DIA

Therapeutic Innovation
& Regulatory Science
2017, Vol. 51(4) 446-459

DOI: 10.1177/2168479017697253
tirs.sagepub.com

Trans-Pacific Partnership Agreement and Its Impact on Accessibility and Affordability of Medicines: A Meta-synthesis

Yan Yee Yap, BPharm[1], Che Pui Wong, BPharm[1], Kah Seng Lee, BPharm, MPhil, MBA[2], Long Chiau Ming, PhD[2,3], and Tahir Mehmood Khan, PhD[1]

Abstract

This article aims to discuss the main consequences of the implementation of the Trans-Pacific Partnership Agreement (TTPA) in the pharmaceutical sector in regard to public health, focusing on the accessibility and affordability of medicines. This paper also looks at the likely impact of the TPP agreement on access to affordable medicines. The potential effects of provisions in the final text are explored based on the context of developed and developing countries. A meta-synthesis study design was used. The thematic analysis technique was used to generate themes and a decision tree of the TTPA meta-synthesis. PubMed, EBSCOhost, Ovid, and Scopus databases from inception until the first week of January 2016 were used. Only peer-reviewed journals that discussed TPPA's impact on the pharmaceutical sector were included. Data were extracted by 2 reviewers and then verified by 3 senior researchers. The extracted data were imported into Excel spreadsheets and coded line by line. Codes were organized into descriptive themes. The identified themes were cross-checked against original articles to ensure consistency. A total of 85 full articles and reports were reviewed and, finally, 32 of them were used in the meta-synthesis. Two central themes to the TTPA emerged: intellectual property rights and transparency. Five subthemes were identified under intellectual property rights: patent subject matter (representing scope of patentability), patent term adjustment for patent office delays (representing patent term extension), protection of undisclosed test or other data (representing data exclusivity), protection of undisclosed test or other data (representing patent linkage), and compulsory licensing. Meanwhile, transparency and anti-corruption-procedural fairness, which presents restriction of coverage program and reimbursement, were identified as the subthemes of transparency. Findings indicate that the TPPA could potentially hinder the affordability and accessibility of medicine, which could increase risks to public health.

Keywords

access to medicine, affordability, health policy, developing countries, intellectual property

Introduction

The Trans-Pacific Partnership Agreement (TPPA) is a free trade agreement that involves 12 Pacific Rim countries: Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, the United States, and Vietnam. On February 4, 2016, in Auckland, New Zealand,[1] the final draft was prepared and signed by the Trans-Pacific Partnership (TPP) countries. The TTPA aims to foster economic growth, transparency, and good governance. It also enhances the protection of labor and the environment as well as for innovation, productivity, and competitiveness. It even plays a supportive role in the creation and retention of jobs, which in turn helps to raise the living standards and reduce poverty in the signatory countries.[2] The TPP countries account for approximately 40.0% of the global economy, with a combined gross domestic product (GDP) of approximately US$30 trillion.[3] Other countries such as Indonesia, Korea, and Thailand have shown interest in joining the TPPA, so it may expand beyond the 12 existing countries.[3,4]

[1] School of Pharmacy, Monash University Malaysia, Selangor, Malaysia
[2] Unit for Medication Outcomes Research and Education (UMORE), Pharmacy, School of Medicine, University of Tasmania, Hobart, Australia
[3] Vector-borne Diseases Research Group (VERDI), Pharmaceutical and Life Sciences CoRe, Universiti Teknologi MARA (UiTM), Shah Alam, Selangor, Malaysia

Submitted 15-Aug-2016; accepted 17-Jan-2017

Corresponding Author:
Long Chiau Ming, Unit for Medication Outcomes Research and Education (UMORE), Pharmacy, University of Tasmania, Private Bag 26, Hobart, 7001 Australia.
Email: longchiauming@gmail.com

Negotiations for the TPPA were carried out in secrecy in the years prior to the declaration of the final TPPA text in 2015. Until then, the only available information was leaked drafts from 2011 onwards, which were intensely discussed and debated by critics. One of the main issues discussed was strengthening Intellectual Property (IP) provisions and its impact on the pharmaceutical sector. The IP provisions stated in the IP chapter (chapter 18) of the final TPPA text is controversial, especially in terms of the impact on pharmaceutical patentability.[5] The TPPA not only integrates the main objectives of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement but also further expands the IP provisions. According to the final TPP text, patents shall be available for any invention, as long as the invention is new or involves an inventive step, and is capable of industrial application.[6] This phrase is not something new as it already exists in TRIPS.[7] Low inventiveness standards creates opportunities for pharmaceutical companies to extend their monopolies in the industries. Consequently, it will delay the introduction of generics into the market. The absence of generic competitors will then prompt patent holders to increase drug prices for their own profit. Thus, a delay in the price fall can be predicted.

TPP also introduced patent term extension, which did not feature in TRIPS.[7] As stated in the final text, in order to avoid absurd delays, patent applications should be processed in an efficient and timely manner.[6] Unreasonable delay includes a delay in the issuance of a patent of more than 5 years from the date of filing of the application, or 3 years after a request for examination of the application has been made.[6] Extension can also be granted for any marketing approval. Thus, any unreasonable delay in approving and marketing a new drug can lead to the extension of patent terms.

In addition to that, under the Protection of Undisclosed Test or Other Data in the TPP intellectual property rights (IPR) chapter, there are two issues that were not in TRIPS, namely, data exclusivity and patent linkage. In the final TPP text, it is stated that if the company with a newly patented product submits data on the product safety and efficacy, it will be given 5 years of clinical trials' data protection.[6] For previously approved drugs with new indication, formulation, or administration, an additional data protection of 3 years is given. Besides, the expansion of the scope of data exclusivity given to biologics to either 5 or 8 years with other measures, such as the regulatory procedure or administrative actions, will be implemented as well.[6] As for the newly introduced patent linkage system, drug regulatory authorities would need to delay approval for generic applicants until the patents protecting the original product become invalid or expire.[6,8] The original purpose of the patent linkage system was to link marketing approval from the drug regulator to the patent status of the drug.[9] All these can delay access to low-cost generics and lead to more patent abuse since the financial benefits of deterring generic market entry may outweigh the risks or penalties.[10] Consequently, doctors and thus patients are deprived of affordable alternatives.

The existing TRIPS agreement includes compulsory licensing as one of the flexibilities on patent protection. However, the implementation of TRIPS has constrained this flexibility. The Doha Declaration, which was adopted in 2001, offered an interpretation of the TRIPS agreement's flexibilities.[11] This interpretation aims to ensure governments understand the terms and are capable of using the flexibilities.[11] Similar to TRIPS, the TPP provides exceptions to the exclusive rights of a patent. However, the IP chapter of the TPP provides limited space for exceptions by limiting compulsory licenses to cases where the compulsory license does not "unreasonably conflict with a normal exploitation of the patent."[6] Even if the compulsory license is issued, the generic manufacturers are still required to wait for the "data monopoly" to expire.[12] The scope and issuance of compulsory licenses will be restricted, and threats to grant compulsory licensing will be much less effective.[13]

The TPP final text also includes an annex on Transparency and Procedural Fairness for Pharmaceutical Products and Medical Devices under Transparency and Anti-Corruption Chapter (chapter 26).[6] The text states that the international minimum standards for domestic regulation will be extended beyond intellectual property and into health policy itself.[14] This had never been proposed for any developing country. Implementation of TPPA will weaken countries' policy space to adopt and enforce therapeutic formularies, reimbursement policies and other price-moderating mechanisms within public health systems.[15]

As a whole, TPP has restricted the flexibilities provided by previous TRIPS agreement and other Free Trade Agreements (FTAs). The review aims to discuss the main consequences of the implementation of the TPPA on the pharmaceutical sector in regard to public health, focusing on the accessibility and affordability of medicines. Moreover, to date there is hardly any summative evidence that scrutinize the impact of TTPA on the access to affordable medicines. Through this paper, we also aim to assess the likely impact of the TPPA on the access to affordable medicines. We explore the potential effects of provisions in the final text and provide insights for both developed and developing countries.

Methods

The current systematic review was done using a meta-synthesis approach. This method is used for our qualitative research on the impact of TPPA on the pharmaceutical sector. It attempts to merge results from various inter-related qualitative studies. The technique utilizes interpretive approaches, which is different from the meta-synthesis of quantitative studies.[8] Qualitative meta-synthesis' is the process of amalgamation of a group of similar qualitative studies with the aim of developing an explanation for their findings. In this case, the meta-synthesis approach was used to develop a fuller understanding and to facilitate new knowledge by bringing together qualitative findings on TPPA and its impact on accessibility and affordability of medicines.

Search and Information Sources

The literature search was conducted using 4 databases, including PubMed, EBSCOhost, Ovid, and Scopus, from inception

until the first week of January 2016. The search terms started off with "Trans-Pacific Partnership Agreement" and then narrowed down to "Trans-Pacific Partnership Agreement AND Pharmaceutical." Appendix A shows the search strategies that were developed and applied for the databases used in this review. Besides, reference lists of obtained papers were screened to check for relevant articles to be included in the meta-synthesis (refer to Appendix B: PRISMA 2009 Checklist). The search terms were discussed by the 2 reviewers (C.P. and Y.Y.) and approved by the 3 senior researchers (K.S.L., L.C.M., and T.M.K.). At the beginning of our information search, we managed to obtain articles related to how the provisions in the draft TPPA text affect medicine affordability and accessibility for data extraction. After we completed the data extraction for the included articles, the final TPPA text was officially released, but the provisions in the final text do not deviate much from the draft text. Hence, both texts were analyzed and used to provide an insight regarding TPPA implementation.

Study Selection

The two reviewers (C.P. and Y.Y.) searched for full-text articles of any study design, in any setting, and without any language restriction, which measured the impact of the Trans-Pacific Partnership Agreement on the pharmaceutical sector. Articles published prior to April 1, 2016, were included. The titles and abstracts, followed by full texts of the relevant articles, were separately screened by the 2 reviewers (C.P. and Y.Y.). The 2 reviewers discussed and decided on the inclusion and exclusion criteria after consulting 3 senior researchers (K.S.L., L.C.M., and T.M.K.). Then, both reviewers worked together on the selection of appropriate articles based on the decided inclusion and exclusion criteria. Only peer-reviewed qualitative articles that discussed TPPA's impact on the pharmaceutical sector were included. Papers in the form of news, report, talks, factsheets, and policy briefings were excluded. Articles that discussed the impact of TPPA on public health but focused on tobacco control were also excluded. Any disagreements were resolved through discussion among the two reviewers (CP and YY) and 3 senior researchers (KSL, LCM and TMK).

Data Extraction

Initially, data concerning aims, settings, and outcomes from the included studies was extracted independently by 2 reviewers (C.P. and Y.Y.). Then, extracted data were tabulated and the information was paraphrased to preserve meaning. To ensure data integrity, 2 reviewers (C.P. and Y.Y.) thoroughly examined and discussed the extracted data together. The reviewers also double-checked for consistency and validation. This was done to make sure the data were not misinterpreted and were free of researcher bias. Lastly, the finalized table was reviewed by the 3 senior researchers (K.S.L., L.C.M., and T.M.K.). The entire extraction was performed using a structured data extraction form.

Qualitative Synthesis of Data

After screening and extracting all the required data, the reviewers (C.P. and Y.Y.) discussed and identified all the issues regarding the impact of TPPA on the pharmaceutical sector. Based on the frequency of occurrence, reviewers (C.P. and Y.Y.) included the main issues raised and categorized them into appropriate themes and subthemes for thematic analysis. Then, the name for each theme and subtheme was finalized after the approval of 3 senior researchers (K.S.L., L.C.M., and T.M.K.). In the results section, themes and subthemes were sufficiently defined. The descriptions were written and illustrated with a few quotations from the original text to facilitate understanding for the readers.

Results

Initially, a total of 296 citations were retrieved from the databases and manual search of reference lists and citations. After reviewing the titles and abstracts, 143 articles were removed because of duplication and 68 articles for failure to address the selection criteria. The remaining 85 articles were viewed in full text. A further 53 articles were excluded because of irrelevance or failure to fulfill the inclusion criteria. Ultimately, 32 articles were taken forward for further review. Figure 1 shows a PRISMA diagram of the systematic review.

Figure 2 further explains the characteristics of the included articles. It is shown that most of them were published in 2015 (41%), followed by 2014 (28%) and 2016 (3%). The remaining articles (28%) were published before 2014. Only 16% of the literature was about Asia, with 50% about non-Asian countries, including the United States, Canada, Brazil, New Zealand (NZ), and Australia, with the remaining 34% only discussing TPPA in general.

To present our findings in a more structured form, we grouped them into two main themes: (1) IPR (T1) and (2) Transparency (T2). Each theme is further categorized into subthemes explaining more in depth about the themes. The summary of the different themes in each article is presented in Table 1.

All themes and subthemes in Table 1 were synthesized based on the interplay between TPPA and the pharmaceutical sector, which could have a significant impact on the accessibility and affordability of medicines. Each theme and subtheme is further discussed below.

Theme 1: Intellectual Property Rights

IPR can be defined as a government intervention in the market to grant monopoly exclusions in exchange for new technology. In other words, the status of property is granted to a person's idea, invention, and creation.[16] The property inventors will receive certain exclusive rights via IPR that enable them to

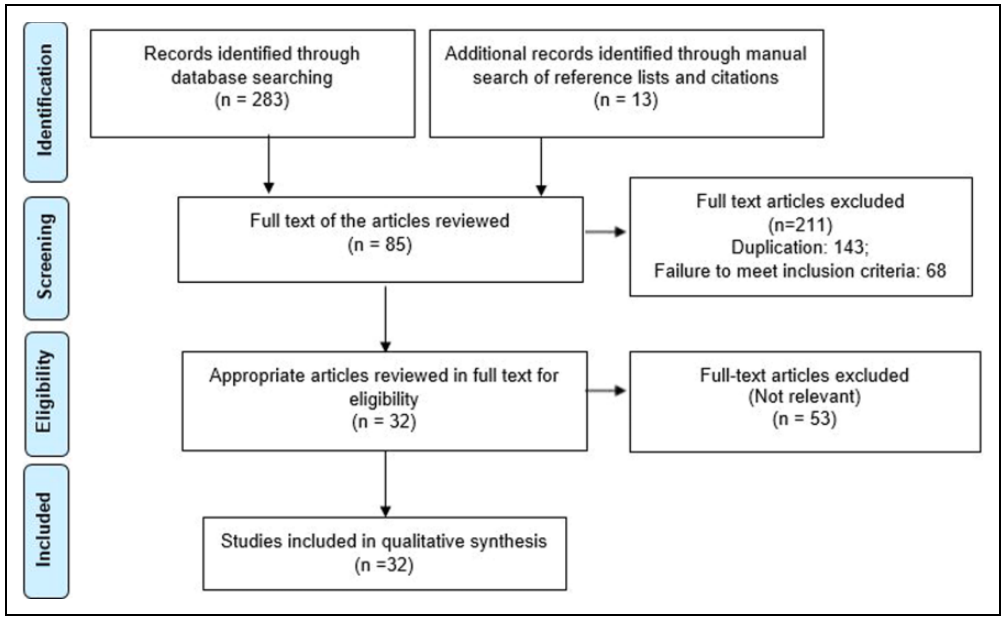


Figure 1. PRISMA flow diagram of systematic review process.

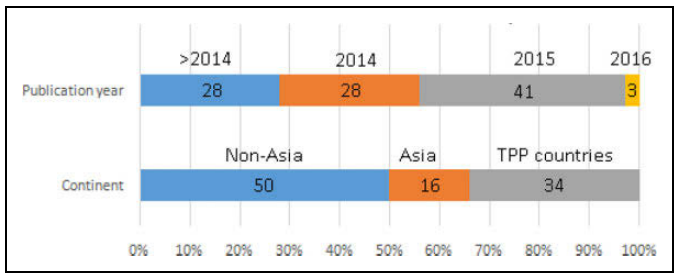


Figure 2. The summary of characteristics of the 32 articles included. The numbers on the bars show the percentage of articles involved.

obtain commercial benefits from their efforts or reputation.[17] Since 1995, the World Trade Organization (WTO) agreement on TRIPS has been in force, which is the most comprehensive multilateral agreement on IPR as it introduces global minimum standards for nearly all forms of IPR protection and enforcement.[18] However, the intellectual property obligations suggested by TPPA goes well beyond the minimum standards of the multilateral WTO agreement on TRIPS, which can have a significant impact on public health.[8] Issues arising from the provision of IPR that would potentially affect accessibility and affordability of pharmaceuticals includes low inventiveness standards, patent-term extension, patent linkage, data exclusivity, and restriction of compulsory licensing. These are the 5 subissues under IPR provision that has been detected in the meta-synthesis.

Low inventiveness standards

Because of the low inventiveness standards in the TPPA IPR chapter, the practice of "evergreening" is often employed to gain longer patent monopolies. With only minor variations to original drugs, companies will be given a new patent for another 20 years, which means that the cumulative period covered by all the different patents, which includes the original and "evergreening" patent, can add up to more than 40 years. By contrast, a different law is adapted in India, as Kapczynski explains:

> India allows patents on new drugs but not on new uses of old drugs or new forms of known drugs that do not increase therapeutic efficacy. These provisions have paved the way for generic versions of lifesaving drugs.[19]

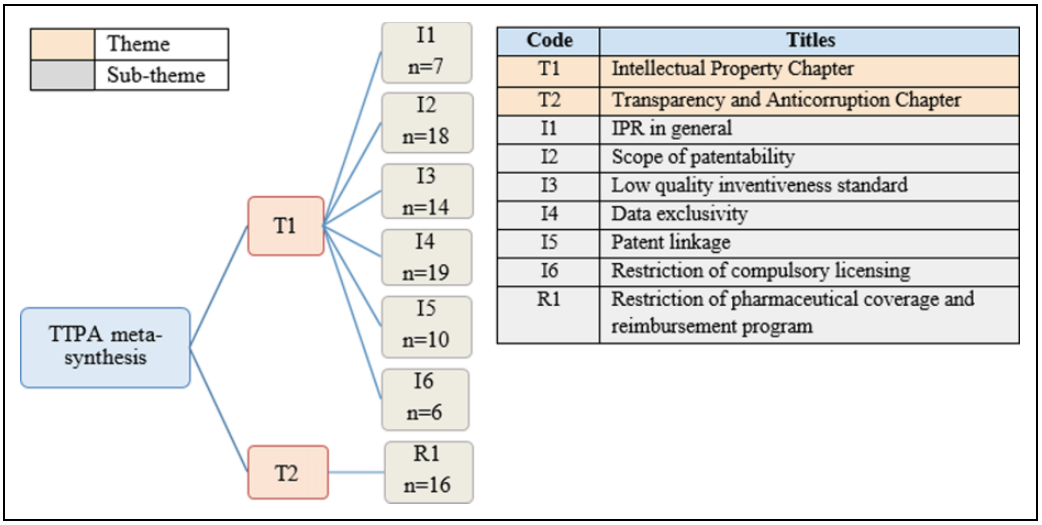
India is not part of the TPP countries but many other countries have shown interest in joining TPPA in future, creating a new baseline for future international negotiation.[19] Therefore, if India or other developing countries were to sign the TPPA, it would significantly affect the accessibility and affordability of medicines.[19]

Patent term extension

Patent term extension provides additional monopolies to the innovators for any delay in the issuance of patent or marketing approval. As stated in the article by Linh et al, with reference to a study conducted by Kessomboon et al,

> In Thailand, a recent study projected that if a 10-year patent term extension had been granted, medicine prices would have increased by 32%.[20]

As seen above, the extension of patent terms is likely to delay market entry of affordable generic medication, limiting the availability of life-saving medications. This will put countries that have not adopted this provision or have an inefficient



Code	Titles
T1	Intellectual Property Chapter
T2	Transparency and Anticorruption Chapter
I1	IPR in general
I2	Scope of patentability
I3	Low quality inventiveness standard
I4	Data exclusivity
I5	Patent linkage
I6	Restriction of compulsory licensing
R1	Restriction of pharmaceutical coverage and reimbursement program

Figure 3. Thematic analysis decision tree of the TTPA meta-synthesis. TTPA, Trans-Pacific Partnership Agreement.

process in issuing a patent or marketing approval of a new drug at a disadvantage.

Data exclusivity

The data exclusivity provision provides an additional form of protection to the innovators as it forces generic manufacturing companies to duplicate clinical trials in order to be marketed, which is said to be unnecessary and unethical. According to Flynn et al, TPPA means

> an additional three-year term of exclusivity for data submitted for approval of a new use or form of an approved chemical entity . . . meaning that data exclusivity, like patents, can be evergreened.[21]

The innovator companies tend to rely on the "evergreening" approach to obtain new patent terms, so that they are granted an additional 3 years on top of the 5 years' data exclusivity of the original product. Consequently, this further restricts the generic applicants from having access to original clinical data within the exclusivity period. They have no choice but to replicate the clinical trials or wait for the exclusivity period to end in order to submit an application for approval. Thus, this provision is not only inconsistent with medical ethical standards against duplication of trials, but it also causes patentlike monopolies, which limits access to affordable generics.

Patent Linkage

This linkage system creates an additional pathway that benefits the innovators by blocking the introduction of generic medicines into the market without the need to sue generic manufacturers in order to implement patent rights. As reported by Flynn et al,

> Linkage systems reverse the onus, forcing the generic company, blocked from access to the market, to affirmatively sue the patent holder in order to gain market access.[21]

Thus, this system not only restricts the generic introduction into the market, which can have a great impact on public health, but it also creates a huge financial burden for generic companies if they were to get involved in court cases, especially before the product is being marketed.

Restriction of Compulsory Licensing

A compulsory license is an authorization granted by the government to authorize the use of patented products without the consent of the patent holder. This is to enable accessibility to life-saving medications during national emergencies. Since the implementation of TRIPS, the capability of countries to issue compulsory licenses has been restricted.[22] With the further strengthening of IPR under TPP, it is obvious that the granting of compulsory licenses will become even harder. According to a study conducted by Linh et al,

> Even in case of emergency, TPP doesn't allow the Vietnamese government to use compulsory licenses. (Vietnam Chamber of Commerce and Industry [VCCI] representative)[23]

Thus, the restriction in issuing compulsory licenses will limit a government's flexibility in addressing a public health crisis and lead to a delay in accessing affordable essential medicines in an emergency situation. It is especially worrying in developing countries such as Vietnam and Malaysia where most of the people cannot afford the expensive medical treatment.

Theme 2: Transparency

Within this theme, the main issue that can impact the accessibility and affordability of medicines is the restriction of pharmaceutical coverage and reimbursement programs.

Table 1. Summary of 32 Articles Based on Different Themes and Subthemes.

Continent	Author	IPR						Transparency and Anti-corruption- Procedural Fairness (26) (restriction of coverage program and reimbursement)
		General	Patent Subject Matter (18.37) (scope of patentability)	Patent Term Adjustment for Patent Office Delays (18.46) (patent term extension)	Protection of Undisclosed Test or Other Data (18.50) (data exclusivity)	Protection of Undisclosed Test or Other Data (18.51) (patent linkage)	Compulsory license	
Asia	Lee (2014)	✓						
	Linh et al (2015)		✓	✓	✓	✓	✓	
	Lee et al (2016)		✓		✓			
	Moir et al (2014)		✓	✓	✓	✓	✓	
	Manaf et al (2014)		✓		✓	✓		✓
Non-Asia	Freeman (2015)	✓			✓[a]			✓[b]
	Faunce et al (2011)			✓	✓	✓	✓	✓
	Lofgren (2011)		✓	✓	✓	✓		✓
	Gleeson et al (2012)		✓		✓			
	Babar et al (2014)			✓				✓
	Monasterio and Gleeson (2014)			✓	✓			✓
	Schram et al (2014)		✓					
	Beard (2015)							✓
	Gleeson et al (2015)		✓	✓	✓		✓	
	Neuwelt et al (2015)	✓						✓
	Ribeiro (2015)	✓		✓				
	Ruckert et al (2015)		✓					
	Thow et al (2015)	✓						✓
	Walls et al (2015)		✓					✓
	Gleeson et al (2013)		✓	✓	✓	✓		✓
	Monasterio et al (2014)			✓				✓
TPP countries in general	Jorge (2013)				✓			
	Lopert et al (2013)		✓	✓	✓	✓		✓
	Greenberg et al (2014)		✓					
	Wise (2014)	✓						
	Kapczynski (2015)		✓		✓			
	Krist (2015)		✓		✓	✓		✓
	Luo et al (2015)		✓		✓			
	Gleeson et al (2013)	✓						
	Mitchell et al (2015)		✓	✓	✓		✓	✓
	Fergusson et al (2013)			✓	✓	✓		✓
	Flynn et al (2013)		✓	✓	✓	✓	✓	

Abbreviation: IPR, intellectual property rights.
[a]A new subtopic given under "Regulatory Data Protection" (RDP).
[b]But they link ISDS as a mechanism to restrict reimbursement.

Restriction of pharmaceutical coverage and reimbursement programs

Pharmaceutical coverage and reimbursement programs play an important role in providing affordable access to generic medicine and ensure public health care expenditure is worth the money.[24] Developed countries like Australia and New Zealand have well-established national pharmaceutical coverage and reimbursement programs, known as the Pharmaceutical Benefits Scheme (PBS) and Pharmaceutical Management Agency (PHARMAC), respectively. The annex to the transparency chapter of TPPA would impose limitations on these pharmaceutical coverage and reimbursement programs.[25] As stated by Monasterio and Gleeson,[26] in reference to Gleeson et al[24] and the Public Interest Analysis done by Flynn et al,[27]

> the TPPA would confer additional privileges on the pharmaceutical industry through mandating procedural changes to pharmaceutical coverage programs . . . the transparency chapter of the TPPA endanger effective pricing strategies such as therapeutic reference pricing.

The quote above indicates the possibility of the implementation of TPPA in affecting a country's policy in moderating the price of drugs for public health interest.[26] As for those countries that have not established such coverage and reimbursement programs, the adoption of TTPA could potentially restrict a government in establishing new health regulatory policy in future. Not only that, TPPA means changes may be imposed to existing regulatory systems way beyond the IPR does, which is likely to compromise public health.

Discussion

This is the first meta-synthesis that explores the impact of TPPA on the pharmaceutical sector: how the strengthening of IPR (Theme 1) and the restriction of coverage and reimbursement programs (Theme 2) affect the affordability and accessibility of medicines. This section aims to discuss a few issues that could arise after the implementation of TPPA, providing an insight for both developed and developing countries.

Strengthening of IPR Leads to Restricted Access to More Affordable Generic Drugs

Stronger IPR provision claimed by the US in the TPPA has created widespread alarm since 2011, when the first draft was leaked.[28] The leaked data, particularly on the IP chapter, has been one of the most contentious areas of dispute, as it is said to delay access to more affordable generic drugs.[28] This delay not only challenges the survival of the smaller generics companies but developing countries specifically will face significant difficulties accessing essential medications, thus having a serious impact on public health. However, stronger IPR is important to encourage innovators to participate in research and development (R&D) for new inventions. Hence, a balance between both is the key: providing sufficient incentives in term of monetary and intellectual protections to the innovator as well as providing unlimited access to affordable medicines to the public.

For example, in the US, total expenditure on health as a proportion of GDP was estimated at 17.1% in 2013, indicating the strong influence of the pharmaceutical sector.[29] In 2011, pharmaceutical industries in the US spent almost US$50 billion for R&D, much higher than Japan (11.5 billion), Germany (5.2 billion), and France (3.7 billion).[30] All R&D in the US is conducted by big US pharmaceutical companies. Most of these companies are registered under the Pharmaceutical Research and Manufacturers of America (PhRMA), which is an industry association representing the country's leading biopharmaceutical researchers and biotechnology companies.[31] PhRMA, together with other US associations, lobbied aggressively in claiming stronger IPR.[32] They stated that strengthening IPR can create productivity, boost economic growth, and increase job availability and living standards.[32] However looking at the trend of prescription drugs, 75.0% of prescribed drugs in the US were generics in 2009 as compared to 57.0% in 2004.[33] The increasing trend for generic usage indicates that the US is now highly dependent on generics. Similar to the US, in Malaysia, generic drugs are estimated to account for approximately 70.0% of the drugs consumed in the country.[3] Hence, if the TPPA provision leads to a delay in the generic market, it will potentially increase the cost of health care and can affect the public health not only in developing countries but also developed countries that rely on generics.

From the thematic analysis, it was found that the issues related to IPR expansion that were frequently discussed in most of the studies are low inventiveness standards, patent term extension, data exclusivity, and patent linkage. These are further discussed below.

Inventiveness Standards

"Evergreening" creates problems especially in countries with low patentability standards such as Australia and the US. Based on a study conducted by Amin et al from the two Human Immunodeficiency Virus (HIV) drugs that has been granted with patents (ritonavir and lopinavir/ritonavir) in the US, there are 82 secondary patents granted and 26 pending applications, which mostly involved only minor variation from primary patents.[34] This scenario clearly proves the significance of multinational companies utilizing "evergreening" practice to gain longer patent extension on brand-name drugs. By doing this, an additional 20 years of secondary patent can be obtained in addition to the original patent of 20 years.

Hence, the implementation of TPPA with low inventiveness standards will make further prevention of "evergreening" approach even harder.

On the other hand, India's strong stance on minor drug innovations is able to prevent innovators from relying on the "evergreening" method to obtain prolonged monopolies, hastening the genetic introduction into the market. For example,

Gleevec, marketed by Novartis, expired in 2015.[35] Foreseeing this, Novartis "evergreened" in order to prolong their monopolies.[35] However, India's Supreme Court rejected Norvatis's application as they did not meet the standard of inventiveness set by Indian patent law.[35] Norvatis and similar companies claimed that this action may discourage innovative drug discovery.[35] Even though India is not a part of TPP, the TPPA IP chapter is going against India's patent law.[19] This is because other countries have started to follow India's lead.[19]

> The Indian ruling is not an isolated one; we are seeing in Canada, courts are under pressure to strengthen their patent standards. What we are seeing is that the developed world is taking a cue from developing countries in drafting patent norms.[36]

Hence, the TPPA will set the low patentability standards in concrete and make further prevention of the "evergreening" tactic even harder.

Issues Relevant to Patent Term Extension and Data Exclusivity

Patent term extension due to unreasonable delay is almost impossible if a country has established an efficient system to process the application to approve new drugs. In the US, since the implementation of the Prescription Drug User Fee Act (PDUFA) I in 1993, FDA has constantly used PDUFA resources and has reduced the time to process and approve new drugs without compromising its strict standards for drug safety and efficacy.[37] In the latest PDUFA, PDUFA V, FDA has created a new review program, "The Program."[38] In fiscal year 2013, 56 applications were made under The Program.[38] By September 30, 2014, 96.0% of these applications were acted on within the deadline set, indicating the efficiency of The Program.[38] On the other hand, in Australia, Pharmaceutical Patent Review (PPR) 2013 stated that 58.0% of new molecules listed on PBS from 2003 to 2010 received an extension, and out of the 58.0% that were granted an extension, 47.0% received a full 5-year extension.[38] The cost of these extensions from 2012 to 2013 is estimated at approximately AU$240 million in the medium term and can double in the long term.[39]

According to a report written by the Malaysian Ministry of International Trade and Industry (MITI) on the impact of TPPA on the Malaysian economy, there will be a minimal effect from patent term extension as Malaysia's processes are efficient.[3] Sources from the National Pharmaceutical Control Bureau stated in 2014 that 100% of a total of 85 applications were evaluated within a target of 245 days.[3]

This shows the importance of creating an efficient regulatory body to assess and approve new drugs, to gain quicker access to new breakthrough drugs and to reduce unnecessary costs due to delay. Thus, patent term extension can be seen as a threat if the government does not have a well-established system in approving new drugs.

Data exclusivity is not new and has been practiced in both developed and developing countries. However, the TRIPS agreement specifically recognized the "protection of undisclosed information" as one of the subtopics under IPR.[40] This is because the innovation of a drug involves a considerable amount of time and money; it may take as long as 15 years and cost as much as US$500 million in industrialized countries.[40] If the data were easily accessible and used by third parties, it would mean that the inventor would have no benefits.[40] In addition, the development of biologics requires a longer time and more money for R&D compared to small-molecule drugs. A fixed data exclusivity period enables pharmaceutical companies to regain their costs and to predict earnings expiry. This privilege is important for innovators to carry out R&D in the first place.[40]

On the other hand, one of the main concerns about the introduction of data exclusivity is that duplication of clinical trials for obtaining generic marketing approval by the less experienced generic companies will add additional risk to humans and animals. Moreover, this act is against ethical law and it seems rather unnecessary to include the additional costs of generic production on repeated clinical trials as the safety and efficacy results are expected to be similar to the innovator's clinical trial results.[10]

In the final TPP text, the scope of data exclusivity to biologics was expanded, which can cause major changes to the law in 9 of 12 TPPA countries.[41] The American Association of Retired Persons (AARP) is against long-term exclusivity, and stated that the shortening of data exclusivity from 12 to 8 years would be "a critical element of any comprehensive effort to contain healthcare costs" as the biosimilars are usually priced 40% lower than the original biologics.[41] It is not surprising that developing countries with lesser resources will face difficulties adopting a policy when even a developed country like the US can hardly afford it. As stated in the report *Health at a Glance* by the Organization for Economic Development and Cooperation and the World Health Organization, the implementation of data exclusivity on biologics in Vietnam will definitely increase the burden for patients and the government because half of the overall health spending is on pharmaceuticals.[42]

The early introduction of biosimilars is said to reduce health care cost. According to a statistical report in Australia titled "Expenditure and Prescriptions twelve months to 30 June 2014," the introduction of the first biosimilar version of adalimumab (Humira) listed in PBS led to a reduction of as low as 16% of cost on all variations of the product.[28] This indicates a significant reduction in taxpayer costs in the first year, and further savings are expected in subsequent years because of the disclosure of price.[28] However, the threat of data exclusivity toward public health will be significantly less in developing countries as they only have a limited number of biopharmaceutical manufacturers.[3]

Nevertheless, the introduction of data exclusivity in general will lead to the late introduction of generics into the market,

limit the accessibility to affordable generics and biosimilars, and also add the unnecessary costs of duplicating clinical trials.

Patent Linkage

Patent linkage is especially worrying in developing countries that rely on generic products to survive. A study was done on the impact of the TRIPS-plus provisions of Jordan-USFTA. IPR strengthening including patent linkage caused 20% of overall price increase from 2001 to 2006, and also accounted for 79% of the delay in the entry of generics produced by 21 pharmaceutical companies from 2002 to mid-2006.[43] This is because pharmaceutical companies can effectively have another platform to prevent launching of generic medication through this linkage system. In the US, the "Orange Book" system usually allows an estimated period of 30 months for the approval of generic products by the drug regulator body.[9] However, the implementation of patent linkage under TPPA could cause an additional 3 to 4 years' delay for generics to enter the market as they do not have a formal system.[9] This would benefit innovators and delay the launch of generics, preventing patients from accessing more affordable alternatives.

In Canada, of all the international trade agreements signed, TPP appears to be the first agreement that requires patent linkage.[44] However, Canada itself has its own existing patent linkage system.[44] Thus, the introduction of patent linkage under the TPP IPR chapter would seem not to have any significant impact to the country.[44] Having said that, while prior to signing TPPA Canada was free to reform or even eliminate the existing patent linkage system, elimination or reform of this system for cost-saving purposes is almost impossible.[44]

The consequences toward public health through the implementation of this linkage system is obvious. In fact, European and Asian countries do not have any fixed patent linkage systems, as their negative impact on drug costs is well understood. The Philippines is one of the Asian countries that used to have a fixed patent linkage system, but the government eliminated it through the Government Administrative Order in 2006.[45] Since the Philippines does show interest in signing TPPA, this could result in a disadvantage in the country by increasing health care expenses and causing long delays as well as economic injury.[45]

Access to Affordable Medicines

With the implementation of the TPP Transparency Annex, most pharmaceutical companies will be granted additional privileges such as mandating procedural changes to the pharmaceutical coverage programs, precluding use of effective pricing mechanisms, and more leverage in the pharmaceutical reimbursement programs listing decisions.[46] This will restrict governments from implementing effective pricing strategies like "therapeutic reference pricing" and providing effective public subsidies for prescribed medicines as well as making decisions about which medicines are subsidised.[24]

In Australia, the implementation of the clause in the TPP Transparency Chapter has the potential to increase the cost of medicines, so the government has to set a greater budget for PBS. This will disadvantage patients because of higher copayments and reduced access to new, expensive treatments.[47] In New Zealand, people of low socioeconomic status who are unable to pay for additional costs are likely to face financial hardship because of the rise in copayments.[24] Besides, the expansion of IPR based on the TPPA provisions could prolong the monopoly periods of the original innovators and the market entry of generics would be delayed. This would severely compromise a pharmaceutical reimbursement agency's ability to source low-cost generic drugs.

In Asia, pharmaceutical coverage and reimbursement programs are available in India, Singapore, Hong Kong, Thailand, Malaysia, Vietnam, the Philippines, and Indonesia.[48] Nevertheless, pharmaceutical reimbursement is treated differently in different countries and each reimbursement program varies from one another according to whether the product is a locally made generic, imported generic, or brand-name product.[48] As seen in richer countries like Singapore and Hong Kong, pharmaceutical products are generally reimbursed at higher prices because of the countries' well-defined drug reimbursement system.[48] On the other hand, for countries who have announced an interest in signing TPPA, such as Thailand, the escalating drug costs would be their concern as it will affect the country's pharmaceutical reimbursement program.[49] This is because Thailand has limited financial resources for health care and the decision making for the program has been based on pharmacoeconomics to create rational policies or allocate resources efficiently.[49] However, in recent years, many physicians in Thailand like to prescribe nonessential drugs that are costly and without subsidies from the less-defined drug reimbursement program.[50] This leads to a reduction in the cost-effectiveness of the reimbursement.

Also, for countries like Malaysia and Vietnam with less developed pharmaceutical coverage and reimbursement programs than the Australian PBS, the impact could be insignificant but the government might face restrictions in establishing new systems or more established reimbursement programs to suit the national context and priorities in the future. The "Annex on Transparency" in TPPA is likely to adversely impact these countries by increasing a government's pharmaceutical expenditure and hindering access to affordable medicines.[51,52] These barriers would result in decreased medication use for disease treatment and greater hospitalization risk, eventually leading to unfavorable patient health outcomes and greater financial burden for the government.[24] Therefore, for countries that have yet to sign the agreement, a health technology assessment agency should be established to conduct a pharmacoeconomic evaluation and budget impact analysis of drugs to

ensure cost effectiveness. As for those countries that have signed TPPA, these governments should create a policy or strategy that can balance the procedural changes to these pharmaceutical coverage programs and maintain the use of effective pricing mechanisms.[49]

Post signing of TPPA, signatory countries are given 2 years to rectify respective domestic legal procedures to align with the agreement provisions, particularly on intellectual property legislation. Developing countries such as Brunei, Chile, Malaysia, Mexico, Peru, and Vietnam need to take a holistic approach and restrategize their health care policies around TPPA during the rectification process to ensure access to cheaper medicine, and the availability of generic medicines is not delayed. Most countries welcome the TPPA as a springboard to encourage the development of more innovative medicines through the strengthening of IPR, but not at the expense of increasing the healthcare expenditure and impeding medicines access. Generic medicine use and health equality policies should be strengthened and barriers to the development of these policies should be removed. These policies could create an environment that promotes the use of generic medicines and foster competition in medicine prices, effectively driving down the prices of medicines. Furthermore, policy makers need to unravel the conundrum of novel life-saving high-cost medicine such as cancer drugs, hepatitis C drugs, and biologic drugs, concomitantly making these medicines accessible and safeguarding a sustainable health care budget. Managed entry agreement, an innovative arrangement between a payer and manufacturer, may be adopted as a tool to enable early access to these medicines while maintaining sustainable pharmaceutical expenditure.[51,52]

On a similar note, in situations of national emergency or extreme urgency, signatory countries are able to issue a compulsory license to enable a patented product to be either manufactured locally or to invoke the "Rights of Governments" provision to import generic medicines at a lower price. This is in accordance with TRIPS declaration, a reference to the 2001 Doha Declaration, for countries to exclude the patentability obligation during public health crisis, including those relating to HIV/AIDS, tuberculosis, malaria, and other epidemics. Participating countries have the right to determine what constitutes a national emergency or other circumstances of extreme urgency. Although these provisions were rarely being invoked, in 2004, Malaysia issued the world's first compulsory license under TRIPs to allow the importation of HIV/AIDS medicines, effectively reducing the cost of these medicines. Policy makers may consider a similar measure in tackling the persistently high price of hepatitis C medicines such as Gilead's Sovaldi (sofosbuvir), AbbVie's Viekira (dasabuvir, ombitasvir, paritaprevir, and ritonavir) and Merck's Zepatier (elbasvir and grazoprevir).

The present review is not without limitations. First, all the studies included in this review are expert opinion as the TPPA has not yet been formally in force and the impacts discussed are projections based on the economic and health care demand. Even though expert opinion is not regarded as a high level of evidence, in the absence of research studies, it is the best reference and evidence. Second, most of the studies reviewed were published before the release of the official, full TPPA text on November 2015. TPP negotiation was classified, and a majority of the included studies relied on the leaked documents. It must be noted that we have counterchecked these variations, which are negligible as the primary TPPA provisions remain unchanged.

Conclusions

This meta-synthesis has revealed the main issues related to the implementation of TPPA, which includes the expansion of IPR and the restriction of pharmaceutical coverage and reimbursement programs. Strengthening of IPR creates prolonged monopolies for the innovator companies, at the same time delaying the introduction of generics into the market. The restriction of pharmaceutical coverage and reimbursement programs due to the implementation of TPPA would cause higher copayment and increase governments' financial burdens. These key findings indicate that TPPA carries a potential in hindering the affordability and accessibility of medicine, meaning greater risks to public health.

For countries that show an interest in signing TPPA, it is important for the government to take precautionary steps to ensure the agreement does not overpower its own policies and jeopardize national interests. Both benefits and threats of TPPA should be analyzed before coming to a final decision about signing the agreement. As for countries that have signed the agreement, ongoing "risk management" is required to create balance between the promotion of pharmaceutical economic growth and public access to affordable medicines. With effective approaches in handling TPPA, this will benefit all parties: the government, pharmaceutical industry, and public.

Appendix A

PubMed, PMC, Ovid Medline, EBSCO Host, and Scopus search strategies for Trans-Pacific Partnership Agreement

Database	PubMed
Date	5/1/2016
Strategy	#1 and #2
#1	"Trans-Pacific Partnership Agreement" OR "Trans Pacific Partnership Agreement"
#2	"Pharmaceutical"
Database	PMC
Date	5/1/2016
Strategy	#1 and #2
#1	"Trans-Pacific Partnership Agreement" OR "Trans Pacific Partnership Agreement"
#2	"Pharmaceutical"
Database	Ovid Medline
Date	5/1/2016
Strategy	#1 and #2
#1	"Trans-Pacific Partnership Agreement" OR "Trans Pacific Partnership Agreement"
#2	"Pharmaceutical"
Database	EBSCOhost
Date	5/1/2016
Strategy	#1 and #2
#1	"Trans-Pacific Partnership Agreement" OR "Trans Pacific Partnership Agreement"
#2	"Pharmaceutical"
Database	Scopus
Date	6/1/2016
Strategy	#1 and #2
#1	"Trans-Pacific Partnership Agreement" OR "Trans Pacific Partnership Agreement"
#2	"Pharmaceutical"

Appendix B

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Not applicable

(continued)

Appendix B (continued)

Section/topic	#	Checklist item	Reported on page #
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Not applicable
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Not applicable
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13 -18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Not applicable
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7):e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Acknowledgments

The authors would like to express their gratitude to the Ministry of Higher Education, and Universiti Teknologi MARA, Malaysia, for financial support for this research.

Declaration of Conflicting Interests

No potential conflicts were declared.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by LESTARI grants: 600-IRMI/DANA 5/3/LESTARI (0006/2016).

References

1. Ustr.gov. Trans-Pacific Partnership Ministers' Statement [Internet]. https://ustr.gov/about-us/policy-offices/press-office/press-releases/2016/February/TPP-Ministers-Statement. Published 2016. Accessed October 19, 2016.
2. Ustr.gov. Summary of the Trans-Pacific Partnership Agreement [Internet]. https://ustr.gov/about-us/policy-offices/press-office/press-releases/2015/october/summary-trans-pacific-partnership. Published 2015. Accessed October 19, 2016.
3. PwC Advisory Services Sdn Bhd. Study on potential economic impact of TPPA on the Malaysian economy and selected key economic sectors. 2015.
4. Will the TPP transform intellectual property regulation in Asia? [Internet]. East Asia Forum. http://www.eastasiaforum.org/2016/02/17/will-the-tpp-transform-intellectual-property-regulation-in-asia. Published 2016. Accessed April 15, 2016.
5. Trans-Pacific Partnership Agreement [Internet]. Electronic Frontier Foundation. https://www.eff.org/issues/tpp. Accessed April 15, 2016.
6. Intellectual Property—The Trans-Pacific Partnership [Internet]. US Trade Representative. https://medium.com/the-trans-pacific-partnership/intellectual-property-3479efdc7adf#.m8wfs3u34. Published 2015. Accessed April 15, 2016.
7. TPP, US, and TRIPS IP Law Comparison [Internet]. 1st ed. Hong Kong. https://www.law.cuhk.edu.hk/en/research/cfred/download/TPP_US_IP_Provision_Comparison.pdf. Published 2016. Accessed April 18, 2016.
8. Implications for Access to Medicines and Public Health [Internet]. Geneva: UNITAID; 2014. http://www.unitaid.eu/images/marketdynamics/publications/TPPA-Report_Final.pdf.
9. Sha DG. Intellectual property watch. Impact of the TPP on the pharma industry [Internet]. http://www.ip-watch.org/2015/12/02/impact-of-the-tpp-on-the-pharma-industry/. Published 2015. Accessed October 21, 2016.
10. Public Citizen. Trans-Pacific Partnership Agreement: harmful provisions for access to medicines [Internet]. https://www.citizen.org/documents/specific%20provisions%20final%20draft%20w.o.pdf. Accessed October 19, 2016.
11. WTO intellectual property (TRIPS)—TRIPS and public health: Compulsory licensing of pharmaceuticals and TRIPS [Internet]. Wto.org. https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm. Published 2016. Accessed April 19, 2016.
12. Trading away health: how the U.S.'s intellectual property demands for the Trans-Pacific Partnership Agreement threaten access to medicines [Internet]. 1st ed. MSF Access Campaign; 2012 https://www.msfaccess.org/sites/default/files/MSF_assets/Access/Docs/Access_Briefing_TPP_ENG_2012_update.pdf. Accessed April 19, 2016.
13. Knowledge Ecology International. KEI TPP Briefing note 2015:1 Compulsory licenses on patents and the 3-step test. Knowledge Ecology International [Internet]. Keionline.org. http://keionline.org/node/2231. Published 2015. Accessed April 19, 2016.
14. Flynn S, Kaminski ME, Baker BK, Koo JH. Public interest analysis of the US TPP proposal for an IP chapter. PIJIP Research Paper Series [Internet]. Paper 21. http://digitalcommons.wcl.american.edu/research/21/. Published 2011. Accessed April 19, 2016.
15. Implications for Access to Medicines and Public Health [Internet]. UNITAID; 2014. http://www.ftamalaysia.org/article.php?aid=333.
16. Fields of intellectual property protection. *WIPO Intellectual Property Handbook: Policy, Law and Use* [Internet]. 2nd ed. Geneva: WIPO Publication; 2004. 17-160. http://www.wipo.int/export/sites/www/about-ip/en/iprm/pdf/ch2.pdf. Accessed April 19, 2016.
17. Saha CN, Bhattacharya S. Intellectual property rights: an overview and implications in pharmaceutical industry. *J Adv Pharm Technol Res* 2011;2:88-93.
18. World Health Organization. WTO and the TRIPS agreement [Internet]. http://www.who.int/medicines/areas/policy/wto_trips/en/. Published 2016. Accessed October 15, 2016.
19. Kapczynski A. The Trans-Pacific Partnership—is it bad for your health? *N Engl J Med*. 2015;373:201-203.
20. Kessomboon N, Limpananont J, Kulsomboon V. Impact on access to medicines from TRIPS-Plus: a case study of Thai-US FTA. *Southeast Asian J Trop Med Public Health* 2010;41:667-77.
21. Flynn SM, Baker B, Kaminski M, Koo J. The U.S. proposal for an intellectual property chapter in the Trans-Pacific Partnership Agreement. *Am Univ Int Law Rev*. 2013;28:105-205.
22. Moir H, Tenni B, Gleeson D, Lopert R. Assessing the impact of alternative patent systems on the cost of healthcare: the TPPA and HIV treatment in Vietnam. Paper presented at the Asia-Pacific Innovation Conference, University of Technology, Sydney, 2014. http://papers.ssrn.com.ezproxy.lib.monash.edu.au/sol3/papers.cfm?abstract_id=2536254M.
23. Linh NN, Huong NT, Thuy HT. Evolving trade policy and the Trans-Pacific Partnership Agreement: does it threaten Vietnam's access to medicine and its progress towards scaling up HIV prevention, treatment and care? *Glob Public Health* 2015;10(suppl 1):S149-S160.
24. Gleeson D, Lopert R, Reid P. How the Trans Pacific Partnership Agreement could undermine PHARMAC and threaten access to affordable medicines and health equity in New Zealand. *Health Policy*. 2013;112:227-233.
25. Gleeson D. Analysis of the June 2011 leaked TPP Transparency Chapter Annex (Annex on Transparency and Procedural Fairness for HealthCare Technologies) [Internet]. Submission to the

Department of Foreign Affairs and Trade; 2012. https://dfat.gov.au/trade/agreements/tpp/negotiations/Documents/tpp_sub_gleeson_120911.pdf. Accessed April 19, 2016.
26. Monasterio E, Gleeson D. Pharmaceutical industry behaviour and the Trans Pacific Partnership Agreement. *N Z Med J*. 2014;127:6-12.
27. Flynn S, Kaminski M, Baker B, Koo J. Public interest analysis of the US TPP proposal for an IP chapter, draft version 1.3, December 6, 2011. Program on Information Justice and Intellectual Property, American University Washington College of Law, at 3.
28. Gleeson D, Moir H, Lopert R. Costs to Australian taxpayers of pharmaceutical monopolies and proposals to extend them in the Trans-Pacific Partnership Agreement. *Med J Aust*. 2015;202:306-308.
29. World Health Organization. United States of America [Internet]. http://www.who.int/countries/usa/en/. Published October 19, 2016.
30. OECD Indicators. Research and development in the pharmaceutical sector. *Health Glance*. 2015;188-189.
31. Phrma.org. About PhRMA. PhRMA [Internet]. http://www.phrma.org/about. Accessed October 19, 2016.
32. PhRMA. PhRMA urges President Obama to secure an ambitious Trans-Pacific Partnership Agreement. http://www.phrma.org/media/releases/phrma-urges-president-obama-secure-ambitious-trans-pacific-partnership-agreement#sthash.3cUGSZjJ.dpuf [Internet]. http://www.phrma.org/media/releases/phrma-urges-president-obama-secure-ambitious-trans-pacific-partnership-agreement. Published 2012.
33. Policymed.com. Prescription Drug Sales 2009 - IMS Data - Policy and Medicine [Internet]. http://www.policymed.com/2010/04/prescription-drug-sales-2009—ims-data.html. Published 2010. Accessed October 19, 2016.
34. Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. *Health Aff*. 2012;31:2286-2294.
35. Ehrlich & Fenster: Patent & Trademark Attorneys. The Novartis decision: "evergreening" and the future of Generics [Internet]. http://www.ipatent.co.il/the-novartis-decision-evergreening-and-the-future-of-generics/. Published 2013.
36. Rajagopal D. EU, Australia, Canada may follow India's Patent Law. India times [Internet]. http://articles.economictimes.indiatimes.com/2013-04-04/news/38278712_1_patent-act-patent-protection-patent-quality. Published 2013. Accessed April 19, 2016.
37. Fda.gov. PDUFA Performance Reports [Internet]. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm2007449.htm. Accessed October 19, 2016.
38. Food and Drug Administration. FY 2014 Performance Report to Congress for the Prescription Drug User Fee Act [Internet]. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/UCM440181.pdf. Published 2014.
39. Harris T, Nicol D, Gruen N. Pharmaceutical Patents Review Report, Canberra, 2013. https://www.ipaustralia.gov.au/sites/g/files/net856/f/2013-05-27_ppr_final_report.pdf.
40. Harvey EB. Encouragement of New Clinical Drug Development: The Role of Data Exclusivity [Internet]. Whole Health Organisation 2000. www.who.int/intellectualproperty/topics/ip/en/DataExclusivity_2000.pdf. Accessed October 21, 2016.
41. Kilic B, Pine C. Inside views: decision time on biologics exclusivity: eight years is no compromise [Internet]. Intellectual Property Watch; 2015. http://www.ip-watch.org/2015/07/27/decision-time-on-biologics-exclusivity-eight-years-is-no-compromise/.
42. *Health at a Glance: Asia/Pacific 2012*. Paris: OECD Publishing; 2012. http://www.oecd-ilibrary.org/docserver/download/8112131e.pdf?expires=1461030060&id=id&accname=guest&checksum=70031FDBE9DFA0A17526CD07ED52979D.
43. All costs, no benefits: How TRIPS-plus intellectual property rules in the US-Jordan FTA affect access to medicines [Internet]. Oxfam Briefing Paper; 2007. https://www.oxfam.org/sites/www.oxfam.org/files/all%20costs,%20no%20benefits.pdf. Accessed April 19, 2016.
44. Behind the Numbers. The TPP and the cost of drugs [Internet]. http://behindthenumbers.ca/2015/10/09/the-tpp-and-the-cost-of-drugs/. Published 2015. Accessed October 21, 2016.
45. Lexology.com. Patent linkage in Asian countries compared to the US | Lexology [Internet]. http://www.lexology.com/library/detail.aspx?g=73ee9ee5-1873-457e-b24f-8af6e96721ff. Published 2016. Accessed October 21, 2016.
46. Hirono K, Haigh F, Gleeson D, Harris P, Thow AM. Negotiating healthy trade in Australia: health impact assessment of the proposed Trans-Pacific Partnership Agreement. Liverpool, NSW: Centre for Health Equity Training Research and Evaluation, part of the Centre for Primary Healthcare and Equity, Faculty of Medicine, UNSW Australia, 2015.
47. Thow AM, Gleeson DH, Friel S. What doctors should know about the Trans-Pacific Partnership Agreement. *Med J Aust*. 2015;202:165-166.
48. Pacific Bridge Medical. Reimbursement for Pharmaceuticals in Asia [Internet]. http://www.pacificbridgemedical.com/regulatory-services/pharmaceutical/reimbursement/. Published 2014. Accessed October 21, 2016.
49. Ngorsuraches S, Meng W, Kim B, Kulsomboon V. Drug reimbursement decision-making in Thailand, China, and South Korea. *Value Health*. 2012;15:S120-S125.
50. Holloway KA. Thailand: drug policy and use of pharmaceuticals in healthcare delivery. New Delhi: World Health Organization, Regional Office for South East Asia; 2012.
51. Lee KS, Khan TM, Ming LC. Review of data exclusivity provisions in the Trans-Pacific Partnership agreement. *Res Social Adm Pharm*. 2016;12:545-547.
52. Lee KS, Khan TM, Ming LC. Impact of the Trans-Pacific Partnership Agreement on cost of medicine. *Res Social Adm Pharm*. 2016;12:660-661.