INTERNATIONAL LAW ASSOCIATION

JOHANNESBURG CONFERENCE 2016

GLOBAL HEALTH LAW

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FIRST REPORT OF THE COMMITTEE

by Prof. Frederick Abbott and Prof. Brigit Toebes (Part I-IV & VIII), Ms Ellen 't Hoen LLM (Part IV), Dr Xavier Seuba (Parts V & VII) and Dr Ruth Atherton, Dr Helène De Pooter and Prof. Gian Luca Burci (Part VI)

I. INTRODUCTION

The Global Health Law Committee (GHLC) was established in October 2014. Since that date, the GHLC has actively pursued its mandate toward the progressive development of international law relating to health, including to identify and confirm norms that are relevant to the promotion and protection of public health, and to develop proposals for improving the existing legal and policy framework The GHLC held its first meeting in February 2015 in connection with a substantive program on Global Health Security Challenges that it co-organized in Geneva, and its second meeting in March 2016 in London in connection with the UN Secretary General's High Level Panel on Access to Medicines hearings and dialogue.

In October 2015, the GHLC settled upon four tracks for its short to medium-term work program. These are:

1. Legal issues surrounding access to research materials, including: (a) biological materials, including virus sharing; (b) clinical research surrounding potential outbreaks, e.g., Ebola.

2. Legal issues surrounding access to medicines deemed "essential" by WHO.

3. Legal issues surrounding tensions between trade/investment agreements and global public health, including (but not limited to) IP issues addressed in the tobacco cases, Canada patent case and data protection cases; the relationship between ICH guidelines and the TBT Agreement, and; the general relationship between international law and innovation.

4. State obligations in the field of health and links with human rights law, including in the fields of non-communicable diseases (including tobacco) and also (progressively) sustainable development (e.g., obligations to assure clean air and water, and to address climate change).

As can be seen from this report, the GHLC has made strong progress in the areas of its work program.

Contrary to, for example, international trade law, international environmental law and international humanitarian law, global health law is not a well-developed field. There is an urgent need for counterbalancing such interests as international trade, industry and commerce against the protection of the health of individuals and populations worldwide. International standard-setting instruments are, increasingly, successfully employed by international organisations, state authorities and civil society organisations to achieve equity in health. For instance the Framework Convention on Tobacco Control (FCTC) has played a key role in advancing tobacco control at the

domestic level.[1] In terms of its sources, global health law brings together international standard-setting instruments adopted in the context of the WHO and under human rights law, while health-related legal rules, norms and other (non-binding) standards can also be found in several other branches of international law, including under international humanitarian and environmental laws, and in medical ethics and patients' rights.

The human 'right to the highest attainable standard of health' (the 'right to health') features as a key standard in global health law, as it places the emphasis on the protection of individual health worldwide, and because it emphasises the need to strive for equity in health. The right to health is acknowledged in, *inter alia*, Article 12 of the UN International Covenant on Economic, Social and Cultural Rights (the ICESCR).[2] In 2000, the Committee on Economic, Social and Cultural Rights (CESCR) adopted General Comment 14, an explanatory document to the right to health in Article 12 of the ICESCR.[3] Importantly, General Comment 14 recognises that the right to health is not a right to be healthy, but rather a broad human right extending not only to access to healthcare services but also to the underlying determinants of health, including an access to safe and potable water and adequate sanitation, healthy occupational and environmental conditions, and access to health-related education and information.[4] A further important component of General Comment 14 concerns the identification of a set of guiding principles that apply with respect to all health-related services: States are to guarantee the availability, accessibility, acceptability and quality of health facilities (the so-called 'AAAQ').[5] [6] Further, General Comment 14 defines a set of legal state obligations to 'respect, protect and fulfil' human rights.[7] Lastly, General Comment 14 defines a set of legal core obligations, minimum essential levels of health services which States have to guarantee 'at the very least'.[8] These principles and guidelines inspire many of the topics addressed by this Committee, including the topics addressed in this report.

II. Global Health Security Challenges: towards strengthening global governance

On February 19, 2015, a group of experts in law, public health, security and medicines, met in Geneva under the auspices of the GHLC and the Global Health Program of the Graduate Institute|Geneva. The group assembled to discuss the global response to the Ebola outbreak of 2014-2015 in West Africa, and the work that needs to be done in order to improve response to pandemic disease threats. Members of the group were associated with multilateral organizations, academic institutions and nongovernmental organizations (including funders), including those that participated in the response. The meeting was organized as an open-ended sharing of ideas. The participants were acting in their individual capacities, and not as representatives of organizations. This summary is a synthesis of the discussion, and intentionally does not identify individual participants and their contributions.

Several important themes emerged from the day-long meeting.

First, there was a general consensus that the single most effective mechanism to improve prevention of and response to pandemic disease is the strengthening of national health systems, and despite recognition of this by the international community, inadequate systematic attention is being directed to this area. Robust public health systems are needed for the diagnosis and detection of disease outbreaks (i.e. surveillance), and for the implementation of measures in response. The building up of national capacity is called for by the International Health Regulation (IHR), but most countries have not implemented the IHR requirements.

Donor governments appear to have priorities other than building up national health infrastructure. The agencies in donor governments responsible for allocating funds are often economic development agencies that do not see a short-term benefit from investments in public health.

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[1] Adopted by the World Health Assembly on 21 May 2003, and entered into force on 27 February 2005.
[2] Other right to health provisions can be found, *inter alia*, in Article 12 of the Convention on the Elimination of all forms of Discrimination against Women (CEDAW, 1979) and Article 24 of the Convention of the Rights of the Child (CRC, 1989) and Article 25 Convention on the Rights of Persons with Disabilities (CRPD, 2006).
[3] Committee on Economic, Social and Cultural Rights, *The Right to the Highest Attainable Standard of Health*, UN General Comment No 14 (2000), UN Doc E/C12/200/4 (11 August 2000). While this document is not legally binding and can thus be characterised as a 'soft law' instrument, it is considered authoritative by many scholars and practitioners from the field
[4] General Comment 14 *supra* note 3.
[5] Ibid.
[6] Ibid. Accessibility has four overlapping dimensions: non-discrimination, physical accessibility, economic accessibility (affordability) and information accessibility.
[7] Ibid.
[8] Ibid. These essential service also include the right to essential medicines.

The rules governing international procurement organizations may allow flexibility for using a percentage of funding to build up local capacity, but such funding is not sufficient to materially address the gaps. Moreover, the problem of health system capacity is also a matter of training the necessary personnel, and this may be as difficult as finding the funding for such an endeavor.

Insufficient attention is paid to encouraging private sector support and investment in building up national health systems in developing countries. Breakdowns in health systems may have significant adverse consequences for enterprise interests, and investments in preventing such breakdowns should be encouraged as prudent business planning.

The question was raised whether a human-rights based response to pandemics and other global health security threats may be useful.

As a consequence of weak national health systems in fragile countries, when urgent circumstances have subsided the transition from donor/international organization pandemic response to the national and local government control can introduce elements of instability. In some cases, dangerous public order situations have arisen.

Some expressed the view that the Ebola crisis may provide impetus for directing resources towards building up national health system capacity, but that this momentum will dissipate as it typically does following an immediate crisis.

Second, there are a number of important issues to address in relation to vaccines, treatments and diagnostics necessary to prevent and control pandemic disease. The potential for outbreak appears to be increasing as pathogens are more frequently jumping the animal to human barrier.

It is important to accelerate the potential development of new vaccines and treatments, and this includes streamlining clinical testing and regulatory evaluation processes. But, in all cases, a baseline of health security must be followed as experience indicates that prospective treatments may be more dangerous than even urgent circumstances would warrant. Vaccines and treatments to address pandemics are often developed with substantial government funding, and there is some question whether high prices for the resulting products are justified. While acknowledging that producers may have opportunity costs for manufacturing facilities, it nevertheless should be possible to arrange purchases on a cost plus basis. Determining cost can be difficult, and establishing advance purchase commitment pricing similarly can be difficult, but these are not insurmountable obstacles. Recognizing that there are multiple mechanisms for funding and development, it is important that vaccines and treatments be priced in a way that permits their distribution to those requiring them.

Point-of-care diagnostics are a very important element of pandemic response, and more attention should be paid to development and distribution of such diagnostics.

Cooperation among national and regional drug regulators has been good, and there does not appear to be substantial need for a new organization or legal mechanism to make that cooperation work. WHO, in particular, is suffering from a lack of adequate financial support for its drug regulatory unit, and faces a shortfall of personnel. This is a serious immediate concern.

Lack of transparency by developers of vaccines and treatments poses problems for R&D efforts, as well as regulators. Some private-sector companies have begun providing more information. National security interests may be playing a role in the lack of transparency, and it is difficult to address this aspect.

There was substantial attention paid to the potential role of convalescent blood plasma (i.e. from patients who had recovered from disease) which appeared to be very promising in the treatment of Ebola. Convalescent blood has an important advantage in not requiring regulatory approval (or clinical testing) because virtually all blood donors have recovered from some diseases, and use of blood and plasma from such donors is routine. With respect to outbreak of almost any pathogen, convalescent blood may be a logical rapid choice for treatment pending other developments.

The timeline between identification of a new pathogen outbreak and development of a vaccine or treatment needs to be accelerated. While substantial advances have been made in modeling and use of pre-existing platforms, there will still remain a period during which effective treatments are not available.

Drugs, vaccines and diagnostics to address pandemic disease share characteristics with those for “neglected diseases”, but with the distinction of being needed to prevent outbreaks in higher income countries. Therefore, funding is made available by high income countries and their enterprises to address pandemics. However,

because of the absence of the typical demand pull for treatments, this is an area in which alternative models of R&D may be usefully explored. If such alternative models can be developed and implemented, they may show the way toward new models for more conventional infectious and noncommunicable diseases.

Third, there was an evident lack of coordinated response to the Ebola outbreak. Subsequently, the role of WHO as lead for health emergency response has been confirmed. But, it is worrisome that governments are not inclined to provide significant financial support to WHO consistent with the urgency evidenced by the Ebola Resolution. There is a strong current of thought that major prospective funding governments are not anxious to relinquish authority to WHO in addressing crises.

It was unusual for a nongovernmental organization (MSF) to request military support in terms of personnel and logistics to confront the outbreak in West Africa. However, there was not enough human capacity available to confront the situation, including because a number of the first responders had died from the disease. Money was not the problem. It was human resources.

WHO is not organized to directly act as an emergency responder. It does not have the personnel or resources for that function. Moreover, it is doubtful that member states will be inclined to pay personnel to await a pandemic outbreak.

Communication with the public is an important part of pandemic response. WHO has been paying considerable attention to this area. There is a difficult line between providing adequate warning and triggering potentially excessive reaction. Communications must be very rapid, clear, and accurate, particularly because the public looks to WHO as an authoritative source, and alternative sources may provide unreliable information. The wide adoption of social media communication has heightened the difficulty of messaging during a pandemic outbreak.

The response of the UN Security Council was also unusual, though not necessarily unwelcome because it elevated the profile of pandemic response. That said, the Security Council did not coordinate with WHO, and the establishment of UNMEER effectively bypassed a number of existing UN and other agencies already established to address international emergencies, including of a humanitarian nature. In this regard, the response to the Ebola outbreak appeared to be disorganized and lacking in coordination.

There was largely a consensus against the need for establishing a new international organization to address potential pandemic outbreak. Already there are a proliferation of organizations, and adding another bureaucracy may not improve matters. There are UN agencies mandated to address humanitarian crises, in addition to WHO, and a number of nongovernmental organizations with substantial capacity in this area. What is apparently needed, however, is an improved mechanism for coordination of response. Also, while it is not unusual for military capacity to be used to provide logistical support in response to international emergencies, there should be an understanding about how military forces are used, and how their role differs in relation to civil police forces and customs/border authorities.

A core problem at WHO is the lack of "untied" donor funding. Government donors do not appear to be particularly interested in funding pandemic response. NGOs are acting as first and primary responders, and are also providing large-scale funding to WHO. NGO funders, as government funders, are playing a role in determining the direction of WHO programs. The area of pandemic response cannot be realistically addressed without taking into account the role of non-state actors.

III. GHLC Participation in the UNLP High Level Panel Process

In November 2015, the UN Secretary General appointed a High Level Panel on Access to Medicines (HLP) with a mandate "to review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies." The HLP was called upon to deliver a report to the Secretary General by June 2016. In December 2015, the HLP issued a call for contributions to the global public, with such contributions to address the subject matter of its mandate and, in particular, that "promote research, development, innovation and increase access to medicines, vaccines, diagnostics and related health technologies to improve the health and wellbeing of all, as envisaged by Sustainable Development Goal 3, and the 2030 Agenda for Sustainable Development more broadly." The call for contributions contemplated an accelerated time-line, with contributions due for submission in February, a date that was thereafter extended into March. Recognizing a unique opportunity to make a contribution to the development of international law, the GHLC decided that its members might prepare contributions in response to the HLP's call. Two contributions were submitted to the HLP. As a consequence of the relatively short time-line for preparing and submitting the contributions, the GHLC indicated on those contributions that they did not necessarily reflect the views of all of the Committee

members, and the contributions included identification of their specific authors.[9] Both contributions were selected for presentation at the hearing of the HLP in London on March 9, 2016, which preceded the GHLC meeting held in London on March 11.

At the hearings before the HLP and its Expert Advisory Group (EAG)[10] in London, GHLC Rapporteurs Ellen 't Hoen and Xavier Seuba presented the contributions and responded to questions. Each of the contributions was well received by the hearing panel, [and we await to see whether either or both of the proposals is taken up in the report of the HLP due in June].

The following two sections of this report (IV and V) originated in the context of development of contributions to the HLP. Both address subject matter that had earlier been identified by the GHLC as part of its work program.

IV. LEGAL ISSUES SURROUNDING ACCESS TO ESSENTIAL MEDICINES[11] [12]

This section offers a summary of a GHLC contribution to the HLP, incorporating several proposals regarding access to essential medicines, as amended after the presentation and discussions of the proposals at the hearing of the UN High Level Panel held on 9-10 March in London. The amendments reflect the support of several stakeholders to expand the mandate of the Medicines Patent Pool to include all essential medicines. Substantial additional work is required to develop the proposals in detail. The GHLC proposes to do this after the publication of the report by the UNHLP.

The WHO Essential Medicines Concept and the challenges of ensuring access to new Essential Medicines as a component of the right to health in a post TRIPS era

The right to essential medicines is a key component of the right to health as guaranteed under international human rights law. The most important treaty is the International Covenant on Economic, Social and Cultural Rights (ICESCR, 1966) enshrining the right to health in Article 12. This provision is further interpreted in the non-binding yet authoritative General Comment 14 (2000), which defines the State's legal obligation to provide essential medicines. Other important right to health provisions are contained in the Convention on the Elimination of All Forms of Discrimination Against Women (CEDAW), the Convention on the Rights of the Child (CRC and General Comment 15), and the Convention on Persons with Disabilities (CPD). The WHO Constitution states in its preambular declaration of basic principles "The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition."

According to the WHO, essential medicines are: '[T] hose that satisfy the priority health care needs of the population.... selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness… [and] intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford'.[13] (The term Essential Medicines here refers to medicines included in the WHO Model List of Essential Medicines and national Essential Medicines List.)

The WHO published the first Essential Medicines List (EML) in 1977 and has updated the list every two years. The WHO EML guides countries in the selection and provision of essential medicines. Countries are encouraged to develop their own EML and to implement policies to ensure access to these medicines. Today, more than 150 countries have an EML.[14]

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[9] Stating: "The perspectives in the submission made to the UNHLP may not necessarily reflect the totality of views of each member of the GHLC. It is intended to further public dialogue and the development of needed options. Peter Beyer, as current staff at WHO, has recused himself from this submission."

[10] Prof. Abbott, a member of the EAG, also disclosed his role as co-chair of the GHLC.

[11] Report based on the submission to the UN High Level Panel on Access to Medicines (UNHLP) prepared by Ellen 't Hoen LLM, Prof dr Brigit Toebes, Katrina Perehudoff MSc, LLM, and Prof Frederick M Abbott available here: http://www.unsgaccessmeds.org/inbox/2016/2/22/contributionglobal-health-law-committee-of-the-international-law-association.

[12] Dr. Ruth Atherton has recused herself from this portion of the submission.

[13] http://www.who.int/medicines/services/essmedicines_def/en/ . Accessed February 2016.

[14] Hogerzeil, Hans. "Essential Medicines and Human Rights: What Can They Learn from Each Other?" *Bulletin of the World Health Organization Bull World Health Organ* 84.5 (2006): 371-75. http://www.who.int/bulletin/volumes/84/5/371.pdf. Accessed February 2016.

Access to essential medicines is a key component of the fulfilment of the human right to health. A study of 186 national constitutions shows that 135 (73%) include provisions on health or the right to health. Some constitutions specifically mention access to medicines.[15] The SDGs include achieving Universal Health Coverage (UHC) and emphasise access to essential medicines and vaccines for all.[16]

Essential medicines should be available, accessible, acceptable and of assured quality.[17] Essential medicines policies have traditionally been rooted in policies to encourage the availability of generic medicines. Countries have sought to keep the prices of essential medicines low by excluding them from patentability. The Andean Community, in 1991, adopted a decision providing that "inventions related to pharmaceutical products included in the List of Essential Drugs of the WHO" shall not be patentable.[18]. India excluded medicines from patentability until 2005.[19] This encouraged the development of a generic pharmaceutical industry that has served as the 'pharmacy of the developing world'.[20] When the Uruguay Round of trade negotiations was launched in 1986, 49 of the 98 parties to the Paris Convention excluded pharmaceutical products from patent protection.[21] Countries varied in the periods of protection granted and/or set out conditions that restricted patent holders' rights.[22]

Adoption of the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 1994 diminished the legal space through which the availability of generic medicines might be assured. TRIPS set out minimum standards for the protection of intellectual property rights. Members of the WTO may no longer exclude entire fields of technology, such as medicines, from patentability,[23] and a minimum 20-year patent term is obligatory.[24]

The 19th EML edition (2015) contains several important medicines including for the treatment of cancer, tuberculosis (TB) and hepatitis C (HCV) that are widely patented and highly priced.[25]. The high prices of the new essential medicines illustrate the challenges to access in the post-TRIPS era.[26] When WHO labels a medicine as essential governments must act to ensure availability.

Yet, mandatory patenting of new essential medicines has entrenched price-setting power within the commercial industry, reducing the effective authority of governments. Monopoly pricing routinely precludes wide access. There is an embedded conflict between government obligations under human rights law and obligations under IP law.

Political coherence of States' obligations under international intellectual property treaties and obligations to ensure the human right to health.

The introduction of TRIPS coincided with the emergence of the HIV/AIDS pandemic, which fuelled a global campaign for access to medicines.[27]

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[15] Perehudoff, S. K., Laing, R.O., and Hogerzeil, H. V., "Access to Essential Medicines in National Constitutions." *Bulletin of the World Health Organization Bull. World Health Organ*. 88.11 (2010): 800. http://www.who.int/medicines/areas/human_rights/Perehudoff_report_constitutions_2008.pdf. Accessed January 2016.
[16] UN Sustainable Development Goal 3.8 and 3.b. https://sustainabledevelopment.un.org/sdg3 . Accessed February 2016.
[17] 'AAAQ', see General Comment 14, para 12.
[18] See Article 7(e) of Decision 344, Common Regime on Industrial Property. http://www.sice.oas.org/trade/JUNAC/decisiones/DEC344e.asp . Accessed February 2016.
[19] Indian Patents Act 1970.
[20] SciDevNet. http://www.scidev.net/global/medicine/analysis-blog/private-sector-india-generic-drug-wars.html . Accessed February 2016.
[21] WIPO, Negotiating Group on Trade-Related Aspects of Intellectual Property Rights, including Trade in Counterfeit Goods, "Existence, scope and form of generally internationally accepted and applied standards/norms for the protection of intellectual property," *Note prepared by the International Bureau of WIPO*, Revision 15 September 1988 (Original published 5 May 1988), MTN.GNG/NG11/W/24/Rev.1.
[22] Graham Dutfield, *Intellectual Property Rights and the life science industries: A Twentieth Century History (Globalisation and Law)*, Hampshire, England. Ashgate Publishing: July 2003.
[23] TRIPS Article 27. Least Developing Countries can delay their obligation under TRIPS with regards to granting and enforcing pharmaceutical patents until at least 2033. See: https://www.wto.org/english/tratop_e/trips_e/ldc_e.htm . Accessed February 2016.
[24] TRIPS Article 33.
[25] http://who.int/mediacentre/news/releases/2015/new-essential-medicines-list/en/
[26] Gray, Andy L., Wirtz, Veronika J., 't Hoen, Ellen F.M., Reich, Michael R., and Hogerzeil, Hans V., "Essential Medicines Are Still Essential." *The Lancet* 386.10004 (2015): 1601-603.
[27] 't Hoen, Ellen., Berger, Jonathan., Calmy, Alexandra., Moon, Suerie., "Driving a Decade of Change: HIV/AIDS, Patents and Access to Medicines for All." Journal of the International AIDS Society J Int AIDS Soc 14.1 (2011): 15

The global mobilization around HIV focussed on a number of flexibilities contained in TRIPS to bring down the price of medicines. These flexibilities include compulsory licensing (CL), parallel importation, delay and/or non-enforcement of medicines patenting and regulatory data protection by least developed countries, defining patentability criteria to reward meaningful innovation and prevent 'ever-greening' of patents, and implementing exceptions to patent exclusivity.

In 2001 the WTO adopted the Doha Declaration on TRIPS and Public Health expressly acknowledging these flexibilities and making clear that IP protection must not interfere with the protection of public health[28] *[16]*. Paragraph 4 reads: "*We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all*."

Consistent with the Doha Declaration, developing countries that had ARV patents have widely used TRIPS flexibilities to procure generic ARVs, mostly from India where these products were not patented. In 2010 the Medicines Patent Pool was created to ensure that generic versions of new ARVs continue to be available. Today, first line ARV regimens are available from generic suppliers for US$ 95 – 158,[29] a steep decrease from US$ 10.000 - 15.000 a decade and a half ago. It is estimated that 80% of the people receiving HIV treatment access generic prequalified ARVs. This progress is the result of unprecedented global mobilisation and the absence of medicines product patents in India until 2005.

The use of flexibilities for non-HIV products seems to be more difficult and politically more sensitive. For example when India issued a CL for a cancer medicine it provoked an out-of-cycle review by the US Trade Representative.[30] The MPP has recently expanded its mandate to include HCV and TB, but challenges remain for countries outside the scope of the MPP agreements. For other new essential medicines such regularized access strategies are lacking.

TRIPS-plus requirements (i.e. standards of IP protection higher than those mandated by TRIPS) in regional and bilateral trade agreements roll back much of the positive momentum represented by the Doha Declaration.[31] Investor to State Dispute Settlement (ISDS) mechanisms, often contained in such agreements, are being used by the pharmaceutical industry to contest decisions by national patent offices and courts.[32]

The trend in international norm setting for patents reflects the IP agenda of corporations that seek expansion of their monopoly positions in the market through patents and other market exclusivity mechanism. For example: test data protection rules that prevent the marketing authorisation of generic and biosimilar medicines by a medicines regulatory agency for a certain period of time or marketing exclusivity granted under orphan drug laws.

The progress in access to ARVs has been the result of a unique and unprecedented global mobilisation. Other diseases have not sparked responses at the same scale, which raises the question of how to ensure access to new treatments for hepatitis, tuberculosis (TB), cancer, diabetes and other non-communicable diseases in the face of expanded patent and exclusivity rights. Affordable essential medicines are crucial to the success of UHC, an important target under the SDGs.

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[28] Declaration on the TRIPS Agreement and Public Health. World Trade Organization. WT/MIN(01)/DEC/2. 20 November 2001.

[29] Untangling the Web of antiretroviral price reductions: 17th Edition. Médecins sans Frontières. July 2014. http://www.msfaccess.org/sites/default/files/MSF_UTW_17th_Edition_4_b.pdf . Accessed February 2016.

[30] Médecins sans Frontières (MSF) Access Campaign, "Persistent US Attacks on India's Patent Law & Generic Competition," January 2015, https://www.msfaccess.org/sites/default/files/IP_US-India_Briefing%20Doc_final_2%20pager.pdf . Accessed February 2016.

[31] Sell, Susan K. "TRIPS-plus free trade agreements and access to medicines." *Liverpool law review* 28.1 (2007): 41-75. Preferential trade agreements (PTAs) such as the signed but not yet ratified TPP typically contain reference to the Doha Declaration and its paragraph 4 formula regarding non-interference with measures to protect public health, but do not specifically address how conflicts between newly-negotiated and tighter restrictions on use of pharmaceutical and health technologies, and the Doha principles, will be resolved. There are no clearly defined mechanisms for that, and conflicts are inevitable. Future work of the GHLC may include examination of how references to the Doha Declaration in PTAs can most effectively function in addressing TRIPS-plus requirements.

[32] See: http://www.theglobeandmail.com/report-on-business/international-business/us-business/lilly-ramps-up-nafta-fight-over-loss-of-patents/article13223813/ .Accessed January 2016.

The human right to access to essential medicines – who is responsible for the fulfilment of this right?

Obligations of States parties

States are the primary duty holders under the international human rights treaties. Based on Article 12 ICESCR, they are under a legal obligation to take measures necessary for the prevention, treatment and control of diseases and for creating conditions assuring access to medical services.[33] General Comment 14 explains that States should ensure that medical services, including essential medicines, are available, accessible, acceptable and of good quality ('AAAQ').[34] It identifies access to essential medicines as a legal core obligation of the right to health[35]. According to General Comment 14, the legal core obligation to provide essential medicines is 'non-derogable', which means that non-compliance would result in a *prima facie* violation of the ICESCR.[36] They are also under a legal obligation to ensure that the pharmaceutical industry does not limit people's access to essential medicines (State's 'obligation to protect').[37]

Obligations of the international community of States

States and the international community of States at large are under an obligation to facilitate access to essential medicines in other countries and to provide the necessary aid when required.[38] They are to assist developing countries in realizing their core obligation to provide access to essential medicines to their population.[39] States should prevent third parties, including the pharmaceutical industry, from violating the right to health in other countries.[40] They should ensure that their actions as members of international organizations take due account of the right to health.[41]

Responsibilities of the pharmaceutical industry

The preamble to the Universal Declaration of Human Rights calls on 'every individual and every organ of society' to promote and respect human rights. Similarly General Comment 14 recognizes that the private business sector has responsibilities under the right to health.[42] In line with this it is widely recognized that the pharmaceutical industry carries responsibilities under the right to health.[43] Based on the 'Ruggie Principles' (2008), endorsed by the Human Rights Council in 2011, pharmaceutical companies have the corporate responsibility to respect human rights. This means that they should avoid infringing on the human rights of others and should address the adverse human rights impacts of the activities in which they – or their business relationships – are involved.[44]

Enforcing responsibilities to the human right to health

The tension between IP and human rights is perpetuated by the differences in how these two frameworks are enforced. IP rights enjoy binding enforcement mechanisms at the international level through the WTO Dispute Settlement Mechanism and through ISDS. While both IP and human rights standards are legally enforceable and binding on State parties, the authority of human rights norms is not often recognised within the IP framework. Although WTO dispute settlement no longer insists on a self-contained regime approach, human rights have yet to play a material role. On the other hand, States are held accountable to human rights norms in several authoritative, albeit often non-binding, fora (i.e. CESCR).

Access to medicines as part of the human right to health has been increasingly enforced before domestic courts, with one of the most prominent cases filed by the Treatment Access Campaign seeking access to ARVs in South Africa.[45] Domestic enforcement is highly contingent on a functional national judiciary and patients' own access to justice - both of which may be lacking in countries where access urgently needs to be scaled up. In successful

[33] Article 12(2) (c) and (d) ICESCR.
[34] CESCR General Comment 14, para 12.
[35] CESCR General Comment 3, para 10; General Comment 14, para 43(d).
[36] CESCR General Comment 14, paras 47 and 48.
[37] CESCR General Comment 14, para 35.
[38] Article 2(1) ICESCR; CESCR General Comment 3, paras 13 & 14, General Comment 14, para 39.
[39] Article 2(1) ICESCR; CESCR General Comment 3, paras 13 & 14, General Comment 14, para 45.
[40] CESCR General Comment 3, paras 13 & 14; General Comment 14, para 39.
[41] CESCR General Comment 3, paras 13 & 14; General Comment 14, para 39.
[42] CESCR General Comment 14, para 42.
[43] Hunt, Paul., Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Health, Paul Hunt, Annex: Mission to GlaxoSmithKline, UN Doc. No. A/HRC/11/12/Add.2 (2009). Available at http://www.who.int/medicines/areas/human_rights/A_HRC_11_12_Add_2.pdf . Accessed February 2016.
[44] Ruggie report 2011, para 13.
[45] Hogerzeil, Hans V., Samson, Melanie., Vidal Casanovas, Jaume., and Rahmani-Ocora, Ladan. "Is Access to Essential Medicines as Part of the Fulfilment of the Right to Health Enforceable through the Courts?" *The Lancet* 368.9532 (2006): 305-11. Available at http://www.sciencedirect.com/science/article/pii/S0140673606690764

cases where patients cannot afford their medicines, the courts often shift the financial burden from the patient to the State, which must pay for expensive, sometimes patented, medicines, rather than address the root causes of high prices. For example in Brazil, where unplanned government spending on court-mandated medicines grew by 11 times over 2 years, reaching US$47,8 million in 2009.[46] In these circumstances, achieving UHC and health system sustainability becomes a major concern. These shortcomings show that a more equitable solution is needed to address the core issue of how health systems can provide high-priced, essential medicines rather than ease only the symptom of patient affordability through the courts.

A global public policy response that rebalances obligations under human rights law with obligations under IP law is needed to address patent challenges to access to new essential medicines.

Proposals to realign obligations under human rights treaties and IP treaties.

Access to essential medicines is a key component of the right to health. Essential medicines should be available "at a price the individual and the community can afford."[47] The patent status of an essential medicine can be an impediment to achieving an affordable price and to a government's obligation to fulfil its population's right to essential medicines. This is the case when the patent holder refuses cooperation through equitable pricing or licensing of the relevant patents.

The GHLC made the following proposals aimed at reconciling access to essential medicines under the right to health and patent rights for consideration by the High-Level Panel. The proposals should be seen in the context of proposals for reform of the global pharmaceutical R&D framework to ensure financing for R&D while maintaining prices within reach of the people and communities that need access to the innovations.

Establish an Essential Medicines Patent Pool (EMPP) supported by the UN
The EMPP could be modelled after the MPP and hosted by the MPP and pursue public health focused licence terms and conditions.[48] [49] The unmet need for treatments for both communicable and non-communicable diseases justifies the application of the patent pool model beyond only a few infectious diseases.

Companies should license their patents related to essential medicines to the EMPP, which would align with their responsibility to promote and protect human rights.

Both voluntary licensing and CL (Proposal 2) through an EMPP should be coupled with a tiered royalty system to remunerate the patent holder and contribute to R&D expenditure at levels proportionate to GDP. The WHO and UNDP have provided guidelines for the remuneration of non-voluntary use of medical technologies that could be used or further adapted for that purpose.[50]

A patent owner's refusal to license an essential medicine to the EMPP would satisfy the CL grantee's requirement under article 31 of TRIPS to have made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions, recognizing that there is no prior negotiation requirement in cases of national emergency, extreme urgency or public non-commercial use.

The right of states to exempt essential medicines from patenting should be authoritatively recognized by the WTO (Proposal 3), including taking into account obstacles that could arise in the implementation of the EMPP. This would assure that the priority needs of individuals, in accordance with basic human rights principles, are given first priority among interests.

National governments should establish effectively automatic non-voluntary licensing of patents related to medicines on the WHO EML or their national EML
The UN and its specialised agencies in collaboration with the WTO should develop guidance for countries including model legislation to implement the effectively automatic provision of CL for essential medicines. This

[46] Biehl, João, et al. "Between the court and the clinic: lawsuits for medicines and the right to health in Brazil." *Health Hum Rights* 14.1 (2012): E36-52.
[47] See: WHO definition of Essential Medicines, http://www.who.int/medicines/services/essmedicines_def/en/ . Accessed January 2016.
[48] For details see: www.medicinespatentpool.org . Accessed February 2016.
[49] Frederick M. Abbott, Intellectual Property and Public Health: Meeting the Challenge of Sustainability. *The Graduate Institute*. Geneva (2011).
[50] http://www.who.int/hiv/amds/WHOTCM2005.1_OMS.pdf . Accessed February 2016.

effectively automatic non-voluntary system should be implemented immediately and should be integrated with the EMPP when the latter is established.

Compulsory licensing of patents related to essential medicines is possible under TRIPS. The Doha Declaration specifies: "Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted." While Article 31 (a) of the TRIPS Agreement requires that CLs should be considered on their individual merits, a legal mechanism meeting that requirement may employ identification as an essential medicine as the means through which the individual merits of a licence are determined.[51] [52] Export of the predominant part of essential medicines produced under such a CL should be understood to fall within the August 30 2003 'waiver'/pending amendment inserting article TRIPS 31*bis*, satisfying the requirement for authorization of export of medicines produced under a CL.

Authorize exemption of essential medicines from patenting
The WTO Ministerial Conference should provide an authoritative interpretation of articles 27 and 30 of TRIPS to allow Members to exclude essential medicines from patentability. The UN General Assembly should adopt a resolution urging the WTO to take this action.

The priority needs of individuals for access to essential medicines should take precedence over commercial interests, and should be facilitated. The recommended authoritative interpretation would demonstrate unqualified recognition by the international community of the priority of human rights over commercial interests.

Conclusion

Impact on policy coherence and advancing human rights
All three proposals will increase policy coherence by strengthening the human rights aspects of access to medicines and by providing effective remedies to patent barriers to generic low-priced essential medicines.

Impact on public health
The impact on public health is expected to be significant. High prices are a serious impediment for providing new essential medicines as is evidenced by the global rationing of new antivirals for the treatment of HCV, challenges of access to new ARVs in countries excluded from voluntary licence agreements and the lack of cancer treatment. While affordability is only one aspect of ensuring access to medicines, lack of affordability is often the single most important barrier.

V. THE FRAMEWORK CONVENTION ON PHARMACEUTICAL INNOVATION[53][54]

The GHLC submitted to the HLP a proposal for the adoption of a Framework Convention on Pharmaceutical Innovation, followed by optional protocols touching upon intellectual property management, funding for innovation, regulatory aspects of pharmaceutical approval processes, and international cooperation in science and technology.

The changing landscape for pharmaceutical innovation

Innovation policies, processes and structures must be adjusted to respond to technological and social changes taking place in a rapidly evolving global society. The linear innovation model has been replaced by a more complex framework, where many actors intervene at several different stages of the innovation chain. Scientific and technological advances, pressing social needs, increased competition, and the ever-evolving role of the state, have prompted the emergence of innovation models pulling together competences and talents of very diverse stakeholders. Innovation has become highly cumulative, and frequently requires collaboration in open, inclusive, and enabling environments. As such, innovation reaches unprecedented levels of sophistication. However, the

[51] Cf. Reichman, J.H., Hasenzahl, C., Non-voluntary Licensing of Patented Inventions Historical Perspective, Legal Framework under TRIPS, and an Overview of the Practice in Canada and the USA. Issues paper number 5; Geneva: UNCTAD-ICTSD Project on IPRs and Sustainable Development. 2003
[52] Correa, Carlos María. *Integrating public health concerns into patent legislation in developing countries*. Geneva: South Centre, 2000. Available: http://apps.who.int/medicinedocs/pdf/h2963e/h2963e.pdf Accessed February 2016.
[53] See: http://www.unsgaccessmeds.org/inbox/2016/2/22/contributionxavier-seubaon-behalf-of-global-health-law-committee-of-the-international-law-association.
[54] Dr. Ruth Atherton has recused herself from this portion of the submission.

needs of large segments of the population remain unmet and the overall sustainability of the pharmaceutical innovation system is at stake.

Pharmaceutical innovation refers to the introduction of new products and processes that create value for health. While innovation is difficult to measure, this definition is a useful starting point. Presently, networks of innovators, often of a global nature, have recourse to a wide range of legal and managerial tools that integrate the innovation toolbox. Such a toolbox exists and is administered in the context of specific policy, economic, legal, regulatory, and cultural settings, both of national and international scope. Indeed, both "proximal" (or downstream) and "distal" (or upstream) determinants of health, including health innovation, may be conditioned by international treaties.[55]

Tools and stakeholders relevant to innovation give a sense of the magnitude of the challenge. Numerous tools have been deployed to promote pharmaceutical innovation, mention commonly being made to public funding, intellectual property, regulatory processes, availability of venture capital, ownership of innovation 'platforms' and 'infrastructure', science and engineering education, technology transfer, competition, prizes, 'open' strategies, and liability rules.[56] On the other hand, the range of actors in the production of innovative goods mirrors that of stakeholders involved in the policy aspects of innovation. International organizations, states, companies, and researchers pursue complementary goals, including the provision of public goods, the maximization of social welfare, the enhancement of firms' competitiveness, and the advancement of science. The promotion of policy options that strengthen interaction and complementarity between those tools and stakeholders is crucial both at the national and international levels.

Framework Convention

Innovation in the area of health is produced and governed by a combination of national and international policies and regulations in a wide array of areas, and spans across several legal regimes, notably international health law, human rights law, and international economic law.

The model of a framework convention followed by protocols is often pursued in contexts of technical complexity and uncertainty. The framework convention is in fact an umbrella treaty that enshrines core values and fundamental principles, facilitating initial consensus on a number of central points while leaving technically complex aspects for additional protocols.

A core element of the Framework Convention on Pharmaceutical Innovation would be the portrayal of pharmaceutical innovation as a common interest of mankind. It would also identify core principles, relevant stakeholders, and the areas of relevance to pharmaceutical innovation where further normative action is required. Specific and complex topics relating to intellectual property management, regulatory aspects of pharmaceutical approval processes, funding, and international cooperation in science and technology, would be approached independently in additional protocols.

Previous proposals to set up a treaty on pharmaceutical innovation have been of varying scope and have targeted a wide array of topics, including clinical trials, medical ethics, transparency, open innovation, funding for research, and international cooperation on science and technology.[57] Global common values and objectives cut across these proposals and the proposed Framework Convention on Pharmaceutical Innovation.

The proposed treaty would be a public health and human rights-based global instrument. First, it would recognize that innovation in the area of pharmaceuticals is a common interest of mankind. Second, the right of everyone to the enjoyment of the highest attainable standard of physical and mental health[58] provides a useful

[55] D. W. Bettcher, *et al.,* "Global trade and health: key linkages and future challenges", *Bull World Health Organ*. 2000; 78(4): 521–534.
[56] S. M. Benjamin, A. K. Rai, 'Fixing Innovation Policy: A Structural Perspective', *The George Washington Law Review*, vol. 77, 2008, p. 2.
[57] See, for all, WHO, *Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, 2011, 28 (2.3) (c); WHO, R*esearch and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination, Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination*, 2012.
[58] Enshrined in Article 12 of the International Covenant on Economic, Social and Cultural Rights, Dec. 16, 1966, 993 U.N.T.S. 3; and elaborated further in Committee on Economic, Social and Cultural Rights, *General Comment nº 14, The Right to the highest attainable standard of health*, 11/08/2000, E/C.12/2000/4.

legal basis and analytical framework to address practices, regulations, and policies with an impact on health, including pharmaceutical innovation. Pursuant to this right, its interrelated and essential elements' and the legal obligations resulting from it, states have the obligation to cooperate –including by means of normative action– and to act locally to enhance meaningful and accessible health innovation to prevent, treat and control epidemic and endemic diseases.

Protocol on intellectual property management

Intellectual property is a tool to stimulate innovation provided that it is finely combined with social norms, government intervention, and competition.[59] Fulfillment of the instrumental purpose of the intellectual property system depends on its actual design and management of intellectual property assets. Some key elements should be included in the Protocol on intellectual property management.

First, patent statutes have commonly adopted broad language with respect to patentability. This room to maneuver needs to be preserved, since it is ultimately related to innovation output, which is both product and country-contextual. In this regard, the Framework convention would explicitly acknowledge such freedom.

Next, a reminder of the flexibility existing with respect to patent post-grant measures of relevance to innovation would be also meaningful. In the Framework Convention these references may be broad and merely quote the Doha Declaration on the TRIPS Agreement and Public Health, whereas more detail could be provided in the proposed protocol on intellectual property management. In this same context, patent approval processes may also be enriched by giving special status to patents relating to priority health needs.

Third, collaborative innovation models, based on cooperation to foster the development of knowledge, rely heavily on intellectual property management and balancing of stakeholder incentives. In this sense, new approaches to intellectual property sharing and management are currently instrumental to promote efficiency and cooperation. Successful international models include the Medicines Patent Pool, which could be supplemented by key principles to adjust intellectual property management to contemporary values and needs, in particular transparency with respect to patent status and licensing conditions.

Protocol on pharmaceutical innovation financing

The proposals for financing innovation, in particular the identification of a sustainable source of funding, put forward in 2012 by the Consultative Expert Working Group on Research and Development could be the starting point for the 'financing protocol' of the Framework Convention on Pharmaceutical Innovation. They included discussion on a 'governmental agreement to contribute to the global cost of R&D, considering each nation's level of development, size of economy and capacity to pay' and delinkage between the costs of innovation and the price of pharmaceuticals, a key concept bridging access and innovation. Whether the funds collected would be devoted to prizes, grants or directly publicly-funded research should be addressed in the protocol.[60]

Protocol on administrative and technical measures

Medicines' regulatory agencies and entities responsible for financing drugs play a relevant role in innovation policies. Their specificities and topics of regulation (technical standards, medicines purchasing) deserve independent attention. On the one hand, there are policy, governance, and normative aspects relating to international quality, safety, and efficacy of medicines that need to be addressed. This is particularly the case of the inclusiveness of international standard-setting processes and the way certain standards impact the development of new drugs. On the other hand, a range of instruments and measures normally implemented at the national level could gain additional recognition in an international treaty. These instruments and measures include procurement agreements, advanced market commitments, conditions of access to government funded research, priority review vouchers, and free access to test data information.

Protocol on science and technology cooperation

[59] WIPO, *World Intellectual Property Report – Breakthrough Innovation and Economic Growth*, Geneva: WIPO, 2015, p. 14.
[60] Evidence shows, however, that direct subsidization may be the most effective response to inadequate innovation incentives and costly adaptation. K. Maskus, *Research and Development Subsidies: A Need for WTO Disciplines?*, E15Initiative. Geneva: ICTSD&WEF, 2015.

International scientific cooperation is key to fulfill the potential of pharmaceutical research. Proposals on the adoption of an international treaty to facilitate and promote the development of science and technology have been on the table for the last two decades,[61] while bilateral agreements and scientific programs also promote scientific and technological international cooperation, and may be a source of inspiration and funding. The protocol on science and technology cooperation could address i) rules on research subsidies in areas of public health interest; ii) an agreement to place 'into access pools the patented results of publicly funded research that develops knowledge capable of supporting applied science and R&D, especially in areas of common global concern';[62] iii) measures enabling cooperation between research centers; iii) compromises to facilitate international mobility of scientists; iv) design of agendas of common interests and priority setting in accordance with public health priorities; v) measures to stimulate technology transfer between developed and developing countries; vi) criteria and to support and access to publicly funded research and tax advantages; and vii) facilitating access to scientific resources.

Which international structure and adoption process

An instrument of this caliber needs broad international support, including states with research-based economies, emerging economies, as well as countries with pressing health needs. It also requires involvement of numerous international organizations, companies supplying different segments of the pharmaceutical market, scientists, and non-governmental health organizations.

Prior complex international normative processes were materialized through a range of conferences over a considerable number of years. In the case of pharmaceutical innovation, discussion has advanced since the nineties. The proposal put forward aims at providing the structure and mechanisms, and some update, to proposals previously made. Already existing initiatives, developed by multiple stakeholders in international organizations, civil society, the private sector, and academia, would fall under the scope of the proposed new regime. The task would be twofold: coordinating and going further when necessary, while constructing broad-ranging stakeholder incentives to participate.

The Framework Convention, negotiated in the context of international conferences, could establish a light coordination mechanism in charge of monitoring the action of concerned stakeholders. The coordination mechanism could be based on the recommendations put forward by the Consultative Expert Working Group on Research and Development and stakeholders described therein, and could also benefit from the experience of already existing small and functional international authorities or regulatory groups.

VI. LEGAL ISSUES SURROUNDING ACCESS TO GLOBAL HEALTH RESEARCH MATERIALS

Overview

Recent Ebola outbreaks and pandemic risks[63] underscored significant gaps in global preparedness for outbreak prevention and response[64]. These events highlighted the lack of available treatments, vaccines and diagnostics to assist communities and individuals exposed to pathogens. Unfortunately, product research and development timelines and economics[65] infrequently align with the accelerated needs of affected individuals and communities in the context of a public health outbreak or emergency. Product development efforts are optimally effective when enabled long prior to the needed interventions. These efforts begin with access to research materials.

J. H. Barton, 'Integrating IPR Policies in Development Strategies', Stanford University ICTSD-UNCTAD Dialogue, The Rockefeller Foundation's Bellagio Conference Center, 30 Oct.-2 Nov. 02, p. 3; T. Hubbard T, J. Love, 'A new trade framework for global healthcare R&D', *PLoS Biol* 2004: 2(2): e52. doi:10.1371/journal.pbio.0020052.

[62] K. Maskus, K. Saggi, *Global Innovation Networks and their Implications for the Multilateral Trading System*, E15Initiative, Geneva: ICTSD and World Economic Forum, 2015.

[63] Jonas, O., World Development Report (2014) Background Paper Pandemic Risk http://www.worldbank.org/content/dam/Worldbank/document/HDN/Health/WDR14_bp_Pandemic_Risk_Jonas.pdf

[64] Moon, et al. Lancet (2015) 386, 2204-21; Gates, B. N Engl J Med (2015) 372:1381-84 ; personal interviews on were also conducted with members of University of Nebraska Medical Center, including within the center's Pathology, the Public Health Laboratory, Biocontainment Unit, international research, legal, compliance, regulatory and leadership teams. See http://www.unmc.edu/; http://www.unmc.edu/publichealth/news/ebola-community.html ; http://www.nebraskamed.com/biocontainment-unit/ebola

[65] See e.g., Pronker, E. S., Weenen, T. C., Commandeur, H., Claassen, E. H. J. H. M., & Osterhaus, A. D. M. E. (2013). Risk in Vaccine Research and Development Quantified, *PLoS ONE*, *8*(3), e57755; see also Adams, C. P. and Brantner, V. V. (2010), Spending on new drug development. Health Econ., 19: 130-141.

From a legal perspective, this public health need is confronted with the absence of one or more dedicated international instruments addressing access to a breadth of human pathogens and biological research materials in general terms (the Pandemic Influenza Preparedness (PIP) Framework being an exception to this gap); and the lack of uniform legal environment to promote medical research for global health accompanied by swift product development, particularly in the context of a public health emergency of international concern (PHEIC) or other health emergency. This is in contrast with other areas where states have established multilateral normative schemes to manage resources of common interest, as for example the FAO International Treaty on Plant Genetic Resources for Food and Agriculture. The lack of dedicated instruments means that the legal status of human pathogens and clinical samples and the rights and obligations of states with regard to their management, exploitation and sharing, fall under a number of existing international legal instruments and regimes largely established and implemented for the pursuit of interests and objectives other than public health. This situation, in turn, raises the risk of fragmentation and possible conflicts among different rules, and of unpredictability as to whether and how human pathogens will actually be made available for public health purposes.

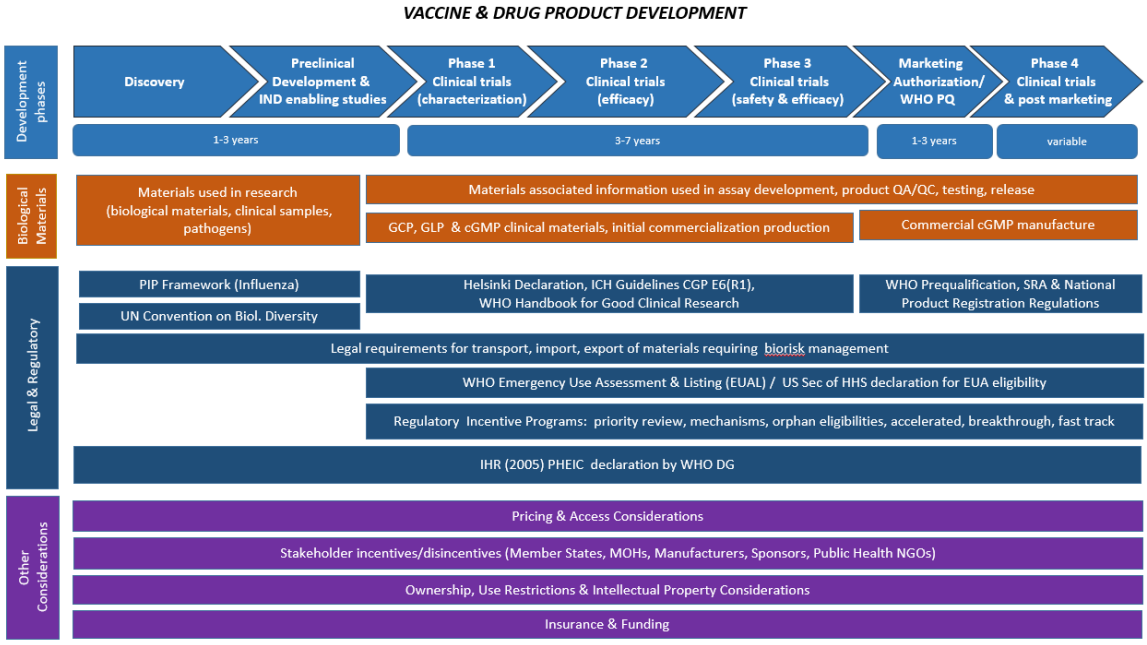
This section examines the legal and contextual issues surrounding access to global health research materials in the context of product development aimed at global health and identifies potential benefits to amending existing instruments or developing new instruments or tools.[66]

These include:

- The need for prompt and safe sharing of biological materials, data and information, including human pathogens and clinical samples to facilitate research and development of therapeutics, vaccines, diagnostics aimed at public and global health measures;
- The legal, regulatory and contextual considerations that overlay global product development and the need to balance bio-risk management; and
- Consideration of incentives to drive products development aimed at beneficial global health outcomes.

Product Development Overview & Uses of Global Health Research Materials

Acknowledging the important public health benefit of affordable and accessible therapeutics, vaccines and diagnostics, the sharing of biological materials for global health research is examined here in the context of the product development process. As illustrated in Figure 1, product development begins in the discovery phase encompassing research to elucidate disease biology, targets and molecules that have the potential to ameliorate, prevent or detect a disease of interest.[67]



[66] This paper is not intended to provide a compilation of all laws, regulations and considerations related to access to global health research materials, but is intended to highlight areas for consideration in the context of benefiting global health stakeholders and communities.

[67] Special thanks to Murray M. Lumpkin, MD, MSc. for input and critical review of paper.

Product development targeting infectious and pandemic disease requires access to biological materials which are the causative agent of the disease. In the case of vaccine development, for example, access to the pathogen is essential to provide antigens, nucleic acids and sequence information essential to identifying potential vaccine candidates, assays and diagnostics. Concomitantly, as discussed further below, the need for biosafety and biosecurity remain central to the management, sharing and use of these materials.

Following the discovery phase, and before progressing into humans, molecules with the highest potential are extensively studied in animal and *in vitro* models during pre-clinical research. Pre-clinical research seeks to minimize the risks of introducing product candidates into humans. In the US, for example, these studies form the basis for an Investigational New Drug (IND) application, a prerequisite to the clinical development phase.

If successful in the preclinical phase, product candidates may enter clinical development phases. During clinical phases, product candidates are characterized and examined for safety and efficacy in human subjects (beginning with health volunteers and progressing into an applicable patient populations). Biological samples from human subjects (such as blood, sputum or other tissue samples) collected attendant to clinical trials can provide insights to understanding the etiology, pathology and epidemiology of the disease. These materials, as well as portions of the pathogen and information derived from each, may also be used in assay development, product quality assurance/quality control, and product release in support of manufacturing.

Upon achieving clinical evidence of safety and efficacy through phase 3 trials and if the product can be produced in a quality manner in compliance with cGMP standards, marketing authorization for the product may be sought from the applicable regulatory agency (usually in the country of manufacture or a stringent regulatory agency that will be a reference agency for follow-on authorizations), followed by WHO Prequalification if applicable, and national registrations in the countries where the product will be used. Finally, if required, phase 4 trials and post marketing studies will follow product registration. The timeline for the product development and its cost have been detailed by others, but is generally understood as taking close to a decade with average costs in the hundreds of millions of dollars (USD) or more[68].

Legal and Regulatory Frameworks Applying to Biological Materials for Global Health Research

As described above, access to pathogens is a critical initial step in the development of therapeutics, vaccines and diagnostics. Similarly, human biological samples provide critical insights in product development. As pathogens and human biological materials for global health research have both overlapping and different legal considerations, we example them separately.

Pathogens

Public health is largely confronted with the absence of one or more dedicated international legal instruments requiring states and other actors to cooperate and share human pathogens for the benefit of public health (the PIP Framework being an exception to this gap)[69]. In the case of pathogens, such as viral agents, several legal constructs provide context.

The UN Convention on Biological Diversity (CBD)[70] is based on the principle of sovereignty over genetic resources and the right of each Party to regulate access to them through mutually agreed terms. The primary purpose of the CBD was to fight biopiracy and ensure both effective management and preservation of a shrinking pool of genetic and biological resources as well as access to benefits for countries sharing them. The CBD is based on a bilateral approach to sharing of resources between states. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (NP)[71] implements in detail the benefit access and sharing provisions of the CBD. Its Article 4 para. 4 foresees a carve-out from its applicability in the following terms: "*Where a specialized international access and benefit-sharing instrument applies that is consistent with, and does not run counter to the objectives of the Convention and this Protocol, this Protocol does not apply for the Party or Parties to the specialized instrument in respect of the specific genetic resource covered by and for the purpose of the specialized instrument*."[72] Accordingly, the CBD and NP leave open the question of whether certain pathogens, particularly those which could lead to the

[68] See e.g., DiMasi et al., J. Health Econ. (2003) 22: 151–185; Drug Inf. J. 2004; 38: 211–223; Adams, C. et al, J. Health Econ. (2010) 19: 130–141; Avorn, J. .N Engl J Med (2015) 372:1877-1879

[69] See e.g., Abbott, F. "An International Legal Framework for the Sharing of Pathogens: Issues and Challenges" (2010)

[70] Adopted in 1992, 196 parties as of early June 2016.

[71] Adopted in 2010, in force as of October 2014, with 77 Parties as of early June 2016.

[72] Under the CBD, "Genetic resources" means genetic material of actual or potential value. "Genetic material" means any material of plant, animal, microbial or other origin containing functional units of heredity.

declaration of a PHEIC (or potentially those requiring higher levels of biosecurity), should fall outside the scope of the CBD and whether an alternate legal framework could serve as such a specialized instrument.

The PIP Framework[73] addresses the need for pandemic influenza pathogens[74]. This non binding instrument regulates the sharing of influenza viruses both within and outside the existing network of WHO laboratories and collaborating centres. It also establishes channels to ensure the sharing of benefits deriving from the use of viruses and/or the services of the network for both preparedness and response in case of pandemic flu outbreaks. The framework embodies an innovative approach, including private companies, laboratories and academic institutions in its scope besides states. It contemplates the conclusion of legally binding Material Transfer Agreements (MTAs) between parties providing and accessing the virus as the tool to guarantee the fulfilment of the objectives of the Framework. The UN General Assembly has recently recalled the importance of the cooperation at the global level in fully implementing the PIP Framework (A/RES/70/193).

Future possibilities and areas of research:

- *Clarify whether the PIP Framework constitutes or may provide the basis for a 'specialized instrument' under NP Article 4.*
- *Revision of the PIP Framework: expansion of its scope (pathogens other than pandemic influenza viruses) and development of further incentives to encourage industries to conclude MTAs.*
- *Alternatively, negotiation of a new international treaty along the lines of the FAO Treaty establishing a multilateral mechanism to share human pathogens.*
- *Inclusion in the IHR of a clear obligation to share pathogens.*

Clinical Materials

Unlike pathogens, the biological materials from human subjects (including clinical samples) are subject to laws, regulations and guidelines[75] aimed at the protection of individual subjects' rights, safety and well-being. While international principles, standards and guidelines including the Declaration of Helsinki [76] and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) [77] are broadly accepted, human subjects research is regulated nationally[78]. The simultaneous application of these international and national regulations, as well as the application of different national standards and processes can significantly increase the complexity of multi-site, multi-jurisdictional trials and similarly impact the management and subsequent use and sharing of biological materials collected attendant to such trials.

Use restrictions on human biological materials are also directly impacted by the context of their collection, the specific patient informed consent and the potential biohazards the sample may create. These cells and tissues are typically collected in different contexts, including: during treatment/diagnosis, as donations for another recipient, in research (including human subjects research, clinical trials and educational purposes) or the manufacture of biological products[79]. These contexts together with the applicable patient informed consents serve as legal and

[73] Adopted by the World Health Assembly (WHA) in 2011 under Article 23 of the WHO Constitution.

[74] Due to their high mutation rate, new strains evade immunity obtained from prior vaccinations and necessitate biannual refinement of the antigenic composition of the vaccine to address current circulations of the virus, http://www.who.int/wer/2012/wer8747.pdf

[75] See International Compilation of Human Research Standards, 2016 Edition, complied by: Office for Human Research Protections, U.S. Department of Health and Human Services

[76] In US, the Declaration of Helsinki is embodied in the Common Rule (45 CFR part 46, and FDA counterparts 21 CFR 50 and 21 CFR 56) which details the protection of human research participants. These regulations requires IRB review and informed consent for research obtaining private information from living individuals. Human biological materials are governed by Department of Health and Human Services, Office for Human Research Protections (OHRP) http://www.hhs.gov/ohrp/. In the EU, clinical trials are governed by Regulation No. 536/2014 of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use. Human biological materials are further governed by Directive 2004/23/EC on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage, and Distribution of Human Tissues and Cells, which also calls for mandatory consent.

[77] Global principles of clinical trial conduct include International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), which assure that the principles of the Helsinki Declaration in protection of subjects' rights safety and well-being. GCP is typically a prerequisite to marketing authorization. ICH Guidelines for Good Clinical Practice E6(R1) describe the responsibilities of all participants including investigators, sponsors (including their CROs), monitors and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) and include the requirement for informed consent of trial subjects. Additional international guidelines include WHO's Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation (2005) and CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

[78] *Fundamentals of U.S. Regulatory Affairs, 8th Ed (2015).*

[79] *C. Petrini J Blood Medicine 2012:3 87-96; Fundamentals of U.S. Regulatory Affairs, 8th Ed (2015), at 337.*

ethical covenants between patients and researchers and define the parameters of allowable use that will follow the human samples[80]. For example, informed consent may detail the destruction, storage and the allowable or impermissible secondary uses of the samples[81]. Within the bounds of the uses permissible under the patient informed consent, human samples must also be managed in accordance with the applicable biohazards guidelines[82].

Accordingly, to enable sharing for broad scientific and R&D purposes, clinical researches optimally anticipate the potential future uses and seek patient consent accordingly. However, given that individuals within single or multiple-site trials may consent to different scopes of use, the subsequent research, sharing and analysis of these samples and information can be significantly constrained.

In the recent Ebola virus outbreaks, the lack of existing therapies, vaccines and diagnostics highlighted the misalignment between product development timelines and the needs of patients and public health systems in the context of a public health emergency. Given no products approved for Ebola Virus Disease (EVD) existed at the time of the outbreak, the global health community and regulators were required to rely upon clinical trial procedures or emergency use authorizations in order to provide specific new treatments to patients.

Emergency Use Authorizations

Recognizing the need for applicable regulatory and public health bodies to act swiftly for the benefit of patients, emergency use authorizations serve to mimic marketing authorizations, but apply specific temporal and use limitations. While emergency use does not supplant the need for full clinical trials, nor imply approval by a Stringent Regulatory Authority or WHO pre-qualification, these procedures import clinical trial elements, including risk-benefit analysis, data collection and evaluation, informed consent and national sovereignty over drug/vaccine/diagnostic approvals. For example, in the US, FDA's Emergency Use Authorization (EUA) procedure[83] is allowable following the Department of Health and Human Services (HHS) Secretary's issuance of a determination of public health emergency or significant potential for public health emergency. During the Ebola emergency, WHO adopted a similar principles of emergency use, known as Emergency Use Assessment and Listing (EUAL)[84] which are allowable in the context of a PHEIC when no licensed medicine, vaccine or diagnostic is available and certain minimum requirements are met, including Good Manufacturing Practices (GMP)[85] manufacture and intent to seek WHO PQ in the future. Data is assessed for reasonable likelihood that quality, safety and effectiveness outweigh foreseeable risks and uncertainty in light of the PHEIC. The EUAL process may also include from an expert Advisory Committee (AACEUM).

These hybrid tools may be essential in public health emergencies when time is of the essence for vulnerable patients and affected public health systems. Emergency use recognizes the need for applicable regulatory and public health bodies to promptly act in public health and other emergency situations, with a presumption that failure to act may be deemed unethical. It also encompasses the perspective that the community, when faced with a public health emergency, is willing to tolerate a greater risk of the unknown (less available of data) given the counterbalance of the known significant risk inherent in the public health emergency. In such settings, in light of the potential increased clinical risks, informed consent becomes even more critical, but what constitutes that consent and how it is obtained in the context of a public health emergency demands an approach, like the emergency authorization itself, that recognizes the realities of the public health emergency and the risks, not only to the individual patient, but to the community at large that an individual patient may represent.

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[80] In the absence of express agreements to the contrary, US Courts have generally held that ownership rights over clinically excised or donated tissues is relinquished by the patient or research subject. *See* Allen et al Clinical Chemistry 56:11 1675-82, at 1678 (2010). Further, while secondary research with such tissue may be subject to IRB approval, patient consent may on a case-by-case basis, be waived by the applicable IRB, particularly in cases where individually identifiable information is dissociated from the materials. *Fundamentals of U.S. Regulatory Affairs, 8th Ed (2015).*

[81] See e.g., http://www.who.int/rpc/research_ethics/informed_consent/en/; http://www.who.int/rpc/research_ethics/Informed%20consent%20for%20sample%20storage.doc?ua=1

[82] See e.g., http://www.cdc.gov/vhf/ebola/healthcare-us/laboratories/specimens.html

[83] http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMLegalRegulatoryandPolicyFramework/ucm411445.htm

[84] http://www.who.int/medicines/publications/druginformation/issues/WHO_DI_29-3_NormsStandards.pdf?ua=1; http://www.who.int/medicines/news/EUAL-vaccines_7July2015_MS.pdf

[85] http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/ ; http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

Given the complexity, cost and perceived liabilities of international clinical trials, little incentive exists for private sector biotechnology and pharmaceutical entities to serve as sponsor[86] of clinical trials in the context of a PHEIC. From a product development perspective, a gap also exists between the emergency use and conventional approval processes, since the emergency use authorization ceases upon termination of the emergency declaration. This gap serves as a disincentive for product developers in the context of health emergencies, particularly as patients may already face high mortality and morbidity due to the underlying pathogen. To fill such a gap, in recent Ebola PHEIC, WHO recently took on an expanded role in a clinical trial aimed at ameliorating Ebola Virus Disease when no other sponsor was willing to conduct the trial in Guinea[87].

This role for WHO was also arguably consistent with the IHR. Under the IHR, adopted by the WHA in 2005, states must develop capacities for surveillance, assessment and response. While the IHR do not address sharing of pathogens or clinical trials and associated biological materials, it calls for WHO's unique role as the guardian of public health[88]. IHR entrust the WHO to detect, assess and respond to public health emergencies of international concern and other public health risks. Indeed, states have often looked to WHO to play a coordinating and normative role in this regard, or even to assume an operational role for the approval and distribution of vaccines and medicines.

Future possibilities and areas of research:

- *Consider the potential benefit of WHO further defining an optional role in clinical trials (such as serving as a clinical trial sponsor) in the limited circumstances when a product manufacturer is unable or unwilling to do so.*
- *Consider whether the role of WHO in serving as a clinical trial sponsor might be relevant in other circumstances taking into account potential advantages for public welfare.*

Transport & Transfer of Materials: Biosafety, Biosecurity and Biorisk management[89]

While it is generally recognized that the conditions of transport, storage and use of pathogenic biological agents must meet the appropriate biosafety[90] and biosecurity[91] requirements in light of the specific biorisk[92] presented, national and subnational/local standards vary widely and can create operational barriers that impede research or result in the spoilage of research materials. Developing as well as developed countries are not exempted from criticism or operational challenges regarding their biosecurity and biosafety standards.[93]

Over the past decade, increased attention to scientific, operational and legal guidelines have been applied to biorisk management. While not meant to be an exhaustive review, the following provide example of frameworks and standards that warrant consideration as related to the transport of materials.

In 2003-2004, the laboratory-acquired SARS-CoV infections in Singapore triggered a demand for international biosafety guidance. In response, the WHA in 2005 adopted resolution WHA58.29 on Enhancement of laboratory biosafety[94]. The WHO further developed guidance on biorisk management[95] as well as a *Strategic Framework*

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[86] A "Sponsor" of a clinical trial is the company, person, institution or organization that takes responsibility for the initiation, management and/or finance or resources for the clinical trial. *Fundamentals of U.S. Regulatory Affairs, 8th Ed (2015);* https://www.clinicaltrialsregister.eu/doc/EU_Clinical_Trials_Register_Glossary.pdf

[87] Henao-Restrepo, Ana Maria et al. Lancet 2015:386: 857-66.

[88] *See* Gostin and Friedman Retrospective (Lancet 2015:385:1902-09) – Envisioning a global health framework with robust national health systems with "an empowered WHO at its apex."

[90] Biosafety (which concerns the "containment principles, technologies and practices that are implemented to prevent the unintentional exposure to biological agents or toxins or their accidental release) more directly addresses the protection of researchers and actors along the product development pathway (http://apps.who.int/iris/bitstream/10665/70878/1/WHO_HSE_2012.3_eng.pdf).

[91] Biosecurity (which describes the "protection, control and accountability for biological agents and toxins … to prevent their loss, theft, misuse, diversion of or unauthorized access or intentional unauthorized release") extends the zone of protection to the national and international public (*id.*)

[92] http://www.cdc.gov/biosafety/publications/bmbl5/BMBL5_sect_IV.pdf

[93] In 2015, the Hudson Institute published its analysis of the US national state of defense against biological attack and infectious disease, finding the nation "dangerously vulnerable" to a biological event. In a 2008 publication by the House of Commons, the Veterinary Laboratory Agency underlined that some current biological containment facilities in the UK "require significant capital investment to bring them to acceptable bio-containment standards." See House of Commons, Innovation, Universities, Science and Skills Committee, *Biosecurity in UK research laboratories*, Sixth Report of Session 2007-08, vol. II.

[94] WHA58.29 on Enhancement of laboratory biosafety (2005).

[95] WHO, *Biorisk management: Laboratory Biosecurity Guidance*, WHO/CDS/EPR/2006.6, September 2006.

for Action (2012-2016)[96] aiming towards the development of sustainable global, regional and national plans relating to laboratory biorisk management. Similarly, in Europe, the *Laboratory Biorisk Management Standard (CWA 15793:2011)*[97] is registered with the European Committee for Standardization (CEN). In Canada, the Canadian Biosafety Standards, recently updated, sets out managment requirements for the safe handling and storing of human and animal pathogens and toxins.[98] In the US, the Federal Select Agent Program[99] oversees the storage, use and transfer of human and animal biological agents and toxins which have the potential to pose a severe threat to public health, including viral agents such as Ebola virus.[100]

The *UN Model Regulations on the Transport of Dangerous Goods (18th ed)* [101] issued by the Committee of Experts on the Transport of Dangerous Goods (UNCETDG) – a committee of the UN Economic and Social Council – set forth international modal regulations on air, rail, sea, road and post. Parts 2, 4, 5 and chapter 6.3 relates to infectious substances[102]. Many states have adopted the *UN Model Regulations* in their entirety or with varriation, to stand as their national dangerous goods legislation.

In addition, independent quality systems such as ISO 17025:2005 and ISO 9001:2000 as well as trade organizations[103] provide further guidance and assurance that valid audit trails and verifiable storage systems exist for all dangerous pathogens received at, transported and held within organizations[104].

Future possibilities and areas of research:

- *Compilation of legal and regulatory requirements, or development of a uniform set of biorisk standards in order to increase consistency in the application of biosafety and biosecurity measures across different services and laboratories.*

Bioterrorism & Synthetic Biology

While vaccine development has traditionally relied on molecular biology techniques as means to capture and elucidate viral antigens from pathogens for use in vaccines, an additional layer of complexity is given by advances in biotechnology, in particular genetic sequencing and molecular biology. In view of the increasing ability of many scientific institutions to sequence and synthetically reconstruct nucleic acids, proteins and biomolecules, reliance on sharing physical samples for such research may one day be fully obviated. Progress in biotechnology may soon make synthetic construction of complex pathogens and biomolecules based on publically available genetic sequences and information, a concrete reality.

The first synthetic virus creation (polio) was reported in 2002[105]. Subsequent laws, such as the variola amendment[106] enacted in the US in 2004 banned the synthesis, use, transfer or possession of the smallpox (variola) virus with penalties of 25 years to life in prison. Similarly, the WHO Independent Advisory Group mentioned below recommended that the recreation of variola virus should be prohibited[107]. While legal prohibitions to such research may impede a biorisk concerns from compliant actors, a legal instrument may not achieve avoidance of intentional bioterrorism acts. In 2015, a WHO Independent Advisory Group on Public

[96] WHO, *Laboratory Biorisk Management: strategic Framework for Action 2012–2016*.
[97] CWA 15793:2011. Guidelines for the Implementation of the CWA 15793:2008 (CWA 16393:2012) have been adopted to assist States in understanding the CWA 15793.
[98] http://canadianbiosafetystandards.collaboration.gc.ca/
[99] http://www.selectagents.gov/
[100] http://www.selectagents.gov/SelectAgentsandToxinsList.html
[101] ST/SG/AC.10/1/Rev.18 (Vol. I) & (Vol. II), 2013. These *UN Model Regulations* are subject to biennial amendments. In December 2014, UNCETDG agreed on further changes for the 19th revised edition (ST/SG/AC.10/1/Rev.19 (Vol. 1) & (Vol. II), 2015), which will come into force in 2017.
[102] These recommendations are addressed to governments and to the international organizations concerned with safety in the transport of dangerous goods. For the purpose of the *UN Model Regulations*, "infectious substances"(*i.e.* "substances known or reasonably expected to contain pathogens. Pathogens are defined as microorganisms (including bacteria, viruses, rickettsiae, parasites, fungi) and other agents such as prions, which can cause disease in humans or animals") are assigned UN numbers and proper shipping names according to their hazard classification and their composition. The packaging, labelling and documentation requirements vary from a category to another. The shipper, the carrier and the receiver have specific responsibilities in ensuring successful transportation. The WHO has provided for an overview of the roles of these actors in its *Guidance on regulations for the Transport of Infectious Substances 2015-2016 (*WHO/HSE/GCR/2015.2), applicable as from 1st January 2015.
[103] See e.g., http://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx
[104] House of Commons, Innovation, Universities, Science and Skills Committee, *Biosecurity in UK research laboratories*, Sixth Report of Session 2007-08, vol. II.
[105] http://www.sciencemag.org/news/2002/07/poliovirus-baked-scratch
[106] 18 U.S. Code § 175c
[107] http://www.who.int/csr/resources/publications/smallpox/synthetic-biology-technology-smallpox/en/

Health Implications of Synthetic Biology Technology Related to Smallpox prepared a report[108] to the WHO DG detailing the health implications of a synthetic smallpox development. The Scientific Working Group concluded that "it would be possible to recreate variola virus" from relatively simple chemicals and laboratory equipment. Accordingly, the report emphasized the "importance of the core capacities required by the International Health Regulations (2005)" calling for increased capacity for detection, disease control, biosecurity and risk communication. The report highlighted the need for "increased biosafety and biosecurity in laboratories stock inventories, strengthened regulatory frameworks and their implementation, coordination between sectors including health, judiciary, law enforcement and customs." In the context of biorisk management, bioterrorism must be integral in the considerations as applied to biological materials. Therefore, in addition to the legal frameworks, diligence and coordination of the global community must seek to ensure biorisk management of this and similar pathogenic agents is achieved.

Future possibilities and areas of research:

- *Increase awareness of biorisk through trainings and clear guidelines.*
- *Consider the potential benefit and learnings from smallpox virus, including limited number of authorized repositories capable of ensuring appropriate biorisk management.* [109]
- *Consider the importance of integrating genetic sequencing and molecular biology of highly pathogenic agents into regulatory and policy development on biosecurity and on limiting access to dangerous pathogens solely for public health purposes.*

Other Considerations

Ownership, Use Restrictions & Intellectual Property

Ownership and use restrictions, including intellectual property, need express consideration when contemplating the sharing of biological materials for global health research. An initial step to this analysis requires answering the questions of 'what use limitations must be accounted for when contemplating sharing for the intended purpose?' In the absence of express agreements to the contrary, US Courts have generally held that ownership rights over clinically excised or donated tissues are relinquished by the patient or research subject[110]. However, as described herein, patient consents may detail use limitations.

Intellectual property also plays a role along phases of R&D. While the development of pharmaceutical patents may occur along the product development phases, many occur in the earlier end of the product development timeline (such as during the discovery of new molecules and methods). Accordingly, the contemplated research uses must be analyzed in light of the desired activities and in light of the jurisdictional limitations of the applicable patents, if any. For the purpose of this discussion, however, an IP analysis is merely one component that needs consideration.

At a different normative level, existing contractual practices impact the conditions upon which biological materials are shared. The widespread practice among laboratories, research centres, universities and private companies is under cover of a material transfer agreement (MTA) or similar agreement. Such agreements are customary in the transfer of biological samples and detail the responsibilities of the parties in providing, receiving and safely managing the materials. In many cases these MTAs may contain clauses that specify the permissible use of the biological material or detail the intellectual property rights related to the materials or their use. By way of example, the ownership claims and restrictions imposed by the MTA[111] of Erasmus Medical Center to share the MERS-CoV virus was well publicized and noted by the WHO DG.[112]

Incentives/disincentives for stakeholders

The development of therapeutics, vaccines and diagnostic for global health applications requires a spectrum of stakeholders including academic and clinical researchers, clinical researcher organizations, product manufacturers, regulatory agencies, members states, distributers, NGOs, funders, intergovernmental organizations and agencies, including WHO. Each of these stakeholders play a unique role along the product

[108] http://apps.who.int/iris/bitstream/10665/198357/1/WHO_HSE_PED_2015.1_eng.pdf

[109] http://apps.who.int/iris/bitstream/10665/198357/1/WHO_HSE_PED_2015.1_eng.pdf ; see also House of Commons, Innovation, Universities, Science and Skills Committee, *Biosecurity in UK research laboratories*, Sixth Report of Session 2007-08, vol. II: calling for "a secure system for assuring protection to those put under pressure from outside to source material from a containment facility" and "Training staff in biosafety [as] an essential element for the safe operation of any high containment facility"

[110] See Allen et al., Clinical Chemistry 56:11 1675-82 (2010)

[111] http://www.twn.my/title2/intellectual_property/info.service/2013/ipr.info.130512/22227717951a47369b9515.pdf

[112] http://www.who.int/dg/speeches/2013/world_health_assembly_20130527/en/

development and delivery pathway. Creating an environment that encourages sharing of research materials and product development aimed at global health must also take into account the existing stakeholder incentives and disincentives beyond the legal considerations. While not the focus of this discussion, these include, among others, the cost of and timelines of product development, product liability and indemnification concerns of product developers,[113] pricing considerations balancing with broad product accessibility. Accordingly the importance of operational and incentive alignment with legal frameworks must not be overlooked.

VII. REGULATION, TRADE AND PUBLIC HEALTH[114]

International standard-setting in pharmaceuticals

International harmonization

A range of activities are conducted at the international level to guarantee the safety, quality, and efficacy of medicines. These activities include, among others, the harmonization of pharmaceutical nomenclatures, the standardization of pharmaceutical compositions, the adoption of harmonized guidelines relating to activities in the preclinical, clinical, production and distribution phases of the medicines' chain, and the harmonization of documentation submitted for approval of pharmaceutical products.

International harmonization of information concerning medicines' tests and trials fulfills an important public health objective. In effect, harmonization avoids the repetition of tests already carried out, or tests very similar to other already carried out. Such a repetition gives rise to avoidable risks for human health and generates unnecessary expenses. Despite these widely shared objectives, international harmonization can hardly be total. Diverging standards are justifiable and sometimes necessary from the public health point of view in a number of areas and for a number of reasons, including genetic differences, climate conditions, or different scientific approaches to quality, safety, and efficacy. However, the risk and unintended consequence may be the use of technical standards to erect entry barriers to foreign competitors.

Harmonization of technical standards relating to pharmaceutical products has historically taken place in multilateral, regional and bilateral forums of public nature, and also in the context of public-private partnerships and initiatives. In addition to the normative dimension, harmonization has an institutional side. Cooperation between health agencies in matters relating to drug registration and control is more and more frequent, and different initiatives have been developed in parallel, frequently involving regulatory agencies where similar market conditions and public health situations prevail.

In this context, it is timely to reflect upon the so-called international standards of reference, and the current prominence, in that regard, of the standards adopted by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). The ICH is not only a very original initiative and the most productive source of international pharmaceutical standards, but it also underwent very relevant changes in 2015. After briefly describing the ICH, its guidelines and recent reform, the relationship between a number of pharmaceutical standards and norms on ethics, human rights, and trade will be addressed. For that purpose, the World Trade Organization (WTO) Agreement on Technical Barriers to Trade (TBT) will play a crucial role.

International standard-setting organizations

Even though institutional sources of international pharmaceutical regulation are not too numerous, there exists still a rich diversity. In addition to the World Health Organization (WHO) and its two major experts' committees dealing with pharmaceutical standardization (the WHO Committee on Biological Standardization and the WHO Committee on Specifications for Pharmaceutical Preparations), the International Organization for Standardization (ISO), the Organization for Economic Co-operation and Development (OECD), and the already mentioned ICH, to name the most relevant ones, adopt international standards of relevance in the pharmaceutical sector .[115] There are also professional organizations such as the World Medical Association (WMA) and the *Council for International Organizations of Medical Sciences* (*CIOMS*) that develop important pharmaceuticals standards, in particular standards relating to good clinical practices.

[113] In the US, US National Childhood Vaccine Injury Act (NCVIA) of 1986 (streamlined 'no-fault' compensation system) and the National Vaccine Injury Compensation Program (VICP)[113] addresses adverse events due to VICP covered vaccines provides a model aimed at encouraging vaccine manufacture. http://www.hrsa.gov/vaccinecompensation/index.html

[114] Dr. Ruth Atherton has recused herself from this portion of the submission.

[115] Moreover, some initiatives of national nature have great influence on activities conducted abroad. This is the case of some pharmacopeias, notably the U.S. Pharmacopeial Convention, the European Pharamocopoeia and the British Pharmacopoeia.

Mapping active stakeholders in the area of international standardization reveals the diverse nature of standard-setting organizations. Some of them are multilateral organizations of either unrestricted membership, such as the WHO, or close and limited membership, this being for instance the case of the OECD. Others, by contrast, are private non-profit organizations, of heterogeneous membership, namely ISO, WMA and ICH.

International Council for Harmonization

The ICH is the most interesting and influential standard-setting organization in the area of pharmaceuticals. In 25 years of action it has adopted about 90 guidelines[116] that have been regularly updated and generally implemented both in ICH Member states and in many other countries that do not participate in the ICH process. In fact, the influence of ICH standards expands well beyond its actual members for a number of reasons. Indeed, non-ICH regulatory authorities may decide adopting ICH guidelines, they may be considered the international standards of reference pursuant to WTO law, or they may be endorsed by other international standard setting organizations, this being notably the case of the WHO.

Among the features of the ICH, the high level of implementation of the guidelines it adopts, as well as the dynamism and productivity in terms of the number of the guidelines produced, stand out. Regulatory members participating in the ICH are engaged in implementing the ICH standards, which do not go through any further internal discussion once adopted. Another feature of the ICH is the sophistication of its standards. There is consensus that the ICH standards are in themselves both of great quality and demanding. This does not exclude, however, concerns regarding the coexistence of some ICH guidelines and international trade norms, human rights norms, and ethical standards.

Changes at the International Council for Harmonization

The ICH is an interesting organization in terms of nature and membership. Up until October 2015, only innovative industry associations of the United States, Japan and the European Union, together with regulatory authorities of the same countries and region, were full members of the ICH. The WHO, Canada and the European Free Trade Association (EFTA) were just observers. The "ICH process" was essentially a closed one, with the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as Secretariat. For contemporaneous accounts of independence and conflicts of interest that situation was hardly sustainable, not to mention the absence of regulatory authorities of the rest of the countries of the world, and the absence of representatives of generic industry associations.

The ICH has gone through very relevant changes in recent times. These changes have impacted on its nature as organization, its membership, the name of the managing bodies, and the norm-setting process, among other aspects.

First, the ICH is not anymore a "process" administered by IFPMA but a non-profit association. Second, regulatory members and industry members are not anymore on equal footing, since the latter have lost the power to propose and adopt standards -however, they can still appoint experts to all regulatory projects, which gives considerable leverage. Third, new regulatory members have been included on equal footing as the three foundational regulatory members. This is the case of the regulatory agencies of Canada and Switzerland, and it will probably be also the case of the other regulatory authorities of EFTA member states, and also the EFTA itself. Moreover, the door is open to a limited number of other regulatory authorities that must, however, fulfill demanding conditions.[117]

The impact of these changes may be crucial for the global acceptance of the ICH guidelines. Some aspects however may be contentious. First, previous guidelines remain untouched, and with them, the discrepancies with respect to the actual need of some standards and their relationship with trade, human rights, and ethical norms, and with policies aimed at promoting the local production of pharmaceuticals in developing countries. Second, the new 'Council' will be scrutinized for its inclusiveness of countries, companies, and consumers that had no representation in the previous 'Conference'. In this respect, the demanding conditions to become (non-founding)

[116] About 30 on safety, plus numerous annexes; 12 on quality; 20 on efficacy; and 8 multidisciplinary documents. *See* the ICH production at http://www.ich.org/products/guidelines.html (accessed May 2016)

[117] They must have made substantive contributions to previous ICH guidelines and must accept and implement key ICH guidelines. The latter include six guidelines on stability, the critical guidelines on good manufacturing practice and the delicate guidelines on good clinical practice. More analysis is needed in this respect, but taking into consideration the participation on the three last assemblies of the ICH, candidates include Republic of Korea, Brazil, China and Singapore.

regulatory and industry members, as well as observers, are key. In this respect, it is worth mentioning that since 2014 some regulatory authorities in emerging economies -Argentina, Brazil, India and Colombia- have discussed the creation of a parallel standard-setting process. Third, the relationship between the ICH and the WHO presents some important questions. Perhaps the most fundamental among these, if WHO has the constitutional mandate to adopt the same type of guidelines that the ICH adopts,[118] should WHO merely observe and endorse the ICH guidelines or, rather, should it become the alternative and truly global standard-setting process?

Relationship with other areas of international law

The impact that international pharmaceutical standards have on ethics, human rights, and trade norms is of central importance. Whereas the stated purpose of harmonization is to reduce the costs of developing medicines, ensure the quality, safety, and efficacy of medicines, and avoid the repetition of preclinical and clinical assays, the content of the harmonized standards may be in tense relationship with ethics, human rights, trade and competition norms.

With respect to ethics and human rights, the guidelines on good clinical practice adopted by the ICH are the case in point. This is an area where a rich normative *acquis* existed when the ICH started its work. In the last fifty years professional and scientific organizations have adopted rules that apply to many steps of the drug development process, and in particular to clinical assays. The guidelines of the WMA and CIOMS are particularly well-known, but are not, by any means, the sole ones. Moreover, a reduced but very important in substance number of international treaty and customary norms apply to clinical assays, some of them dating back to Nuremberg trials. However, in a number of aspects, the ICH guidelines seem to depart from these norms. For instance, ICH E6 does not address, or seems to addresses differently, important ethical requirements stipulated in the Declaration of Helsinki relating to the use of placebos[119] and also regarding the continuation of therapies once the trial is concluded.[120]

With respect to effects on international trade, the use of technical standards to restrict international trade is a matter of concern. Think for instance about a standard relating to purity. If such a standard does not impact on safety and efficacy, it should be of no interest whether the requirement of purity is set at 99% or 98.8%. However, adopting one or the other percentage may impede the entrance of products into the national market and be considered, therefore, a protectionist measure. Indeed, if the ICH adopts such a standard, if it becomes the international standard of reference, and members transform it into national regulations, activities taking place in countries that did not adopt the ICH guideline will be affected. For instance, the trade of companies based in non-ICH countries with ICH members will be disrupted.

The relevance of the WTO Agreement on Technical Barriers to Trade

The TBT is aimed at ensuring that national regulations do not become unnecessary barriers to trade. In order to do so, it establishes that national regulations –by definition, mandatory- cannot be more trade–restrictive than the levels established in international standards of reference. The latter are not identified, nor are international standard-setting organizations. On the contrary, the TBT Agreement sets forth some basic criteria. Fundamentally, it establishes that national regulations must satisfy the "necessity test", that is, they cannot be more trade-restrictive than necessary to fulfill a legitimate objective. Pursuant to Article 2.5 of the TBT, whenever a technical regulation is adopted to achieve one the legitimate objectives explicitly mentioned, including the protection of human health, and the national regulation is in accordance with relevant international standards, it shall be rebuttably presumed not to create an unnecessary obstacle to international trade.

In this regard, with respect to the "international standard of reference", the increasing importance of the ICH, the declared objective of expanding guidelines to non-ICH states (and the fact that some non-ICH states actually adopt them), the consensus that generally characterizes the adoption of the standards, and the fact that the WHO is also endorsing ICH guidelines, may result in the perception that ICH are, in effect, the international standards of reference.

This is very important because national regulations will have in principle to be based on the ICH guidelines. Certainly, the TBT is concerned about trade restriction. For instance, it would be applicable if good

[118] *See* Article 2(u) of the WHO Constitution

[119] While Article 32 of Declaration of Helsinki provides for the limited use of placebo in clinical trials, the ICH GCP and ICH Choice of Control Group guidelines adopt a more open stance and accept the use of placebo may change in different jurisdictions

[120] While the Declaration of Helsinki establishes that specific recommendations should be made for the continuation of treatments beyond the trial, these requirements are absent from ICH guidelines.

manufacturing practices adopted internally were more demanding than those existing in international standards of reference. For this reason, states where sophisticated pharmaceutical companies are based may be tempted to increase the level of exigency of international standards using their leverage in the ICH. In this way, they will be able to endorse national regulations that satisfy international standards and that only some companies can satisfy. Situations may be, however, more complex. What happens, however, if the standards adopted are not more demanding but just different? This may occur in areas where, even if some international standards exist, countries hold different views. Likewise, what happens if those standards are just more competitive? In those cases, and contrary to the argument of some companies in recent battles relating to biosimilar products regulations, ICH standards would just not apply.

VIII. Conclusion and Future Work

This report includes the initiation of GHLC study of global health security challenges, and the results of its first meeting on this subject; an analysis and recommendations with respect to access to essential medicines that reflects a contribution made to the UN HLP, as amended based on stakeholder suggestions; an elaborated proposal for a Framework Convention on Pharmaceutical Innovation and related protocols, also reflecting a contribution made to the UN HLP; a detailed analysis and recommendations with respect to access to research materials, and; a study and suggestion for further exploration regarding key regulatory issues affecting the production and distribution of medicines, including trade-related aspects. GHLC members recognize the urgency of addressing issues involving the links between health and human rights law, issues concerning noncommunicable diseases, and obligations to protect the environment and address the health impact of climate change. The GHLC expects to further address all of these issues as it continues with its work program. We have made a good start.