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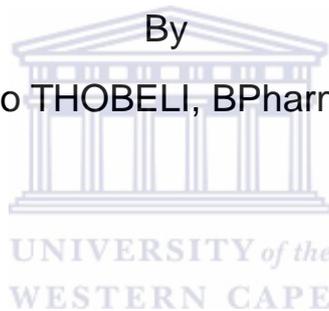
Hibernia College, Ireland



A Literature Review on Pharmacovigilance Systems in Off-Label Use of Medicines

By

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A Literature Review on the Pharmacovigilance Systems in the Off-Label Use of Medicines



ABSTRACT

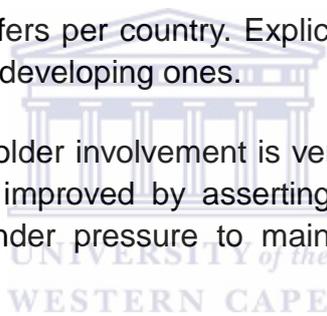
Problem and significance: Off-label use of medicines is not illegal; however, it can be risky and harmful, or beneficial and innovative. The main problem of this practice is the lack of systems for monitoring adverse drug reactions, since the drugs are used in a manner that is not approved by regulatory agencies. For this reason public health protection is not guaranteed.

Purpose: To identify the various systems employed in different regions to monitor/manage the risks and benefits of off-label use; and to ascertain their extent of implementation.

Method/search strategy: Electronic and manual literature search was done. Articles referring to off-label medicine use were reviewed. The literature included journal articles, national MRA guidelines, international guidelines, etc. The articles were sourced from databases such as Pubmed and Google Scholar. Data was collected from both developed and emerging markets. There was no limit to publication date.

Findings: Pharmacovigilance systems for off-label use do exist although the degree of commitment and advancement differs per country. Explicit off-label laws are present in the developed countries but not in the developing ones.

Implications of findings: Stakeholder involvement is very important in monitoring off-label use. Reporting of ADRs can be improved by asserting the role of off-label PV in drug repositioning. The regulator is under pressure to maintain public trust through efficient control of off-label use



DECLARATION

I declare that this thesis that I now submit for assessment on the programme of study leading to the award of Master of Science Pharmacy Administration and Pharmacy Policy Specialising in Regulatory Sciences has not been submitted as an exercise for a degree at this or any other college. It is entirely my own work and has not been taken from the work of others, save the extent that such work has been cited and acknowledged within the text of my work.

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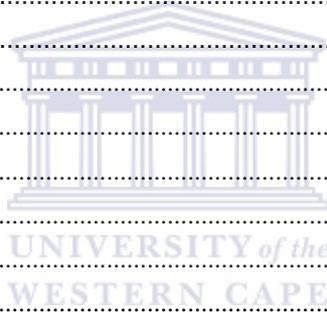
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LIST OF ACRONYMS

ADR / ADE	–	Adverse Drug Reaction/Event
AIDS	-	Acquired Immune Deficiency Syndrome
ANVISA	-	Agência Nacional de Vigilância Sanitária (Brazil)
CMV	-	Cytomegalovirus
CPA	-	Consumer Protection Act
CTD	-	Common Technical Document
EMA	–	European Medicines Agency
EU	–	European Union
FDA	–	Food and Drug Administration (USA)
FDAAA	-	Food and Drug Administration Amendments Act
FDCA	-	Federal Food, Drug and Cosmetics Act
GVP	-	Good Pharmacovigilance Practice
HIV	-	Human Immunodeficiency Virus
ICH	-	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	-	Individual Case Safety Reports
MA	-	Marketing Authorisation
MCC	–	Medicines Control Council (South Africa)
MHRA	–	Medicines and Health Products Regulatory Authority (UK)
MRA / DRA	–	Medicines / Drug Regulatory Authority
NHA	-	National Health Act
NME	-	New Medical Entity

OLU	–	Off-label Use
PAHO	-	Pan American Health Organisation
PSMF	-	Pharmacovigilance System Master File
PSUR	-	Periodic Safety Update Report
PV	–	Pharmacovigilance
SA	–	Republic of South Africa
SACAWG	-	South African Childhood Asthma Working Group
SASA	-	South African Society of Anaesthesiologists
SPC	-	Summary of Product Characteristics
TB	-	Tuberculosis
TRU	-	Temporary Recommendations for Use
UK	-	United Kingdom
UMC	–	Uppsala Monitoring Centre
US	–	United States of America
WHO	–	World Health Organisation



1. Introduction

1.1. Background

The World Health Organisation (WHO), in (WHO, 2002) and Pal, Duncombe, Falzon, and Olsson, (2013), defines pharmacovigilance (PV) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. According to WHO, the aims of PV are;

- To strengthen patient care and public safety with regards to the use of medicines
- To support public health programmes through provision of reliable, balanced information for proper risk-benefit profile assessment of medicines, thereby encouraging their safe, rational and more effective (including cost-effective) use.

Off-label use of medicines on the other hand, is described by Stafford (2008) as the prescription of medicines in a way that is different from that approved by the regulatory authority such as the Food and Drug Administration (FDA) of the United States; that is, the medicine is used outside the provisions of the Summary of Product Characteristics (SPC) as described by Horen, Montastruc, and Lapeyre- Mestre (2002).

Stafford (2008) and Gillick (2009) state that off-label use of medicines is legal and common in many countries and entails the prescription of a drug in different populations, conditions and even in varying doses than those it was licensed for. Gillick (2009) also highlights the benefits of off-label prescribing such as its use in paediatrics and finding new uses for existing drugs (drug repurposing). The disadvantages of this practice however, as stated by Gillick (2009), are the concerns about patient safety with drugs that have a high potential for toxicity as well as economic issues when these drugs are costly. The use of drugs in unregistered situations is pervasive. For instance, it is estimated in Walton, Schumock, Lee, Alexander, Meltzer and Stafford (2009) that off-label medicines use in the

US is more than 20% of out-patient prescriptions. A European study done in five countries, as discussed in Morales-Carpi, Estañ, Rubio, Lurbe, Morales-Olivas (2010), found that 67% of patients that were interviewed got at least one off- label prescription; and up to 90% of patients in neonatal intensive care wards receive off-label prescriptions.

1.2. Statement of the problem

Granted, off-label use has both advantages and disadvantages. However, the concern is that as much as off-label use is not illegal, systems and efforts are not put in place to extensively monitor the adverse drug effects in these situations. Thus the patients and the general public are not protected, but exposed to potential harm due to treatments that are not based on proven evidence. After the benefits have been identified, what are the risks and are they monitored and reported?

In Mukattash, Millership, McElney and Collier (2008), Gillick (2009) and Rodwin (2013), it is mentioned that off-label use exposes patients to a considerable degree of risk especially in the paediatric population and when the drugs have a high potential for toxicity; they also contribute to increased medical costs. The authors further state that there are also legal and ethical implications if the patients are not informed of the potential risks and the harms actually occur.

PV systems and activities to regulate and monitor safety of off-label medicines use are not in place. These activities include availability and implementation of the relevant regulatory framework such as legislation, policies, guidelines, education and training.

Rodwin (2013) indicates that the public policy that is currently available 'fails to track, evaluate, or manage off-label drug use effectively', and as a result the regulatory authorities that are meant to protect the public and regulate the pharmaceutical industry may become corrupted and hence put the public health in danger.

1.3. Significance and relevance of the study

The World Health Organisation (WHO, 2002) also states that the science of PV includes other issues such as the use of drugs in unapproved conditions for which there is not enough scientific evidence. This study will ascertain if this WHO recommendation is applied. As highlighted by Barratt and Frai (2012) and Boguski *et al* (2009), off-label medicine use as a drug repurposing mechanism offers a more cost effective and environmentally friendly method of drug development as it seeks to maximise the potential benefits of a drug that is already in the market. Therefore, as stated by Boguski (2009) and Flower (2013); the initial aims of PV of detection and characterisation of only adverse drug effects are broadened as the side effects are now positively exploited in drug development; this is termed 'type 2' PV or repurposed PV.

1.4. Purpose of the study

The aim of the study is to determine the availability of pharmacovigilance systems employed in the regulation and monitoring of off-label use of medicines in the different parts of the world. The identified activities are also ascertained for whether they are implemented, in the pipeline, or just recommendations.

In the process, the study also aspires to highlight the importance of PV or post- marketing surveillance in off-label drug use and to emphasize the growing importance and dynamism of PV.

2. Off-label use of medicines

2.1. Background

The regulation of medicines came about due to a number of historical disasters related to drug use; notably the use of thalidomide in pregnancy, which resulted in babies born with limb deformities in the late 1950s and early 1960s. This resulted in a rapid increase in

medicine regulation laws and establishment of medicine regulation authorities (MRAs). In South Africa, the Medicines and Related Substances Act 101 of 1965 was promulgated and gave rise to the regulatory body, the Medicines Control Council (MCC) CTD module (Hibernia College 2012).

MRAs are responsible for protection of public health through registration (or licensing) of medicines to ensure that when they are marketed, they meet three basic requirements of good quality, safety and efficacy CTD module (Hibernia College 2012) and, Regulatory affairs module (Hibernia College 2012). Medicines are approved only when the potential benefits outweigh the potential risks. Therefore, according to Boos (2003) and from CTD module (Hibernia College 2012), for their drug to be marketed, pharmaceutical companies have to submit to the MRA, pre-clinical (animal studies) efficacy and safety data, and the results from the clinical studies to prove the claimed safety profile and the efficacy for the intended use.

In the Regulatory Affairs module (Hibernia College 2012), it is mentioned that the FDA also adds drug labelling, i.e. whether the drug is labelled as meeting the standards, as the fourth medicine registration requirement. Dresser and Frader (2009) also add that the label includes the following approved information;

- Indications
- Dosage
- Route of administration
- Patient population
- Age group

Off-label use of medicines consequently implies that the above elements are defied. As indicated earlier, the practice of off-label use is legally and clinically acceptable; Boos (2003) and Tarbarok (2000) indicate that the MRAs regulate the registration process and

the label, but not how the medicines are prescribed. According to Leroose, Musto, Aieta, *et al.* (2012) and Lindell-Osuagwu, Korhonen, Saano, *et al.* (2009), off-label use of medicines is a global phenomenon, most common in populations where it is difficult to conduct clinical research such as in paediatrics and oncology.

A Finland study by Lindell-Osuagwu *et al.* (2009), found that the use of off-label drugs in the paediatric wards studied was very common and as pervasive as those described in other regions. In Gillick (2009), it is also stated that one study showed that five mostly prescribed oncolytics were for off-label indications in half of cases. According to several reports, as highlighted by Leroose, *et al.* (2012) and Fallon (2008), the most drugs commonly used in an off-label manner are antipsychotics, oncolytics, antibacterials, anticonvulsants, antiasthma, and cardiovascular drugs.

2.2. Implications of off-label use

As already alluded to, off-label use of medicines has both advantages and disadvantages; which in the end, according to DeMonaco, Ayfer, and von Hippel (2006), raise a lot of ethical, legal, economic, regulatory and safety issues. Stafford (2008, 2012) asserts that the different stakeholders, namely; the pharmaceutical companies, the public, the prescribing doctors and the payers of medical services, have different and conflicting views in terms of these issues arising from the off-label use of medicines. An attempt is made to discuss the issues separately below even though it was a bit of a challenge as there is an overlap e.g. ethico-legal issues.

- **Ethical issues:** the patients that receive OLU drugs are exposed to risk due to lack of sufficient safety data. As discussed in the Ethics module (Hibernia College, 2012) and by Kling (2011), the principle of non-maleficence is breached when the patient suffers an adverse drug reaction from this use. On the other hand, if the patient

benefits from OLU, the principle of beneficence is upheld as the prescriber exercises her duty and responsibility of promoting health. Rosoff (2011) and Molyneux and Bogaert (2010) further emphasize that in the case where the patient is not informed of the benefits and risks of OLU before administering and thus cannot make an informed decision, his autonomy is violated. In Italy for example, Molyneux et al, (2010) indicate that prescribers may be charged for criminal conduct if they do not obtain informed consent, especially if the patient is harmed in the process. In South Africa, Kling (2011) states that the requirement for informed consent applies only to the use of unregistered drugs, not OLU.

Another violation of the patient's right is being misled into participating in clinical research. In Rosoff (2011) and Bennett (2004), the untested OLU of medicines is seen as experimental treatment of which patients have to undergo without their knowledge when the prescribers do not disclose the important safety facts about the drugs. Therefore, Bennett (2004) recommends that informed consent should be issued and approved by the ethics committee. Other dilemmas that are raised by Kling (2011) and Rosoff (2011) are how much and how detailed information to give to the patients regarding OLU, and also sometimes both the prescriber and the patient may be ignorant of the off-label status, and hence the efficacy and safety, of the medicine.

- Legal issues: OLU of medicines is not illegal; however, careful consideration must be taken especially with other laws that deal with public safety. For example, in South Africa, the Consumer Protection Act (CPA) and The National Health Act (NHA) have a direct bearing on the OLU of drugs with respect to the conduct of prescribers and protection of patients. CPA stipulates that a health care practitioner in the process of marketing a product, may not give exaggerated,

misleading or deceptive information, and must correct any patient misunderstandings. Thus potential risks and benefits must be communicated and informed consent must be sought to protect the patient and avoid litigation (SASA, 2012). The NHA also requires that the patient must be thoroughly informed of risks and benefits of OLU (SASA, 2012). In many jurisdictions including South Africa and the United States, it is illegal for pharmaceutical companies to promote the OLU of medicines; however, the FDA does allow for circulation of journal articles and scientific references on unregistered new uses of registered medicines – this, according to Jansen (2009), is not permitted in SA. It is stated in Ventola (2009) that promotion of off-label use information also forms another bone of contention among the regulator (state), prescribers and the pharmaceutical companies. There is the point of view that dissemination of this information promotes transparency with regard to treatment choices against the view that the information poses a risk to public health. Jansen (2009) says that dissemination of this information by manufacturers is illegal in South Africa.

- Economic issues: Gillick (2009) states that OLU of medicines can be costly if it is not efficiently regulated, since newer and more expensive drugs such as biotechnology products, may be used indiscriminately. An example is mentioned in Mesgarpour *et al* (2012) where it stated that in one study off-label use of factor VII was found to be more common than its use in approved conditions. The issues of cost-effectiveness and justifiable evidence are very important in controlling the general use of medicines. Scarce resources are wasted when unproven medicines and those with insufficient scientific evidence are funded by the state. Gazarian (2007) also suggests that the resources could instead be used in to fund essential drugs and even the needed research.

According to Molyneux *et al* (2010), the EU law explicitly states that financial considerations should not affect the decision to obtain informed consent for OLU of medicines. DeMonaco *et al* (2006) indicate that pharmaceutical companies also gain financially through the increased sales of their drugs being used off-label, even though they do not publicly endorse this practice.

- Regulatory issues: there is a view that OLU of medicines undermines the regulatory system and thus threatens public trust in the MRAs. In Boos (2003), it is estimated that more than 50% of treatment with any medicine is off-label, which implies that the regulatory requirements are violated; hence it can be inferred that the label has no role in the marketing of the drug. According to Molyneux *et al* (2010), the OLU of medicines is comparable to the different kinds of amendments to a marketing authorisation (MA), known as variations. In Regulatory Affairs module (Hibernia College 2012) and EU variations (2008) it is stated that variations are classified as minor or major depending on the level of risk to public health and the effect it has on the quality, safety and efficacy of the drug product. Molyneux *et al* (2010) assert that OLU of medicines constitutes a major variation and thus requires prior MRA approval since there is an additional new indication, inclusion of a new target population, etc. Gillick (2009) on the other hand sees an opportunity in that OLU bypasses the prolonged and costly process of label modification with the FDA. In Pandolfini, Impicciatore *et al* (2002), it is stated that PV as a regulatory activity is extremely important in order to detect any drug related problems, especially when they are used outside their summary of product characteristics.
- Clinical and Safety issues: as suggested by Stafford (2012) and Borzo (2009), the use on medicines off-label may be beneficial in situations where standard 'on-

label' drugs have failed; for example in treating multi-drug resistant tuberculosis and HIV/AIDS. Stafford (2012) further suggests that it may also be the only treatment available and accessible for rare, orphan and neglected conditions, cancer and populations not studied in clinical research.

Deviation from the provisions of an MA, on the other hand, according to Molyneux, *et al* (2010), Gillick (2009) and Bennett (2004), exposes patients to increased harm since they may have a high potential for toxicity, and the risks of the OLU are not well documented. As a result, Molyneux *et al* (2010) indicates that the prescribers must conduct a benefit/risk assessment per individual as the risk factors may not be universal. Palčevski, Skočibušić and Vlahović-Palčevski (2012) highlight that OLU of drugs may result in benefit, no therapeutic effect or adverse drug reaction; however, if a prescriber is unwilling to use a drug in an off-label manner, patients may be denied of potentially effective treatment. Mehta (2011) mentions that adverse drug reactions (ADRs) pose a great threat to the public health; however, many are predictable and preventable through a more rational use; except, for example, in off-label use because of insufficient data on safety profile. Horen *et al* (2002) write that in some studies, the results showed that a third to half of ADRs occurring in children were as a result of off-label use. Because very few drugs are tested on children, their medicines are mainly used off-label; and according to Okechukwu *et al* (2009), their doses are generally extrapolated from the approved adult doses. However, as argued by Okechukwu *et al* (2009), children are not small adults, their vital organs are not fully developed hence their capacity to metabolise drugs is not fully developed. Tomlin and Morris (2009) further state that elimination half-lives for preterm and neonates are normally three to nine times

longer than in adults. Thus there is an increased inclination for children to risks of ADRs.

- Drug repurposing: Bisgin *et al* (2012) define drug repurposing as the system of discovering new uses or indications for existing drugs; and for the purpose of this discussion, the existing drugs are the ones approved by the relevant MRA. According to Boguski *et al* (2009) and Sekhon (2013) drug repurposing has the advantages of exhausting the full benefits of a drug, and of offering a cheaper, shorter and environmentally friendly drug development system. Dolgin (2011), Napolitano *et al* (2013) and Barrat *et al* (2012) assert that large amounts of money are continuously invested in the conventional drug discovery and development but the number of newly approved drugs keeps declining. In Barrat *et al* (2012), it is further stated that the number of new medical entities (NMEs) that are approved by the FDA has remained the same at about 25 items per annum, meanwhile, the drug research and development cost have gone up to over 50 per cent in the last ten years.

OLU, viewed as creative and flexible by Gillick (2009) facilitates innovation and the discovery of new and important indications for old established drugs, as stated by Stafford (2012) and Gillick (2009). For example, beta-blockers were initially approved for hypertension and arrhythmias, their off-label use led to their use in congestive heart failure. Boguski (2009) classifies OLU of medicines as a form of drug repurposing.

In WHO (2002) and Yang (2011), it is stated that ADRs or side effects can be used to determine structure-activity-relationships, as well as pharmacological and genetic factors affecting the medicines' activity. Thus they contribute to the discovery of other new indications. Side effects are unwanted effects due to the drug's ability to

bind to a number of different targets apart from its intended target, report Haupt *et al* (2013).

Therefore, the basic concept as explained in Yang (2011) and Bisgin (2012) is that drugs that have a common side effect profile are likely to be effective in treating the same conditions, even possibly at a lower risk profile. Hence, as discussed by Haupt *et al* (2013), Sekhon (2013) and Bisgin *et al* (2012) this presents an opportunity to find new indications for existing drugs. For example, methotrexate, an anticancer drug, lists cytomegalovirus (CMV) infection as a side effect; CMV infection results from immunosuppression. Drugs that suppress the immune system are often used in patients who have undergone organ transplant to prevent rejection. Yang *et al* (2011) mention that methotrexate has been reported as used off-label to prevent organ rejection. They also mention that the side effect on its own can be used to hint on a new indication by changing the drug formulation and controlling the dose, instead of it being dismissed as an unwanted effect.

Therefore, as suggested by Haupt *et al* (2013) and WHO (2002), it is imperative to do away with the negative perception of ADRs and side effects, and to develop measures that will allow clinical, pharmaceutical and chemical information to be applied to better improve the understanding of the mechanisms of action of drugs.

The one challenge with drug repurposing as highlighted by Sekhon (2013) and Boguski *et al* (2009) is regarding the complexities of intellectual property protection, since the success of a repurposed drug seems to depend on whether the patent has expired or not and on regulatory exclusivity. Apparently, as stated in Boguski *et al* (2009), pharmaceutical companies are not willing to invest in costly clinical trials for repurposed drug without a patent protection.

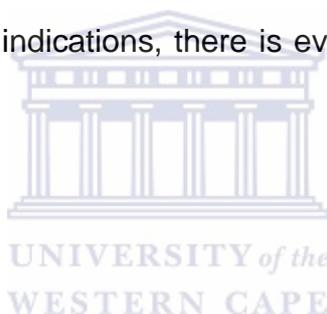
WHO (2002) indeed recognises the importance of monitoring off-label use by widening the scope of PV to include the use of medicines in unapproved conditions for which there is insufficient clinical evidence. Hence, PV is extremely important throughout the mentioned issues. Detection, assessment, understanding and prevention of adverse drug reactions ensure reduced rate or severity of harmful effects of drugs. Consequently, public health is safeguarded, health care and drug development costs are reduced, and there is an increased availability of treatment options. Mehta (2011) and Boguski et al (2009) argue that PV and public health protection are not only the obligations of the drug regulators; all stakeholders, i.e. drug manufacturers, the health care workers and the public itself should be all responsible in their own right to understand, reduce and manage potential risks in order to attain the goal of public health protection. It is discussed in the PV module (Hibernia College 2012) that manufacturers are already mandated by the regulators to submit risk management plans and other periodic safety reports on their products, prescribers and patients on the other hand only report voluntarily and sporadically. The different roles of stakeholders are as follows:

- Public and patients: according to Flower (2013) and Boguski et al (2009) it has been discovered that consumer health groups can play a big role in educating the general public about drug safety and also in research. In Boguski et al (2009), it is stated that potential beneficial side effects of old drugs can be discovered online through a social networking tool known as 'crowdsourcing'.
- Industry may facilitate research by funding the needed studies.
- Prescribers – according to Edwards (2011), clinicians need to know about the risk-benefit balance of drugs, their pharmacology and toxicology. They should make a habit of reading the drug SPCs. In general, health professionals must communicate among themselves and they should report both failures and successes of off-label

use. DeMonaco *et al* (2006) also believe that prescribers, as product users, are crucial to innovation. The authors further state that product users are the actual innovators rather than the manufactures, hence they support drug repurposing through off-label use.

- Regulators must ensure compliance to the laws, and they must foster stakeholder engagement.

The underreporting of ADRs is a big challenge globally, as reported by WHO (2002), and this for approved uses of medicines. It is hence the intention of this study to insist that the minimum requirement for any ADR reporting should be on the off-label use of medicines; the rest will follow; for as aptly expressed by Stafford (2008:1429), “If there are substantial safety concerns about approved indications, there is even greater uncertainty with regard to off-label uses”.



3. Methodology

3.1. Study design

Electronic and manual search of literature published in English was done. Articles referring to off-label medicine use alone and also with PV were reviewed. ‘Unregistered’ and ‘incorrect’ uses were search terms used synonymously with ‘off-label’ use. Other alternative ‘PV’ terms used were ‘post-marketing surveillance’, ‘adverse drug reactions/events’. Other keywords included in the search with the word ‘drug or medicine’ were ‘benefits, risks, safety, repurposing, repositioning’, Summary of Product Characteristics (SPC) and non-compliance/breach, and regulation / control / innovation in off-label use.

The literature included journal articles, national medicine regulatory authorities (MRA) guidelines, international guidelines, grey literature, and so on. MRA and PV websites (e.g. FDA, Uppsala Monitoring Centre¹) were also explored.

The articles were sourced from databases such as Pubmed, Google Scholar (through access to the Hibernia College library), and general internet search. Manual search was conducted at my workplace resource centre. There was also communication by email with South Africa's national PV office to inquire about any PV activities that related to off-label use of medicines. No other country PV office was contacted. An attempt was made however to contact the Uppsala Monitoring Centre; no response was received.

Articles that were included in the study were those that discussed off-label use alone or with PV and monitoring systems. Those that discussed PV only were excluded because they discussed general PV. The study was also only limited to off-label use of already marketed drugs and not those that are unlicensed². However, articles that discussed unlicensed use were also considered in the review as the problems and management strategies were similar. There was no restriction as to the type of off-label use, origin of the article, or publication period. A fairly global representation of literature was sought i.e. South Africa, North and South America, Europe, Asia, etc. also bearing in mind to include information from both developed and emerging markets. There was also no limit to the publishing date, but from the articles collected, none was published before the year 2000.

Limitations: The biggest challenge was that many promising articles could only be accessed through subscription. At times the abstracts were not sufficient as they were not detailed;

¹ Uppsala Monitoring Center (UMC) is a WHO Collaborating Centre for International Drug Monitoring.

² Unlicensed medicines are those that have not been approved for marketing by the regulatory authority in a given country or region (e.g. tablets of an adult medicine crushed and made up into a suspension for oral administration to a child).

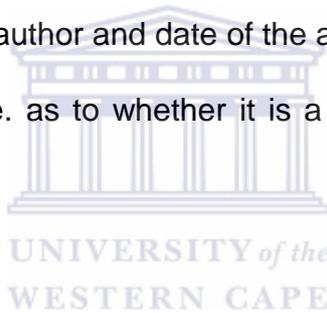
hence I only used the abstracts that had the required information. Other challenges encountered were finding relevant articles on OLU studies from the African region as the intention was to determine the availability of such systems especially in African countries.

Most of the articles that linked off-label use and repurposing were accessible through subscription and the abstracts were not very helpful.

3.2. Data collection and analysis

From the articles collected, any activity or system that spoke to monitoring and management of off-label use and drug repurposing was noted. The following information was also noted;

- The source of data, i.e. the author and date of the article
- The type of intervention, i.e. as to whether it is a law, policy, guideline, education / awareness tool, etc.
- The region or country
- Implementation stage or status, i.e. whether the PV system is already in operation or a proposal
- General recommendations that were not specific to a region



The results were tabulated into two tables; promulgated laws and soft laws such as guidelines, policies and statements. The activities or systems were explained per region or country. There were also articles that gave recommendations and suggestions on how to manage without being specific to a country. These were discussed separately.

4. Results

Most articles were obtained through access to the Hibernia College library. The total number of full articles that met the search criteria was forty two and the abstracts were

eleven. In addition, other publications such as books, reports and other documents from different jurisdictions were sourced to consolidate the information collected from the articles and to get a feel of general opinion on the off-label use of medicines. From the search, eight regions were found to have the relevant systems, namely: South Africa, Australia, Brazil, Canada, Italy, UK, US and EU. The results of the search are displayed in two tables below.

Table 1: The laws relating to OLU which have been promulgated in different regions

Source	PV system	Type	Status	Region
Martens, M & Carbonnelle, N (2012)	Regulation No. 1235/2010 & Directive 2010/84/EU	Law	Implemented (2012)	EU
Palčevski et al (2012) and Lindell-Osuagwu, L. et al (2009)	Regulation (EC) No. 1901/2006 as amended	Law	Implemented (2007)	EU
Molyneux, C.G. & Bogaert, P (2010) and Bernardi, A. & Pegoraro, R. (2008)	Law 648/96, Law 94/98 & Decree Law	Law	Implemented	Italy
Dresser, R. and Frader, J. (2009)	FDA Amendments Act of 2007 & FDCA	Law	Implemented (2007)	US

Table 1 shows the binding laws that regulate OLU are only available in Europe and the US. Each region has at least two laws. Italy also has its own laws in addition to the ones passed by the EU.

Table 2: The soft laws relating to OLU which have been adopted in different regions

Source	PV system	Type	Status	Region
Tomlin, S. & Morris, H. (2009)	Prescribing unlicensed medicines to children	Guidelines	Implemented	UK
Pulver, L. Gazarian, M. et al (2013)	Guiding principles for OLU	Guidelines	Proposal	Australia
Dos Santos, L. & Heineck, I. (2012)	Off-label PV programs	Policy	Proposal	Brazil
MCC website	Reporting post-market ADRs	Guidelines	Implemented	South Africa
SA Society of Anaesthesiologists	Position statement	Information tool	Implemented	South Africa
Ogilvie, K. & Eggleton, A (2014)	Official report	Information tool	Implemented (2007)	Canada
Nature medicine (2011) and FDA website	FDA Sentinel Initiative	Policy	Launched (2008)	US

Hospital	Off-label case	Information	Implemented	US
Pharmacy Journal	studies	tool		

Table 2 shows the available OLU management systems which are non-binding in the UK, Australia, Brazil, South Africa, Canada and the US. They range from policies and guidelines to information tools.

The information from both tables was extracted from different articles stated under 'Source'. The name of the activity or system was noted, the type (e.g. law, policy, guide, etc.) was also noted as well as whether it is practised and from which region it came.

More information on PV legislation from different regions was also sourced from the PV module (Hibernia College 2012); these laws are found in the annexure segment of this report.



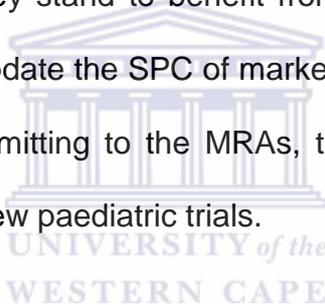
European Union

The EU Laws Regulation No1235/2010 & Directive 2010/84/EU were amended to affect a number of PV requirements such as;

- The definition of an ADR is now wider in scope and includes effects also caused during OLU, misuse, abuse and medicine errors.
- Pharmaceutical companies must maintain and make available a PV system master file (PSMF) which must have detailed information on safety data of a product that is available globally. This applies to those medicines which were registered from July 2012.
- The periodic safety update reports (PSUR) requirements have also been revised.
- Improved transparency

- New good pharmacovigilance practice guidelines (GVP) to replace Eudralex Vol9A³ in 2013.
- MRA may demand post-marketing studies to be done at any time, depending on circumstances.

Regulation (EC) No. 1901/2006 as amended, also known as the Paediatric Regulation is an EU law aimed at improving child health protection. It regulates the development and licensing of drugs intended for use in children from zero to seventeen years. This goal will be achieved through a number of systems including ensuring that conduct of research for paediatric medicines is ethical and of good quality. Children must not be exposed to clinical trials unnecessarily, only when they stand to benefit from the drug. Also, through the law, pharmaceutical companies may update the SPC of marketed drugs that are used off-label in children. This is achieved by submitting to the MRAs, the cumulative safety and efficacy data on children and conducting new paediatric trials.



Other regulations employed in the EU for OLU of drugs include the Regulation (EC) No.141/2000 for orphan drugs and International Conference on Harmonisation (ICH) guidelines that relate to risk management and PV plans (Regulatory Affairs & PV modules, 2012).

Italy

In Italy, OLU of medicines is regulated by three laws namely;

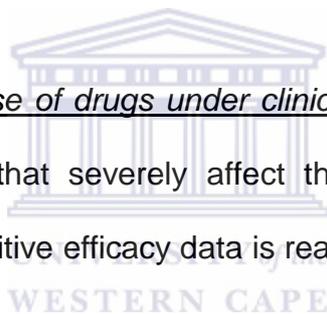
Law 648/96 specifies the kind of drugs which are freely accessible to the patients in the absence of alternatives and the therapeutic proposal is acceptable. These are (a) innovative drugs that are available in the EU but not in Italy, (b) drugs which have

³ Eudralex Vol 9A. – PV guidelines for medicines used in humans published by the European Commission

undergone phase II clinical studies and their results are available, regardless of whether they are registered for the disease or not, and lastly, (c) drugs that will be used for a condition other than the labelled one. The drugs for OLU should be those that have substantial scientific evidence of efficacy and safety even if they have not been registered for that purpose yet.

Law 94/98 controls the OLU of medicines in individual cases but does not allow pervasive use, otherwise it is deemed illegal. It supports the prescriber in using a drug in an off-label manner provided there is no 'on-label' alternative, there is evidence of efficacy from globally reputable sources, the patient is under the direct care of the physician and informed consent is obtained.

Decree Law on the therapeutic use of drugs under clinical investigation provides for life-threatening conditions or those that severely affect the quality of life, to be treated by experimental drugs as long as positive efficacy data is readily accessible.



For all the above provisions of OLU of medicines, continuous monitoring of adverse effects is mandatory.

United Kingdom (UK)

The UK has developed a number of strategies to deal with prescribing in children. The above guidance addresses the prescribing of unlicensed medicines to children but it also addresses off-label use. One of the goals is to improve communication between the prescriber and the parent (and patients) through informed consent, so that risk to patients is minimised. The parents must be told why they are given medicines off-label and they are encouraged to report any ADRs that may occur during use. It also requires that all discharge letters (e.g. from one level of care to another) for prescriptions must be thorough

and have information that includes name of drug, dose, frequency, length of treatment, strength and dosage form. Recognising that sometimes OLU of medicines in children is unavoidable, prescribers are advised on steps to follow in order to avoid harm to patients and litigation, namely:

- Exhaust all possible approved medicines.
- Ensure there is sufficient scientific evidence, experience or both to support that the drug is safe and effective.
- Document in the patient's records, the reasons why such a treatment was given.

The UK through its MRA, Medicines and Healthcare products Regulatory Agency (MHRA), has quite an extensive PV program as seen on its website. ADR reports can be accessed and a lot of different reports e.g. drug analysis prints, can be drawn from there. A report of misoprostol was generated out of interest to see what the format of the report looks like, and because it is used in South Africa for termination of pregnancy; a use not registered with the MCC. This report is extensive (38 pages long); and lists all ADRs (according to system organ class) and total reports on misoprostol, as a single agent or in combination, from 1963 to date!

Australia

Gazarian, Kelly *et al* (2006) identified that although there is plenty of literature on the prevalence and consequences of off-label prescribing, there is not much in terms of guiding the prescribers on how to make informed decisions about the proper manner of such a practice. Thus they are expected to use their own judgment to determine whether they should prescribe a drug off-label or not. The report explains the development of a guide for health care workers, policy makers and funders of health care. The guidelines are meant to show the difference between OLU that is supported by high quality evidence and that which

may be justified in individual exceptional cases. The report explains how the development process unfolded, and what the recommendations were. Apparently the recommendations were adapted by the Department of Health and many hospitals. The algorithm developed identifies three general elements of appropriate OLU, namely; use that is justified by high quality evidence, use within the context of a formal research proposal, and exceptional use. This use must be monitored for effectiveness, outcome and adverse effects. A poster summarizing the guidelines and highlighting this process was developed in 2013.

Brazil

The Pan American Health Organisation (PAHO, 2011) indicates that PV in Latin America and the Caribbean is still in the early developmental stage. And like other countries, it faces challenges of underreporting, redundant reports of already known effects, and irrational use of medicines including OLU.

A paediatric study by Dos Santos and Heineck (2012) in a Brazilian hospital showed that the rate of unlicensed and off-label drug prescriptions was the same as the global trend. This is considered as high. A number of drugs used commonly for off-label were identified and listed, such as salbutamol. There are few studies in Brazil on the OLU of medicines, and the high prevalence of OLU is a concern for Brazil's regulatory authority, ANVISA. According to Dos Santos *et al* (2012), the authority aims to employ PV systems and reporting of ADRs in order to identify these drugs.

South Africa (SA)

The guidelines for the reporting of adverse drug reactions to the regulatory authority, Medicines Control Council (MCC), relate to the Regulations of the Medicines and Related Substances Act 101 of 1965 as amended. The definition of an ADR in the guidelines includes the off-label use of medicines. The main form of post-marketing surveillance is the

spontaneous reporting. Mehta and Dheda *et al* (2014) also mention other forms that include PV systems for immunisation, HIV and TB programs, and dermatology. The challenges include lack of collaboration among the programs and resource constraints. There is no specific off-label use surveillance program except through extraction from the spontaneous reports.

There are also position statements on off-label use of medicines that come from medical societies in SA, such as the SA Society of Anaesthesiologists (SASA) and the South African Childhood Asthma Working Group (SACAWG). According to Kling (2011), SACAWG in publishing their childhood asthma guidelines realised that some of the drugs were used off-label hence a disclaimer was added stating that 'some of the medications used in this guideline are used off-label but with the best evidence available'. SASA (2012), in its statement, acknowledges all the concerns relating to the off-label use of medicine and links them to the various Acts in SA that relate to public protection such as;

- the Consumer Protection Act 68 of 2008 – informed decision making by the patient in a language that they understand; risks to be effectively communicated
- the National Health Act 61 of 2003 as amended – informed consent for medical treatment
- Medicines and Related Substances Act 101 of 1965 – pharmacovigilance requirements

They also draw on regulations by the World Medical Association on the Relationship between Physicians and Pharmacists in Medicinal Therapy of 1999, as amended in 2010, and the Health Professions Council of SA Ethical Rule 2006, as amended.

Canada

Fuller and Saibil (2005) highlighted political and economic challenges that limited effective post-marketing surveillance systems in Canada, and a major dependence on spontaneous reporting by healthcare workers and the public. The public, however, through consumer health groups have made a great impact in raising awareness to ADRs. Fuller and Saibil (2005) also mentioned that the low rate of reporting makes it difficult to monitor drug effects and take prompt action. Political directives were also issued to employ faster approval systems for new drugs; but no directives to improve post-marketing surveillance of drugs came forth.

'Prescription pharmaceuticals in Canada: off-label use' is the title of the report included in table 2. It is one of the four phases undertaken by the government on prescription medicines and it seeks to present to parliament, the current state of monitoring off-label prescribing, to raise awareness to issues of concern (ethical, economic, clinical, etc.) and offer recommendations. It states for example, measures that Health Canada has taken to collect safety data on drugs prescribed for children (Canadian Surveillance Paediatric Program and Pediatric Expert Advisory Committee) but with very poor results.

The report explicitly states that there is no system in place in the country to monitor OLU of medicines; and there is no official procedure for documenting and monitoring whether the drugs used in this way are effective. The report also uses other countries as benchmarks; for example, it is mentioned that in South Africa, off-label data is collected by mandating the prescribers to supply the indication for which a drug is prescribed. Also, in France, a newly registered drug may be issued a Temporary Recommendations for Use (TRUs). TRUs can be valid for up to three years, during which the drug can be used off-label for stated conditions subject to some conditions and monitoring and collection of data.

United States (US)

The US was found to have numerous articles and publications (including a reference book titled 'Guide to off-label prescription drugs') on the off-label use of medicines, including its role in drug repurposing. According to Ventola (2009), the FDA also publishes policies that deal with off-label information in aspects such as regulation, distribution, evaluation, etc. The systems listed in this report are by no means exhaustive.

The FDAA Amendments Act (FDAAA) 2007 made a number of changes to the Federal Food, Drug and Cosmetics Act (FDCA) which have a bearing on the OLU of medicines as follows;

- It has strengthened the post-marketing surveillance system that regulates approved drugs by increasing funding to the FDA unit responsible for monitoring safety of approved drugs, and to the adverse event reporting system. The aim is to create an active monitoring system to reduce reliance on spontaneous reporting. Furthermore, the FDA will be able to use information from large clinical records to assess product safety and OLU of drugs. Manufactures may also be requested to perform post-marketing research to identify risks on time. As a result patient information and evidence base on OLU can be gathered.
- The Act facilitates access to study information on OLU by providing for the public registration of industry sponsored studies. This will deter the manufactures from covering up unfavourable results of those studies.
- The Act also authorises the FDA to step in where there is a threat to public safety, for example, the agency can mandate modifications to the drug label to reflect any newly identified risks.

Other relevant laws include Best Pharmaceuticals for Children Act, to amend the Federal FDCA to improve the safety and efficacy of pharmaceuticals for children. It offers six

months of additional patent life to drugs tested on children. The Paediatric Research Equity Act on the other hand authorizes the FDA to require drug manufacturers to conduct research in children.

The Sentinel Initiative comes as a result of the passing of the FDAAA. It is the first point discussed above. This is an active surveillance system whereby safety information relating to drugs and devices will be pooled from an electronic database of patients. It is meant to strengthen and not replace the current post-market PV systems. It is a public-private-partnership that includes data partners, patient and health advocacy groups, academic institutions, health insurance companies and regulated industry. When it was launched in 2008, it was implemented in phases aiming at accessing data from 25 million people in 2010, and 100 million by 2012. The 2010 milestone was achieved. The idea is to have 'near real time' safety information including adverse events due to off-label use, so that timely decisions can be made.



The Hospital Pharmacy Journal is an independent, peer-reviewed publication. It is intended for health practitioners and is committed to the promotion of safe use of medicines. One of the standing items in the journal is a section called 'Off-label drug uses'. This is where case studies of medicines used in an off-label manner are discussed in detail including the number of participants, the doses given for the OLU and safety information.

5. Discussion

There is a hierarchy of laws in the different jurisdictions as discussed in Regulatory Affairs module (Hibernia College 2012). For example in the US, Laws are passed by the US Congress; they are most authoritative and are binding. Below them are Regulations and then Guidances. Regulations apply the Law hence they are also binding, however,

Guidances are not binding. In the EU, in a descending order, the laws are as thus: Treaties, Regulations and Directives, which are all legally binding. Soft Laws are at the bottom and include recommendations, guidelines and opinions; which are all not obligatory.

The EU and US health laws are very progressive and prompt, especially in relation to safeguarding public health. The two regions have very established PV systems and there are many publications and surveillance systems that address the issue of OLU of medicines. Monitoring and control of OLU is facilitated and enabled by its entrenchment into the binding laws, and not just in soft laws or guidelines, in which the issues of ethics, finance, regulation, safety etc. are addressed and thus ensure compliance to international guidelines such as the Helsinki Declaration. Patent issues are one of the obstacles in drug repurposing, the US law addresses that in the Best Pharmaceuticals for Children Act.

From the EU as a central authority, the individual European countries also have measures that are legally binding to deal with OLU and protect public health.

The Italian laws for example, highlight the principles of non-maleficence and beneficence as they promote the need to weigh the benefit /risk ratio and to monitor the effects of the drugs; they also promote respect for patient autonomy through informed consent, and finally, providing the drug freely upholds the principle of distributive justice where every patient who qualifies to be treated is not restricted on the basis of affordability. However, Bernadi *et al* (2008) highlight moral challenges in applying the law, such as when oncology drugs have little evidence of efficacy but are used in the final stages of the disease. Or when the law does not specify the degree of evidence needed to justify OLU, or when there is scientific evidence of efficacy and safety but the government cannot approve its use due to high cost. Those who may privately afford the treatment may be exposed to increased harm as they will be outside the safety monitoring system. The TRU system in France, as stated in

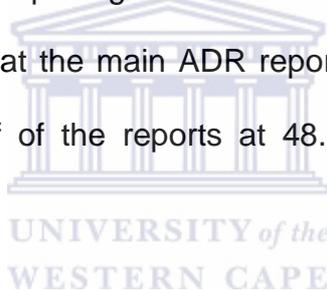
the Canada report, has not been running long enough to measure its impact. Off-label prescribing is more common for older drugs; therefore a system of following the off-label use of new drugs will take a long time before significant effects and extent are noted.

According to Pal *et al* (2013), all countries essentially rely on the spontaneous reporting of ADRs for their monitoring of drug safety. However, in PAHO (2011), it is stated that reporting is voluntary in all countries except Spain and France where it is compulsory. Therefore, for the developing markets, new systems do not necessarily have to be introduced; the spontaneous reporting can be used to actively draw up information on off-label use, especially in instances where such reporting includes indications and doses, such as in South Africa. This was also used by the Canada report as a benchmark model. It is also encouraging to note that in the absence of explicit regulations on OLU of medicines in South Africa, medical associations use the other available Acts that speak to protection of public health to guide their practice of OLU.

Gazarian (2007) mentions that there are no published studies, similar to those done in the developed world, that assess the magnitude of off-label or unlicensed medicines use in the paediatric population in the developing world setting. The report further speculates the reasons for this as due to either a lack of awareness or interest about this issue amongst health care professionals in the developing world. Certainly this picture is changing as during the literature search for this report, there are studies that were encountered such as the one by Okechukwu *et al* (2009) on prescription pattern of unlicensed and off-label use of medicines in Nigerian children. The article also recommends more extensive studies to be conducted in Nigeria and the rest of Africa. Other articles although specific to a particular region, were able to offer solutions and recommendations of monitoring off-label use that are applicable in any setting, such as the ones found in Ventola (2009) listed below:

- Industry self-regulation
- Prescriber self-regulation and monitoring
- “Sunshine laws” that require declaration of conflict of interest such as financial relationship between prescribers and manufacturing companies
- State registration of medical sales representatives so that they can have a professional code of ethics to ascribe to

From the results above, explicit OLU laws and Acts are only found in developed markets, whereas the soft laws can be found in both developed and emerging markets. This implies that there is more OLU control and regulation in the developed countries than in the developing ones. This is hardly surprising as it is evident in the UMC Vigibase figure 1 below (UMC, 2015) that shows that the main ADR reporters are the developed countries. The US accounts for almost half of the reports at 48.2%, while emerging markets are covered in the 18.3% of ‘other’.



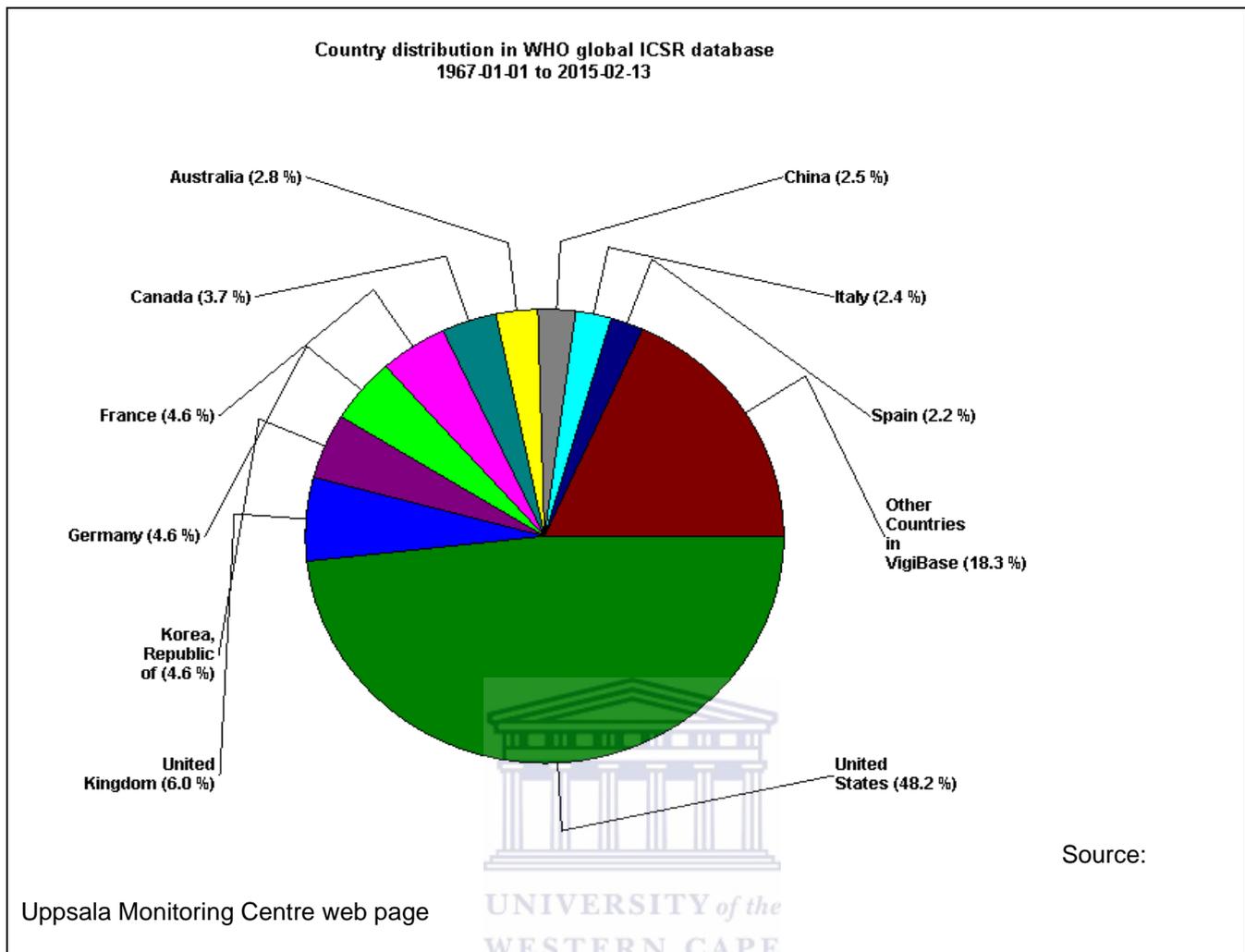


Figure 1: UMC VigiBase⁴ graph showing ADR reporting distribution by country from January 1967 to February 2015

The World Health Organization (WHO, 2010) estimates that medicines contribute 15% to 30% of middle income national health budgets, and 25% to 66% in developing countries. It further states that in some countries, medicines are the largest health expense for poor families.

This leads to problems of availability and affordability of medicines. Promotion of rational use of medicines is an important initiative in improving access to medicines; hence efficient off-label pharmacovigilance is an essential tool to achieve this objective.

⁴ VigiBase[®] is the name of the WHO Global ICSR database; it consists of reports of adverse reactions received from member countries since 1968. VigiBase is updated with incoming ICSRs on a continuous basis.

6. Conclusion

There are systems and activities for off-label use pharmacovigilance in place. Some are efficient and advanced; while others need a boost of resources and political will to thrive. Drug repurposing measures can flourish where systematic off-label information is accessible. Consequently, reporting of adverse drug reactions will improve.

However, off-label use of medicines poses a regulatory science nightmare. Without proper, solid laws and regulations, it becomes very complex for regulatory authorities to manage it and at the same time ensure the public that it has screened all marketed drugs for quality, safety and effectiveness thus protecting them from harm. These regulations instil confidence in the MRAs as they alleviate the concerns discussed earlier that relate to ethics, finance, safety, etc. It is recommended that further studies should be done on the following;

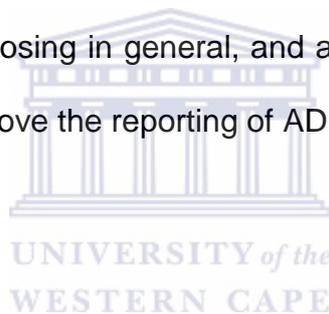
- monitoring the impact of off-label PV activities
- Prevalence and outcomes of PV type 2
- off-label use in African countries

7. Recommendations

The following measures are recommended to improve the management of off-label use of medicines;

- Stakeholders at all levels must be involved in the safety monitoring of medicines, whether they are used off-label or not.
- International bodies such as WHO, must endorse and encourage pharmacovigilance in off-label use through their publications; how about, '*A practical handbook on the pharmacovigilance of off-label use of medicines*'

- South Africa should continue to benchmark from other regions especially in augmenting the current systems. Also, noting that there is a proposal for a policy on PV systems, off-label use must be included explicitly.
- The Australian guidelines on OLU are simplified in the form of a poster. These should be globally embraced especially in the developing world where there are no systems in place to control off-label use.
- The WHO definition of pharmacovigilance should be revised to include its role in drug repurposing (Flower, 2014).
- Risk management plans with regard to the use of medicines in general, should be mandatory at all levels of health care.
- The concept of drug repurposing in general, and as a form of beneficial OLU, should be asserted in order to improve the reporting of ADEs.



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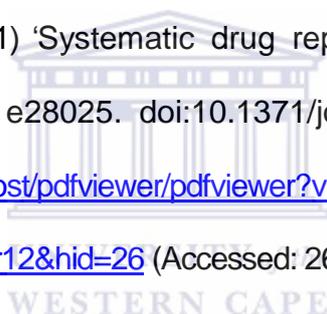
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9. Annexures

Research proposal

SA ADR reporting form

B-R legislation notes

Research Proposal

**MASTER OF SCIENCE IN REGULATORY SCIENCE
CONTINUOUS ASSESSMENT COVER PAGE**

Name: Khopotso Thobeli

Student Number: MRESC003

Student Cohort: April 2012

Assessment Title: Research Proposal

Word Limit as per CA details: 500 – 1000

Assessment Word Count: 588
(excluding title page & bibliography)



Submission Date: 18th November 2013

I agree that I have researched and written the work submitted in this assessment, and that the work submitted is my own. Any information and opinions drawn from other sources are attributed by means of a reference to that source.

√

TITLE

Pharmacovigilance systems in off-label medicines use

INTRODUCTION

The World Health Organisation (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO, 2013). WHO further stipulates the aims of pharmacovigilance as follows:

- To strengthen patient care and public safety with regards to the use of medicines.
- To support public health programmes through provision of reliable, balanced information for proper risk-benefit profile assessment of medicines.

Off-label use of medicines is described by Stafford (2008) as the prescription of medicines in a way that is different from that approved by the regulatory authority (e.g. FDA), that is, the medicine is used outside the provisions of the Summary of Product Characteristics (SPC) (Horen, 2002). It is a common practice and it is legal since according to Boguski (2009), the FDA regulates the system of drug approval but not how the drug is used (i.e. physicians can prescribe medicines for any indication they see fit as long as they have run out of standard options).

Off-label use has both advantages and disadvantages. However, the concern is that as much as off-label use is not illegal, systems and efforts are not put in place to extensively monitor the adverse drug effects in these situations. Thus the patients and the public at large are not protected but exposed to potential harm due to treatments that are not based on proven evidence. Risk-benefit ratio balance: the benefit is identified, what is the risk and is it monitored?

The study is inspired by the concept of drug repurposing (from the Research Methods module assessment). As indicated by Barratt *et al* (2012) and Boguski *et al* (2009), traditional drug development methods are costly and cumbersome; drug repurposing, or 'drug recycling' is a cost-effective and environmentally friendly strategy of drug development that seeks to exhaust the potential benefits of an already marketed drug. Off-label use of prescription medicine is a form of drug repurposing (Boguski *et al*, 2009); however, from my experience and observations, systems are not in place to monitor the effects of the drugs used in this way.

This brings in the issue of pharmacovigilance. Medicines can be harmful to patients; and normal reporting of adverse drug events is very poorly done in my work environment. Therefore, I feel that pharmacovigilance systems and activities should be stepped up for use of medicines in unregistered situations whereby there is no evidence of efficacy and safety. Also with the advent of drug repurposing, the additional aims of pharmacovigilance seem to emerge; to detect, assess, and understand favourable side effects or expanded spectrum of activity that may be identified during drug development or use (Boguski *et al*, 2009).

Hypothesis / research question: pharmacovigilance systems and activities to regulate and monitor safety of off-label medicines use are not in place.

The activities in question are: availability and implementation of the relevant regulatory framework such as legislation, policies, guidelines, and education and training.

METHODOLOGY

Systematic literature review of studies conducted to investigate both good and bad effects of off-label medicine usage.

Data will be collected from databases such as Cochrane, Embase, Pubmed and other different journals, publications and proceedings.

Data analysis will be qualitative. The relevant activities will be identified and assessed with regards to whether they are available, implemented or not, and whether there are any in the pipeline.

ETHICAL CONSIDERATIONS

The study will not infringe on any ethical issues as it will be based on publicly available information, i.e. published articles and public documents.

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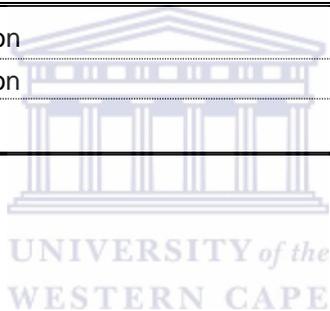
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SA Adverse Drug Reactions Reporting Form



Version 1: Released for implementation	May 2003
Version 2: Released for implementation	November 2004
Version 3: Updated contact details	April 2011



ADVERSE DRUG REACTION AND PRODUCT QUALITY PROBLEM REPORT FORM

(Identities of reporter and patient will remain strictly confidential)

 <p style="font-size: 1.2em; font-weight: bold; margin: 0;">health</p> <p style="font-size: 0.8em; margin: 0;">Department: Health REPUBLIC OF SOUTH AFRICA</p>	<p style="font-size: 1.1em; font-weight: bold; margin: 0;">NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE NADEMC</p> <p style="font-size: 0.8em; margin: 0;">The Registrar of Medicines Private Bag X 828 Pretoria , 0001</p>	<p style="font-size: 0.8em; margin: 0;">Fax: (021) 448-6181 Tel : (021) 447-1618</p> <p style="font-size: 0.7em; margin: 0;">In collaboration with the WHO International Drug Monitoring Programme</p>
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PATIENT INFORMATION

Name (or initials): Patient Reference Number:
 Sex: M F Age: DOB:/...../..... Weight (kg) Height (cm)

ADVERSE REACTION / PRODUCT QUALITY PROBLEM (tick appropriate box)

Adverse reaction and/or Product Quality problem Date of onset of reaction:/...../.....
 Time of onset of reaction:hour.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES / VACCINES / DEVICES (include all concomitant medicines)

Trade Name & Batch No. (Asterisk Suspected Product)	Daily Dosage	Route	Date Started	Date Stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/> death <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage	<input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalisation <input type="checkbox"/> Other.....	<p>Reaction abated after stopping medicine: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> N/A</p> <p>Event reappeared on rechallenge: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> Rechallenge not done</p>	<p>Recovered: <input type="checkbox"/> Y <input type="checkbox"/> N</p> <p>Sequelae: <input type="checkbox"/> Y <input type="checkbox"/> N</p> <p>Describe Sequelae:..... </p>
---	---	--	--

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. PRODUCT QUALITY PROBLEM:

Trade Name	Batch No	Registration No	Dosage form & strength	Expiry Date	Size/Type of container

Product available for evaluation?: Y N

REPORTING HEALTHCARE PROFESSIONAL:

NAME: QUALIFICATIONS:.....
 ADDRESS:
 Signature Date

Postal Code: TEL: (.....).....

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- medications (drugs, vaccines and biologicals)
- medical devices (including in-vitro diagnostics)
- complementary / alternative medicines (including traditional, herbal remedies, etc)

Please report especially:

- adverse drug reactions to newly marketed products
- serious reactions and interactions with all products
- adverse drug reactions which are not clearly reflected in the package insert.

Report Product Quality Problems such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labelling
- therapeutic failures

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Important numbers:

Investigational Products and Product Quality Problems:

- fax: (012) 395-9201
- phone: (012) 395-9341

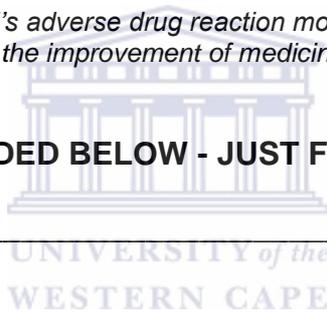
Adverse Events Following Immunisation:

- fax: (012) 395 8905
- phone: (012) 395 8914/5

Confidentiality: Identities of the reporter and patient will remain strictly confidential.

Your support of the Medicine Control Council's adverse drug reaction monitoring programme is much appreciated. Information supplied by you will contribute to the improvement of medicine safety and therapy in South Africa.

PLEASE USE ADDRESS PROVIDED BELOW - JUST FOLD IN THIRDS, TAPE and MAIL



Postage will be paid
by the Addressee
Posgeld sal deur die
geadresseerde betaal
word

No Postage stamp
necessary if posted in the
Republic of South Africa
Geen posseël nodig nie
indien in die Republiek van
Suid-Afrika gepos

**BUSINESS REPLY SERVICE
BESIGHEIDSANTWOORDDIENS**

Free Mail Number: BNT 178
Vryposnommer:

**DEPARTMENT OF HEALTH
DEPARTEMENT VAN GESONDHEID
REGISTRAR OF MEDICINES
REGISTRATEUR VAN MEDISYNE
PRIVATE BAG / PRIVAATSAK X828
PRETORIA
0001**

Benefit-Risk Assessment Legislation Notes

Legal drivers for B-R assessment

EU Regulation (EC) 726/2004

Recital (14): Indicates that provisions related to Benefit-Risk (B-R) assessment described in Directive. 2001/83/EC are applicable. It should be possible to assess the B-R balance of all medicinal products when they are placed on the market, at the time of the renewal of the authorisation and at any other time the competent authority deems appropriate.

New pharmacovigilance (PV) legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council in December 2010.

New PV legislation-EU

Directive 2010/84/EU

Regulation 1235/2010

- PV-related changes applicable to all products, irrespective of approval procedure, for all European Economic Area (EEA) countries
- Came into effect 2 July for Centrally Authorised Products (CAPs) and 21 July for all other products, 2012

Impacts on the move from Periodic Safety Update Report (PSUR) to Periodic Benefit-Risk Evaluation Report (PBRER) include the need to provide:

- Summaries of data relevant to the benefits and risks, including results of all studies with a consideration of the potential impact on the marketing authorisation (MA)
- Scientific evaluation of the B-R balance
- All data relating to the volume of sales of the medicinal product and any data relating to prescription volume and population exposure estimates
- ICH E2 (R2) will provide the guidance and template.

New PV legislation - US

US Food and Drug Administration Safety and Innovation Act (FDASIA) Prescription Drug User Fee Act (PDUFA) V

PDUFA V goals include 'Enhancing benefit-risk assessment in regulatory decision making.'

FDA's commitments:

- Publish a five-year plan that describes FDA's approach to implement a structured B-R framework by 31 December 2012 and begin execution by 30 September 2013
- Conduct two public workshops on B-R from the regulator's perspective that will begin by 31 December 2013
- Develop an evaluation plan to ascertain the impact of the B-R framework

- Revise templates (such as review, decision and memo) as appropriate to incorporate FDA's approach

B-R Assessment Initiatives

US	EU	Global
<p>PDUFA V Goals Letter and FDA Framework Plan to conduct workshops</p> <ul style="list-style-type: none"> • Patient perspective • Decision making • Piloting framework on six new molecular entities (NMEs) in 2012 <p>Institute of Medicine (IOM) Calls for the FDA to develop a single, comprehensive document that tracks B-R and Risk Management (BRAMP) over the life cycle</p> <p>Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit Risk Action Team (BRAT) framework Development of a flexible framework to promote transparent, systematic B-R assessments and enhance communication among stakeholders</p>	<p>European Medicines Agency (EMA) B-R Methodology Project Work packages completed:</p> <ul style="list-style-type: none"> • Models and methods in use • Tools and processes • Field testing • ProACT framework • Final work package will make recommendations to incorporate into routine practice <p>EU Good PV Practice B-R assessments in:</p> <ul style="list-style-type: none"> • Periodic reporting • RMPs • License renewals <p>Innovative Medicines Initiative (IMI) PROTECT Focused work stream on B-R assessment and the development of B-R visualizations</p>	<p>ICH E2C Draft Guidance PBREER will replace periodic safety evaluation reports (PSURs) Emphasis on integrated B-R evaluation Focus on qualitative framework</p> <p>Japan Three-year project to enhance risk management, including approaches to B-R assessment</p> <p>COBRA/CASS Initiative* Qualitative B-R pilot project to develop and implement a framework for use among regulatory agencies, including Canada, Australia, Singapore and Switzerland</p>

Several B-R initiatives have been initiated globally over last 15 years and momentum has increased exponentially with time.

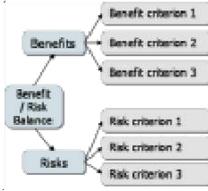
Despite regional preferences, there is momentum toward a standardized, global approach that includes the:

- Development and rise of frameworks for organizing data and structuring B-R discussions
- Introduction of more specialized quantitative methodologies

Visualization and communication of B-R assessments are key outcomes for these initiatives.

The recognition of the important differences in perspective (patient, prescriber, regulator or payer) for any given B-R assessment has emerged.

Leading Frameworks: 2012

	FDA	EMA	COBRA/CASS	BRAT																		
Characteristics	<p>Structured qualitative approach identifying key issues for B-R deliberations</p> <table border="1"> <thead> <tr> <th>Consideration</th> <th>Evidence and Uncertainties</th> <th>Conclusions and Reasons</th> </tr> </thead> <tbody> <tr> <td>Indication/Condition</td> <td>Summary of evidence</td> <td>Conclusions (justifications for decisions)</td> </tr> <tr> <td>Unmet Medical Need</td> <td>Summary of evidence</td> <td>Conclusions (justifications for decisions)</td> </tr> <tr> <td>Clinical Benefit</td> <td>Summary of evidence</td> <td>Conclusions (justifications for decisions)</td> </tr> <tr> <td>Risk</td> <td>Summary of evidence</td> <td>Conclusions (justifications for decisions)</td> </tr> <tr> <td>Risk Management</td> <td>Summary of evidence</td> <td>Conclusions (justifications for decisions)</td> </tr> </tbody> </table>	Consideration	Evidence and Uncertainties	Conclusions and Reasons	Indication/Condition	Summary of evidence	Conclusions (justifications for decisions)	Unmet Medical Need	Summary of evidence	Conclusions (justifications for decisions)	Clinical Benefit	Summary of evidence	Conclusions (justifications for decisions)	Risk	Summary of evidence	Conclusions (justifications for decisions)	Risk Management	Summary of evidence	Conclusions (justifications for decisions)	<p>PrOACT-URL Problem Objectives Alternatives Consequences Trade-offs Uncertainty Risk tolerance Linked decisions</p>	<p>Qualitative framework to support regulatory decision making in CASS countries</p> 	<p>Structured, transparent framework for assessing and communicating the B-R profile</p> <p>Value Tree Example with Identified and Potential Benefits and Risks</p> 
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Background	<p>Developed with the goal of improving transparency in decision making</p> <p>Better communication</p> <p>Which B&R were considered</p> <p>How evidence is interpreted</p> <p>How B&R were weighed</p>	<p>B-R Methodology Project introduced in 2009</p> 	<p>Commissioned in 2008</p> <p>Led by Centre for Medicines Research (Stuart Walker)</p>	<p>Progressively developed over a six-year period using hypothetical and real-world examples</p>																		
Status	<p>Piloted via six case studies of past regulatory decisions</p> <p>Road tested with an additional two cases studies</p> <p>Currently being evaluated in 'live' reviews with consideration for implementation into the review process</p>	<p>The Committee for Medicinal Products for Human Use (CHMP) assessment templates have included a list of B-R criteria since Oct. 2009</p> <p>B-R Methodology Project aims to adapt or develop tools for B-R assessment</p>	<p>Currently being piloted</p>	<p>PhRMA Pilot Initiative completed 2011</p> <p>BRAT Framework transitioned to the Centre for Innovation in Regulatory Science (CIRS) in 2012 for broadened input and further development</p>																		

FDA

The B-R framework is designed to 'tell the story' of the regulatory decision, with the therapeutic area questions to be addressed.

Severity of condition

What is the condition that is treated or prevented by the drug?

What are the clinical manifestations of the condition; what is the natural history; does severity vary across sub-populations?

Unmet medical need

What other therapies (approved and off-label therapies, including non-pharmacological) are available?

How effective or well tolerated are alternatives, and what is the evidence?

Clinical benefit

It is more product specific and utilizes questions such as:

- What trials (including strengths and weaknesses) were conducted to establish efficacy?
- What endpoints were evaluated; are they clinically meaningful?
- Did the benefits vary across sub-populations of responders?

Risk

Characterize the safety concerns identified in the clinical trials, including:

- Incidence of a particular risk in study population or variation in sub-population
- Range in the severity of the risk, noting if it changes with continued exposure, and if it is reversible when treatment stopped

How might incidence of risk change in the post-approval space? Is further characterization of risk needed?

Risk management

Which risks (if any) require mitigation or further characterization? What tools or methods are best to assess or mitigate these risks? What is the expected contribution of each methodology or tool to the overall RMP?

What would be the ideal risk management plan? How should effectiveness be measured? If the desired impact is not achieved, at what point should the risk management plan be re-evaluated?

EMA

The EMA uses a qualitative framework (**ProACT-URL**) for structured decision making, which is useful with or without additional quantitative methodologies, it includes 8 steps:

1. Problem: Determine the nature of the problem and its context.
2. Objectives: Identify criteria of favourable and unfavourable effects.
3. Alternatives: Identify the options to be evaluated against the criteria.
4. Consequences: Describe how the alternatives perform for each of the criteria.

5. Trade-offs: Assess the balance among favourable and unfavourable effects.
6. Uncertainty: Assess the uncertainty associated with the effects.
7. Risk tolerance: Judge the relative importance of the decision maker's risk attitude.
8. Linked decisions: Consider the consistency of this decision with past decisions.

COBRA/CASS

- Coordinated by the Center for Innovation in Regulatory Science, CASS is a consortium of regulatory agencies from Canada, Australia, Switzerland, and Singapore (CASS). The objective of the CASS initiative is to develop a systematic and standardized approach to benefit-risk assessment in order to facilitate joint or shared reviews among the four agencies. The consortium has established project teams at the respective agencies, developed a draft electronic summary and pro forma template that summarizes and contextualizes B-R decisions, and undertaken demonstration projects using the draft pro forma with agency pairs assessing the same drug at the same time. The CASS initiative has been renamed COBRA: (Consortium On Benefit Risk Assessment)

BRAT

A structured, transparent approach for B-R assessment is the 'BRAT framework'. The BRAT framework is a six-step process with an adaptable structure that can be used for a broad range of pharmaceutical B-R assessments. The framework comprises a set of processes and tools that guides decision makers in selecting, organizing, summarizing, and communicating evidence relevant to B-R decisions. It is designed for use throughout the life cycle of a drug for decision making and as a means to improve dialogue with regulators and other stakeholders.

