Report of the Conference on Clinical Drug Trials

30 September 2016 | Geneva, Switzerland

Organised by:

Public Eye

Berne Declaration

hai Health Action International

Example – distorted attrition rates
CONSENT TO PARTICIPATE IN A STUDY
TITLE OF STUDY: A Double-Blind, Randomized, Placebo-Controlled Study of GS4104 (R)
64-0796) for Prophylaxis Against Human Influenza Virus (HCF7554)
Payment
You will receive $300 for participating in and completing the study. No payment will be made to you
if you withdraw from the study for personal reasons. An additional payment of $25 will be made
each time you are cultured for an influenza type illness. Full payment will be made if you are removed
from the study for medical reasons after receiving the study treatment. Other costs such as travel
expenses or parking fees resulting from your participation will be your responsibility and are not
reimbursable.

Introduction

Clinical trials are at the core of fundamental decisions that are taken on a regular basis in the field of public health by regulatory authorities – such as marketing authorisation procedures.

For pharmaceutical companies, clinical trials are thus at the heart of fierce commercial interests as a marketing approval can represent huge money for its producer, said Patrick Durisch, Health Programme Coordinator at Public Eye, in his introductory remarks. As published literature extensively shows, clinical drug trials are subject to manipulation and biases, putting at risk not only the participants but also the population at large if the efficacy of the product is being overplayed or side-effects downsized, said Durisch. Concerns have also been raised about lack of transparency on trial results and unethical behaviour in the conduct of clinical trials.

*For pharmaceutical companies, clinical trials are thus at the heart of **fierce commercial interests** as a marketing approval can represent huge money for its producer, said Patrick Durisch*

Despite their importance, clinical trials as such are however rarely debated in public. To discuss these issues in depth and facilitate dialogue on the way forward, Health Action International (HAI) and Public Eye (former Berne Declaration) organised a public conference on 30 September 2016 in Geneva. The all day long event convened up to 100 participants from the NGO, regulatory, academia and industry sector. The session was divided in three keynote speeches and four panel sessions, which included short presentations from experts and an open debate between the panellists and the audience.

Keynote Address by Tom Jefferson

Tom Jefferson | Honorary Research Fellow, Centre for Evidence Based Medicine & Cochrane Acute Respiratory Infections Group

Tom Jefferson, honorary research fellow at the Centre for Evidence Based Medicine and long-standing contributor to the Cochrane Collaboration, kicked off the session with a keynote speech in which he highlighted that well-designed clinical trials are the closest we can get to pure experiment and warned against the perils of badly-designed trials. In a well designed and honestly reported trial, any observed difference between arms are most likely to be due to the differences between intervention and control, he said, drawing on his vast experience. He gave some common examples of distortion such as poorly worded objectives, shaky rationale, selection biases in the recruitment of population, non-randomisation, blinding failures and loss of participants at follow-up.

Another possible cause of distortion is the choice of the comparator: “If you are worried about harms, choose and active comparator; if you are worried about effectiveness, choose a weak comparator”, Jefferson said. He concluded his keynote address by refering to the RIAT (Restoring Invisible and Abandoned Trials) call to publish, formally correct or republish abandoned trials, as unpublished and misreported studies make it difficult to determine the true value of a treatment.

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First Panel

The Globalisation of Clinical Drug Trials & Ethics

Panellists:
Patrick Durisch | Health Policy, Public Eye
Ayman Sabae | Right to Health Researcher, Egyptian Initiative for Personal Rights
Samia Hurst | Director, Institut Ethique Histoire Humanités (iEH2), University of Geneva
Françoise Jaquet | Head, Clinical Trials Division, Swissmedic

The issue of ethics in clinical trials was addressed in detail during the first panel session. Patrick Durisch, Health Programme Coordinator at Public Eye, opened up the session with his presentation about the increasing off-shoring of clinical trials to low and middle income countries (LMICs). According to Durisch, at least 1/3 of international clinical trial participants are from LMICs. Pharmaceutical companies are often attracted by lower costs and weaker regulatory frameworks in those countries, which in turn poses a number of concerns from an ethical perspective. Various reports as well as published literature have revealed issues concerning the scientific rigour of trials conducted in those settings, suboptimal informed consent procedures and lack of compensation of participants in case of adverse events. In addition, access to treatment in the post-trial phase is very limited. In fact, recent studies show that only about 40% (South Africa) to 60% (Latin America, India, Egypt) of the drugs that made it to a high-income market were effectively registered in the LMIC where tested. Ethical guidelines deem trials unethical and exploitative if the product tested is not benefitting i.e. made available to the population concerned, Durisch concluded.

Sabae referred to the particular situation of industry-sponsored clinical trials in Egypt, where participants often take part in studies due to poor financial means to undergo treatment but access and affordability of treatment post-trial remains suboptimal.

This information was corroborated by Ayman Sabae, Right to Health Researcher at the Egyptian Initiative for Personal Rights. Sabae referred to the particular situation of industry-sponsored clinical trials in Egypt, a country where 23% of the population is under the poverty line and where 62% of healthcare costs are paid out of pocket. Like in other LMICs, participants often take part in trials due to poor financial means to undergo treatment but access and affordability of treatment post-trial remains suboptimal. Research reveals that the monthly treatment for some medicines tested in the country costs more than 20 times the official monthly minimum wage of the public sector. According to Sabae, whilst the research infrastructure in Egypt is increasingly attractive, the legislation protecting the rights of patients, and clinical trial participants in particular, is poor. Amongst his recommendations on the way forward, he called for the establishment of a single, robust legislative framework with a functional independent control system that sets clear conditions for trials. He also called for the set-up of an online, up-to-date public registry of trials and cautioned the government against approaching clinical research as a mere vehicle for the delivery of unproven treatments to participants with limited financial resources.

According to Samia Hurst, Director, Institut Ethique Histoire Humanités (iEH2), University of Geneva, the principles of research ethics are quite stable but their application is a work in progress. She referred to some benchmarks for ethical research like seeking permission from local communities and involving them, taking their social values into account, respecting enrolled patients by ensuring informed consent, confidentiality and results sharing. Although the principles remain the same, international research with human subjects raises distinct difficulties because usual protections might be more difficult to apply in some settings due to asymmetric power relations, deep inequalities, cultural differences and lack of local capacity. Nonetheless, progress is being made in some ethical standard guidelines such as the Declaration of Helsinki or CIOMS, e.g. on the notion of vulnerability and its related protection mechanisms. Capacity building in research ethics is increasing as well as requirements for compensation. Nonetheless, more needs to be done to ensure international coordination in the oversight of research and a fair deal to trial participants.

Françoise Jaquet, Head, Clinical Trials Division at Swissmedic provided the regulatory perspective of a high-income country on the issue of ethics in clinical trials. In line with previous interventions, she referred to a changing landscape, with high-income countries still dominating the space for clinical trials but more and more of them moving to middle income countries, in particular to regions such as Asia. She referred to Good Clinical Practice (GCP) Guidelines as the "golden" standard in clinical research. Compliance with these guidelines ensures that the rights, safety, well-being of trial subjects are protected, and that the clinical trial data are credible and reliable. Swissmedic supervises the quality of clinical trials by performing on-site inspections for trials conducted in Switzerland and also by reviewing the documentation submitted by companies during marketing authorisation applications. In particular, the agency checks whether the study has been performed according to the protocol, if the study report is based on what the protocol and the statistical analysis plan (SAP) outlines, whether investigators are qualified and if the study protocol and patient information documents have been reviewed and approved by an independent ethics committee.

TAKEAWAY MESSAGES

1. There is an increasing trend to off-shore clinical trials to Low and Middle Income Countries (LMIC)

2. Pharmaceutical companies are attracted by lower costs, weaker regulatory frameworks and ethical standards in those countries

3. Concerns have been raised about the lack of scientific rigour of industry-sponsored trials, poor trial transparency and insufficient protection of participants

4. Usual protections in international research are more difficult to apply in these settings due to asymmetric power relations, deep inequalities, cultural differences and lack of local capacity

5. Recommendations on the way forward include: better coordination in the oversight of clinical research at international level, strengthened ethical control by host countries and high-income countries (including, but not limited to, inspections by the latter), enhanced protection for vulnerable participants by trial sponsors, clear definition of benefit sharing mechanisms before the clinical trial starts and enhanced transparency at all levels.

Second Panel

Transparency & Access to Clinical Trial Data

Panellists:
Jan Stadler | Legal Officer, Inquiry Coordination Unit, European Ombudsman
Ancel.la Santos Quintano | Policy Advisor, Health Action International
Ghassan Karam | International Clinical Trials Registry Platform, World Health Organization
Tom Jefferson | Honorary Research Fellow, Centre for Evidence Based Medicine & Cochrane Acute Respiratory Infections Group

The second panel session was entirely dedicated to the issue of clinical trial data transparency.

Evidence shows that only half of all completed trials are published. Tom Jefferson referred to the non-publication of clinical trials as a major threat to independent systematic reviews, as well as the misleading description of the study design, conduct and results of trials (reporting bias). Jefferson emphasised that 50% of Cochrane reviews showed suspicious signs of selective reporting of efficacy outcomes and 63% of safety outcomes. The comparison between different types of documents for reporting clinical trials reveals that Clinical Study Reports (CSRs) submitted for regulatory purposes – which can amount up to thousands of pages – provide the most reliable and detailed information on each clinical trial. CSRs have been made available on request by the European Medicines Agency (EMA) under its 2010 retroactive release policy but data redactions remain a real threat. The critical appraisal industry is based on the production of assessment and reporting checklists which have so far completely ignored regulatory documents, despite growing evidence of the unreliability of journal reports of pharmaceutical trials. This may be due to conservatism, lack of appreciation or latent conflicts of interest.

Following up on the question of public access to regulatory documents, Jan Stadler, from the European Ombudsman's Inquiry Coordination Unit, spoke on the importance and value of transparency in the area of public health. Transparency opened the work of public bodies such as the European Medicines Agency (EMA) to public scrutiny and allowed for more information being provided to patients, researchers and health care professionals. Therefore, the European Ombudsman Emily O'Reilly welcomed EMA's new policy on the proactive publication of clinical trial documents. At the same time, citizens continue to be able to request documents from EMA. Information in such documents could only be withheld to protect certain clearly defined interests, such as patients' personal data. To a limited extent, commercial interests of pharmaceutical companies may also justify some redactions unless there existed an overriding public interests, such as the need to protect and promote public health. As the Ombudsman stated in a recent decision related to documents on the approval of Humira (adalimumab), where information in a clinical study report had implications for the health of individuals, the public interest in disclosure should generally defeat any claim of commercial sensitivity.

In her presentation, Ancel.la Santos, Policy Advisor at HAI, explained that in the last five years, discussions about access to clinical trial data seem to have intensified, with increasing claims for greater transparency. Santos referred to the adoption of a new Regulation on Clinical Trials in 2014 as an important milestone on data transparency. Notably, the Regulation mandates that Clinical Study Reports submitted for marketing authorisation have to be made publicly available and emphasises that, in general, information in these reports should not be considered commercially confidential. In the same year, the EMA adopted a new policy for the proactive publication of clinical reports. Whilst acknowledging the importance of these initiatives, she emphasised the need to monitor closely the implementation of these policies and remain vigilant about redactions on the grounds of commercial confidentiality and aggressive anonymisation techniques promoted by the industry, which are completely out of balance and threaten the clinical usefulness of the data.

In line with previous interventions, Ghassan Karam, from WHO, emphasised that registration of clinical trials is both a scientific and ethical duty. According to Karam, data transparency can help to improve accountability, public trust, identify gaps in research and avoid unnecessary duplication of clinical trials. He introduced the audience to the WHO International Clinical Trials Registry Platform (ICTRP), a global platform that links clinical trial registries to facilitate trial identification. Primary Registries in the WHO platform need to meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Other requirements include, for example, that the register is managed by a non-for-profit agency and has the government's support to act as the main primary registry for the country/region. In line with other pro-transparency initiatives, the WHO published in April 2015 a new statement on Public Disclosure of Clinical Trials Results which defines clear reporting timeframes, calls for results-reporting of older but still unpublished trials and outlines steps to improve linkages between clinical trial registry entries and their published results.

TAKEAWAY MESSAGES

- *Non-publication of clinical trials and selective reporting of trial results are common practices in biomedical literature which pose a major threat to independent systematic reviews and informed decision on treatment*
- *Publication of clinical trial data is important from a scientific and ethical standpoint*
- *Clinical Study reports provide the most reliable and detailed source of information on clinical trials*
- *Important pro-transparency initiatives have been adopted in the European Union and WHO in the last couple of years*
- *Data redactions are a real threat. Close monitoring of policy implementation is needed.*
- *Public health should always outweigh commercial interests*

Keynote Address by Teresa Alves

International Policy Advisor, La Revue Prescrire

The second keynote speech of the day was given by Teresa Alves, International Policy Adviser at Prescrire. The focus of her presentation was trends in marketing authorisation in Europe, namely the role of regulators. Ratings from the independent drug bulletin Prescrire show that 47% of new indications authorised in France between 2005-2011 didn't offer anything new when compared to the available treatments and 20% were not acceptable (i.e. products without evident benefit but with potential or real disadvantage). Timelines for drug licensing have halved over the last 20 years and lower evidence requirements for marketing authorisation are being accepted by regulators, such as the use of surrogate markers, methodological shortcuts and evidence from shorter trials wuth less participants. Premature approval of medicines raises concerns as it has been associated with higher rates of post-marketing safety warnings. Although modalities available to provide faster access to medicines require the conduct of additional studies, pharmaceutical companies do not always honour post-marketing commitments. Whilst there is a trend to shift the burden of proof to the post-marketing phase, measures to ensure appropriate use once a drug is in the market are often limited, if not inadequate. According to Alves, whilst RCTs are the best design on which to base therapeutic recommendations efforts are being made to tarnish the gold standard and push for a lesser evidence agenda. Although observational studies can generate important data, they also have several methodological limitations. The solution, she said, is better RCTs instead of shaming RCTs. In 2015, 83% of the overall budget of the European Medicines Agency came from industry fees. The agency's conflict of interest policies fall short and experts with ties to pharmaceutical companies are invited to share their views on pharmaceutical products. Alves also raised additional concerns about the provision of early scientific advice to companies, the role of regulators as co-developers and cautioned against regulatory capture.

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Third Panel

Evidence Generation for Marketing Authorisation & Adaptive Pathways

Panellists:
Hans-Georg Eichler | Senior Medical Officer, European Medicines Agency
Beate Wieseler | Head, Drug Assessment Department, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Jörg Schaaber | Past-President, International Society of Drug Bulletins, BUKO-Pharma Kampagne
Mónica Cavagna | BEUC (European Consumers' Organisation)
Sophie Le Pallec | Chair, Amalyste

Evidence requirements for marketing authorisation were further discussed during the following session on Adaptive Pathways (AP). Adaptive Pathways is defined by the European Medicines Agency as a prospectively planned, iterative approach to bringing medicines to market. Under this approach, drug development is initially targeted towards a well-defined group of patients that is likely to benefit most from the treatment. Initial licensing is then followed by iterative phases of evidence gathering and progressive licensing adaptations. Between March 2014 and August 2016, the EMA ran a pilot to explore the practical implications of the Adaptive Pathways concept with medicines under development.

According to Hans-Georg Eichler, Senior Medical Officer at the EMA, the ''access vs evidence'' question is an ethical and scientific conundrum which Adaptive Pathways attempts to solve. AP, he explained, harnesses existing tools, such as conditional marketing authorisation, Risk Management Plans, scientific advice provided to companies, patient registries and adaptive pricing and reimbursement schemes. Adaptive Pathways is to focus on the authorisation of medicines for a high unmet need (sub) population first, and on products likely to have a major impact for patients. Remaining uncertainties would be reduced as fast as possible through an established iterative development plan. For this purpose, the full evidence spectrum would be taken into account (e.g. RCTs, observational studies). According to Eichler, recent experience shows that the current pharmacovigilance system is robust and compliance with binding post-marketing studies generally good (although start of some studies is slow). He acknowledged that subsequent data may not confirm the initial promise of high effect size but that 'exit' scenarios can be applied by regulators and payers. Aware of the fact that Adaptive Pathways has drawn some criticism, he called upon critics to come up with alternative, better ideas to Adaptive Pathways that provide solutions to current problems.

The German Health Technology Assessment (HTA) body, IQWiG, a key player in the evaluation of medicines effectiveness, is one of the stakeholders that has raised concerns about Adaptive Pathways. During her intervention, Beate Wieseler, Head of the Drug Assessment Department at IQWiG, expressed reservations about the need of further accelerated approval pathways beyond procedures currently available, and about the scope of Adaptive Pathways (i.e. whether it will be restricted to situations of true unmet medical need). According to Wieseler, even at present, there is often insufficient data to describe the benefits of a drug for patients, and HTA bodies have coped with some negative experiences in dealing with early access schemes and post approval-evidence generation. IQWiG is particularly concerned with the emphasis that AP puts on observational studies due to the uncertainties of non-randomisation and difficulties to control confounding variables. Wieseler recalled the EMA that, under its pilot project, the majority of development plans to collect real world data to supplement RCTs were found to be vague and insufficient detail was provided about how to refine the safety profile and even less about how efficacy could be confirmed or augmented in the post-authorisation phase. She recommended the EMA to use the advantages of randomisation whilst avoiding the shortcomings of many current RCTs, enhance clinical trial data transparency and explore the use of observational studies for situations in which RCTs are really not possible.

To Jörg Schaaber, Past-President, International Society of Drug Bulletins and Managing Director, BUKO-Pharma Kampagne, companies' interests are the drivers behind Adaptive Pathways. According to a conceptual paper on Adaptive Pathways, the potential benefits for companies of this scheme would be an earlier revenue stream than under a conventional licensing pathway and less expensive and shorter clinical trials. Evidence shows that the pharmaceutical industry has already been the business sector with the highest average profit margin for years, without such benefits necessarily being channelled to prioritise research and development activities. Schaaber told the audience about NEWDIGs, a think tank group established at the Massachusetts Institute of Technology's (MIT) Center for Biomedical Innovation (CBI) in the US. NEWDIGs brought together industry, academia and regulators who developed the concept of Adaptive Pathways. H.G Eichler himself participated in NEWDIGs as a visiting scholar in 2011. To Schaaber, a key concern of Adaptive Pathways has to do with the fact that regulators become co-developers of medicines – and the inherent risk of institutional capture that emerges therein. He also showed some conflicting messages in different pro- AP papers about the definition of unmet medical need and its scope, with a conceptual paper even referring to AP as the future common pathway for drug approval. Instead of weakening evidence requirements, Schaaber called for better designed RCTs, comparative data against therapeutic standard, better surveillance of adverse drug reactions and therapeutic advance as market entry criterion.

The lack of clarity about what constitutes an 'unmet medical need' under the EMA's pilot project on AP is also an issue of concern to the European Consumer Organisation (BEUC). The representative of the organisation, Mónica Cavagna, highlighted a passage of the EMA's report on the pilot project which reads that in the context of Adaptive Pathways ''a broader acceptation of the term unmet medical need is considered''. BEUC is also concerned about poor compliance with post-marketing studies, which is particularly relevant for medicines with an early authorisation. In fact, studies show that obligations imposed by the EMA after drug licensing are fulfilled by companies with delays and discrepancies. In addition, the EMA has acknowledged that it has proven challenging to identify sound strategies of real-world evidence collection. To BEUC, it is not clear the extent to which patients and doctors would be fully aware about increased levels of uncertainty associated to drugs authorised under Adaptive Pathways. Effective control of off-label use of drugs authorised for small subpopulation groups could also prove challenging. Another issue that the EMA's project on Adaptive Pathways does not clarify according to BEUC is how patients would be protected in case of harm. Cavagna emphasised that through Adaptive Pathways, risks are comparable to those in clinical trials but without similar guarantees (e.g. damage compensation). She also referred to critical positions about AP from HTA bodies and payers and questioned how these medicines – for which there will be limited data – and their post-marketing studies would be financed. Cavagna finalised her presentation by reminding that the EU legislation already provides for mechanisms that allow patients to get faster access to medicines. To BEUC, faster approval procedures should be the exception, not the rule.

To Sophie Le Pallec, from Amalyste, earlier marketing of a drug means that serious and rare adverse drug reactions (ADRs) will be detected after the clinical trial. Amalyste is an organisation representing patients with Lyell and Stevens-Johnson's syndromes, generally caused by ADRs. Le Pallec questioned whether patients are fully aware of the impact of earlier market access to their rights, and regretted that liability issues are not being addressed in the Adaptive Pathways debate. She reminded the audience that under the existing legislative regime, compensation to victims of (unexpected) drug induced harm outside clinical trials falls within the general EU liability regime on defective products, in which the victim must prove the causal relationship between the product (in this case, the medicine) and the damage caused. Compensation rights expire 10 years after the product is placed on the market and 3 years after the occurrence of the damage. Proving a causal relationship is very hard for a patient who does not have access to clinical trial data and drug-induced victims, she said, rarely get compensation. Amalyste recommends that clinical trials liability regimes are extended to the post-authorisation phase and cover all unexpected ADR victims, development risk exemption are suppressed for drugs and consumers are adequately informed about medicines' risks.

TAKEAWAY MESSAGES

- *Adaptive Pathways is defined by EMA as a prospectively planned, iterative approach to bringing medicines to market. Drug development is initially targeted towards a high unmet need (sub)population first, and on products likely to have a major impact for patients. Initial licensing is followed by iterative phases of evidence gathering and progressive licensing adaptations. For this purpose, the full evidence spectrum would be taken into account (e.g. RCTs, pragmatic trials, observational studies). According to EMA, AP harnesses on existing tools.*
- *Consumer, patient and HTA representatives raise concerns about the need of further accelerated approval pathways beyond procedures currently available. Early market access should be the exception and not the rule.*
- *Contradictory information from EMA about the question of the 'unmet medical need' and the scope of Adaptive Pathways.*
- *The emphasis that AP puts on observational studies is seen as problematic, due to the uncertainties of non-randomisation and difficulties to control confounding variables.*
- *Caution against shifting the burden of proof from pre to post-marketing phase: patients and healthcare professionals not fully aware about risks; pharmaceutical companies do not honour post-marketing commitments.*
- *Adaptive Pathways seen as an industry-driven concept.*
- *Liability regimes are particularly relevant in early market schemes, but patients' protection is weak. Under AP, patients' risks are comparable to clinical trial participants, but without similar rights on compensation for damage.*

Fourth Panel

The Way Forward for Needs-driven Public Health Research

Panellists:
Silvio Garattini | Founder, Mario Negri Institute for Pharmacological Research
Joel Lexchin | Professor, Faculty of Health, York University (Toronto, Canada)
Katy Athersuch | Policy Adviser, Médecins Sans Frontières Access Campaign
Nathalie Strub-Wourgaft | Medical Director, Drugs for Neglected Diseases Initiative (DNDi)

The fourth panel session aimed at discussing recommendations and initiatives for a public-health driven biomedical innovation system. Silvio Garattini, Founder of the Mario Negri Institute for Pharmacological Research, opened up the session by referring to some of the pitfalls in clinical trials – such as abuse of placebo, inappropriate comparators, non-inferiority design, surrogate endpoints, overlook of adverse drug reactions, selective publication and reporting. He advocated for adequate training of clinical investigators in RCTs, focusing on patient-centred outcomes and comparative effectiveness and data transparency. He mentioned the example of the Italian medicines agency's (AIFA) support to independent clinical research through a fee charged to pharmaceutical companies, equivalent to 5% of their marketing expenditure. Almost 190 projects were funded between 2006-2009. ECRIN is another interesting initiative. This public, non-profit organisation links scientific partners and networks across Europe to facilitate multinational clinical research. Strict transparency rules are applied which include trial registration in a public register, trial results posting, publication of results irrespective of findings, sharing anonymised raw data with the scientific community and declaring conflicts of interest. According to Garattini, the European pharmaceutical legislation needs to incorporate criteria on added therapeutic value in addition to quality, safety and efficacy standards. Marketing authorisation procedures should be supported by at least two pivotal trials, one sponsor-driven RCT and an independent one.

Along the same line, Joel Lexchin, Professor, Faculty of Health, York University (Toronto, Canada) called for therapeutic innovation that meets real public needs and that is affordable. Even if clinical trials are publicly funded, he argued, pharmaceutical companies still set priorities for what drugs are researched and developed. They will never do clinical trials for off-patent drugs and unprofitable diseases, so alternative models for R&D need to be explored to cover these and other unmet needs. He talked about priority review vouchers, product development partnerships (PDPs), prize funds, advanced market commitments and an R&D treaty as mechanisms that have been under discussion. Changes can also come from the regulatory side to promote true innovation. For example, conditioning marketing authorisation to the use of hard clinical outcomes (and not surrogate endpoints), superiority trials and clinical trials use in 'real world' patients. The patent system should also be re-considered: for example, no patents granted for minor variations of existing agents with no added therapeutic value or for tweaks to drug delivery devices with no major added functionality. No public funding should be granted for drugs that do not offer: added therapeutic value (more effective in general or in specific populations), greater safety, new useful formulations (e.g., paediatric formulations) ; novel characteristics (e.g., vaccines that don't require a cold chain) and improved compliance. He acknowledged that there are no simple answers and that any solution requires multiple approaches.

The concept of de-linkage was introduced by Katy Athersuch, Policy Advisor at the Médecins Sans Frontières (MSF) Access Campaign. In a needs-driven model of innovation, set priorities respond to health-needs and collaboration and data sharing are encouraged. The result is competition, as opposed to monopolistic positions, and fair prices. Athersuch talked about the more than a decade long- process that took place at the WHO, resulting in various reports and policy papers documenting the pitfalls of the current patent-driven R&D model. Among these was the Consultative Expert Working Group (CEWG), whose report released in 2012 recommended concrete mechanisms to finance research and development to meet the needs of people in developing countries, including the need to delink the cost of R&D from the endproduct's price. The CEWG also recommended WHO Member States to reach a global agreement (R&D convention) that sets priorities, coordinates research, ensures financing and defines norms for access. Lack of political will prevented significant advances for a while, but emerging challenges have put it back to the spotlight. For example, the Ebola outbreak and the absence of existing treatment, rising levels of antimicrobial resistance (AMR) and high prices blocking access to medicines in Europe and the US. All these global issues have become high on the political agenda, in discussions in the EU and amongst the G7 and G20. In parallel, in 2016 the UN High Level Panel on Access to Medicines (UNHLP) published a report calling again for the need to achieve a binding R&D convention that delinks the costs of R&D from end prices, a code of principles in biomedical R&D, innovative financing mechanisms and transparency of clinical trial data. MSF urged decision-makers to move from statements to concrete change.

Product Development Partnerships (PDPs) have been proposed as alternative, public-health driven models of R&D. A very-well known PDP is the Drugs for Neglected Diseases Initiative (DNDi). Nathalie Strub-Wourgaft, DNID's Medical Director, introduced the R&D model of the organisation, which is driven by the principles of non-profit, patient-needs driven research, independence and pragmatic policies on IP to ensure that medicines are ultimately affordable to patients who need them. To date, 7 new treatments have been made available through DNDI and 15 new chemical entities are in the pipeline. Clinical trials conducted by the organisation focus on unmet medical needs and respond to a product development plan that has to meet a disease specific ''target product profile'' developed with public health partners. Strub-Wourgaft emphasised that a key challenge is that trials are conducted in endemic countries with often poor, voiceless and vulnerable patients, investigators with little or no experience in the field, poorly resourced ethics committees/national regulatory authorities. DNDI's approach to the conduct of trials in those settings is to use and strengthen research capacities in the region. In her view, remaining challenges include ethical concerns around vulnerability of patients, the capacity of national regulatory agencies to review CTs, technical, cost and timing issues around transparency, considerations on whether or not a disease deserves a priority review in the medicines marketing authorisation process and post-approval safety detection issues. Recommendations for the future include defining public health priorities and expected value of new drugs, promoting inclusive collaborative procedures with public health actors and set up an R&D observatory and fund.

TAKEAWAY MESSAGES

- *The limitations of the current, monopoly-driven (patent-driven) R&D model have been clearly documented.*
- *Access to medicines has become a global issue. Even high-income countries have started limiting the reimbursement of new treatments due to their exorbitant prices (e.g. cancer or hepatitis C).*
- *The misalignment of financial incentives of the present R&D model with the public health priorities results in the dire absence of effective and affordable medicines to treat neglected diseases/patients.*
- *The call for a global R&D Convention on the coordination, financing and development of health technologies has been reiterated several times, most recently by the UN Secretary-General's High-Level Panel on Access to Medicines (UNHLP). Decision-makers should move from statements to concrete changes.*
- *Pharmaceutical legislations need to incorporate criteria on added therapeutic value in addition to quality, safety and efficacy standards.*
- *Marketing authorisation procedures should be supported not only by sponsor-driven data, but also by at least one independent pivotal clinical trial to minimise commercial distortion.*

Keynote Address by Ruth Dreifuss

Co-chair, United Nations Secretary General's High-level Panel on Access to Medicines

The last keynote speech of the day was given by Mrs Ruth Dreifuss, former President of the Swiss Confederation and Co-Chair of the UN Secretary-General's High-Level Panel on Access to Medicines (UNHLP). In its report released in September 2016, the UNHLP, whose mandate was 'to recommend solutions for remedying the policy incoherences between the justifiable rights of inventors, international human rights laws, trade rules and public health in the context of health technologies', addressed several old and new challenges pertaining to access to medicines. Dreifuss explained the work and the atmosphere prevailing in the UNHLP, and recalled some of the recommendations made by the Panel, such as:

- Intellectual property (IP) laws and access to health technologies: making full use of policy space available in the TRIPS Agreement, balancing the priorities in Free Trade Agreements, publicly funded research serving public health
- New incentives for R&D: more public funding to address unmet health needs, test and implement new models for financing and rewarding R&D, binding R&D Convention that delinks the cost of R&D from end prices
- Governance, accountability and transparency:
    - Governments to review the situation of access to health technologies in their countries in the light of human rights principles
    - Private sector companies to disclose the costs of R&D, production marketing and distribution of their products
    - UN General Assembly to convene a Special Session, no later than 2018, on health technology innovation and access

Directly relevant to this conference was also the recommendation of the UNHLP that data on all completed and discontinued clinical trials be made publicly available regardless of whether their results are positive, negative, neutral or inconclusive. The UNHLP also called for governments to require that study designs and protocols, data sets, test results and anonymity-protected patient data be available to the public in a timely and accessible fashion to facilitate open collaboration.

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Closing Remarks by Tim Reed

Executive Director, Health Action International

In closing, Tim Reed, Executive Director of Health Action International, teased out four key messages that had resonance during the day.

1. That we should be giving greater emphasis to the fact that the drugs we take in Europe may well have been trialled unethically – without consent, without any opportunity for on-going treatment and without proper support to patients. He suggested that consumers choose fair-trade clothing and fair-trade food, and that we should be aware that the drugs we take may be tainted at best by unethical practice and at worst may have caused harm.

2. Clinical trial data – transparency of any data that is in the public interest – must be a gold standard which we demand each and every day. The EU transparency regulation should be welcomed, but transparency in and of itself is not enough. In the end, it is we, the technocrats, bureaucrats and advocates that must exploit transparency and convert it into meaningful intervention in the public interest.

3. Adaptive Pathways – Dr Reed questioned the motivation of the initiative, and on whose behalf it is being proposed? Ever since the 1970s, it has been the goal of the pharmaceutical industry to 'reduce the regulatory burden' of licencing. The concertation process, accelerated approval, and now Adaptive Pathways, have all been attempts to shave a little off the regulatory timeline. And yet we know, the consequence of reduced regulatory timelines implies greater uncertainty about treatments' effects and safety concerns. We have a perfectly good mechanism for unmet medical need, so why Adaptive Pathways?

4. We don't hear much about regulation for innovation - regulation that insists on therapeutic value as part of the licence application, and we need a move to restructure regulation that promotes real public health needs.

Dr Reed closed the day by thanking all the speakers for their expert inputs and the audience for a lively and interesting discussion.

Trust no one?
Restoring invisible and abandoned trials (RIAT) declaration (from Doshi et al
PUBLIC CONFERENCE ON CLINICAL DRUG TRIALS

Conference Materials

All conference materials, including slide presentations and the Conference Agenda, are available online at:

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