Potential Patent Protection Related to Bedaquiline



*Update patents

Source: The authors. Estimates based on 20 years patent term counted from the international filing date. Scenario based on patents filed or granted in selected countries.

Patent	Type of opposition (Country/Organization)	Year
Patent 2 WO 2005/117875A1 Use of substituted quinolone derivatives for the treatment of drug-resistant mycobacterial diseases	Third Party Observations* (Thailand/AIDS Access Foundation And Thai Network For People With HIV/AIDS)	2020
Patent 3 WO 2006/067048A1 Quinoline derivatives for the treatment of latent tuberculosis	Third Party Observations* (Thailand/AIDS Access Foundation)	2020
Patent 5 WO 2008/068231 Fumarate salt of (alpha S, beta R)-6-bromo-alpha- [2-(dimethylamino)ethyl]-2-methoxy-alpha -1-naphthalenyl -beta-phenyl-3-quinolineethanol	Pre-grant (India/Network of Maharashtra People Living with HIV - NMP+)	2013
	Pre-grant (India/Nandita Venkatesan and Phumeza Tisile - TB survivors)	2019
	Pre-grant (Brazil/Working Group on Intellectual Property - GTPI)	2020
	Third Party Observations* (Thailand/AIDS Access Foundation and Thai Network For People With HIV/AIDS)	2020
Patent 6 WO 2016/120258 Dispersible compositions	Pre-grant (Ukraine/100 Percent Life)	2020
	Third Party Observations* (Thailand/AIDS Access Foundation)	2020
Patent 7 WO 2017/066053 Combination antibacterial composition and short-course antibacterial regimen	Pre-grant (India/Eldred Tellis And Ganesh Acharya)	2020
	Pre-grant (India/Delhi Network of Positive People - DNP+)	2020
Patent 8 WO 2019/012100 Long-acting formulations	Pre-grant (India/Ganesh Acharya and Delhi Network of Positive People - DNP+)	2021

Lessons from BDQ long-acting injectable patent application

- **Pharmaceutical composition**

- administration by intramuscular or subcutaneous injection
- API (or its salts, such as fumarate) in the form of a suspension of micro- or nanoparticles
- Ingredients needed for the formulation

- **Process to produce pharmaceutical composition**

- **Use**

- long-term treatment of *Mycobacterium tuberculosis* (such as the latent/dormant form) or *Mycobacterium leprae*
- Treatment time intervals
 - intermittently at a time interval of one week to two years
 - at least one month to one year
 - range of one week to one month, or in the range of one month to three months, or in the range of three months
 - to six months, or in the range of six months to twelve months, or in the range of 12 months to 24 months
 - once every two weeks, or once every month, or once every three months

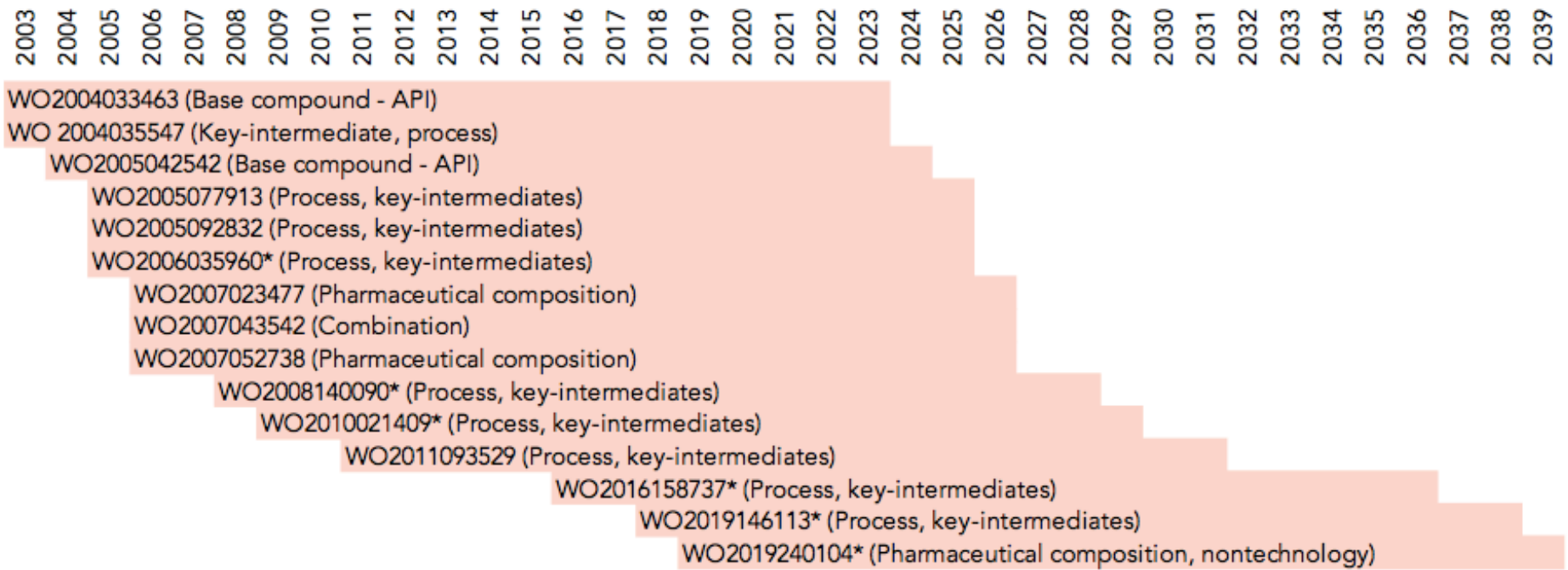
Main conclusions

- Where granted, the patent covering the base compound (API) is expected to expire in 2023, and the one related to the fumarate salt (WO 2008/068231) is expected to expire in 2027. Therefore, it is likely to be the main barrier for the development of and access to long-acting formulations.
- One patent was identified related to a long-acting formulation (pharmaceutical composition) for administration by intramuscular or subcutaneous injection of bedaquiline

Delamanid

- 15 patent/applications
- Patenting trends
 - majority focus on the API or its synthetic routes (processes) and key-intermediate (11)
 - pharmaceutical compositions (3)
 - Combination (1)
- WO 2019/240104: pharmaceutical composition
 - process to obtain the API in submicron particles
 - Use for the production of **oral solid preparation** (tablet or capsule)
 - **Delamanid particles with an average size of 350 nanometers or less**

Timeline of Potential Patent Protection Related to Delamanid



* Update patents

Source: The authors. Estimates based on 20 years of patent term counted from the international filing date. Scenario based on existing patents filed or granted in countries.

Main Conclusions

In relation to potential barriers to the development of and access to long-acting formulations of delamanid:

- Where granted, the patent on the API is expected to expire in 2023 and is likely to be an important barrier.
- There are a number of patents/applications related to synthetic routes and key-intermediates that might have an effect on the synthesis of the API. They seem to be related to a similar synthetic route.
- WO 2019/240104 is related to an oral pharmaceutical composition involving delamanid in submicron particles; the average particle size of the delamanid particles is 350 nm or less. Although this is unlikely to block the development of long-acting injectables, it should be assessed if the protection of submicron particles of delamanid claimed in this patent overlaps with the development of nanoparticles for use in long-acting injectables.

**Preliminary and Non-Exhaustive List of Patents
and/or Patent Applications Related to
Nanotechnology and Pharmaceutical
Composition by the University of Liverpool**

Previous publications

- MPP and UoL: Collaboration Agreement & Patent and Know-How License (2015)
- MPP Intellectual Property Report on Long-acting Technologies (2018)
- 13 patent/applications
 - No mention to APIs of the present research
 - Pharmaceutical compositions involving **nanoparticles of API**
 - Several on antivirals, including prodrugs (TDF, TAF)
 - Some specific mention to long-acting formulations

Patent search

- 17 patent/applications related to nanotechnology
 - pharmaceutical composition involving a specific API or therapeutic class (5)
 - development of nanoparticles (4)
 - materials for pharmaceutical compositions (4)
 - nanodispersions or nanoemulsions (4)
- September 2021: “Patent and Know-How License” between Medicines Patent Pool and Tandem Nano Ltd
 - WO 2011/128623
 - WO 2017/216564
 - WO 2008/006713
 - WO 2013/030535

Nanodispersions

Some active pharmaceutical ingredients are not soluble in water. To help with the formation of liquid medicines, the APIs may be converted into tiny particles by processes such as milling and then dispersed in water. If the particles are nano-sized, they are called nanodispersions (or nanoparticle suspensions).

Nanoemulsions

An emulsion that has one liquid dispersed within another where the droplets of the dispersed liquid are less than 100 nm.²³ This may lead to enhanced performance of a medicine.

Main conclusions

- Patents on the selected API, and potentially on the processes to produce those API, as described in the previous case studies, might be the main barrier for access to those long-acting technologies in case they get market approval before the expiry date of those patents.
- Although there are no patents filed by the University of Liverpool on long-acting injectables covering the selected API of the present study, knowledge and patents covering the technology platform of SDN by other patents/applications may be applied for the development of the formulation involving those API.
- Scope of LONGEVITY Project: licensing agreements may require negotiations either with originator companies (in the case of glecaprevir and pibrentasvir) and with patent holders of the technology platform adopted (UoL and Tandem Nano Ltd).
- In order to ensure that resulting technologies are available at affordable prices, access issues must be addressed from the beginning of the development process.

Recommendations

- To monitor and follow up at the national level patent filing and status in countries to assess approaches to overcome access barriers.
- In relation to the current MPP license with AbbVie for glecaprevir/pibrentasvir, it is important to review and address concerns previously raised,⁴² to provide clear language with regards to the development of long-acting formulations, and to ensure that sublicensees who eventually develop them are able to commercialize in all low- and middle-income countries. To ensure that any long-acting injectable is made available at an affordable price.
- To promote the adoption and use of TRIPS flexibilities in order to challenge patent barriers; activities may include: a) assessing the national law and the possibility of filing patent oppositions for applications related to both glecaprevir and pibrentasvir (base compounds) patents based on the grounds presented at pre-grant oppositions filed in India as well as other target patent/applications; b) promoting the issuance of compulsory licenses in cases where the patents are granted.
- The so-called “research exemption” or “experimental use,” possible within the scope of Article 30 of the TRIPS Agreement, should be explored in the legislation by countries involved in the LONGEVITY Project, as it may allow the use of patented inventions for research purposes during the patent term. However, access issues, once the technology is approved, should be considered from the beginning of the development process.