The Accelerate Marketing Authorization of New Pharmaceutical Products and the Capture of Pharmacovigilance Activities by Pharmaceutical Companies

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1. Pharmacovigilance as a manipulative tool utilized by pharmaceutical companies

Pharmacovigilance is a scientific field based on observation, focusing on the interaction between a medicine and patients, aiming at proving the possible causal relationship between an adverse event[1] and the product. Its purpose is to identify and rapidly warn adverse reactions exposing patients to risk, with the ultimate objective of preventing these effects from being replicated.

The glossary of the "ISDB/EU Berlin Declaration on Pharmacovigilance"[2] mentions multiple approaches adopted by the World Health Organization (WHO) on the definition of the pharmacovigilance field:

> *"The WHO defines pharmacovigilance as '... the activities involved in the detection, assessment, understanding and prevention of adverse effects or any other drug related problems...' or as 'analysing and **managing the risks of medicinal products'**. Pharmacovigilance is a broad concept, that spans the whole clinical phase of drug development and the postmarketing drug safety surveillance including **risk management** and preventing of drug errors, communicating drug information, promoting rational drug use and crisis preparedness."* (italics added)

Such a multitude of approaches and definitions adopted by WHO when dealing with Pharmacovigilance activities permits the instrumentalization, in the international arena, of the pharmacovigilance concept and its technical tools, especially when pharmacovigilance activities are handled in terms of "risk management systems" led by marketing authorization holders.

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[1] The ISDB/EU Berlin Declaration on Pharmacovigilance's glossary provides the following definitions of adverse reaction and adverse event, based on WHO's definitions:

"ADR/AR = Adverse drug reaction/adverse reaction

WHO defines adverse drug reactions (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function". The causal relation between the drug intervention and the event is at least a reasonable possibility. (…) It has also to be considered that an ADR may be the result of intended or accidental poisoning, drug abuse, or errors in administration or compliance."

"AE/ADE = Adverse event/adverse drug event

WHO defines adverse event (AE) as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment". With respect to pharmacovigilance AE and ADR both have their relevance."

ISDB. **ISDB EU: Berlin Declaration on Pharmacovigilance**, Berlin, January 2005. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[2] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

Given the complexity and the time span necessary to establish the possible causal relationship between an adverse event and a pharmaceutical product, companies see in the pharmacovigilance field the perfect opportunity of postponing stringent regulatory decisions (as modifications to patient information leaflets or the medicine withdrawal), by providing incomplete updates on the safety profile of a given medicine through biased risk management systems and Periodic Safety Update Reports (PSURs).

Marketing authorization holders, while performing pharmacovigilance activities related to risk management systems prioritize managing the product's reputation (a company's asset) to the detriment of known or potential risks posed to patients:

> *"The conception of risk management allows the pharmaceutical companies to adopt a product-oriented "risk management" approach designed primarily to protect the product (their medicines), but not to protect patients from drugs' adverse effects."*[3]

On the side effects of risk management systems, International Society of Drug Bulletins (ISDB) & Medicines in Europe Forum (MiEF)[4] mentions the notorious examples of Acomplia and Chantix, in which risk management systems were tools employed to "manage" unfavourable risk-benefit balances to the detriment of public health:

> *"(…) [Risk Management Systems] RMSs are too often used to reassure the public when inadequately evaluated drugs have been granted premature marketing authorisation. The examples of rimonabant (formerly marketed as Acomplia) and varenicline (Chantix) illustrate this point.*
> *(…)*
> *Rimonabant (formerly marketed as Acomplia) was licensed for the treatment of obesity. But one of its effects is to increase the number of suicides. The European agencies' response was initially confined to setting up a "risk management system", none of the details of which were made public. It took about 2 years after its marketing authorisation was granted for rimonabant to be withdrawn from the market! The US Food and Drug Administration had refused to approve this drug from the outset. Similarly, varenicline (Chantix) has an unfavourable risk-benefit balance in smoking cessation (psychiatric disorders including increased suicide risk, etc.), but for now the only measure has been to operate a risk management system."*

Moreover, pharmacovigilance activities can be utilized by pharmaceutical companies as clinical trials in disguise, mainly when accelerate marketing approvals, as well as post-marketing surveillance activities employing sophisticated data mining tools are involved, allowing the assessment of a great volume of real-world evidence related to new medicines across multiple jurisdictions and many distinct layers of the population.

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[3] HAI Europe, MiEF & ISDB, **New European pharmacovigilance legislation: getting it right. - Response to the European Commission's public consultation on legislative proposals for pharmacovigilance**. 2008.
Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[4] ISDB & MiEF.
Available on: https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

In sum, despite its vital role in health regulatory monitoring and controlling policies, unfortunately pharmacovigilance activities have been undermined and distorted by pharmaceutical companies utilizing the field as an opportunity to manipulate the public opinion through the concept of "risk management systems", perform clinical trials in disguise that are not subject to the due ethical and regulatory scrutiny of competent authorities, as well as jeopardize and postpone the adoption of the required safety measures related to pharmacovigilance signals and proven or probable adverse reactions.

2. The gradual erosion of Pharmacovigilance activities' role in the regulatory framework

The implementation, development and strengthening of pharmacovigilance systems have their roots in public health disasters, as described by HAI Europe, MiEF & ISDB[5]:

> *"The need for continuous monitoring of adverse effects emerged in the early 1960s, particularly after the thalidomide affair, which caused several thousand cases of atrophy of one or several limbs in babies born to women who had taken this drug during pregnancy. A number of subsequent public health disasters have served to remind us that effective pharmacovigilance is crucial for the protection of citizens: the diethylstilbestrol (DES) affair in the 1970s (cancer of the vagina and anomalies of the uterus in women exposed to this drug in the womb), that of triazolam in the 1980s (anterograde amnesia); and more recently, in the 2000s, those of cerivastatin (severe muscular disorders), rofecoxib (fatal cardiac events), so called 'selective' serotonin reuptake inhibitors (SSRIs) (increased risk of suicide), olanzapine (diabetes and metabolic disorders), rosiglitazone (fatal cardiac disorders)."*

Despite the historical disasters caused by adverse effects of medicines and the intrinsic hurdles of proving the causal relationship between an adverse event and a given pharmaceutical product, several recent trends in health regulation are prone to deregulate pharmacovigilance activities, exposing more people to expected and non-expected adverse effects of drugs that sometimes are not even proven to be effective[6]. According to ISDB/EU Berlin Declaration on Pharmacovigilance[7]:

> *"(…) new drugs are being approved for marketing more quickly and without adequate long-term safety studies, supranational marketing is making drugs available to many more people at an early stage, and removal of restrictions on*

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[5] HAI Europe, MiEF & ISDB, **New European pharmacovigilance legislation: getting it right. - Response to the European Commission's public consultation on legislative proposals for pharmacovigilance**. 2008. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[6] "The criterion that a product must be of proven therapeutic efficacy in order to obtain authorisation was introduced after the thalidomide affair in the USA (Kefauver-Harris amendments in 1962), and in Europe in 1965. Only proven therapeutic efficacy can justify exposing the entire population to the risks of adverse effects when a new drug is authorised. It is essential to have an evaluation providing convincing evidence of the drug's efficacy in order to weigh up the risks of adverse effects (known, suspected and expected), in order to answer the question: what adverse effects are we prepared to accept given the drug's proven efficacy? (…)"
HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[7] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

availability is leading to some medicines being used more widely by patients for self-medication."

The progressive deregulation of the Pharmacovigilance field, as well as the increasing control of its activities by the very companies supposed to be monitored and enforced by pharmacovigilance decisions has led the authorities to frequent questionable actions and omissive behaviors. According to HAI Europe, MiEF & ISDB [8]:

"In recent years, several major pharmacovigilance problems have thrown into question not only the effectiveness of pharmacovigilance systems, but also the authorities' commitment to protecting citizens by putting in place the necessary measures, such as quickly withdrawing drugs exposing patients to risks that are too high in relation to the expected benefits."

Simplifying administrative procedures and rationalizing the European pharmacovigilance system, for example, was an excuse given by the European Commission's Directorate General for Enterprise[9], in 2007, to transfer the effective control of pharmacovigilance activities to the private sector, despite all the intrinsic conflicts of interest arising from such a regulatory scenario:

"A series of public health disasters (from thalidomide in the 1960s to rofecoxib (Vioxx) at the beginning of this century) have served to remind us that effective pharmacovigilance is crucial for the protection of citizens. Regrettably, the European Commission's proposed legislative changes, published on 5 December 2007, pose a serious threat to public health.

On the pretext of simplifying administrative procedures and "rationalising the system", the Commission's proposals undermine the European pharmacovigilance system and represent a major backward step for the evaluation of medicinal products."[10]

Indeed, according to the European Commission's Directorate General for Enterprise, the aim of adopting risk management systems and post-authorization studies as a pharmacovigilance strategy is provide business-friendly opportunities to pharmaceutical companies, since "*earlier product authorisation provides faster return on investment and, by reducing the cost of capital the total cost of product development is reduced*"[11]. On the due proper balance of companies' and patients' rights and interests, ISDB & MiEF[12] reminds the following:

"Yet it has been demonstrated that premature licensing is achieved at the expense of proper evaluation, leading to more pharmacovigilance issues further down the

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[8] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[9] In 15 March 2006, the European Commission launched a public consultation on the pharmacovigilance system in place in the European Union.

[10] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[11] European Commission. **Strategy To Better Protect Public Health By Strengthening And Rationalising Eu Pharmacovigilance: Public Consultation On Legislative Proposals**. Brussels, 5 December 2007. Available on: https://ec.europa.eu/health/other-pages/basic-page/public-consultation-draft-legislative-proposals-strengthen-and-rationalise-eu-system_en

[12] ISDB & MiEF. Available on: https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

line. And years of experience show that, in Europe, the US and Canada, pharmaceutical companies generally do not honour their commitments on postauthorisation evaluation. Worse still, post-authorisation studies are too often used as a pretext to market a drug with an unfavourable risk-benefit balance for a few more years, while awaiting the results of the study."

In sum, despite the increasing complexity of the regulatory environment and the fact that more products whose efficacy and safety profiles are poorly known are being approved, the pharmacovigilance systems all over the world have been eroded and increasingly left to be led by the pharmaceutical companies that should instead be monitored and controlled by these very systems, exposing a clear and pervasive conflict of interest in the field. On the dysfunctional EU's pharmacovigilance conjuncture in 2005, the "ISDB EU: Berlin Declaration on Pharmacovigilance"[13] describes the following:

"Systems for pharmacovigilance are not well organized and funded to serve patients and the public optimally. So, for example, the European Medicines Agency (EMEA) is attached to the Enterprise Directorate General (DG) in charge of industry and not to the DG Health and Consumer Protection, an obvious conflict of interest; there is little sharing of information on ADRs between regulatory authorities and health professionals. EMEA and national agencies are funded to a great extent by industry, and so far no law requires that pharmacovigilance be funded by the public part of an agency's budget."

3. Pharmacovigilance and conflicts of interest

3.1. Conflicts of interest involving pharmaceutical companies

Business driven policies regarding Pharmacovigilance tend to keep information about adverse events and adverse reactions undisclosed, a conjuncture that leads the population in general to receive inadequate, delayed and poorly reliable information about the safety profile of pharmaceutical products.

Pharmacovigilance activities controlled by pharmaceutical companies and poorly monitored or scrutinized by public officials disseminate the following pervasive scenario:

"There is insufficient research on ADRs, so that the exact incidence (either population- or prescription-based) of specific ADRs is unknown.
Information about ADRs from the pharmaceutical industry and regulatory authorities is usually not accessible by the public.
Health professionals' motivation for pharmacovigilance is low, there is little encouragement for them to be involved in the process and ADRs are generally under-reported.
Reports directly from patients, the only ones to actually experience the ADRs, are often not accepted by professionals in established monitoring centres and by regulatory authorities."[14]

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[13] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[14] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

It is expected that pharmaceutical companies will have no incentive to bring to light proofs against their own products and questionable conducts. When a major pharmacovigilance case emerges, the value of the manufacturer's shares on the stock market plummets. Expecting the pharmaceutical companies to perform the task of gathering and diligently analyzing negative data about their (sometimes innovative and blockbuster) products, issuing warnings and informing authorities, health professionals and the public in general about their pharmaceutical products' adverse effects is to put them in an untenable position with a major conflict of interests[15]. That scenario put the marketing authorization holders in the condition of both judge and defendant, which is not at all a sustainable one:

> *"(…) Drug representatives may hesitate to forward ADR reports because they could harm the company, or because their own income depends on sales figures. Financial liabilities can be so important that when ADRs lead to a drug crisis the company may primarily inform the stock market rather than health professionals and the public, as Bayer did in the case of cerivastatin (Baycol/Lipobay) and Merck Sharpe & Dohme in the case of rofecoxib (Vioxx)."* [16]

Other strategies that can be used by pharmaceutical companies while trying to cover-up undesirable adverse reactions of medicines is the use of different codes for the same clinical findings, a procedure useful to hide signals. Or the design of risk management systems that do not identify rare long-term adverse effects, a strategy able to deliberately exclude from periodic reports unexpected or delayed adverse effects, even when severe[17].

Additionally, pharmaceutical companies normally fail to conduct essential relevant studies designed to clarify the efficacy and safety profiles of their products. The experience and recent studies[18] have shown that the pharmaceutical companies do not keep their promises when it comes to mandatory post-authorization studies:

> *"Pharmaceutical companies have little interest in conducting long-lasting and expensive epidemiological studies to clarify the risks of particular drugs or to*

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[15] *"The recent cases of rofecoxib (Vioxx) and olanzapine (Zyprexa) are a reminder of the extent to which pharmacovigilance data can be damaging to the pharmaceutical companies, which will attempt to conceal the data for as long as possible. In 2000, for example, the data from the VIGOR trial revealed an excessive number of heart attacks in patients taking rofecoxib, an anti-inflammatory drug. The firm then put forward the hypothesis that the comparator drug used in this trial had a favourable cardiovascular effect. The time lost between these initial results and the withdrawal of rofecoxib, four years later, resulted in tens of thousands of sometimes fatal cardiovascular events. Another more recent example: in 2007, Lilly paid out several tens of thousands of dollars compensation each to 28,000 plaintiffs in the United States, who accused the firm of not having informed them of the adverse effects of olanzapine, a neuroleptic which turned out to cause diabetes and severe metabolic disorders, even though Lilly was aware of this problem."* HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[16] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[17] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[18] AHIP. **New Studies Show: Americans Are Paying for Unproven Drugs**. December 6, 2021. Available on: https://www.ahip.org/news/articles/new-studies-show-americans-are-paying-for-unproven-drugs

establish long-term safety. It appears that fewer than half of the postmarketing studies that companies have made commitments to undertake as a condition of approval have been completed and many have not even been initiated. (…)"[19]

Moreover, pharmaceutical products are commonly subjected to marketing campaigns put in place precisely to cover-up potential or even detected negative aspects of the product:

"(..) To capture market share pharmaceutical companies emphasise the drug's efficacy in their "information" and minimize the significance of ADRs, e.g. classifying them as unproven events (AE). Anything to do with harms tends to remain buried, because of the commercially sensitive connotations. Thus, while the VIGOR trial raised concerns about the cardiovascular toxicity of the non-steroidal anti-inflammatory drug rofecoxib, Merck Sharp & Dohme proposed – in the absence of any evidence – that the explanation of the observed worrying increase in the risk of myocardial infarction was the "cardioprotective potential" of the comparator drug used in VIGOR, naproxen."[20]

Besides this, pharmaceutical companies tend to use litigation and other aggressive dissuasive strategies aiming at keeping products in the market, in cases in which proven or unproven adverse effects correlated to their products are brought to light:

"Drug companies sometimes wage aggressive campaigns against those who voice safety concerns. Some pharmaceutical companies have used litigation against researchers, editors and publishers in attempts to suppress the publication of information that casts doubt on the safety (or effectiveness) of their products.
If drug companies compensate victims of ADRs the payment is commonly settled out of court with a secrecy clause, so that other people suffering a similar ADR remain unaware of the settlement." [21]

3.2. Conflicts of interest related to regulatory authorities:

Neither the regulatory authorities nor the pharmaceutical companies have real-world incentives to promote in-depth exploration of possible pharmacovigilance strategies, since both sides are intrinsically involved and legally bound with the marketing authorizations exposing products to the population.

The governments' disinterest may arise from the fact that drug regulatory authorities are in a great extent dependent on fees from the pharmaceutical industry. Furthermore, many experts within regulatory authorities have substantial links with pharmaceutical companies, including the revolving door phenomena, pervasive in the pharmaceutical sector.

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[19] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf
[20] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf
[21] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

Additionally, the very authority that granted a (sometimes problematic and criticized) marketing authorization is supposed to monitor the concerned product and eventually determine its withdrawal, recognizing flaws in its own procedures and due diligence:

> *"It may be a hindrance for appropriate action, if the same authority which is responsible for clearing products for approval also has the task of monitoring their safety and, under given conditions, has to remove them from the market. That creates an inherent conflict of interest. Measures may be delayed because they could signal poor quality of approval decisions and the authority may have to explain why it allowed the drug to reach the market. The unwillingness to disclose the information is intensified by the fear that disclosure may threaten a product, affect company profits and share prices, and be followed by litigation."* [22]

An additional problem is the fact that pharmacovigilance units normally only recommend safety actions (withdrawing a product or amending a marketing authorization) to other units or instances within the regulatory structure. In fact, pharmacovigilance authorities normally dependent on the final decision of the marketing authorization unit responsible for the product approval in the first place. Even though marketing authorization officials have an intrinsic conflict of interests when it comes to admit they had made a poor decision in approving a questionable product.

Summing it up, given the lack of incentive that governments perform in-depth and timely pharmacovigilance activities, the pharmaceutical companies see in the current conjecture the perfect opportunity to act in substitution to official pharmacovigilance bodies, distorting and instrumentalizing pharmacovigilance tools so they are able to keep unsafe and unproven effective products in the market, while these companies mine and assess data arising from the exposure of multiple layers of the population to that sort of (sometimes clearly experimental) products.

3.3. Companies' infiltration in public regulatory systems - the ICH case in the European Union:

Developing the authorities' intellectual independence from pharmaceutical companies involves re-assessing the position of the "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use" (ICH)[23], a regulatory forum founded in 1990 by the regulatory agencies and the pharmaceutical industries' associations of the US, EU and Japan, in the drafting of regulatory guidelines and standards adopted or considered by regulatory agencies. Specifically on the EU case, Prescrire[24] states the following:

> *"Recognised international institutions clearly have a role to play; for instance, the World Health Organization (WHO) has a collaborating centre for international drug safety monitoring.*

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[22] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[23] Formely known as "International Conference on Harmonisation". See: https://www.ich.org/

[24] Prescrire. **Editorial Staff "Contribution to consultation on pharmacovigilance in the EU: the new legislation must be fully applied, and provisions for patient safety and public transparency must be improved"**. Prescrire International, v. 15, n. 84, 2006. 149-53 p.

However, the role of the International Conference on Harmonisation for technical requirements of registration of pharmaceuticals for human use (ICH), created jointly in 1990 by the regulatory agencies and the pharmaceutical industries of the United States, Europe and Japan, appears excessive. Through international conferences and, above all, intensive work by a 14-member committee assisted by industry advisors and administrative experts, but with practically no patient or healthcare professional representation, ICH guidelines have been drawn up and adopted by drug companies and regulatory agencies. (…)

Six of these ICH recommendations on pharmacovigilance were adopted by the EMEA Committee on Medicinal Products for Human Use (CHMP) (4). Although they are not legally binding in the EU, these guidelines exert a major influence and have important implications for the organisation of pharmacovigilance, content of PSUR, and the sharing and analysis of data. The European regulatory authorities do not even control the definition of certain elements that are crucial for the interpretation and exchange of pharmacovigilance data.

The regulatory authorities thus appear to be beholden to the ICH, and ultimately to the industry representatives that participate in ICH. Drug manufacturers obviously favour a minimum of regulatory obligations when it comes to pharmacovigilance (and drug evaluation). It is crucial to restore the conceptual independence of European pharmacovigilance. Guidelines must be drawn up by European and national regulatory agencies, after broad public consultations. After all, this is a topic with enormous public health implications."

When it comes to pharmacovigilance, besides the Eudravigilance database, *"(…) driven by the recommendations of the International Conference on Harmonisation (ICH), developed in partnership with the pharmaceutical industry and the drug regulatory agencies"*[25], the ICH developed the MedDRA dictionary (Medical Dictionary for Regulatory Activities Terminology) intended to standardize adverse effects reporting. According to ISDB & MiEF[26], MedDRA serves to many pharmaceutical companies' interests as it can make the identification of pharmacovigilance signals even more difficult:

"In practice, it requires encoding adverse effects by 'symptom' using the 'lowest level term', at the risk of losing their clinical significance. This risk is particularly high since this 'symptom' must be linked to one or more 'categories' (system organ class, SOC): the data from one patient is therefore spread across several 'categories' making the evaluation of cases difficult. Furthermore, some effects can be made to 'disappear' by linking them to the wrong categories. For example, if the symptom 'weight gain of 20 kg' is encoded in the 'investigations' category, where nobody would think of looking for it, this adverse effect will be concealed."

[25] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[26] ISDB & MiEF. Available on: https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

4. Other systemic pervasive Pharmacovigilance challenges

4.1. Pharmacovigilance and data disclosure

Bearing in mind the public interest, patients' rights and public health policies, full transparency, based on freedom-of-information legislation, should be the paradigm of pharmacovigilance systems. On the subject, the "ISDB EU: Berlin Declaration on Pharmacovigilance"[27] states:

> *"From the day a medicine is marketed, regulators and the pharmaceutical industry must allow access to all relevant data from clinical and pre-clinical trials, including animal studies.*
> *These data need to be publicly available to enable health professionals and drug bulletins to assess the benefit/harm ratio of treatments more thoroughly than can be done from the Summary of Product Characteristics (SPCs) and material industry is willing to provide. Health care providers need to be informed promptly about new findings on ADRs. There must be policies for disclosing potential conflicts of interest wherever they exist."*

Public access to documents held by the regulatory authority has to be in place, all aspects of drug risks, including comparative data, must be openly communicated to all concerned parties (prescribers, suppliers, dispensers, patients etc.). In the case of patients, the information must be available in a patient-tailored manner. Information about adverse reactions and their frequency should be given in a patient-friendly and understandable manner[28].

Moreover, commercial confidentiality should not include clinical trials data or adverse reactions information. The commercial interests of pharmaceutical companies should not be prioritized or restrict access to data whenever drug safety problems are involved[29].

4.2. Incomplete knowledge

Even the total transparency by governments and pharmaceutical companies won't be able to solve all the problems arising from the wide use of medicines (many of them experimental or with incomplete efficacy and safety profiles) by different layers of the population, since previous information gathered through clinical trials do not cover all the possible adverse effects and contexts of use:

> *"At the time a drug is approved knowledge about its risk is incomplete. Tests in animals are necessary and useful to discover toxic effects, but do not allow sufficient conclusions about human safety.*
> *Clinical studies focus on demonstrating efficacy statistically instead of comparing benefits and ADRs with those of existing drugs. The small number of patients involved in, and unsatisfactory length of, clinical studies limit the value of their findings. Thus, pre-approval clinical data include only information about the most*

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[27] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[28] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[29] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

common ADRs. In addition, specific doses are used and patients who may be at greater risk from ADRs are usually not studied during the development of a drug, e.g. young children, elderly people, pregnant or lactating women, patients concomitantly using other drugs or other therapies, patients with complicated disease conditions, sub-populations carrying known and relevant genetic polymorphism and patients of different racial and/or ethnic origins.
Thus, clinical studies give very limited information about risk and efficacy in real life conditions." [30]

Furthermore, clinical trials designed by pharmaceutical companies are not tailored to provide detailed information on the safety profile of medicines, whereas their results are constantly biased when presented to regulatory authorities:

"The design of randomised clinical studies (and later of meta-analyses) - typically made by clinicians and not by experts in pharmacovigilance - usually concentrates on efficacy. Generally, statistical power of a study is calculated for efficacy, not for ADRs. Furthermore adverse events are inadequately and inconsistently reported in most clinical trials, and if the investigators decide that an event is unrelated to treatment it is usually not mentioned at all.
Drug regulatory agencies worldwide routinely rely on selective data presented by companies. The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. (…)"[31]

Detecting a signal[32] of adverse reaction is a complex activity, given problems related to under-reporting of adverse effects and the challenging causal assessment of reports. Such complexity and the time span involved, allows pharmaceutical companies to artificially maintain products in the market, while manipulating risk management reports and further investigating, in their own benefit, the real-world effects of its products.

In fact, several years of active pharmacovigilance, which demands resources, time, political will and absence of conflict of interest, are necessary to get a broad, reliable and clear picture about adverse reactions related to new drugs, drugs used by small populations, real-world pharmaceutical interaction with other active substances, as well as to new or off-label indications which may alter the marketing authorization's benefit-

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[30] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on:
https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf
[31] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on:
https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf
[32] A signal, according to the ISDB/EU Berlin Declaration on Pharmacovigilance, is defined as:
"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information".
"Absence of a signal does not mean that a problem does not exist".
ISDB EU: Berlin Declaration on Pharmacovigilance. Available on:
https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

harm profile. As stated by "ISDB EU: Berlin Declaration on Pharmacovigilance"[33], given the complexity of the theme, when drug safety concerns are involved: *"(…) governmental or non-governmental institutions (for instance insurance companies) should initiate or fund appropriate studies like case-control studies or cohort studies, in order to provide optimal information about drug safety. (…)"*

4.3. Under-reporting of adverse effects and reactions

Besides the real-world difficulties in establishing the causal relationship between an event and the medicine[34], the under-reporting is another major factor contributing for the lack of effective post-marketing control of products:

> *"Limited data exist on the incidence of ADRs. It is generally acknowledged that most ADRs – even fatal ones - are not reported. Under-reporting delays the recognition of new ADRs and leads to the perception that injuries from ADRs are less common than they really are. (…)"*[35]

Spontaneous reporting is the main source of pharmacovigilance systems and vital to their operation, despite the fact that spontaneous reports are usually based on suspicion and not well grounded or documented:

> *"It is available immediately after a new drug is marketed, continues indefinitely and, potentially, covers all patients receiving the drug. It helps to generate safety signals by accumulating data on similar ADRs. The great weakness of spontaneous reporting is health professionals' limited ability to recognise unknown and unexpected adverse events and then their failure to report what they do observe. (…)*
>
> *ADR data from spontaneous reporting are usually based on suspicion, and may be preliminary, ambiguous, doubtful or wrong. The poor quality of data often affects the interpretation. Thus, spontaneous reporting cannot provide definitive answers. (…)"*[36]

In statistical terms, the "ISDB/EU Berlin Declaration on Pharmacovigilance" presents the following general reporting rates of adverse reactions:

> *"Reporting rates in clinical trials and in spontaneous reporting systems suggest that only between 2% and 5% of all ADRs are reported in many spontaneous systems. Dedicated pharmacovigilance centres achieve reporting rates between 10% and 20%.*

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[33] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[34] "In many causality assessment systems, the fact that a reaction is not known substantially decreases the causality score, making such a system less appropriate for the purpose of signal detection. (…)" **ISDB EU: Berlin Declaration on Pharmacovigilance.** Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[35] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[36] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

Deaths due to ADRs are common. For example, fatal ADRs rank from the fourth to the sixth leading cause of death in the United States of America. ADRs are estimated to cause 3-7% of all hospital admissions. (…)"[37]

According that same publication, physicians are structurally reluctant in adverse reaction reporting. Physicians fail to report an estimated 95% to 98% of all adverse events for the following varying reasons:

- ✓ *"they don't think about it because they have not been educated to do so;*
- ✓ *they think the features of ADRs are already well known, especially when the suspected drug is old;*
- ✓ *they interpret ADRs as minor or irrelevant;*
- ✓ *they lack the interest to listen to the patient;*
- ✓ *they have doubts about the causal role of the drug(s) involved and wrongly assume that causality has to be established;*
- ✓ *they suspect that the ADR has never been previously discussed and fear that their suspicion might therefore be wrong;*
- ✓ *they suspect that the ADR has already been reported by a colleague;*
- ✓ *they lack the time;*
- ✓ *they fear a lot of extra work, because of time-consuming requests for additional information;*
- ✓ *they are concerned that the ADR might subject the reporter or others to disciplinary action or a lawsuit;*
- ✓ *they fear they could be sued by the company for 'false' statement and compensation;*
- ✓ *reporting is thought to be ineffective;*
- ✓ *they are ignorant of the requirements for reporting;*
- ✓ *they plan to collect and publish a personal series of cases;*
- ✓ *they lack understanding of what types of ADR should be reported;*
- ✓ *the ADRs simulate a common spontaneously occurring disease or simulate the symptoms of the treated disease;*
- ✓ *relevant information is missing such as drugs prescribed by other physicians or medicines taken without prescription (patients rarely tell physicians about their use of alternative medicines);*
- ✓ *they lack financial compensation for the time and effort of reporting;*
- ✓ *they lack feedback from authorities or medical professionals in the system;*
- ✓ *reporting forms are not to hand."*[38]

As mentioned before, given the under-reporting of adverse effects and the natural difficulty of identifying unknown, long-term or unexpected adverse reactions, pharmaceutical companies take advantage of pharmacovigilance risk management systems to cover-up toxicities and other detrimental impacts arising from the use of their products by the population in general or by specific vulnerable patients.

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[37] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[38] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

5. Making Pharmacovigilance systems reliable

HAI Europe, MiEF & ISDB[39] presented, in 2007, four main proposals to strengthen the European Pharmacovigilance system:

- ✓ *"more stringent marketing authorisation criteria to ensure the approval of medicines offering a genuine therapeutic benefit;*
- ✓ *guaranteeing the transparency of pharmacovigilance data, information and decisions;*
- ✓ *granting authorities the means to be financially and morally independent from the pharmaceutical companies;*
- ✓ *ensuring resources are in place for effective pharmacovigilance systems."*

The first pivotal recommendation, **more stringent marketing authorization criteria**, relates to the lack of comparative clinical trials to show that a pharmaceutical product is more effective or less dangerous than the standard available treatment:

> *"The vast majority of new drugs currently coming onto the market do not offer any real therapeutic benefits, and can even be regressive, needlessly exposing patients to adverse effects. The authorities do not require pharmaceutical companies to demonstrate that their new drug offers "added therapeutic value" compared with those already on the market as part of the authorisation process, even in fields where there are already numerous, acceptable, well-established drugs for the same indication. The entire population is therefore being exposed irresponsibly to the harms of new drugs whose balance of risks and benefits is not properly established, and which becomes unfavourable the moment an adverse effect occurs if the efficacy is not demonstrated. (…)"*[40]

The second pivotal recommendation, **guaranteeing the transparency of pharmacovigilance data, information and decisions**, reflects the fact that the pharmacovigilance authorities must be able to collect or access relevant data on pharmacovigilance, investigating this information efficiently, as well as making it accessible to all the parties concerned.

Pharmaceutical companies, on the other hand, must give health professionals and patients full information about adverse reports received nationally as well as internationally[41].

Putting pharmaceutical companies both as judge and defendant, and subcontracting the interpretation of the collected data to them deprives regulatory authorities of their role and does not enable them to strengthen their competencies, which makes governments

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[39] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[40] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[41] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

even more reliant on the firms. It is the pharmacovigilance authorities' responsibility to process and interpret data[42], as well as to communicate findings and results[43].

Data collected and recorded by pharmaceutical companies should be accessible and monitored by pharmacovigilance authorities. And all report received should be kept recorded, even if the company's conclusion is for the inexistence of causal relationship with the medicine in question[44].

Direct reporting of adverse effects by patients should be allowed, but not directly to the marketing authorization holder[45].

Specifically about the PSURs assessing the harm-benefit balance of the product, that companies must provide regularly to regulatory authorities, the "ISDB/EU Berlin Declaration on Pharmacovigilance" states the following:

> *"(…) [PSURs] should be made available to the public. (…) Moreover, the PSURs should be written in a way that any new information is clearly identifiable. Outdated products whose "risk-benefit balance is not positive under the normal conditions of use" (article 116 of Directive 2004/27/EC) should be removed from the market."*[46]

Besides this, all the data related to post-authorization studies must be available for regulatory assessment instead of exclusively a short report provided by the marketing authorization holder[47].

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[42] The "**ISDB EU: Berlin Declaration on Pharmacovigilance**" provides strategies to remedy the chronic issue of data assessment in pharmacovigilance:
"(…) it is important to have in place arrangements for detecting, identifying, and responding to adverse events (AE; see annex) and adverse drug reactions (ADRs; see annex), remembering that an AE has to be regarded as ADR when the causal relationship between event and the drug cannot be excluded or further investigation as to the event's circumstances and pathophysiology make it plausible that the reaction was indeed a response to the drug in question. Key objectives of such pharmacovigilance which can be briefly defined as the process of evaluating and improving the safety of medicines, are to consolidate what is already known, quickly detect ADRs that were previously unknown or incompletely documented, and to inform about ADRs in order to reduce ADRs and medication errors in future. Through robust pharmacovigilance, the frequency of ADRs can be estimated, balances made between benefit and harm, comparisons made between the ADRs of alternative treatments, and advice given to health professionals and patients on treatment choices. (…)"
Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[43] HAI Europe, MiEF & ISDB. Available on:
https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[44] HAI Europe, MiEF & ISDB. Available on:
https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[45] HAI Europe, MiEF & ISDB. Available on:
https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[46] **ISDB EU: Berlin Declaration on Pharmacovigilance.** Available on:
https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[47] ISDB & MiEF.
Available on: https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

All the Pharmacovigilance decisions should be made public with a clear rational, accessible both to health professional, as well as to patients (provided the due patient-friendly language).

When litigation cases (claims of victims of adverse reactions for compensation) are settled out of court, secrecy clauses should be prohibited. And broad information on the safety issues related to de product must be made public, and internationally accessible[48].

Providing more details on possible strategic improvements to current public pharmacovigilance systems, the "ISDB EU: Berlin Declaration on Pharmacovigilance"[49] suggests that all pre-clinical and clinical data are connected to a worldwide register using a unique international numbering system, besides other strategic policies:

> *"The protocols and results of pre-clinical research (animal studies and toxicology studies) and clinical trials which are registered centrally (nationally or internationally) should be connected to a worldwide register using a unique international numbering system. Registrations should start at trial inception (at the time of ethical approval and/or funding approval) and should cover studies of both drug and non-drug therapies.*
>
> *The full data must be publicly available from the date of first marketing at latest, whether a product has been licensed through the centralised or a national procedure. The registered trials data have to comply with the CONSORT (Consolidated Standards of Reporting Trials) guidelines including the recommendation about reporting harms-related issues. The register must be accessible at no charge. It must be open to all prospective registrants and managed by a not-for-profit organisation. There must be a mechanism to ensure the validity of the registration data, and the register should be electronically searchable.*
>
> *All scientific journals should require, as a condition of consideration for publication, registration in a public trials register (as announced by the International Committee of Medical Journal Editors).*
>
> *Current standards for safety reporting in clinical trials have to be revised and information about all adverse events (AEs) or adverse drug reactions (ADRs) per study arm should be systematically included as well as detailed descriptions of cases with previously unknown AEs/ADRs and the specification of numbers and reasons for study withdrawals.*
>
> *The type and frequency of all adverse events occurring during the development of medicines should be fully declared and mentioned in the Summary of Product Characteristics (SPCs) so that there is no loss of information.*
>
> *If 'compassionate use' of unlicensed medicines is allowed for patients, all information from preclinical (e.g. animal study data) or clinical trials must be given to the treating physician and on request to the patient and drug bulletins. Reporting of ADRs should be obligatory in compassionate use as with any other use."*

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[48] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

[49] ISDB EU: Berlin Declaration on Pharmacovigilance. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

The third pivotal recommendation, **granting authorities the means to be financially and morally independent from the pharmaceutical companies,** reflects the fact that additional restrictions are needed on pharmaceutical companies' influence over safety decisions, pharmacovigilance guidelines, standards and policies, as well as over the officials in charge.

The pharmacovigilance authority must have the power to impose real penalties on companies that do not fulfil their commitments and obligations. For example, "[t]*he Pharmacovigilance authority must be able to impose modifications to patient information leaflets or the withdrawal of products with an unfavourable risk-benefit balance"*[50].

Pharmacovigilance authorities must have mandatory powers instead of keeping on recommending safety actions (withdrawing or amending a marketing authorization) to other instances within the regulatory structure. As mentioned before, Pharmacovigilance authorities normally dependent on the final decision of the marketing authorization unit responsible for the product approval in the first place. Even though marketing authorization officials suffer an intrinsic conflict of interests when it comes to admit they had made a poor decision in approving a questionable product.

Moreover, pharmacovigilance authorities must be able to demand and review post-marketing studies and other methods of active surveillance, and not "*be limited to the evaluation of the data provided by the pharmaceutical companies alone (in PSURs) (…), which could bias their conclusions*"[51]:

> *"(…) to require companies to conduct postmarketing studies when they are granted conditional product approval on the understanding that such studies will be conducted; to conduct independent pharmacovigilance studies; and to evaluate the impact of drug safety decisions."*[52]

Further discussing active pharmacovigilance, the "ISDB EU: Berlin Declaration on Pharmacovigilance"[53] asserts that:

> *"Given the limitations of spontaneous reporting, well-designed epidemiological studies and other methods of active surveillance are required, such as case-control studies and large cohort studies, to investigate and quantify the risks of drugs including safety in at-risk groups (such as elderly people, children, pregnant women and patients in renal failure) and interactions."*

The fourth pivotal recommendation, **ensuring resources are in place for effective pharmacovigilance systems,** resonates the fact that an effective pharmacovigilance system requires significant public funding and genuine political will, *"[s]ince companies'*

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[50] HAI Europe, MiEF & ISDB. Available on: https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[51] ISDB & MiEF. Available on: https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

[52] Prescrire. *op. cit.*

[53] **ISDB EU: Berlin Declaration on Pharmacovigilance**. Available on: https://www.akdae.de/Arzneimittelsicherheit/Weitere/Archiv/2005/85_200501252.pdf

pharmacovigilance systems cannot under any circumstances become a substitute for national public pharmacovigilance systems which unequivocally serve public interest"[54].

As previously mentioned, resources must be in place allowing the development of proactive Pharmacovigilance able to identify and assess signals related to uncommon and unexpected adverse reactions that demand in-depth, complex and long-term investigations:

> *"Spontaneous reporting enables the identification, after a time, of serious adverse effects that correspond to uncommon conditions (congenital malformations, agranulocytosis, anaphylactic shock, acute liver failure, etc.). In recent years however, a number of serious adverse reactions corresponding to common diseases have been identified, but only after a long delay (breast cancer with hormone replacement therapy, cardiovascular effects with cyclooxygenase-2 inhibitors (anti-inflammatory drugs), bone fracture with proton pump inhibitors (anti-ulcer medication), etc.). Because these adverse effects correspond to common diseases, they are seldom reported spontaneously, and were often discovered through observational studies or during clinical trials. Proactive pharmacovigilance is needed as a complement to the spontaneous reporting system: the drug regulatory agencies are responsible for analysing clinical trials (metaanalyses) in order to identify and quantify the risks associated with the use of medicines, and for proactively organising observational studies."*[55]

6. The WHO model and the pervasive influence of B&MGF

6.1. The Smart Safety Surveillance (3S) strategy

Despite the aforementioned recommendations, WHO under the pervasive influence of Bill & Melinda Gates Foundation (B&MGF)[56] is currently developing and recommending to Member States (especially low- and middle-income countries) the Smart Safety Surveillance (3S) strategy, conceived and funded by B&MGF itself. The major objective of the 3S strategy is to convince national pharmacovigilance authorities to focus their scarce material resources and personnel on products authorized through accelerate pathways,

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[54] HAI Europe, MiEF & ISDB. Available on:
https://www.prescrire.org/docus/ConsulPharmacovigJan08En.pdf

[55] ISDB & MiEF. Available on:
https://english.prescrire.org/Docu/Archive/docus/En_PharmacovigBriefingNoteOct2009.pdf

[56] "The WHO pilot project on Smart Safety Surveillance, funded by the Bill & Melinda Gates Foundation (BMGF), will end in 2019. It was noted that the principles of Smart Safety Surveillance are aligned with the principles of 'Smart' regulation of medicinal products; getting 'Pharmacovigilance-ready' for new products ahead of their launch, sharing resources through collaboration, reliance, and recognition of mutual expertise between countries would be the hallmark of this 'Smart' approach. While six countries are being supported through the BMGF grants, funds and resources from other partners (UNITAID, UMC in particular) have been used to integrate the 3S principles in a second set of countries. Members agreed that the principles of 3S should continue to inform the work of the SAV programme. An additional set of countries will be supported in 3S-principles with Global Fund grants in the next phase." (italics added)
2019 Recommendations from the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP). Available on:
https://www.who.int/medicines/regulation/medicines-safety/publications/ACSoMP_16.pdf?ua=1

based on insufficient clinical data about their efficacy and safety profiles[57]. These products generally are first registered in developed countries, according to national regulatory strategies aiming at faster return on pharmaceutical companies' investments, or from their conception intended for first registration in low- and middle-income countries through reliance schemes incentivized by WHO[58], based on non-legally biding scientific opinions or technical assessments performed by "reference regulatory authorities"[59] – an ICH classification adopted by WHO under no formal mandate nor scrutiny by Member States[60].

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[57] "Investments in activities to strengthen countries' capacity to monitor the safety of novel medicines and vaccines can be optimized through the WHO Smart Safety Surveillance (3S) strategy, by focusing on priority products that are exclusive to the country and/or products with limited global experience."
Iessa, N. et. al. **Smart Safety Surveillance (3S): Multi-Country Experience of Implementing the 3S Concepts and Principles.** Drug Safety (2021) 44:1085–1098.
Available on: https://pubmed.ncbi.nlm.nih.gov/34331675/

[58] In 2021, the Fifty-fifth Report of the "WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)" adopted, through its 10th Annex, the first WHO guideline on international reliance mechanisms: the "Good reliance practices in the regulation of medical products: high level principles and considerations". The official document, never scrutinized by Member States, defines "reliance" as:
"The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others." (italics added)
The guideline, as the sentence stressed on the aforementioned definition, makes it clear that the relying authority (Philippine FDA, in the Dengvaxia case) remains responsible and accountable for decisions taken based on another authority's assessment (EMA's scientific opinion, in the Dengvaxia case), whereas no recommendation or debate on the legal liability of the regulatory authority performing and endorsing the assessment taken into consideration (mainly by developing countries lacking of full capacity of appraising the technical information and its real-world consequences), is presented or discussed by WHO. Not a single statement on possible legal liabilities involving "agencies of reference", neither in cases of bad faith, fraud or careless regulatory review, especially when products aiming exclusively at third countries' markets are involved (products targeting tropical neglected diseases, as dengue disease, for example).
Its also important to emphasize that ECSPP is the very Committee utilized by WHO to incorporate ICH documents and standards in its own guidelines and standards aiming at impact all the WHO Member States and the international trade of medical products, even though this very Member States never provided the required mandate for such adoptions, through the World Health Assembly
Available on: https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

[59] WHO. **List of Stringent Regulatory Authorities (SRAs).** 2017. Available on:
https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs

[60] "The WHO has continued with the ICH process for more than 24 years without the close scrutiny of Member States because the issues of norms and standards are considered as technical subjects; therefore, the World Health Assembly never deliberates the merits of the Expert Committee Reports, which contain norms and standards for the regulation of medicine.
The Report of the Expert Working Group is placed before the WHA Executive Board to take note of the Report along with many other expert reports. Normally, the Executive Board takes note of expert reports without any discussion.
The ICH adopts guidelines with political and economic considerations and successfully projects these guidelines as science-based and exported to WHO Expert Committees. The WHO's alliance with ICH facilitates this repackaging."
Gopakumar, K. WHO: **Alliance with industry raises concerns over medicine regulation**. Third World Network, SUNS #7807, 20th of May, 2014.
Available on: https://www.twn.my/title2/health.info/2014/hi140502.htm

While providing further details on the concept, Iessa, N. et. al.[61] clarify that the 3S strategy relates not only to accelerate regulatory review of new medicines based on limited clinical data, but also in new (experimental?) indications for existing drugs that have been streamlined for approval (another common and questionable strategy to accelerate marketing authorization reviews), usually based on reliance schemes incentivized by WHO, which endorse regulatory decisions by US/FDA and EMA:

> *"Access to medicines facilitated through expedited regulatory pathways and early access programmes has been supported by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines agency (EMA) from as early as 1992. Often these programmes are based on limited clinical data to allow accelerated authorization into the market. For example, the novel drug bedaquiline was granted a conditional license by the US FDA in 2010 for the treatment of multidrug-resistant tuberculosis before phase III clinical trials were complete. Drug repositioning (also known as drug repurposing or drug reprofiling) is a process of developing new indications for existing drugs that have been streamlined for approval. However, other safety issues may emerge after a drug is repurposed with changes in posology, when different patient groups such as the elderly and children may get the treatment; the adverse drug reaction (ADR) profile of the drug could change with more extensive use, when lesser known (or less frequent) adverse reactions may surface more prominently. Remdesivir, an antiviral originally designed for treatment of hepatitis C, was repurposed for the treatment of Ebola in 2018 and repurposed again for the treatment of COVID-19 in 2020. Although such expedited processes for licenses in the EU and FDA are primarily for authorization in these countries and regions, low- and middle-income countries (LMICs) often leverage decisions from these reference agencies; the World Health Organization (WHO) also uses the decisions of such reference agencies to inform the work of its programmes such as the WHO prequalification programme, facilitating access to priority products in LMICs. (…)"*

As mentioned before, the 3S strategy involves two categories of products. Products intended exclusively to markets of low- and middle-income countries (that can be subjected to careless regulatory assessment by the so called "reference regulatory authorities", given the companies' pressure for the product clearance and the fact that the real-world consequences of the marketing authorizations will take place in other jurisdictions), as well as products to be introduced simultaneously in high-income and low- and middle-income countries:

> *"Given the finite resources at their disposal and the competing health priorities, LMICs would need to invest judiciously when it comes to pharmacovigilance. Rather than focus on general PV system development, the smarter option would be to focus their PV efforts on two types of medicinal products:*
>
> 1. *Products that are important to the country, introduced to address a high burden disease of public health priority and/or exclusive to the country (e.g. sleeping sickness).*

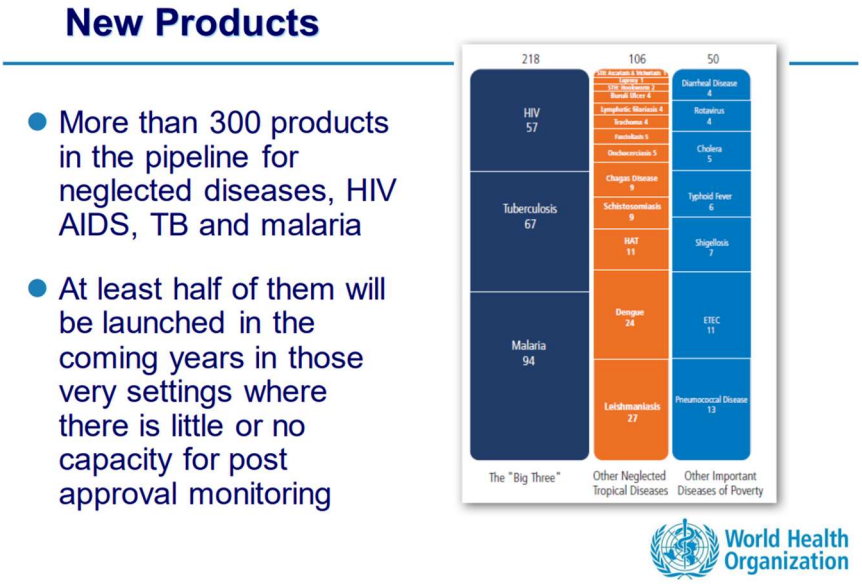
[61] Iessa, N. et. al. Available on: https://pubmed.ncbi.nlm.nih.gov/34331675/

2. *Products with limited clinical data that will be introduced simultaneously, in high-income countries and in LMICs, with little global experience for LMICs to rely on."*[62]

Relevant to stress that Iessa *et. al.*[63] explicitly mention as a tool of accelerate regulatory reviews to be addressed by the 3S strategy, the reliance scheme, incentivized by WHO, based on the article 58 of the Regulation (EC) No 726/2004 (that very reliance scheme led to the death of dozens - maybe hundreds of children - in the Philippines related to the national registration and mass vaccination involving the dengue disease vaccine Dengvaxia, with no legal liability both to the WHO and EMA):

> *"(…) Additionally, the EMA, in cooperation with the WHO, can provide scientific opinions on high priority human medicines, including vaccines, that are intended for markets outside of the European Union (EU). Expedited authorization (accelerated approval in the USA and conditional marketing authorization in Europe) for novel and often urgent treatments or vaccines might be given on the basis of several conditions, including timely completion of post-marketing studies, and should be able to rely upon robust and effective pharmacovigilance (PV) systems for a more thorough understanding and application of these products. Monitoring requirements may be intensive and could even become a barrier for accessing new medicinal products in LMICs with very rudimentary or sub-optimal pharmacovigilance systems."*

To give an idea of the intended dimension of the 3S strategy led by WHO, in a presentation[64] available on the internet, Dr. Iessa, a WHO representative and the main author of the aforementioned paper "Smart Safety Surveillance (3S): Multi-Country Experience of Implementing the 3S Concepts and Principles", cites more than 300 innovative products in the pipeline, to be launched in developing countries, and as a consequence demanding the strengthening of national pharmacovigilance systems:



[62] Iessa, N. et. al. Available on: https://pubmed.ncbi.nlm.nih.gov/34331675/
[63] Iessa, N. et. al. Available on: https://pubmed.ncbi.nlm.nih.gov/34331675/
[64] Iessa, N. **Pharmacovigilance: New Challenges for WHO**. Available on: https://www.who.int/medicines/technical_briefing/tbs/TBS2016_Pharmacovigilance.pdf

6.2. WHO, B&MGF and post-marketing safety assessment of covid-19 vaccines

Finally, it is important to mention that accelerate regulatory reviews were applied in the development of disruptive innovative vaccines against covid-19, as mRNA based vaccines, whose safety profiles are scarcely known and are subjected to considerable scientific and public concern, given the potentially pervasive dangerous nature of mRNAs technologies. According to Lo Re *et al.*[65]:

> *"The first vaccines against the novel pathogen SARS-CoV-2 were deployed just nine months after the covid-19 outbreak was declared a global pandemic. Several types of covid-19 vaccines have been developed using different platforms and adjuvants, including messenger RNA based vaccines, adenovirus based vector vaccines, and inactivated vaccines. As of June 2021, 102 vaccines were under study in phase I-III trials, and 185 were under investigation in preclinical studies.*
>
> *Given the global impact of the pandemic, vaccine development received unprecedented public and political attention, resulting in accelerated regulatory review. However, there has been scepticism about the rigour of evidence supporting comprehensive benefit-risk assessments and concern that breakthroughs in vaccine development have not been accompanied by similar advances in systems to monitor adverse events or communicate safety signals among regulators, public health officials, and healthcare providers. The limited human exposure and follow-up within the pivotal covid-19 vaccine trials, optimised to allow formal conclusions about efficacy, did not permit detection of rare adverse events (occurring in fewer than 1 in 10 000 people) after immunisation, particularly within subgroups under-represented in, or excluded from, those trials (such as pregnant women, children, and frail elderly or immunocompromised people). Public apprehension about the safety of covid-19 vaccines has contributed to hesitancy to receive a vaccine."*

On pharmacovigilance terms, Lo Re *et al.*[66] qualify covid-19 vaccines as an unprecedented opportunity for innovation in post-licensing vaccine safety assessment, both in terms of passive and active pharmacovigilance activities:

> *"The global deployment of covid-19 vaccines affords an unprecedented opportunity for innovation in post-licensing vaccine safety assessment. National regulatory authorities could collaborate on the development of "master protocols" that detail approaches to capture vaccine administration within healthcare databases or vaccine registries with linkage to electronic health records; ascertain events of interest after vaccination using prespecified algorithms; and identify subgroups that were under-represented in trials.*
>
> *(…)*
>
> *The massive rollout of covid-19 vaccines also offers an opportunity to enhance active vaccine safety surveillance systems. This could help overcome existing barriers in ascertaining vaccine exposure and adverse events on a population level.*

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[65] Lo Re, V. et al. **Global covid-19 vaccine rollout and safety surveillance—how to keep pace**. BMJ; v. 373, n. 1416, 2021. Available on: https://pubmed.ncbi.nlm.nih.gov/34144957/
Available on: https://www.bmj.com/content/bmj/373/bmj.n1416.full.pdf

[66] Lo Re, V. et al. **Global covid-19 vaccine rollout and safety surveillance—how to keep pace**. BMJ; v. 373, n. 1416, 2021. Available on: https://pubmed.ncbi.nlm.nih.gov/34144957/
Available on: https://www.bmj.com/content/bmj/373/bmj.n1416.full.pdf

Ideally, these systems should use databases that can be accessed in near real time to identify large numbers of individuals who have been vaccinated, ascertain the vaccine and lot number administered, and detect adverse events using validated coding algorithms, such as those developed by the Brighton Collaboration. These systems could address concerns regarding cases of Bell's palsy observed in phase III trials of the messenger RNA based vaccines developed by Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) by comparing incidence of this outcome against background rates in the general population and matched non-vaccinated comparison groups."

In concrete terms, WHO is involved in the Global Vaccine Data Network (GVDN), a consortium, funded by B&MGF and the US Centers for Disease Control and Prevention (US/CDC), conducting globally coordinated epidemiologic studies of the safety of vaccines, including covid-19 vaccines. According to WHO's website[67]:

"The website of the Global Vaccine Data network is a member of the WHO-led project Vaccine Safety Net (VSN).

The Global Vaccine Data Network is a consortium of research sites ready to conduct globally coordinated epidemiologic studies of the safety of vaccines, including COVID-19 vaccines, as they are introduced. We aim to facilitate collaborative studies of vaccine safety and effectiveness using health data from diverse populations in countries around the world. With international cooperation it is now possible to have a large enough population to conduct robust analyses of rare events following vaccination.

The GVDN website contains descriptions of our goals, the methods we use, and how big data can help assess vaccine safety. It features a list of international partners who participate in our vaccine safety studies, and commentary on topics such as vaccine hesitancy. (…) The GVDN is supported by a coordinating centre based at the University of Auckland in New Zealand[68], where a dashboard that will present the results of our vaccine safety studies is being developed.

(…)

The GVDN received seeding money from the Gates foundation in 2019 and relies on research grants for specific vaccine safety monitoring projects. The GVDN recently received significant funding from the US Centers for Disease Control and Prevention for a 3-year project entitled Global Covid Vaccine Safety (GCoVS). (…)"

Given the unprecedented scale of use of accelerate approved vaccines and medicines related to covid-19 in the entire population, its utterly important that all the pharmacovigilance initiatives (or "post-marketing safety assessments", depending on the publication language) implemented or under development are carefully regulated both from technical and ethical perspectives.

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[67] https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/vaccine-safety-net/vsn-members/gvdn

[68] University of Auckland. **University of Auckland leads Covid-19 vaccine monitoring for the world.** 27 May 2021. Available on: https://www.auckland.ac.nz/en/news/2021/05/27/university-leads-covid-vaccine-monitoring.html

As previously shown, pharmacovigilance structures can easily be converted into platforms in which clinical trials are performed in disguise, not subjected to due technical and ethical legal frameworks aiming at protecting human subjects from abusive experimental procedures.

Specifically about health research and ethics, it's important to mention that also the Council for International Organizations of Medical Sciences (CIOMS), the international, non-governmental organization established jointly by WHO and UNESCO in 1949, whose "*mission is to advance public health through guidance on health research and policy including ethics, medical product development and safety*"[69], has been equally infiltrated by ICH, since ICH's foundation in the 1990 decade, when medicine safety and pharmacovigilance strategies are concerned. Example of such form of pervasive influence by ICH was explicitly given by Tsintis & La Mache[70], back in 2004:

> *"In this article we review the current initiatives by the Council for International Organizations of Medical Sciences (CIOMS) and the International Conference on Harmonisation (ICH) on pharmacovigilance planning that are due for general release during 2004. These initiatives could form the basis for applying concepts of risk management to medicines throughout their life cycle, from preclinical and clinical development to marketed use. The CIOMS VI Working Group (with 28 senior scientists worldwide from drug regulatory authorities and pharmaceutical companies) is currently developing scientific guidance that relates to clinical trials for medicines during development. It recommends a developmental pharmacovigilance concept - a 'living' concept that would start early in drug development supporting the science and ethics of research leading up to licensing (marketing authorisation) and continuing to post-authorisation (postmarketing) pharmacovigilance. This approach is seen as complementary to current ICH initiatives called 'Pharmacovigilance Planning'. ICH will introduce two concepts in pharmacovigilance management of medicinal products: the 'Pharmacovigilance Specification' and the 'Pharmacovigilance Plan'. The 'Pharmacovigilance Specification' will summarise important knowns and unknowns about the medicine. It will include safety risks identified at the licensing stage, potential risks and any key missing information. These elements will be essential to the formulation of pharmacovigilance plans. Dialogue and common understanding between regulators and the pharmaceutical industry will be a key factor for developing pharmacovigilance plans during the life cycle of medicines. Appropriate interaction with health professionals and patients should also be planned for the future as regulatory systems become more transparent. Where no significant issues are apparent at the licensing (marketing authorisation) stage, routine pharmacovigilance practices will be followed during the marketing phase. Where issues do exist or the data are limited, further study, including epidemiological approaches can be planned. All types of medicines (new drugs, biological agents, orphan drugs) may be involved in these concepts, as would major extensions to existing medicines. Currently ongoing CIOMS and ICH initiatives are in line with*

[69] See: https://cioms.ch/.

[70] Tsintis, P. & La Mache. E. **CIOMS and ICH initiatives in pharmacovigilance and risk management: overview and implications**. Drug-Safety 27, 509–517 (2004). https://doi.org/10.2165/00002018-200427080-00004

emerging risk-management strategies in the US, the European Union and Japan aimed at early and proactive pharmacovigilance." (italics added)

Bearing in mind both the covid-19 context and the increasing number of accelerate approvals provided to new medicines (300 in the pipeline, according to WHO, related exclusively to neglected diseases, HIV/Aids, tuberculosis and malaria), it is a remarkable source of concern the fact that the pharmaceutical companies are under the perverse incentive to take control over public pharmacovigilance systems of low- and middle-income countries. Specially if reliance schemes with no legal liability towards regulatory authorities providing technical assessments utilized to support national marketing approvals in more vulnerable third jurisdictions are involved.

The combination of (i) products approved without complete information on efficacy and safety profiles; (ii) short-term clinical trials of new disruptive technologies leading to low detection of probable adverse reactions and no detection at all of mid or long-term effects of the product, creating a nebulous regulatory and scientific scenario in which all the adverse effects eventually reported are necessarily classified as unknown or unexpected; (iii) no effective legal framework covering ethical issues of real-world assessment of the efficacy and safety profile of new products; (iv) the emergence of new real-world technologies (as NTFs, for example) able to monitor in details and in real time patients and control groups all over the world; (v) the ability of marketing authorizations holders manipulate pharmacovigilance signals and assessments through risk management systems and periodic reports, disregarding, among other safety indicators, spontaneous reports classified as with no causality relation with the product; (vi) asymmetry of information among marketing authorization holders, regulators, other public health officials, health professionals and the public in general; and (vii) pharmacovigilance authorities lacking independent mandatory enforcement powers, leads to a troublesome and dangerous scenario that demands from all health authorities across the globe immediate coordinate regulatory action having the protection of human rights and the public health interest as its milestones and ultimate objectives.