Chapter 2
Lost in Regulation

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The aim of regulation in drug safety is to state as clearly as possible and to enforce the legal responsibility of the involved parties (regulators, marketing authorization holders and health care professionals where applicable), and to provide guidance on how the respective duties should be complied with. The guidelines issued have as a significant impact on the outcome as the law itself, as they determine the stakeholders' compliance and performance.

We have seen PV regulation develop from virtual nonexistence[1] into a well-intended but overwhelming collection of documents defining every possible detail of every imaginable contingency. The intent is to ensure the seamless safety surveillance of medicinal products from preclinical testing throughout their lifecycle in order to preserve patients from harm, but what we lack up to the present day is evidence that such extensive, in certain aspects even obsessive regulation is in fact resulting in safer medicines, safer use of medicines, and ultimately, safer patients.

[1] Pharmaceutical regulation up to the middle of the twentieth century focused mainly on manufacturing and sales issues, documentation of efficacy, as is standard nowadays, was not required. A medicine was considered unsafe if contaminated with known toxic agents, but the concept that an active ingredient itself could cause damage to certain patients was not current.

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2.1 All Well, Thanks to Thalidomide?

Thalidomide was and still is a tragedy for over 10,000 children born with congenital malformations and their families. In Europe, it also represents failure all along the line[2]: the granting of marketing authorization; the delayed recognition of the cause of the sudden increase of observed phocomelia; the hesitant approach of the regulatory authorities to investigate the problem and take action; and the failure to recognize the causal relationship between drug and ADR and to communicate openly with victims, health care providers, and the public.

The thalidomide tragedy was a wakeup call that led to a much needed strengthening of the existing regulation and significant improvement in the approval process for new medicines. Several other factors might have contributed to more sensitivity to the safety of medicines. Contrary to many adverse drug reactions, congenital abnormalities are immediately visible harms, which can be considered as possibly attributable to medicines intake affecting a vulnerable population, in this case, newborn babies. This might have contributed to an increase in awareness not only in professional circles but also in the general population that the use of medicines is not free of risk and therefore to a demand for better surveillance. It was, after all, the media coverage that pressured authorities into action.

Rapid scientific and technological progress has helped towards a more reliable investigation of efficacy, safety, and quality, providing better data to decide whether or not to grant a marketing authorization for a product, and the WHO Programme for International Drug Monitoring, the worldwide pharmacovigilance network founded in 1968,[3] has provided the means for rapid identification of areas of concern by collecting, pooling, and evaluating ADR reports from all sources. Industry safety databases have also become more comprehensive over time albeit limited to each company's portfolio. Such databases hold comprehensive pre- and postmarketing safety data but are not accessible to external parties.

All well after thalidomide? Far from it: 50 years later we are still adding to the long list of medicines causing serious harm to high numbers of patients before any regulatory action is taken.

2.2 Does the Current Regulation Work?

Searching for evidence that the current regulatory requirements and practices have indeed led to safer use of medicines and less or less severe drug-induced injury brings one quickly down to earth: these questions have not been answered yet.

[2] The US Food and Drug Administration (US FDA) did not approve thalidomide due to safety concerns, which leads to the conclusion that data pointing at a safety issue were available at the time.

[3] The program started in 1968 with 10 countries willing to share their reports on adverse reactions to medicines and counts 121 full members and 29 associate member as per September 17th 2015. For further information see http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324

The impact of regulation on drug development was looked at in 2007 by Marchetti and Shellens [1], and within the FDA's Sentinel Initiative (http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm) a pilot study was conducted to look at what research had been performed so far to evaluate the impact of FDA's regulatory actions. The researchers focused on the methods used to evaluate impact and not on outcomes, thus not answering the question whether the regulatory actions had any impact at all.

In 2012 Nkeng et al. [2] reviewed Risk Minimization Interventions (RMIs) published from 2000 to 2009 in relation to the publication of regulatory guidance on risk management. The study, limited to the ICH region, showed that only the USA registered a substantial increase in the number of RMIs during the postguidance period, but again the actual impact of these RMIs on patients' outcomes was not addressed in this study.

Bouvy et al. [3] explored if the cost-effectiveness of PSURs of biologicals in Europe can be established and concluded that this kind of analysis can and should be performed but again provided no evidence for safer medicines under the current regulatory practice.

Pacurariu et al. [4] have described the signals submitted to PRAC in the first 18 months (July 2012 to December 2013) after this body was established while also looking at the efficiency of this new process. Eighteen months is probably too short to see the impact the PRAC recommendations have actually had on patient safety, if any. Therefore, although we have experienced in the past the impact of absent regulation, there is so far no evidence that the current regulation leads to better outcomes. If we want regulation to significantly improve patient safety, we need to know if what we are currently doing is effective. If it is not, we must stop wasting time and resources and need to think of better ways to achieve our goals.

2.3 Harmonization: Global Business = Global Safety?

Legislation is national but business is global. This calls for harmonization of regulatory requirements, at least from industry's point of view. International companies need to comply with regulation in all the countries in which their products are marketed and in which they conduct clinical trials. Different requirements lead to an increase in workload, duplication of work, and in a significant investment both in time and resources to assure compliance. The *International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) is a body of representatives of the regulatory agencies and industry associations of Europe, Japan, and the USA and has been working towards common standards and requirements for efficacy, safety, and documentation format since 1990. This body represents 17 countries and approximately 15% of the world population; WHO, Canada, and EFTA (European Free trade Association) hold observer status. ICH Guidelines have also been adopted by regulators of some non-ICH countries. De facto Europe, the USA, and Japan are indirectly driving regulation also outside their own jurisdiction.

Comparable content, common formats, and timelines help to exchange information, which is fundamental for drug safety.

It is recognized that the ICH Guidelines are scientifically sound and fulfill their purpose of establishing common standards in the environment they originate from; however, they have been developed by and reflect primarily the views of industry and regulators of highly industrialized countries excluding those of low and middle income countries. As these ICH guidelines are regarded by the influential ICH countries as the gold standard, there is pressure to implement them worldwide. Expanding ICH standards into non-ICH regions might be a way of "globalizing" pharmacovigilance by facilitating exchange of information worldwide, but countries that have been excluded from the decision making process and do not see their concerns and needs addressed by these guidelines might be reluctant to adopt them.

Many of the countries outside the ICH region have drug regulation systems comparable to those in Europe and the USA. Others have regulatory systems that are still growing and maturing. Some countries struggle with political instability, wars, and natural disasters that put an additional burden on already stretched resources in the public administration, adding to the difficulty of establishing well-functioning pharmacovigilance systems. Under such circumstances, investing resources into harmonizing regulatory requirements with ICH countries can hardly be seen as a priority. The ICH Guidelines themselves, as well as they may meet the needs of the environment that has driven them, are not necessarily the appropriate model for low and middle income countries. This is especially the case where there is no local pharmaceutical industry that can be closely monitored and medicines are provided either through vertical programs or are imported from markets equally insufficiently regulated. Moreover, the underlying diseases, health care structures, and budgets, as well as the drugs used, might need different considerations. Obvious examples of important geographical differences apart from what drugs are available and how they are made available are the state of nutrition and the phenotypes of different populations.

While some non-ICH regions prefer to go their own way, others have opted to adopt recommendations and Guidelines from ICH countries. The Guideline on good pharmacovigilance practices (GVP) for Arab countries (532 pages!) [5] is an example of adoption of the EU GVP in a different region. Yes, the EU GVP guidelines are a comprehensive and monumental opus, but does that per se make them useful in a different setting? Shouldn't there be more room (and courage) for the best possible local adaptation of sound general principles?

In the interest of global pharmacovigilance, we need to develop common standards that are applicable and acceptable worldwide. This is only possible if low and middle income countries are included as active and equal partners in such discussions and decisions. We must find and allow room for local adaptation of common requirements.

2.4 Regulatory Guidance: Help or Obstacle?

Regulation per se is neither bad nor an unnecessary burden, on the contrary. Products are put on the market for profit, not for philanthropy even though the vision and mission statements in the industrial world might want us to believe differently.

Where high profit can be made, the temptation to take shortcuts in quality, efficacy, and safety is huge and if the market for pharmaceuticals were not so profitable, counterfeiting and illegal trade of medicines would be much less of a problem too. Unfortunately we cannot rely blindly on the industry's (whether pharmaceutical or other) ethics and regulations contribute to contain damage, but they can be and are circumvented, despite the efforts and engagement of the many employees driven by high ethical standards. Temafloxacin sales were pushed even when the MAH and the US FDA were already discussing the withdrawal of the drug because of life-threatening ADRs[4] [6], and Volkswagen with their rigging of emissions tests by software in its diesel cars that has come to light in these days is just the latest of many examples of corporate skulduggery. Regulation is necessary, but the question is: are we moving in the right direction?

While legal requirements within the ICH region are on the whole comparable, the amount and kind of guidance provided for complying with these is strikingly different. The US FDA *Guidance for Industry* documents on Good Pharmacovigilance practices and Pharmacovigilance planning, together approximately 50 pages, provide practical advice on content and methodology. The reader is informed that the documents contain nonbinding recommendations, thus leaving room for pragmatic solutions. In section IV B of the *Guidance on Good PV Practices* [7] (Characteristics of a Good Case Report in the US FDA Guidance for Industry), the most important elements of a good quality ICSR are presented clearly. This is what the regulator obviously expects to receive and this is what should also be looked at when a regulator inspects a MAH to assess their compliance with good PV practices.

The US FDA approach shows common sense, after all the pharmaceutical industry is a very diverse world. The monitoring of the newest biologic agent presents different challenges than the surveillance of a product with a safety profile so well established that the product is considered safe enough to be sold at petrol stations and grocery shops.

In contrast to the frugality of the US guidance, the European Guidelines on Good Pharmacovigilance Practices (GVP) encompass 16 modules, 12 with various lengths (9–90 pages), and several addenda are so far finalized and published [8]. GVP describe frames, timelines, and formats in detail, but the attention given to the medical content of safety reports to be submitted to the authority is by contrast minimal. The stoical reader will therefore find in detail how to report but little help on the medical/scientific information essential to investigate issues of concerns and which might help formulate a useful hypothesis. This might be seen as trust in the good judgement of the

[4] Temafloxacin was licensed in Europe and Latin America at the end of 1991. Shortly after approval by the US FDA in February 1992 serious, and in some cases fatal ADRs describing a multiorgan disease involving the hematological, hepatic and renal systems were reported with alarming frequency. After several meetings with the US FDA, the MAH agreed to withdraw the drug On June 5th 1992. Between February and June the sales representatives were not only not informed about the discussions with the regulators but pushed to continue selling the product, according to J. O' Donnell in his book *Drug Injury. Liability, Analysis and Prevention*, 1st ed 2001. The withdrawal was followed by several claims of wrongful death and personal injury filed in the USA and not settled until 1997.

MAH, but it results in a focus on format instead of content with negative consequences for pharmacovigilance activities. The daunting volume and dry, technical and in part legalistic language make GVP hardly a user-friendly manual, not even for electronic wizards or longstanding pharmacovigilance enthusiasts. However, I fully agree with IR Edwards, when he points out in his editorial *Good Pharmacovigilance Practice and the Curate's Egg* written for Drug Safety in 2012 [9], "there is some very good guidance and information here." In fact GVP covers every theoretical possibility or question that might arise in the safety surveillance of medicines and provides every possible answer on how to fulfill regulatory duties – in the correct format of course. The intention is good and the effort put into compiling it is impressive: it is the lack of weighting, of room for pragmatic approaches, and of focus on scientific content and its sheer volume that makes it a well meant big monster: interesting to look at from distance but better kept under lock and key. Better guidance on essential scientific content condensed in a much shorter and more pragmatic document as its US counterpart could turn the monster into a faithful companion.

Efforts have been made to reduce workload at both ends, the regulators and the MAHs. Transferring the responsibility for literature review from the MAH to the European Authority is an important step to avoid duplication of work and will contribute to less duplicate reports in the databases, always provided that this approach works in practice. On the other hand, according to GVP, even all expected nonserious ADRs must now be reported to the authority as ICSRs and the balance between workload and beneficial impact of these requirements is doubtful.

If the regulators want to receive the relevant information for their work, they must ensure that the guidance they provide for reporters, no matter if HCPs or industry, is focused, practical and user-friendly.

2.5 Sacrificing Content for Format

Regulatory authorities have the duty to enforce what legislation dictates and some players need a little bit more "encouragement" than others to comply with legal requirements. Inspections are one way of stimulating the regulatory compliance of a marketing authorization holder. Failure to comply leads to sanctions that can go as far as the withdrawal of a manufacturing license. Major findings at inspection must be watertight, especially in countries where regulatory decisions are legally binding and a company can challenge a regulator's decision in court.

Timelines and formats both of ICSRs or periodic reports are easy to monitor and admonish in case of fault: a timeline is either kept or not, there is not much room for disagreement. If this is listed as a finding of noncompliance, it will be accepted. Whether a scientific evaluation is sound or not is more difficult to assess and criticize and therefore more open to discussion and prone to challenge. If this is at the core of major inspection findings leading to sanctions, it might pave the way to a long and costly legal dispute. To be on the safe side the attention of the inspectors focuses on form and not content and the MAHs act accordingly: fill in the right form

and submit on time, too bad if the information provided is limited to minimal reporting criteria or little more, and does not contain the information relevant for an appropriate clinical assessment.

Risk minimizing measures are often taken based on data from spontaneous ADR reports [10]. Insisting on receiving ICSRs of high quality should therefore be a top priority for regulators. If the focus of regulatory requirements was more on content than format, and if the guidance provided reflected this, it would be easier for inspectors to challenge reports of poor quality and this would act as an incentive for MAH to invest more in better reporting. Strict timelines can be a hindrance to quality of reports as once a report is filed, the pressure to complete it with additional information lessens and the necessity to forward one or more follow-up reports to the authority complicates the workflow and adds to the workload on both sides.

The current focus invariably leads to the submission of individual case safety reports listing the minimal information required to make them valid from a regulatory perspective (reporter, patient, medicinal product, ADR) but little or no information that enables causality assessment. At the Regulatory Authority, receiving reports saying "*On an unknown date, a female patient under treatment with drug X in unknown dosage, developed ADR Y. Medical history, concomitant medication, action taken and outcome are unknown*" is by no means an exception, and such submissions are the daily nightmare of any assessor asked to evaluate if there is a reasonable possibility that drug X can cause ADR Y. What we need are spontaneous reports of high quality, with a detailed description of the events, a complete chronology, the relevant medical history and information on concomitant treatment, how was the differential diagnosis carried out, action taken with the suspect drug, and outcome of the reported ADRs. Providing also time to recovery and treatment of the ADRs reported adds to the knowledge required to give provide important and much sought after information on expected course and outcome. Getting this information is difficult: HCPs are busy people with little time to spare for activities that put a burden they might perceive as unreasonable. Many HCPs do not understand the importance of reporting ADRs and the benefit they and their patient can get out of well-documented reports. A legal obligation to report is not enough: we must make sure that HCPs fully understand the value of reporting and get value back for the time they invest in pharmacovigilance. Prompt feed back to primary reporters with information that is relevant for clinical practice such as causality assessment of the reported ADR-drug association and information from the ADR databases as well as from the scientific literature motivates the medical community to contribute to safer medicines. Providing user-friendly coordination with already existing electronic records will further ease the burden of busy professionals.

Regulators have the duty to provide sound and useful information on the safety of medicines. Patients suffering from an ADR (and their HCPs) are not primarily interested in hearing from a regulator if the ADR of their concern is listed in the product information leaflet or not; they want to know what they can expect in terms of course, severity, treatment, and recovery. Well-documented, clinically focused reports can significantly add to this kind of knowledge, and every possible effort should be made to get them.

One might argue that low-quality reports should not be dismissed too quickly as they do have a role in contributing to disproportional reporting in safety databases and therefore help to highlight potential risks when mining large datasets, but we need to be aware that such reports are utterly useless when it comes to the actual scientific evaluation of the identified issue. If the only information available is that a patient suffered and ADR under treatment a causality assessment is not possible, nor can the combination be characterized in terms of risk factors or populations at risk. This gives MAHs that are not overly motivated to look into potential safety issues, a welcome reason to dismiss spontaneous reports of low quality as unassessable when concerns are being signaled by other parties. The fact that a significant number of such unassessable reports are submitted by MAHs to the authorities and that they are responsible for their content is conveniently overlooked.

We should not forget that collecting poor-quality reports, entering them in a database and transmitting them to the authority require effort, time, and resources that are not available for other, more demanding, and more important safety work. This is not going to change until regulators start putting more emphasis on content than on format. However, such a shift of focus will only lead to a real improvement if it is taken up during PV inspections and enforced.

2.6 Don't Ask for More Than You Can Handle

Marketing authorization holders are mandated to reports ADRs while participation in the safety surveillance of medicines remains voluntary for health care professionals in most instances. Even where they are obliged by law to report ADRs, this requirement is very difficult to enforce. If an authority wants to prosecute a HCP for not reporting, it has to prove in the first place that the HCP in question did in fact suspect that the condition the patient was suffering from might have been an ADR and has not reported it. Now, how are we ever going to prove what went on (or not) in the mind of somebody else? And even if this suspicion has been documented in medical records, which regulator has the capacity to screen all medical records in their jurisdiction? When professionals publish case reports on ADRs in scientific journals but no such case can be identified in the national database, the logical conclusion is that the reporting requirement has not been met; nevertheless, confronting the fallible HCPs will hardly improve reporting culture but probably achieve the contrary by creating resentment and possibly even ridicule. The legal requirement for HCP to reports ADRs does not by itself improve compliance[5]; it can be used as a medium to raise and maintain awareness of drug safety among HCP but not as

[5] In 2002 Switzerland introduced the legal requirement for HCP to reports ADRs and this was broadly communicated to the medical community. The number of reports from HCPs increased rapidly over a short time. When the authority stopped actively promoting ADR reporting on a large scale, the number of reports stabilized more or less, while reports from industry kept increasing significantly. See https://www.swissmedic.ch/ueber/00134/00441/00445/00568/index.html?lang=en

coercion. A legal provision that cannot be enforced is a toothless tiger: it is not taken seriously if it is well recognized that there will be no adverse consequences in case of noncompliance.

As basis for the marketing authorization for a medicinal product, pharmaceutical companies are rightly required to submit all available data on efficacy, safety, and quality. This documentation has become so extensive that electronic submission must be considered a blessing not only by reviewers but also by any logistics team. It is more than reasonable to ask for as much information as possible on a new drug before granting marketing authorization, provided that this information can also be thoroughly evaluated within an appropriate timeline. What is difficult for a regulatory agency in a high income country can become quickly impossible if Western requirements are uncritically adopted in countries where resources are far too scarce to process all the documentation submitted. Under the pressure of limited patent time, it is in the interest of a company to obtain approval as soon as possible and accordingly there is a lot of pressure on regulators. There is also pressure from the public: a regulatory agency is very quickly accused of dragging its feet by patients who are ill and hoping that the new drug will provide cure or at least significant relief.

Drug regulatory authorities are funded partly by taxpayers and partly by fees for services paid by industry. The former is a problem because the same politicians who decide on legislation are too often not willing to allocate the state budget needed for the work the implementation of this same legislation requires and the latter is condemned by those who think that a regulator must be completely independent from industry. This leads in any case to too limited resources for the workload and the depth of data evaluation required. This forces the regulators into a compromise between what is necessary and what is realistic, leaving all parties dissatisfied.

The same applies for postmarketing surveillance. The marketing authorization is granted, individual case safety reports, periodic reports, pharmacovigilance, and risk management plans (and their results!) must be submitted within defined timelines. Again, the rationale for these requirements is perfectly sound: the companies should continuously and reliably monitor the safety of their products and report to the authority. Once again format and timelines are given for ICSRs, periodic reports, PV Plans, and RMPs. The question still remains: are these documents being evaluated appropriately or only cursorily and then archived? Compiling these reports ties up immense resources and if the evaluation at the other end does not or cannot go much further than reading the executive summary or enter unassessed ICSRs into their database, it is pertinent to ask, if regulators should not ask for less but more focused information, appropriately tailored to the products and concentrate on this. This would still leave the option open to ask for more if needed. Do we really need every nonserious ADR reported as ICSR for every product on the market? A more focused, evidence-based approach would free up resources to invest in the scientific work that should constitute good PV practice.

Regulatory requirements should be based on evidence of effectiveness and cost-effectiveness. Requirements that prove effective should be enforced and adequate resources made available, if we want to reduce medicine-related harm to patients.

2.7 Acceptable Risks?

Even optimal regulation cannot eliminate every risk. One question that arises here is *how much risk are we prepared to take?* followed by *who decides on how much risk is acceptable?* The public's voice has been included in some regulatory proceedings,[6] but is this enough? Patients need to be able to make informed decisions. This means that the available information on benefit and risk of drugs must be communicated openly and in an understandable way. As the information must be objective and the MAH will hardly be considered free of bias, preparing and delivering it will be up to the authority.

Everybody has high expectations when it comes to therapeutics: they must be highly efficacious, completely safe, available as soon as discovered, affordable, and possibly funded by insurance or other parties. The competent authority must make sure all this is provided and function like clockwork. All this comes at a price. We must decide what we want and be prepared to pay for it.

2.8 The Regulation of the Future

We should work towards a regulation that is evidence based and cost-efficient, practical, simple, and transparent by

- Openly sharing relevant information in the regulatory environment
  - The first registration of a drug and all the information related to it could be made available to all other regulators, who in their turn could peer-review and add to it. This would reduce duplication of work, lead to leaner and more rapid regulatory processes, adapted to local needs and resources, and encourage a better and more equal collaboration between highly industrialized and low and middle income countries.
- Getting rid of overflowing bureaucracy and allow for flexibility and common sense.
  - Only data that can and will be thoroughly evaluated at the authority should be submitted. This will free up resources for more thorough scientific investigations of safety issues and the timely communication of the results.
- Ensuring that regulatory requirements are evidence based and cost-efficient
  - More efforts need to be put into investigating and documenting the impact of regulatory requirements on the benefit-risk balance for patients as well as the

[6] The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency is composed of representatives of the Member States, scientific experts and one representative of healthcare professionals and of patients' organizations respectively. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp

health care system. A documented positive impact will motivate all stakeholders to strongly engage in pharmacovigilance and to comply with requirements they can perceive as useful and important and not as an additional burden.

And last but not least, all harmonization initiatives should aim at global exchange and integration of knowledge instead of imposing Western standards in regions that need alternative solutions.

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