CPhI Pharma Insights

UBM

Pharma's year of accelerated innovation & convergence

Industry Expert Panel Submissions

CPhI Annual Industry Report 2018

Released at CPhI Worldwide, October (9-11), 2018 in Madrid

CPhI worldwide

P-mec InnoPack icse FDF

www.cphi.com

bio LIVE

CPhI Pharma Insights

UBM

Part 2.

The impact of global regulation and convergence

PANEL MEMBER
Dilip Shah, CEO, Vision Consulting Group and Secretary General, Indian Pharmaceutical Alliance

IPRs in Trade Agreements & Access to Medicines

5-year trend summary

- Global trend towards patent term restoration/extension, e.g. Regional Comprehensive Economic Partnership (RCEP) text seeks to redefine protection period to 20 years from the *date of marketing approval*.
- 'Patent linkage' under Comprehensive and Progressive Trans-Pacific Partnership Agreement (CPTPP) will require [generic company] to gain consent from patent holder prior to use of data in (generic) marketing approval.
- CETA between the EU and Canada has similar patent restoration as does EU-Japan economic partnership agreement.
- The net result of these patent regulations is that patients may need to wait 5-10 years longer for access to generic medicine.
- This will significantly increase the overall cost of healthcare in developed and developing countries by as much as $100 Bn over the next five 5 years[1].
- Unintended consequences: In the medium-term, the pharma industry will likely face a sizeable backlash from the government, health activists, and wider society that may see a fundamental reform of how companies are reimbursed for innovative medicines globally.

Introduction

The new trade regime unleashed by President Trump has heightened trade tensions. The two major trading partners, the US and the EU, are at loggerheads. Trump has frequently attacked the EU for alleged unfair trading practices. His Administration's *Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs* has highlighted "foreign governments free-riding off of American investment in innovations". His focus is on "addressing price disparities in the international market", particularly among the countries that are part of the Organization for Economic Cooperation and Development (OECD). his blueprint states that "U.S. consumer and tax payers generally pay more for brand drugs than consumers do and tax payers in other OECD countries. In effect, other countries are not paying an appropriate share of the necessary research and development to bring innovative drugs to the market and are instead free riding off U.S. consumers and tax payers"[2].

UN Declaration on TB:

As is evident from the fate of UN Declaration on TB, the barriers to access will grow because of many country's reluctance of adding new fronts of conflict with the US. Thus, even without a formal bilateral treaty, the new trade regime unleashed by the US is having its impact on the access to medicines. The draft text of the Declaration[3] shows that it is stripped of the language about the use of TRIPs flexibilities to reduce drug prices under pressure from the US.

Special 301 Report:

The 2018 Special 301 Report released in April 2018 had already indicated a top priority of the Trump Administration "to use all possible sources of leverage to encourage other countries to open their markets to U.S. exports of goods and services, and provide adequate and effective protection and enforcement of U.S. intellectual property (IP) rights"[4]. The report classified Canada, China, Colombia, India, Indonesia and Russia on the Priority Watch List among a list of 12 countries. Their folly:

China
Trade secret theft, online piracy and counterfeiting, high-volume manufacture and export of counterfeit goods, technology transfer requirements imposed as a condition to access the Chinese market, the mandatory application of adverse terms to foreign IP licensors, and IP-ownership and research and development localization requirements.

Canada
The only G-7 country identified in the Special 301 Report. Its downgrade to Priority Watch List reflects a failure to resolve key longstanding deficiencies in protection and enforcement of IP. Counterfeit, pirated goods, weak patent and pricing environment.

India
For lack of sufficient measurable improvements to its IP framework include those which make it difficult for innovators to receive and maintain patents in India. An outdated and insufficient trade secrets legal framework, skepticism about whether India is serious about pursuing pro-innovator and creativity growth policies.

Colombia
Lack of meaningful progress warrants its elevation to the Priority Watch List.

One can go on listing many countries. The common refrain among all of them is "inadequate" IP protection and enforcement. The USTR action on these observations by itself is sufficient to create barriers to access in developed as well as developing economies. The US has been continuously trying to distance countries from any reference to the TRIPs flexibilities: be it Special 301, UN Statement, World Health Assembly or any other forum.

It is against this backdrop that the new trade agreements are taking shape. A preview of some of the key trade agreements indicate hardening of stance on the intellectual property rights (IPRs). This article examines a few of them (CPTPP, RCEP, CETA, EU-JAPAN) to understand how access to medicines will be impacted. The examination is limited to five areas, namely, patent term extension, patent linkage, border measures, protection of undisclosed test data, and use of TRIPs flexibilities for compulsory licensing.

Trade Agreements:

Comprehensive and Progressive Trans-Pacific Partnership Agreement (CPTPP):

The countries have agreed to suspend several IP obligations negotiated earlier under the Trans-Pacific Partnership (TPP). However, there are measures which would have profound impact on the access to medicines. These are:

- **Patent Linkage:** The patentee will be notified of anyone seeking to rely on that drug's clinical trial data prior to granting marketing approval. The agreement provides for adoption of a system that precludes the issuance of marketing approval to a third person, unless consented by the patent holder.
- **Border Measures:** Empowering competent authorities to initiate border measures ex officio[5] with respect to goods in transit that are suspected of being counterfeit trademark goods or pirated copyright goods.
- **IP – An Asset in the Investment Chapter:** Enabling private investors to have the right to use the Investor-State Dispute Settlement (ISDS) mechanism to interpret the IP chapter of the CPTPP and also the TRIPs Agreement.

Regional Comprehensive Economic Partnership (RCEP):

- **Patent Term Restoration:** The RCEP text seeks to redefine the protection period as 20 years from the date of marketing approval. The TRIPs Agreement grants protection of 20 years from the patent filing date. Thus, RCEP proposal could end up granting patent monopoly for more than 30 years.
- **Data Exclusivity:** The RCEP seeks inclusion of Data Exclusivity provision over and above Patent Term Restoration. This would extend monopoly for innovators and delay the launch of generics.
- **TRIPs Plus Enforcement:** It provides for disproportionate damages. It includes any measure of value (lost profits, sales) that the right holder may provide to the judicial authority. It creates obligation on an alleged infringer to provide information about the origin and distribution network of the infringing goods, putting onerous responsibility on a legitimate generic manufacturer.
- **Border Measures:** Border Measures empowers customs authorities to seize goods suspected of infringing patent or trade mark, without the need for a complaint by the rights holder. The TRIPs Agreement empowers competent judicial authorities and not customs officials and also provides for exception in case of goods in transit.
- **IP – An Asset in the Investment Chapter:** The RCEP Agreement may include IP as an asset in its Investment Chapter. It will enable private investors to use the Investor-State Dispute Settlement (ISDS) mechanism to interpret the IP Chapter in RCEP as well as the TRIPs Agreement. There is no such provision in the TRIPs Agreement.

Canada-EU Comprehensive Economic and Trade Agreement (CETA):

- **Patent Term Restoration/Extension:** CETA requires the parties to provide a period of "sui generis" protection to pharmaceutical patents to cover the period between the filing date of the patent application and the date on which the pharmaceutical product was granted authorization to enter the market. This sui generis protection confers the same rights as conferred by the patent and is subject to the same limitations and obligations. It is essentially a patent term extension or restoration for some of the time lost between the filing date of the patent application and the date when the pharmaceutical product was granted market authorization. Though the agreement prescribes certain limitations and exceptions, this provision will allow extended period of patent protection, denying access to affordable generics.
- **Patent Linkage:** CETA provides a "patent linkage" mechanism. Thus, marketing authorization for a generic version is linked to the patent status, thereby denying access to affordable generics.
- **Protection of Undisclosed Test Data:** The Agreement provides six to eight years of protection against generic entry. The only exception is obtaining approval/ authorization from the originator of the data, which rarely works. This clearly goes much beyond TRIPs Agreement and could delay entry of generics beyond expiry of patent.
- **Border Measures:** The CETA provides for suspension or detainment of goods in transit on mere suspicion of infringement of some form of IPRs. This could be done suo moto by the "competent authorities" or on a request of the right holder.

EU-Japan Economic Partnership Agreement:

- **Extension of the Period of Protection for a Patent:** The Agreement provides for "compensatory term of protection" to cover the time taken for marketing authorization. The compensatory term being limited by statute to five years, the extension will deny entry of generic by the extended protection period.
- **Border Measures:** A provision very similar to the CETA ensures suspension or detainment of goods in transit on mere suspicion of infringement of an IPR. This could be done suo moto by the "competent authorities" or on a request of the right holder.

Other Recent Developments:

- Among other developments that would have major bearing on the access to medicines are the outcomes of EU-Mexico negotiations and the NAFTA. The EU-Mexico Agreement in making seems to suggest that it will have "high standards of protection and enforcement beyond TRIPs rules". It has identified three areas, namely, patent term extension, data exclusivity, and protection of plants. These would have significant impact not only on the access to medicines for the people of Mexico, but also the US citizens as many manufacturing plants servicing the US market are located in Mexico and will be governed by the provisions of the EU-Mexico treaty. The Agreement also envisages empowering the customs authorities for targeting alleged IPR infringements.

The other major development relates to NAFTA. At the time of writing this article, the Mexican Secretary of Trade with his negotiating team is in Washington DC. The outgoing President Pena Nieto is keen to strike a deal with the US on NAFTA. It is noteworthy that the USTR is negotiating the NAFTA bilaterally with Mexico, leaving Canada on the sidelines. Any further concession by Mexico would leave Canada in a tight spot.

Summing Up:

It thus appears that going forward, patients may have to wait longer for access to affordable generics. The new trade agreements will delay access to generics. In addition, they would result in higher health expenditure of both the developed and the developing countries. This would be a misfortune for the pharmaceutical industry as a whole. An industry that saves lives of people will unwittingly provide further fodder to the civil society, health activists and the governments to tarnish its image.

References

1 This estimate is based on savings from generics in the U.S. reported by Association for Accessible Medicines (AAM).
2 American Patients First, The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs May 2018
3 Released on 24 July 2018.
4 Released by the Office of the United States Trade Representative in April 2018
5 For greater certainty, that ex officio action does not require a formal complaint from a third party or right holder

PANEL MEMBER
Bikash Chatterjee, President and Chief Science Officer, Pharmatech Associates

As Regulatory Philosphies Diverge, the Technology and Innovation Gap Converges Over the Next Decade

Five-year trend summary

- Innovation convergence and science-based approaches will allow for divergent yet integrated regulatory pathways
- China is issuing new guidelines at a feverish pace and will be harmonised with ICH very quickly. The result is that over the next two to three years poorer quality manufacturers will drop out of the market and China's manufacturers will look to compete in international markets as well as domestic
- Over the next five years big data will catalyse drug discovery with R&D leading to quicker advancement of more targeted therapies
- The future will be constructed on science-based regulatory frameworks – for example, with process validation done for individual patients, not batches. CAR-T and NGS have opened up the a regulatory pathways for even 3-D bioprinting of organs to follow

Introduction

It is difficult to remember a time when we have seen such a rapid escalation of groundbreaking technology and science in our industry. The impact of these advancements would have been far less had they been restricted to academia and research. However, the leap to industry was made deftly, within a decade, which in our industry is light speed, fueled partially by a harmonized global shift toward a more scientific-based, rather than a documentation-intensive, compliance and regulatory philosophy.

The International Committee on Harmonization (ICH) has been a huge catalyst for change within our industry at a technical and drug development level, harnessing and coalescing best practices from Europe, Japan, and the U.S. to establish a suite of guidance documents that are universally recognized for their balanced scientific rigor by global regulatory authorities. Combine this with the propagation of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), whose charter is the establishment of harmonized Good Manufacturing Practices (GMPs), and it's easy to see why there has been so much movement in the field of quality to elevate the minimum standards and ensure safe and efficacious drugs on a global basis. Hand in hand with this initiative

is the long-term potential of access to the major markets including the U.S. and Europe if each qualifying nation chose to invest in meeting these higher regulatory standards.

Beyond access to these markets, regulatory authorities also saw an opportunity to conduct international inspections in a more efficient way. Under the Food and Drug Administration Safety and Innovation Act, enacted in 2012, the FDA has the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determines those authorities can consistently conduct inspections that met U.S. requirements. The FDA and the EU have collaborated since May 2014 to evaluate the way each inspects drug manufacturers and to assess the risk and benefits of mutual recognition of drug inspections. To date, 15 countries have been qualified under this program and the U.S. looks to complete its capability assessment of all EU inspectorates by July 2019.

The second largest market in the world, China, is issuing new guidances at a feverish pace, delivering new updates on almost a monthly basis as they strive to establish standards mirroring ICH. The escalation to a higher standard has had a positive effect in the local and global marketplace in that less reputable manufacturers in China are finding it more difficult to get a foothold. However, the rapid evolution of the compliance and regulatory framework challenges ethical drug manufacturers and, in some cases, even regulators, to keep pace with the new regulations. However, the commitment to a higher standard is laudable and will result in a market that is better poised to compete in the world market in addition to the Chinese market.

Data is King

The debate about clinical trial data transparency has raged for decades with advocates crying for greater transparency to avoid bias in published data. In 2015, the World Health Organization (WHO) published a statement that updates and expands their 2005 position on clinical trials registration and reaffirms the ethical imperative to report the results of all clinical trials. Historically, approximately only 9 percent of the data generated as part of the drug development process is submitted as part of a regulatory filing. The EU was the first major market to attempt to legislate clinical data transparency, sparked by a 2013 report from the European Parliament (EP) stating that one of the major problems with the regulation and performance of clinical trials in Europe is the lack of transparency of results. The report concluded that this lack of transparency has reduced public trust in trials and their findings. The EU is looking to issue its updated clinical trial regulation by October 2018 and will harmonize the conduct of clinical trials in the EU while establishing new transparency requirements for the disclosure of clinical trial information, which will require a portal for the publication of clinical trial data within 60 days of a marketing authorization decision.

The U.S. had ignored the issue of data transparency until this year when the FDA launched a clinical data transparency pilot program aimed at making Clinical Study Reports (CSR) public upon approval. The pilot program begins with the recent approval of nine new drugs. So what was once a key point of divergence in philosophy has converged to address the rising need for data objectivity through transparency.

Unfortunately, the U.S. and Europe have diverged when it comes to the issue of data privacy. The EU has enacted the strictest data privacy regulation in the world with its Good Data Protection Regulation (GDPR), which went into effect in May 2018. This sweeping legislation was immediately enforceable by all EU member states and carries penalties starting at 20 million Euros for violations. The regulation advocates the creation of a Data Protection Officer (DPO) to monitor, enforce, and report on compliance with the tenets of the regulation including such rights as "the right to be forgotten" and the "right to consent" that must be absolutely enforced across the entire information chain, including third party entities.

The U.S. has not moved so aggressively. Previously the U.S. and the EU had regulated information privacy via the International Safe Harbor Privacy Principles developed between 1998-2000 but the European Court of Justice declared this regulation invalid in October 2015. The U.S. put in place the EU–U.S. Privacy Shield as a replacement but this again was found to be very weak as it

pertained to the deletion and collection of data. Complicating matters is the current presidential administration position that U.S. privacy considerations will be extended only to U.S. citizens and residents. Clarity is not likely to come any time soon as it relates to privacy in the U.S. The Supreme Court has ruled in favor of data privacy several times regarding the government's ability to obtain data, but as technology continues to evolve look for these principles to be further tested.

Despite these disparate positions we can look for the intelligent gathering and application of data to transform the healthcare landscape

Artificial Intelligence

Few developments have received as much hype as artificial intelligence (AI). AI is often used to describe anything a computer can do as well as a human often as a byproduct of what is called "machine learning." However, the truth is that in medicine many of the current applications of AI rely upon human developed algorithms to do the analysis. Machine learning by contrast utilizes neural networks that are intended to mimic the human brain and its activity. Machine learning can uncover new and innovative approaches to problem solving and do not rely on programmer algorithms. One of the most innovative ways AI is being used to today is to understand colloquial human speech. These applications are being used to provide medical diagnoses and recommend treatment for remote regions of the world where a physician is not available. Combining this capability with machine learning could provide physicians with insight about likely future health events before they occur and recommend potential courses of treatment.

Big Data

Big Data Analytics is the process of examining large and varied data sets to uncover hidden patterns, unknown correlations, market trends, customer preferences and other useful information that can help organizations make better-informed business decisions. Clinical data derived during the drug development process is one of the richest repositories for hidden drug opportunities. Big Data is slowly gaining traction within the life sciences. Big data allows large amounts of data to be analyzed to provide descriptive, predictive diagnostic or prescriptive analytics. Coupled with open source portals such as www.PatientsLikeMe.com where patients can share their health data, the hope is that researchers and patients alike can influence the treatment of their disease and improve their overall outcomes. Intelligent devices, embedded within drug delivery technology, smart pills, lifestyle solutions and diagnostic technology will fuel a renaissance in disease management insight. The science and tools behind Big Data are well defined and the potential for catalyzing discovery and R&D is limitless at this point.

21st Century Cures Act

One of the most significant U.S. legislations impacting the FDA's approach to drug and medical device approval has been the 21st Century Cures Act (Cures Act). The Cures Act was signed into law on December 13, 2016, and is designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently. The law builds on the FDA's ongoing work to incorporate the perspectives of patients into the development of drugs, biological products, and devices in the FDA's decision-making process. The Cures Act enhances our ability to modernize clinical trial designs and clinical outcome assessments, which in turn,

will hopefully translate into speedier development and review of novel medical products. It also established new expedited product development programs, including:

- The Regenerative Medicine Advanced Therapy, or RMAT, that offers a new expedited option for certain eligible biologics products
- The Breakthrough Devices program, designed to speed the review of certain innovative medical devices

The Cures Act... is designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently.

Most notable was the establishment of a regulatory evaluation and approval path, based upon real world evidence for medical devices[1]. The FDA issued a guidance describing the predicate requirements for pursuing this path and to date the FDA has approved several systems under this regulatory guidance.

The RMAT designation has expedited the approval of many therapies utilizing human tissue, regulating them under Section 351 of the Public Health Service Act, which is considerably less stringent than section 361 for pharmaceutical drug therapies. Many of these products are approved for their mode of action, such as anti-inflammatory or anti-scarring, as opposed to treating a specific disease state. This has broadly introduced such healthcare solutions as a standard of care in for many ailments. The FDA has followed up this legislation with a new guidance regarding Human Tissue that is minimally manipulated, requiring the use of the Biologic License Application (BLA) regulatory pathway to stay on the market. These disease therapies are not going away: they will make the transition to a biologic drug therapy as they present the potential for building on the rapidly growing regenerative medicine marketplace.

EU Medical Device Regulations

The EU has moved in the other direction however, from the U.S. The new EU Medical Device regulations (MDR) have made significant changes that will take full effect by 2020. The MDR will change the way medical device manufacturers bring their devices to the European market, and how they maintain compliance throughout the product's life cycle. The regulation actually modifies the classification of some devices that have been CE marked and approved. The new regulation requires manufacturers to address the additional requirements prior to the 2020 deadline or face having the products withdrawn from the market! Under the MDR, there is a much greater emphasis on more thorough reviews by Notified Bodies to confirm manufacturers are fully compliant and devices are fully supported by adequate data and technical documentation. The MDR's requirements for acceptable clinical evidence are stricter as well so it is very likely you will need new data and updated, robust clinical evaluations for most legacy devices.

Science-Based Regulatory Framework

While there are divergences between the U.S. and EU's regulatory philosophy, they both have their foundation in a desire for risk-based control derived from scientific insight. Next Generation Gene Sequencing (NGS), which was originally approved under a 510K waiver has evolved to where it can meet the requirements of a Pre-Market Authorization as a Companion Diagnostic, allowing physicians the ability to pinpoint the genetic modifications that drive the disease state, and apply a drug therapy specifically designed to target that anomaly. To do so required the FDA to deal with a number of paradigm-shifting issues. Huge data sets are generated as part of the NGS process that is known to be only 97% accurate. Data integrity of 400,000 data point per run had to be developed and explained to the FDA. The assay used control regents with 100-200 oligonucleotide sequences blended together

requiring the agency to shift its expectations of process validation. The same can be said for the latest Chimeric Antigen Response-T Cell (CAR-T) therapies. These CAR-T therapies are personalized to an individual and again required shifting the FDA's expectation regarding process validation as only one batch is made per patient and each batch is unique to that patient.

In the future we will have additive manufacturing being routinely used for medical devices and 3-D bioprinting systems that will be able to build replacement organs that are fully biocompatible with any prospective patient. These technologies are in development today. CRISPR-Cas9 has allowed us to customize DNA sequences and even allowed us to embed technology that replicates them. A team of scientists in 2017 embedded a video in bacteria DNA[2]. The scientific tools available today provide the opportunity for unparalleled insight and understanding that will translate into lower regulatory risk.

Next Generation Gene Sequencing allows physicians the ability to pinpoint the genetic modifications that drive the disease state, and apply a drug therapy specifically designed to target that anomaly.

Conclusion

The foundation for the next generation of drug therapies, devices and diagnostics will rely heavily on data and analytics to drive insight and understanding. The regulatory philosophies of the U.S, and Europe are not completely aligned in their approach to fostering innovation while ensuring patient safety. We have, however, seen groundbreaking drug therapies and diagnostics approved in the last five years that position regulatory bodies to embrace these new innovations. Whether risk is managed via enhanced control and oversight, such as with the EUs GDPR legislation, or is a by-product of intelligently gathered real-world data, as provided under the US's 21st Century Cures Act, the regulatory evaluation in each framework required to evaluate these new technologies will be grounded in today's scientific tools and analytic techniques.

References

1 FDA Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

2 Who needs film when you can store a movie in bacteria DNA? LA Times, http://www.latimes.com/science/sciencenow/la-sci-sn-dna-movie-20170712-story.html