Assessment of medicinal products: A comparative study between Europe and United States of America

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To my family, friends and colleagues - for their continuous care and support

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Abstract

Differences in evaluation practices during the registration of medicinal products in Europe and the United States of America are found. The aims of this research were to compare the outcomes of the evaluations by the European Medicines Agency (EMA) and the US Food & Drug Administration (FDA) and to highlight differences in the approved product information and the differences in the decision-making process between the two agencies using cardiology-related medicinal products as examples. The method used involved: i) All cardiology-related medicinal products assessed by the EMA (1995-2016) were identified using the Anatomical Therapeutic Chemical (ATC) code and matched with the FDA counterparts using active ingredients, branded names and authorisation holder details; ii) The assessment reports (EMA), the reviews (FDA) and initially-approved product information (EMA & FDA) for each identified drug were obtained; ii) A tool was developed and validated by 6 experts to compare the differences in the outcome of the evaluation between the two agencies. Twenty-seven cardiology-related medicinal products were identified. Mipomersen was the only identified active ingredient with a disagreement in the outcome between agencies. Mipomersen was refused by the EMA and authorised by the FDA. The FDA designated the indication with an orphan designation while the EMA did not and this is considered to be the reason for such a difference in the decision-making process for this product. Fourteen products were found to have different indications when comparing the label (FDA) to the Summary of Product Characteristics (SmPC) (EMA). Differences in the indications have been categorised according to the following restrictions: disease states (5), patient characteristics (4), severity of the condition (3), combination (3), previous therapy failure (1) and inappropriate alternative therapies (1). The EMA and the FDA both contributed to indication restrictions. Different clinical scenarios (4) were

identified, where agencies authorised a product for a different clinical setting in view of different efficacy-related clinical studies submitted by the industry. The number of post-authorisation requirements, related to safety and efficacy, for the same products were found to be (73) EMA and the (29) FDA. Details in the information included in the product information and label related to efficacy and safety also vary between regulatory agencies for the same product. Lack of harmonisation in the EMA SmPC and FDA label noted in the 26 products studied included differences in indications (18) and safety (21). Post-authorisation requirement differences (25) have been found between the EMA and the FDA. The regulatory agencies and the pharmaceutical industry are both responsible for this lack of harmonisation which may lead to differences in clinical guidelines, pricing policies, and drug use. It is suggested that there is a need of a framework to ensure more collaboration between agencies and industry to reduce discrepancies in medicine regulation.

Key words: Comparison, EMA, Evaluations, FDA, Medicinal products

List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ATC	Anatomical Therapeutic Chemical
Apo B	Apolipoprotein B
BR	Benefit-Risk
CAP	Centrally authorised product
CDER	Centre for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
CTD	Common Technical Document
CV	Cardiovascular events
CVI	Content Validity Index
DCP	Decentralised Procedure
EC	European Commission
EMA	European Medicines Agency
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HefH	Heterozygous familial hypercholesterolaemia
HofH	Homozygous familial hypercholesterolaemia
ICH	International Conference on Harmonisation

JAR	Joint Assessment Report
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
MA	Marketing Authorisation
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Medicines Regulatory Agency
MRP	Mutual Recognition Procedure
NDA	New Drug Marketing Application
NME	New Molecular Entity
Non-HDL-C	Non-high density lipoprotein-cholesterol
SAG	Scientific Advisory Group
PDCA	Paediatric Committee
PIP	Paediatric Investigation Plan
PMDA	Pharmaceuticals and Medical Devices Agency
REMS	Risk Evaluations and Mitigation Strategies
RMS	Reference Member State
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TC	Total cholesterol
USA	United States of America

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Chapter 1:

INTRODUCTION

1.1 Reflections on pharmaceutical regulation

Medicines have been available since mankind and the concept of how their safety, quality and efficacy are ensured has evolved gradually over time (Rago and Santaso, 2008). Negative and unfortunate public health events gave rise to the development of medicines regulation (Callréus and Schneider, 2013). In 1937, in the United States, over 100 people died of diethylene glycol poisoning which was used as a solvent for a sulfanilamide elixir without any safety testing (Rago and Santaso, 2008; Avorn, 2012; Callréus and Schneider, 2013).

Another catastrophe that influenced the development of medicines was the thalidomide disaster about 25 years after the diethylene glycol incident (Paine, 2017). Thalidomide was a sedative and hypnotic that first reached the market in Western Germany. Between 1958 and 1960 it was introduced in 46 different countries worldwide, resulting in an estimated 10,000 babies being born with phocomelia and other malformations (Rago and Santaso, 2008; Kim and Scialli, 2011; Paine, 2017). The whole regulatory system was reshaped bringing into place intense focus on the importance of rigorous and pertinent testing of pharmaceuticals prior to their introduction into the marketplace (Rago and Santaso, 2008).

Following the thalidomide incident, in the United States, The Drug Amendments Act of 1962 was passed by Congress requiring the Food and Drug Administration (FDA) to approve all new drug applications (NDA) (Lumpkin et. al, 2012; Paine, 2017). For the first time, it was demanded that a new drug should be proven to be effective and safe by including systems of independent product assessment of preclinical, clinical, and

manufacturing data prior to marketing, which is performed or overseen by a government medicines regulatory agency (MRA) (Lumpkin et. al, 2012; Paine, 2017).

Similar changes have been established in other jurisdictions, with Europe (EU) introducing European Commission (EC) Directive 65/65/EEC of January 26, 1965[1], whereby a medicine may only be placed on the European (EU) market after a marketing authorisation (MA) has been granted by at least one competent authority in Europe (Agius, 2017). Since 1965, the EU pharmaceutical legislation framework was further developed with the enactment of Directive 2001/83/EC[2].

1.2 The role of regulatory agencies

Directive 2001/83/EC, defines a medicinal product as being:

"*Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product*."[2]

[1] European Council. Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products [Online]. Official Journal of the European Union 1965; 022: 0369 - 0373 [cited 2017 Jun 05]. Available from: URL: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31965L0065:EN:HTML

[2] European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Online]. Official Journal of the European Union 2001; L311:67-128 [cited 2017 Jun 05]. Available from: URL: http://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32001L0083&from=EN

Based on the above definition by the European Commission, medicinal products are no ordinary consumer goods. People depend on medicinal products for their health and even their survival (Zammit, 2010). Medicinal products, as a result, are amongst the most stringently regulated products in the developed world and are allowed on the market following approval by a regulatory agency (Callréus and Schneider, 2013).

New products established by the pharmaceutical industry as possible beneficial drugs undergo substantial preclinical evaluation followed by clinical trials to assess efficacy and safety in human subjects (Roden and Temple, 2005). Drug regulatory agencies which act as autonomous third parties, are tasked with the assessment of such products based on the evaluation of scientific data.[3,4] Evaluations undergo rigorous control to ensure safety, quality and efficacy of the medicinal product. If these parameters are considered acceptable and a positive benefit-risk balance is identified, approval to market new products or to expand indications for already marketed drugs is allowed (Roden and Temple, 2005; Eichler, 2010).

Decisions to approve a product are relatively straightforward if the new drug shows clear efficacy with little actual or potential risk for serious side effects, and, when the potential addition of the product to the therapeutic choices does not present a major problem (Roden and Temple, 2005). Approval for a new drug will not be granted if efficacy cannot be demonstrated, when significant serious adverse effects are identified and/or when a drug does not contribute to the therapeutic armamentarium in at least some patients (Roden and Temple, 2005).

[3] European Medicines Agency [Online]. c1995-2017 [cited 2017 Jan 08]. What we do. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general
[4] Food and Drug Association [Internet]. c2016 [cited 2017 Jan 08] Development & Approval Process; Available from URL: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm

In many cases though efficacy, safety and quality issues result which make the decision making process difficult and not so clear-cut as the risks may be (or may appear to be) more than marginal, and the sponsor and the regulator may differ in their estimatation of each of these issues (Roden and Temple, 2005). Regulators must find an appropriate balance between ensuring that decision-making is based on rational scientifically valid information and the necessity for accessibility to new medicines through timely approval (Eichler et. al, 2008; Berlin, 2009). Balancing efficacy and safety evidence (with its innate uncertainties), while reflecting on the need for new and improved medicines is also required (Eichler et. al, 2008).

Zineh and Woodcock (2013) considered such a balance between evidence (and its limitations) and the need for newer medicines as a *"regulatory paradox"* and define it *as "an inherent, but reconcilable, tension between aversion to uncertainty and willingness to accept certain unknowns about a drug before its approval"* which can mean the difference between the promotion and oppression of innovation. Eichler et. al (2008) indicates that this challenge in determining a balance is a dilemma which has been attributed to recent experiences, such as the withdrawal of drugs from the market (example cerivastatin (Baycol®) and rofecoxib (Vioxx®)), and post-marketing safety concerns as exemplified by tegaserod (Zelnorm®) and rosiglitazone (Avandia®). Other challenges include concerns over lack of efficacy example gefitinib (Iressa®), or the reliability of clinical trial data, like in the case of telithromycin (Ketek®).

In the past, access to newly accepted drugs was focused on the time interval between the application for approval and the granting of a marketing authorisation (Cohen, 2007). This time lag has been tackled by both the EMA and the FDA through a number

of procedures with the aim to shorten review times. In 1992, the FDA introduced a priority review procedure with the goal to reduce review time from 10 to 6 months while in 2006 EMA developed an approach referred to as the "accelerated assessment procedure" to reduce the review time for medicinal products from 210 to 150 days (Boucaud-Maitre and Altman, 2016). The introduction of shortened regulatory processes applies to marketing authorisations of drugs with potential added therapeutic value (Boucaud-Maitre and Altman, 2016). The approach shows how regulatory agencies develop and adapt to the needs of the public while still maintaining and without compromising the protection to the public.

Currently, regulatory authorities are exploring the use of adaptive licensing. Adaptive licensing seeks to exploit the positive impression of new products on public health by balancing sensible access for patients without compromising the need to provide satisfactory information on the benefits and risks (Shah et. al, 2013).

Eichler et. al (2011) argues that despite the care taken by regulatory agencies, regulatory decisions are established on population-level evidence, with a awareness that the benefit–risk will not necessarily be positive for all concerned patients. Patients are not similarly responsive to these favourable effects, and not equally predisposed to side effects. All stake-holders concerned are aware of patient heterogeneity and that 'one size doesn't fit all'. Regulators would need to direct healthcare professionals to the appropriate patient subpopulations and treatment options.

While often criticised for reducing access to novel beneficial options for cancer patients with high needs, regulators have shown much less rigidity in the approval of certain

drugs in particular therapeutic areas such as in the rare forms of cancer. This is done either by not requiring duplication of clinical trials or by accepting preliminary data from potential but not validated surrogate end points and/or interim analyses (Martinalbo et. al, 2016).

Along the years, regulatory agencies would also issue guidance documents for industry to ensure that adequate standards are implemented in the research and development of novel medicinal products. While regulatory agencies across the world share a mutual goal of protecting public health, since regulatory agencies were developed individually in each country, many variances in specific requirements emerged which result in limited harmonisation (Tobin & Walsh, 2008; Tafuri et. al, 2013). It is acknowledged that such discrepancies pose a barrier to the introduction of novel medicinal products in terms of availability, cost, use and time (Tobin & Walsh, 2008).

Unmet medical needs and medical practices vary in the three major markets of Europe, the United States of America and Japan (Milne et. al, 2016). Different legal influences and health care organisations, with different regulatory and compensation requirements for both conventional and advanced therapies further contribute to differences in the process of evaluation of a medicinal product application (Milne et. al, 2016).

1.3 Regulatory Sciences

The demand of promoting and protecting public health from the global perspective is increasing, and to meet this demand, regulatory science exploration is being directed towards providing the benefits of new and novel technologies to patients while

maintaining product safety, quality and efficacy (Patel and Miller, 2012). During the last decade, several initiatives were taken to interpret and incorporate results of scientific investigation into daily regulatory practice (Kurz, 2017).

Regulatory science with regards to development of medical products, has been a field of growing awareness for both regulators and pharmaceutical industry alike (Spindler et. al, 2016). Regulatory science does not entail the application of laws and recommendations as done in the practice of regulatory affairs. Regulatory science refers to the basic and applied research that aids to assess the benefit/risk assessment in a medical product and so allows for a regulatory decision making process It provides a transparent regulatory decision making process throughout the development and life cycle of any medical product (Callréus and Schneider, 2013; Spindler et. al, 2016).

The regulatory agencies of the three major markets all use the term regulatory science, but while they define it similarly, they apply it in a different manner (Milne, 2016). Regulatory science has the potential to enable more innovative drugs to come on the market through novel analysis of pre-clinical and clinical data (Johannesen et. al, 2014). All three major regulatory agencies have incorporated the principle in the daily processes.

1.4 International Council for Harmonisation

Following the globalised introduction of new regulations and guidelines for the reporting and evaluation of data on the safety, quality and efficacy of new medicinal products, the difference in technical requirements between countries resulted into the

duplication of many time-consuming and expensive test procedures (Tobin & Walsh, 2008; Tafuri et. al, 2013; Singh, 2015). The increase in expenditure on research and health care made it necessary to streamline and harmonise regulation to ensure that safe and efficacious new treatments are released on the international market and made available to patients in the minimum amount of time possible (Singh, 2015).

The concept of harmonisation of regulatory requirements was decided by Europe, Japan, and the United States which gave rise to the International Council (formerly Conference) on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH was established in 1990 at a WHO conference on Drug Regulatory Authorities in Paris (Singh, 2015).

The guidelines introduced by the ICH to streamline the evaluation process and promote a harmonised process are of major importance as the industry and regulatory agencies in the EU, US and Japan have dedicated themselves to follow these guidelines (Abraham and Reed, 2003). Generally, regulatory authorities opt to require standards equivalent to those agreed at the ICH with no further requirement over and above those stated by the ICH (Abraham and Reed, 2003).

The concept of harmonisation has brought benefits to both regulatory authorities and pharmaceutical industry (Singh, 2015; Reggi, 2017). The ICH recommendations helped in preventing duplication of pivotal trials, reducing the use of animal testing, whilst ensuring safety and effectiveness of the proposed product and applying different methodologies to meet different national requirements (Singh, 2015; Reggi, 2017). The recommendations also streamlined the regulatory process for new drug applications,

reducing paper work, development times and optimising assets for drug research and development (Reggi, 2017). The ICH has since its introduction entered the electronic era with a stress on paperless application processes and sharing of real‑time information among stakeholders (Singh, 2015).

ICH has come up with a standardised Medical Dictionary for Regulatory Activities (MedDRA) which incorporates general medical terminology that supports data examination, communication, and data management to share regulatory information, (Singh, 2015). The ICH contributions also modernised the regulatory process for drug applications with the introduction of the Common Technical Document (CTD) which contains the elements of quality, safety, and efficacy information in a common format. The CTD makes regulatory review processes simpler and allows for electronic submission (Singh, 2015). There are five modules in the CTD designed to harmonise submission of new drug applications (NDAs) in the electronic format. The 5 modules include: Module 1 - Administrative and prescribing information; Module 2 - Overviews and Summaries of Modules 3, 4 and 5; Module 3 - Quality (pharmaceutical documentation); Module 4 - Non-clinical reports (pharmacology/toxicology) and Module 5 - Clinical study reports (clinical trials) (Jordan, 2014).

1.5 The drug approval procedure in the United States of America

The US Food and Drug Administration is responsible, amongst its many other duties, to protect the health and safety of American consumers through the safe and effective use of drugs (Ciociola et. al, 2014).

The main FDA division responsible for drug approval is the Centre for Drug Evaluation and Research (CDER). The CDER evaluates all new drugs before they can be authorised in the United States and ensures that both branded and generic medicinal products are safe and effective and that the health benefits outweigh risks (Ciociola et. al, 2014).

In the United States only one procedure is available for medicinal product approval as opposed to the European processes. The sponsor summarizes all of the data obtained from manufacturing, preclinical, and clinical studies into a new drug marketing application (NDA) which is submitted to the FDA.[5] Once received, it is validated to ensure that sufficient information have been submitted to justify the start of its review (Shah et. al, 2013). The NDA proceeds through five review areas: medical, chemistry, pharmacology, statistical and biopharmaceutical (Ciociola et. al, 2014). The agency's reviewers attempt to endorse and confirm the sponsor's outcomes and inferences that the drug is safe and effective for its intended use and meets industrial and quality standards (Shah et. al, 2013; Ciociola et. al, 2014).[5] Typically the process takes between six to ten months.[5] The FDA may require the aid of an advisory committee, consisting of external experts who act on its behalf to provide independent thoughts and suggestions on the approvability of the NDA. Although the FDA takes the suggestions of the advisory committee into consideration, they are not binding (Ciociola et. al, 2014). Upon completion of the NDA review, an FDA Therapeutic Division Director together with management evaluates the scientific reviews and adopts the action the division will take regarding whether to approve or reject the application. A letter is sent to the sponsor with the decision.

[5] Food and Drug Administration [Online]. c-2016 [cited 2017 Oct 23]. Step 4: FDA Review. Available from: https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405570.htm

1.6 The drug approval procedure in Europe

There are three commonly used procedures available for approval of medicinal products in the European Economic Area (EEA) (Kohler, 2011). The decision on the choice of the procedure used is dependent on the nature of the product, the target indication(s), the history of the product, and/or the marketing strategies of the sponsor. These are:

- Centralised procedure
- Mutual recognition procedure (MRP)
- Decentralised procedure (DCP)

1.6.1 Centralised Procedure

The centralised procedure allows the authorisation of a medicinal product on the basis of a sole EU-wide assessment and marketing authorisation which is valid throughout the EEA.[6] Pharmaceutical companies submit one application to the EMA and the Agency's Committee for Medicinal Products for Human Use (CHMP) carries out a technical evaluation of the application and provides a recommendation to the European Commission (EC) on whether or not to grant a marketing authorisation.[6] Once granted by the EC, the marketing authorisation is simultaneously valid in all EEA Member States and allows for the marketing of the product and its availability to patients and health care professionals.[6] The product would typically have one common name with one common product information for all member states.

[6] European Medicines Agency [Online]. c1995-2017 [cited 2017 Oct 23]. The European regulatory system for medicines A consistent approach to medicines regulation across the European Union. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf

The centralised procedure is compulsory for[3]:

- Human medicines containing a novel active substance to treat:
    - Human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
    - Cancer
    - Diabetes
    - Neurodegenerative diseases
    - Auto-immune and other immune dysfunctions
    - Viral diseases
- Medicines resulting from biotechnology processes, such as genetic engineering;
- Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines
- Orphan medicines (medicines for rare diseases)
- Veterinary medicines for use as growth or yield enhancers

The compulsory criteria for the centralised procedure are considered areas of interest in the EEA and have been established to ensure a more harmonised approach in these areas in order to avoid any discrepancies between member states.

The centralised procedure is optional for other medicines which contain new active substances for indications not included in the above, which are of a significant

[3] European Medicines Agency [Online]. c1995-2017 [cited 2017 Jan 02]. What we do. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general

therapeutic, scientific or technical innovation and whose authorisation would be in the interest of public or animal health at EU level.[3]

Following the submission for the medicinal product application to EMA by the applicant or the marketing authorisation holder, there is a validation period where the application and the dossier are reviewed to ensure that the required documentation has been provided. No assessment is carried out during the validation stage. After a positive validation process, the application is presented to the CHMP to start for formal reviewing. One of the members of the CHMP is nominated to act as a rapporteur to coordinate the evaluation while a second member of the CHMP may act as a co-rapporteur (as applicable depending on the type of application).

Both the rapporteur and the co-rapporteur circulate their individual assessment reports to the CHMP members by day 80 (80 days after starting the procedure following validation) (Figure 1.1). The CHMP members provide their comments and following comments and discussions, a final consolidated list of questions is agreed upon by the CHMP on day 120 and submitted to the applicant. The procedure is considered in clock-stop (typically for up to 3 months but may be extended further by another 3 months) until the applicant submits responses to the list of questions as agreed by day 120. On receipt of the responses from the applicant, the clock is re-started (day 121) and a joint assessment report (JAR) of the responses is to be compiled by both rapporteur and co-rapporteur by day 150. Issues are discussed on day 180 and if all issues have been solved a decision may be taken on whether to issue a positive CHMP opinion. If outstanding or unresolved issues are identified or are still pending, the clock is stopped

[3] European Medicines Agency [Online]. c1995-2017 [cited 2017 Jan 02]. What we do. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general

again. On or before day 210, the CHMP adopts its opinion which is done by taking a vote, where there is either a consensus or an absolute majority from its members. An appeal may be triggered by the applicant and the product may be subject to re-examination.

The CHMP may require the assistance of the Scientific Advisory Groups (SAGs) throughout the centralised procedure for a particular application. Scientific Advisory Groups are made up of external experts and/or EMA working parties made up of experts from each competent authority in the EEA. SAGs are loosely comparable to the FDA advisory committees (Shah et. al, 2013).

A key difference between the centralised procedure and the FDA procedure is that in the centralised procedure, following CHMP opinion (either positive or negative), the European Commission has to issue a decision which may or may not be in line with the decision of the CHMP. Shah et. al (2013) discuss that the EU system is a rather complex system because as the European Commission is legally mandated to issue decisions which are then binding to all Member States and because of the bureaucracy that comes with it. The FDA procedure does not make use of a similar phase. Another reason why the EU procedure was considered complex by Shah et. al (2013) is because each member state nominates an expert to the CHMP to provide an opinion, discuss and comment to the committee on the safety, quality, efficacy and risk/benefit balance of the product under consideration. The views and opinions of all members are exchanged and discussed at meetings to build a consensus. Irrespective of the decision taken, whether positive or negative, the CHMP opinion is transmitted to the sponsor and to the EC to issue a final decision which is legally binding. Shah et. al (2013) also argue that such a

complex system is in place as the EC is accountable to all citizens of all member states. The centralised procedure has the disadvantage of possible delays as compared to the FDA counterpart, but it also has the advantage that a medicinal product application receives a detailed and rigorous evaluation through different perspectives and experiences from all nominated experts from the different member states.

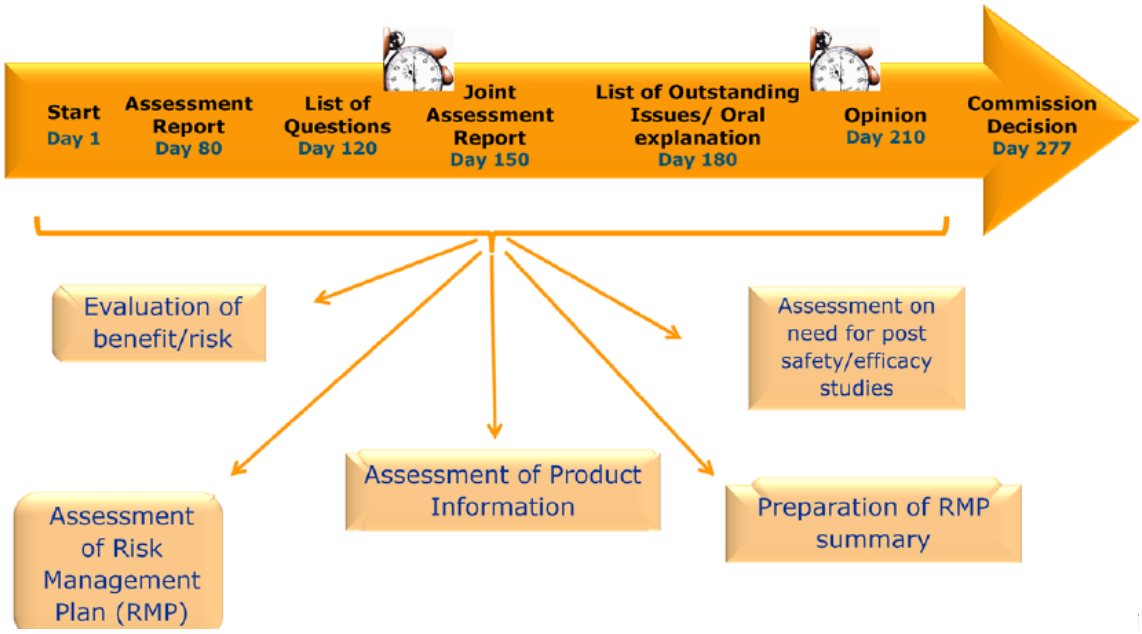

Figure 1.1: The Centralised Procedure Timetable. (Reproduced from: Medicines Agency [Online]. [cited 2017 Oct 23]. The Centralised Procedure at the EMA. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/02/WC500201043.pdf)

1.6.2 Decentralised & Mutual Recognition procedure

When using the MRP or DCP, the applicant must select how many and in which EU member states to seek approval (Kohler, 2011). Not all member states may be chosen for the procedure unlike the centralised route, where all member states are compulsory. In the case of a MRP, the applicant must ensure that the product already has an

authorisation in at least one Member State on a national basis in order to be used.[7] The DCP may be used if the product is either not already authorised in any Member State, but there is no intention to use the centralised procedure, or when the product is not eligible or no mandatory need for the centralised procedure.[7]

One of the intended Member States will offer to act as Reference Member State (RMS) by the applicant. The RMS does the lead evaluation of the product concerned and issues a draft assessment report. The other countries, known as the Concerned Member States (CMS), either agree with the RMS's evaluation or they ask further questions/raise objections (Koher, 2011; Mitra & Schiff, 2012). If all the issues are set and the application is positive, each Member State will then produce a MA for that product allowing it to be marketed in the member state.[7] In view of the different conditions required to fulfil the appropriate procedure, the procedure timetable varies between the DCP and the MRP procedure.

The DCP is divided into five steps[8]:

- Pre-procedural step, including validation phase
- Assessment step I
- Assessment step II
- Discussion at the CMDh, if needed
- National step

[7] Heads of Medicines Agency [Online]. [cited 2017 Oct 23]. Medicines Approval system Marketing Authorisations for Medicinal Products within the EU. Available from URL: http://www.hma.eu/medicinesapprovalsystem.html

[8] Heads of Medicines Agency [Online]. [cited 2018 May 23]. DCP Decentralised Procedure Members States' Standard Operating Procedure . Available from URL: http://www.hma.eu/92.html

The pre-procedural step involves discussion with the potential RMS regarding date of submission of the application, allocation of procedure number and including scientific advice. The applicant submits an application together with the dossier to the National Competent Authorities of each MS where a marketing authorisation is required. A 14 day validation period takes place to ensure that all required documents have been submitted and all necessary requirements have been fulfilled by all member states concerned.

Following a positive validation period, the procedure officially starts and the scientific information is assessed. This step is called Assessment step I and cover Day 0 till Day 120. The RMS would forward a Preliminary Assessment Report (PrAR), including comments on the product information, to the CMSs and the applicant within 70 days after the start of the procedure.

By Day 100, CMSs should communicate any comments regarding the procedure. The RMS should inform the applicant on all comments raised. The RMS may consult with the CMSs to discuss the comments raised. The clock is stopped by the RMS at Day 105 and forwards the questions raised by the RMS and CMS, to the applicant in the form of a Request for Supplementary Information (RSI). The responses should be forwarded within a 3 month period which may be extended for a further 3 months.

Following the responses, the RMS will restart the clock at D106 and by Day 120; distribute a Draft Assessment Report (DAR) on the basis of the information available at that period of time. On Day 120, the RMS starts the assessment step II by sending the Draft Assessment Report (DAR) together with the draft product information, to the

CMS concerned and the applicant. During assessment step II, the procedure can be finalised at any time-point before Day 210 if consensus is reached by all parties concerned that the product is approvable.

Between Day 145 and 150, the RMS consults with the CMSs to discuss the comments raised. If consensus is not reached, the RMS communicates such issues with the applicant. Additional clarifications should be submitted by Day 160 to the RMS and circulated to the CMSs by Day 180. A Break-Out Session (BOS) may be held at the European Medicines Agency with the involved MSs to reach consensus on the major outstanding issues. At Day 210 the RMS closes the procedure including its position of whether the product is approvable or not through a Final Assessment Report (FAR).

If by Day 210, a CMS(s) cannot endorse the positive RMS assessment report and the product information, on the grounds of a Potential Serious Risk to Public Health PSRPH, the CMS(s) shall notify all parties involved. The RMS will refer the matter to the Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and all member states should settle all points of disagreement. If consensus is reached, the procedure is closed. If no consensus is reached at the level of CMDh, the RMS informs the European Medicines Agency and a final absolute decision is taken.

If the procedure is approvable, the national phase takes place where there is a period of 30 days where individual member states issue a Marketing Authorisation for the product. The date of authorisation may be different in the different member states.

The timetable for an MRP is shorter than the DCP or the centralised procedure as the product is already authorised in a member state and has been already assessed by that member state to acquire authorisation. Little to no assessment is carried out by the RMS. Prior to submission of the dossier to the new CMSs; the RMS is informed by the applicant to update the original Assessment Report.

In accordance with the CMDh website, the applicant submits the dossier to new CMSs while the RMS circulates the updated AR with the relevant product information.[9] Validation of the application by CMSs takes place, which takes up to 14 days. Day 0 starts after all CMSs have positively validated the submission. Within 30 days from the start of the procedure, the CMSs should submit their comments to the RMS and applicant. By Day 40, the applicant should submit responses and the RMS evaluates such responses within 8 days. The CMSs can further comment on the responses. At Day 60, the procedure may be closed if no further issues are identified. If further clarifications are needed, a 30 day period is allocated to solve clarifications. If agreement is reached by Day 90, it is positively closed and the national phase starts as in the DCP. If there is still disagreement, the procedure is forwarded to the CMDh and the EMA like in the DCP.

1.7 Benefit-risk balance

The benefit-risk (BR) balance is a valuable regulatory tool used by all stakeholders for the past fifty years (Mt-Isa et. al, 2014). Stakeholders like competent authorities are concerned in defining the BR balance of medicines but they may have different

[9] Heads of Medicines Agency [Online]. [cited 2018 May 23]. MRP/RUP. Available from URL: http://www.hma.eu/93.html

perspectives, values and priorities, resulting in differing evaluations by different agencies and evaluators (Mt-Isa et. al, 2014). Differing evaluations in the BR balance is especially important since regulators make these decisions in an isolated, fragmented and, to a large extent, subjective manner (Bellanti et. al, 2015).

The determination of the BR balance of a medicinal product is one of the most important stages in a medicines development, evaluation, and post-authorisation re-evaluation (McAuslane et. al, 2017). The key advantage of a consistent approach in the determination of a BR balance is that the review is more foreseeable, reliable, transparent and simplifies building standards into the decision-making process, thus ensuring faith in the regulatory procedure across agencies and ultimately with health care professionals and patients (McAuslane et. al, 2017).

Proficient assembly and use of data are needed to reply to the clinical questions that arise with new therapeutic options (Bellanti et. al, 2015). One needs to identify efficiency from clinical response and understand the additional worth compared to other products. These are multidimensional problems which require clear thought of how data will be produced and how benefit and risk will be calculated (Bellanti et. al, 2015). A strong framework for benefit–risk assessment is still absent during drug development and at the time of regulatory authorisation (Bellanti et. al, 2015). Consequently, decision making at significant mileposts in R&D and at submission remains erratic and more often than not, non-transparent (Bellanti et. al, 2015).

In 2009, recognising that there is no standard procedure that is used to aid regulatory decisions on the benefits and risks of medicines, the EMA began a three-year project on

benefit-risk methodology with the aim to identify decision-making simulations that can be used in the agency's work.[10] It was recommended to improve the procedure in how the outcome of benefit-risk assessments is untaken, and was implemented through minor changes to the CHMP assessment reports.[10]

The use of an effect table by the EMA in the assessment report is aimed to improve the transmission of the benefit-risk balance for an evaluated product. The effect table is a tool to summarise the principle benefits and risks together with the uncertainty of the present data to be used as a supplement to the benefit-risk section of the CHMP assessment report. Its aim is to present a compact and consistent layout of the data and uncertainties that are drivers of the decision making process.[11] The effect table as a regulatory tool would be of use to patients and health care professionals.

1.8 Collaboration between regulatory agencies

In this modern age, medicine manufacture and distribution are becoming more globalized, resulting in complexity in processes related to pharmaceutical products (Skerritt et. al, 2015; Luigetti et. al, 2016). It is common that different manufacturing steps take place in different countries far from each other while similar elements are included in the dossiers in different jurisdictions (Luigetti et. al, 2016). Some regulators may lack the resources or competences to carry out assessments of products before they are put on their markets especially since novel agents are becoming more complex

[10] European Medicines Agency [Online]. c1995-2017 [cited 2017 Oct 23]. Benefit-risk methodology. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp#section3

[11] European Medicines Agency [Online]. c1995-2017 [cited 2018 May 30]. Benefit-risk methodology project Update on work package 5: Effects Table pilot (Phase I). Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/02/WC500162036.pdf

(Luigetti et. al, 2016). In such an environment, collaboration among regulators is vital to avoid replication of work, release scarce resources to be used in more critical areas and speed up access to new and/or affordable products (Skerritt et. al, 2015; Luigetti et. al, 2016).

Regulatory collaboration may be achieved through data and/or work-sharing and mutual recognition of assessment and inspection results (Luigetti et. al, 2016). Mutual recognition agreements which require the foundation of a strong legal framework are desirable and should be implemented whenever possible (Luigetti et. al, 2016). It takes time to set up a collaboration between agencies, as the regulatory systems involved need to show equivalency in the respective processes before implementation (Luigetti et. al, 2016). An EMA-FDA confidentiality arrangement took place in 2003 to increase awareness and further facilitate the collaboration between the two agencies (Garrett, 2011).

A mutual recognition agreement between the EU and the US reached on the 1st November 2017 enabled the recognition of inspections conducted at manufacturing sites for human medicines conducted in their respective regions.[12] The first eight EU Member States to be recognised by the FDA were Austria, Croatia, France, Italy, Malta, Spain, Sweden, and United Kingdom.[12] The mutual recognition agreement between the EU and the USA was considered exceptional as the FDA has never acknowledged another country's procedures; a key milestone towards closer collaboration to encourage the use of available resources to safeguard quality and safety of medicines.[12]

[12] European Medicines Agency [Online]. c1995-2017 [cited 2017 Nov]. EU-US mutual recognition of inspections of medicines manufacturers enters operational phase. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002842.jsp&mid=WC0b01ac058004d5c1

Luigetti et. al in 2016 discussed that an alternative method to achieve collaboration and reducing duplication of work is through reliance. Collaboration is achieved through the sharing of work done by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses the already assessed work according to its own technical information and regulatory procedures and retains its own regulatory responsibilities.

There are still barriers to overcome with regards to collaboration which include legal (e.g. lack of legal framework, confidentiality issues), technical (e.g. lack of secure IT systems for information sharing), and non-technical (e.g. political issues, lack of faith) (Luigetti et. al, 2016).

1.9 Comparisons between regulatory agencies

Different regulatory agencies do not always agree on the interpretation of data for a drug's safety and efficacy and so comparing the agencies may provide potential learning opportunities to improve performances (Makuch & Shi, 2014). Moreover, Makuch & Shi (2014) state that awareness about differences in the regulatory systems, environments and processes may decrease the amount of discrepant approvals and withdrawals.

A comparison between the EMA and FDA found that there was agreement on the conclusions for ~80% of new molecular entities (NMEs) when dossiers were submitted

within 12 months from each other.[13] It was observed that there was little divergence on priority NMEs as opposed to standard NMEs and it is regarded as not surprising given the lower public health need of standard NMEs.[12] Many of these conclusions are near verdicts (i.e. minimal but statistically significant efficacy and safety concerns).[12]

The FDA completes regulatory reviews faster than the EMA when novel therapeutic agents are concerned (Downing et. al., 2017). This finding was based on a review of products authorised by both authorities between 2001 and 2010.

FDA and EMA members attributed the difference in the decision making process to a number of factors which include: (i) different evaluation of clinical end points, (ii) differences in collaboration with the companies, (iii) time lag between dossier submissions, (iv) different regulatory guidelines and requirements and (v) potentially different cultural roots and attitudes (Tafuri et. al., 2014). Other key areas of concern which result in differences in the decision making process include wording of drug indications, time for drug approval, benefit-risk assessment and post-marketing requirements (Goodman, 2012; Lis et. al., 2012; Howie et. al., 2013). There are other driving forces resulting in heterogeneity in the approval processes which may include economic, political and sociocultural factors (Trotta et. al, 2011). Comparisons found in literature have been mostly related to the field of oncology most likely due to the perceived public health needs in the field of oncology (Mason et. al, 2010, Roberts et. al, 2011, Trotta et. al in 2011, Shah et. al 2013). No study has conducted a thorough

[13] Food and Drug Administration. New drug review 2009 updates. Presentation by Jenkins JK. FDA/CMS Summit, 3 December 2009. Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM192786.pdf (Last accessed 9th July 2017)

evaluation of differences in the characteristics of medicinal products approved by FDA and EMA (Alqahtani et. al, 2015).

Classically, studies have been conducted by comparing the reviews and approvals between agencies (Hiraku et. al, 2007). Shah et. al in 2013 argues that in general these focused on comparing the timelines between the two with limited emphasis on the differences in regional legislation and the impact of these differences.

In the case study of rivaroxaban, conducted by Arif and Bilfaqi in 2013 it emerged that the FDA requested more safety and dropout data from the manufacturer to help make its conclusion while the EMA felt that the data from the phase 3 trial was sufficient to grant an approval. While generalisability cannot be assumed as only one case was compared, it gives another insight to another potential factor. The authors do not discuss why the FDA requested the additional information.

Regulatory differences can impede the development of pharmaceutical markets (Sifuentes and Giuffrida, 2015). Differences either physical and/or functional between the FDA and EMA necessitate proper planning to ensure requirements to manufacture and commercialise medical products internationally (Sifuentes and Giuffrida, 2015). Future regulatory standardisation between agencies is essential to decrease redundancy and hasten the review process capacity for the benefit of all stakeholders (Sifuentes and Giuffrida, 2015). Such differences in evaluation and authorisation of pharmaceuticals may lead to discrepancies in clinical guidelines, pricing policies, and drug use (Alqahtani et. al, 2015).

Milne et. al (2016) argued that without some determined intervention by the public health agencies of Europe, Japan, and the United States in the next few years, to harmonise regulatory pathways and parameters related to risk assessment, the discrepancies in the technical, regulatory, and funding uncertainties will continue to appear while visions for significant change will remain insignificant for the future.

Industry often decides to pursue different routes with the same medicinal product in different countries such as different indications and so differences are bound to result (Alqahtani et. al, 2015). These may not only reflect variances in the regulatory agency needs and processes but pharmaceutical companies' intention to implement marketing strategies to adapt their medicinal product to the marketplace in each geographic area (Alqahtani et. al, 2015).

1.10 Aims and objectives

The aims and objectives of this research were to:

- Compare the evaluation for the approval of medicinal products by the European Medicines Agency (EMA) and the US Food & Drug Administration (FDA) from the efficacy and safety perspective.

- Highlight differences in the decision making process and information presented in the approved product information between the two regulatory agencies using cardiology-related medicinal products as examples.

Chapter 2:

METHODOLOGY

2.1 Methodology Overview

The study was divided into 5 phases:

1. Mapping of changes in the European Public Assessment Report (EPAR) over time
2. Identifying new active substance medicinal products evaluated by the European Medicines Agency (EMA)
3. Matching of the identified products with those submitted to the US Food & Drug Administration (FDA)
4. Developing and evaluating a tool to collect information necessary for data collection
5. Comparing the evaluation of medicinal products of both regulatory agencies

2.2 Mapping the changes of the European Public Assessment Report over time

The European Public Assessment Report (EPAR) is a regulatory tool which contains the technical conclusions and the judgement reached by the EMA's Committee for Medicinal Products for Human Use (CHMP), following the regulatory review process (Berntgen et. al, 2014; Papathanasiou et. al, 2016). Commercially confidential information is omitted from the document. An EPAR is developed for any product that is submitted for evaluation at the EMA, and is made available in the public domain. The methodologies of the studies and the applicability and significance of the results are included and the report is concluded with a transparent, impartial, and clear description of the benefit–risk balance for the proposed indication (Berntgen et. al, 2014; Wai Yeen et. al., 2014; Papathanasiou et. al, 2016). An EPAR is always made available regardless of the decision taken and so are available for both approved and rejected medicinal products.

The EPAR is a summary of the evaluation of a medicinal product. The EPAR includes only the essential information regarding the product with no mention to confidential information. It is based on the information present in the various assessment reports constructed during the evaluation of the medicinal product (refer to section 1.6.1). The EPAR is different from the report generated by the FDA where all information is included and the confidential information is blotted out.

The European Public Assessment Report is a key document which may have the potential to be used to compare the evaluations between the two regulatory agencies. Over time, the structure and format of the EPAR has changed together with the various assessment reports from which the EPAR is based on. In anticipation of the changes that took place, it was required to identify what were/are the criteria and information that are included in the document and the changes which took place. Identifying the changes in the EPAR is needed in order to verify whether the EPAR can be used to collect the information needed for purposes of the study and to see whether such information was consistent throughout the years.

Since the EPAR is a summary and is based on other assessment reports produced during the evaluation process, it was required to identify the guidances and templates for the assessment report on which the EPAR is based on. The European Medicines Agency uploads the most recent templates and guidance documents required on how to build an assessment report. Specific guidance documents are available for both new and generic

applications. The latest templates and the guidance documents for the Day 80 (D80) overview, non-clinical, and clinical sections were extracted from the EMA website.[14]

The D80 templates and guidances were used to compare the changes of the EPAR since they reflect the Assessment Report format and design that the rapporteur and co-rapporteur use for the Day 80 meeting. The D80 assessment report is the first document that is generated for products being evaluated through the centralised procedure and further assessment reports are built from the D80 Assessment Report. Guidance documents for the D80 assessment report templates are available which helps assessors build the assessment report and so use of the D80 template justifies why such documents have been used in the study.

The latest version of the D80 template and guidances were obtained from the EMA website. The European Medicines Agency was contacted to provide previous templates and guidance documents.[15] The previous templates and guidances were in fact provided. The EMA was approached to provide the previous templates and guidances as only the latest version of the D80 Assessment Report template and guidance is uploaded on the EMA website. The Agency was asked by the investigator to provide all the versions of the D80 documents and the equivalent documents (to cater for possible changes that may have taken place in the naming of the documents). The comparison process of the D80 documents was dependant on the material that was provided by the European Medicines Agency.

[14] European Medicines Agency [Online]. c1995-2017 [cited 2017 Sept 19]. Assessment templates and guidance. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000337.jsp&mid=WC0b01ac0580022719

[15] European Medicines Agency [Online]. c1995-2017 [cited 2017 Sept 19]. Send a question to the European Medicines Agency. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid

The templates and guidance documents were compared to identify the differences over the years. The different sections that make up the Assessment Report and the content and detail that is required to prepare the report were compared.

2.3 Identification of new active substance medicinal products evaluated by the EMA

In Europe, there is more than one registration route for a marketing authorisation for a medicinal product as opposed to the United States of America where there is only one route. For this study, focus on medicinal products authorised through the centralised procedure took place. Products authorised through the centralised route typically tend to have more public health need or special interest for the community compared to other registration routes.

The centralised approved medicinal products were selected for the study because the evaluation is the same for all member states which results in medicinal products with the same medicinal product name, the same product information and the same decision (authorised or rejected) throughout Europe. In the other registration procedures in Europe, not all member states may be involved, the product name may be different in the different member states, product information may be different and not all member states would agree to authorise the product which would make it more difficult to compare.

A list (in the form of an Excel sheet) of all medicinal products assessed by the European Medicines Agency was extracted from the EMA website on the 8th January 2017.[16] Cardiology-related medicinal products, with an outcome in the centralised European marketing authorisation procedure were identified. An outcome was considered as being either a positive or a negative recommendation following assessment of the proposed medicinal product. Such information is available to the public domain. Cardiology products were identified using the Anatomical Therapeutic Chemical (ATC) code. The first hierarchical levels which are related to cardiology include levels B (for blood and blood forming organs) and C (for cardiovascular system). Products with an ATC code that included hierarchical levels B and C were extracted from the complete list of products using the filtering system of the Microsoft® Office™ Professional Plus 2010 package - Excel.

The area selected for the study is cardiology. Cardiovascular diseases are the leading cause of death in the EU.[17] The pharmaceutical industry tends to be more willing to identify innovative treatments in cardiovascular field, in view of the public health need and more likely to harvest advances in healthcare, with first-in-class therapeutics that address unmet public health needs and "me too" drugs (Downing et. al, 2012). A number of studies focusing on the evaluation of products have been conducted on oncology medication (Mason et. al, 2010, Roberts et. al, 2011, Trotta et. al in 2011, Shah et. al 2013). The selected area to cardiology may prove to identify aspects which have not been previously identified through the oncology field and continues to add-on

[16] European Medicines Agency [Online]. c1995-2017 [cited 2017 Jan 02]. European public assessment reports. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

[17] Eurostat [Online]. c2016 [cited 2007 Jan 11] Cardiovascular diseases statistics Available from URL: http://ec.europa.eu/eurostat/statistics-explained/index.php/Cardiovascular_diseases_statistics

to existing knowledge by involving and studying other therapeutic areas. No studies related to cardiology have been identified.

The WHO considers the use of the ATC classification system is considered as a gold standard for international drug utilisation research and is intended as a tool for exchanging and comparing data at international levels.[18] The ATC classification system involves the use of different groups to classify drugs based on the target area and mode of action including the chemical and therapeutic characteristics (Chen & Jiang, 2015). The use of the ATC code was considered the most appropriate method to use since the medicinal products obtained from the EMA website contains the respective ATC codes which allows easy filtering of products according to the respective category and so facilitated the identification of cardiology-related medicinal products.

Exclusion criteria (Table 2.1) were established since some products, have different criteria for assessment depending on a number of characteristics and could introduce a number of bias in the study.

[18] WHO Collaborating Centre for Drug Statistic Methodology International language for drug utilization research. 9th May 2017. Available from: https://www.whocc.no/ [Accessed 11th June 2017].

Table 2.1: The exclusion criteria used for the study

Exclusion Criteria	**Notes**
Innovative biological medicinal products	Examples include vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, monoclonal antibodies and recombinant proteins
Biosimilars and generic medicinal products	A biosimilar defined as a biological product which is similar in characteristics to the reference biological product (Genazzani et. al., 2007). A generic medicinal products defined as a product with the active ingredient having identical qualitative and quantitative composition and same pharmaceutical form as the reference product[19]
Medicinal products containing more than one active ingredient	With the exception when a new molecular entity is introduced only in combination
New application for an already existing active ingredient	Applicable to products were the active ingredient is not a new molecular entity but the product is not considered a generic medicinal product.
Duplicates	The same product submitted for the assessment under a different brand name or using the generic name
Medicinal products with an outcome following 31st December 2016.	To establish a cut-off period

[19] European Medicines Agency [Online]. c1995-2017 [cited 2017 Jan 01]. Generic and hybrid applications. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000170.jsp&mid=WC0b01ac0580514d5c

The administrative information on the EPAR was used to identify the legal basis of the medicinal products to ascertain whether the product meets the requirements of the exclusion criteria. The legal basis of a medicinal product is the category in accordance with the Law under which a particular medicinal product falls under. The legal basis helps to confirm whether the medicinal product in question is to be included in the study or not. If the medicinal product fits in either one of the categories of the exclusion criteria, then it was excluded from the study. The older versions of the EPAR do not contain information on the legal basis but information available through the Malta Medicines Authority was used to confirm legal basis.

Biological medicinal products were excluded from the study since they are different from traditional chemical based medicinal products. Biological agents differ from chemical agents in three main areas; through the use of living source materials used for its production, the impact of the manufacturing processes on the produced biologic, and complexity of the biologic molecules (Table 2.2) (Geigart, 2013).

Identification of chemical active ingredients, is done through analytical techniques such as mass spectrometry and nuclear magnetic resonance with the ability to detect impurities and contaminants (Genazzani et. al, 2007). In contrast, the biopharmaceutical products are analysed on the basis of less sensitive assays, such as electrophoresis and biologic assays (Genazzani et. al, 2007). Biologics are manufactured using highly sophisticated processes, the changes of which can potentially result in alterations that lead to differences in clinical response (efficacy and safety) (Li et. al, 2015). The differences among manufacturers together with sensitivity to the manufacturing

conditions result in disparity, were a product is similar but not identical to the reference product (Geigart 2013; Li et. al, 2015).

From a regulatory standpoint, the biological product requires additional quality related information in order to be assessed. The difference in assessment translates into a different regulatory framework and so different approval pathway. Such quality related information was considered difficult to use for this study since detailed information about the drug substance and drug product (which are quality related information) are not fully available as detailed information is omitted for the public. Information related to quality is considered commercially confidential information with general information made available only.[20] The same scenario is applicable to biosimilars.

A generic application may be submitted when data exclusivity period expires i.e. when the additional market protection for the originator product expires (Zulfikari et. al, 2015). Since the originator would have already been on the market for a period of time, when applying for a marketing authorisation of a generic, there is no need to provide pre-clinical tests or clinical trials to prove efficacy if the indication is the same as that of the originator.[1] Instead, literature is used to cover the required information in the dossier. To ensure that the product is indeed comparable to the original, bioavailability studies are needed unless exempt in accordance with guidelines.[1] Since there is a

[20] Heads of Medicines Agencies & European Medicines Agency [Internet]. c2012 [2017 July 14] HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation (MA) application – Release of information after granting of a marketing authorisation Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf

[1] European Commission. Directive 2001/83/EC of The European Parliament and of The Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended. Official Journal of the European Union 2001; L311:67-121.

difference in the regulatory process for generic drugs, it was decided that generic medicinal products should be excluded from the study.

Combination products as stated in article 10b of Directive 2001/83/EC, pre-clinical tests and clinical trials are required related to the combination of the active ingredients involved and there is no need to provide scientific information on the individual active ingredients.[1] There would be inconsistent data comparison if these are reviewed with products authorised through other legal basis.

Products with an active ingredient already available on the market and intended for a different application from the originator product were excluded from the study. In the legislation, this is considered as a 10(3) application also known as hybrid application. In 10(3) dossier, reference is made to the efficacy and safety documentation included in the dossier of the chosen reference product including the Summary of Product Characteristics (SmPC) (Vogel, 2012). Only data that is specifically required to establish the properties of the new product need to be provided in the application dossier (Vogel, 2012). Since there are various degrees of information and data which can be provided for a 10(3) application, it was deemed necessary to exclude it from the study.

A duplicate product (article 10(c)) authorised based on a dossier of an already approved product to which it is considered identical in terms of quality, safety and efficacy. Since the same information is submitted for review, duplicate products were not included in

[1] European Commission. Directive 2001/83/EC of The European Parliament and of The Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended. Official Journal of the European Union 2001; L311:67-121.

this study. When a duplicate was identified, the date of authorisation was used as a guide to identify which product was authorised first. There were cases when the applicant would submit more than one application in parallel, in such cases, the product with the branded name was considered. The date 31st December 2016 was selected as the cut-off point from which no further products were selected for the study.

2.4 Matching with the FDA approved counterparts

The centrally authorised products (CAP) identified from the EMA website were matched with the FDA approved counterparts through the FDA website.[21] A number of sources of information were used which included: (i) the name of the product, (ii) the marketing authorisation holder and (iii) the information in the European Assessment Report were used to ensure that the correct counterpart product was identified. If a counterpart could not be identified using the above system, it was excluded from the study.

2.5 Tool development to collect and compare information (CCI)

A CCI tool was developed to collect and compare the information collected about the evaluation process from the EMA and the FDA (Appendix 1). The tool facilitates the understanding of how the decision process was conducted and identifies which factors were taken into consideration while ensuring a harmonised and reproducible approach and minimising intra-individual variability and investigator bias in the comparison process. The tool was intended to be used by the investigator.

[21] Food and Drug Association [Internet]. c2016 [cited 2017 Feb 26] Drugs@FDA: FDA Approved Drug Products; Available from URL: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

The CCI tool was designed using Microsoft® Word 2010 and consists of six sections:

- **Section 1:** Including administrative information such as legal status, date of submission, date of approval and rejection.
- **Section 2:** Relates to essential non-clinical information.
- **Section 3:** Includes the essential information regarding clinical aspects.
- **Section 4:** Addresses the benefit risk balance.
- **Section 5:** Relates to risk minimisation plans and risk evaluation and mitigation strategies.
- **Section 6:** Incorporates relevant sections taken from the product information.

The CCI tool was developed using articles and guidelines. The online databases were used to identify articles were ScienceDirect, PubMed and EBSCO. Articles were not limited to a specific type like peer reviewed articles only but were extended to other forms to identify all possible areas related to the study.

Keywords used included the following in various combinations: European Medicines Agency, EMA/EMEA, U.S. Food and Drug Administration FDA, U.S.A, Japan, PMDA, assessment, evaluation, differences, comparison, public health, authorisation, review, regulatory/regulation, decision, drug approval, affairs, Centre for Innovation in Regulatory Science, CIRS, restriction, marketing authorisation, application, medicines, medicinal product, drugs, risk-benefit, cardiovascular, process, harmonisation, International Conference for Harmonisation, ICH, innovation, new chemical/molecular entities, NCE, registration, safety, efficacy, clinical, non-clinical.

The content included in sections 2 and 3 reflects the parameters listed in the "notice to applicants guideline on the content of a dossier[22]" which is a guideline available on the European Commission website to help applicants. This guideline includes details for applicants on how the backbone of the dossier should be constructed for European applications. Information in section 5 was taken from the "Questions and answers on the risk management plan (RMP) summary"[23] issued by the EMA. Section 6 was developed using the information found in the "Quality Review of Documents (QRD) Product Information template"[24] which is publically available since the EPAR includes product information. The information found on the SmPC was used in the tool since the information in the PL reflects that of the SmPC but in layman's terms. The contents in the checklist consist of standard sections and sub-sections.

Additional questions were included in each sub-section to better understand how the decision process was conducted and which factors were taken into consideration that gave rise to the final decision. The developed CCI tool consisted of fifty-four pages.

2.5.1 Psychometric evaluation of the CCI tool

Developed data tools need to be psychometrically robust by establishing validity before initiating data collection to ensure that the research design is vigorously sound (DeVon et. al, 2007). The validity of an instrument is the degree to which the components in the

[22] European Commission [Internet]. [cited 2017 Mar 25] Vol 2: Notice to Applicants Human; Available from URL: https://ec.europa.eu/health/documents/eudralex/vol-2_en

[23] European Medicines Agency [Internet]. [cited 2017 Jul 23] Questions and answers on the risk management plan (RMP) summary; Available from URL: www.ema.europa.eu/docs/en_GB/document_library/Other/.../WC500166101.pdf

[24] European Medicines Agency [Internet]. [cited 2017 Jul 23] QRD product-information annotated template (English) version 10; Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf

tool/s actually measure what they are intended to measure regardless of the responder (Smith, 2002; Smith, 2010; Kazi & Klahid, 2012). A validated tool will help gather better quality and credible data (Kazi & Klahid, 2012).

2.5.1.1 Content Validity

Content validity of an instrument refers to the extent to which elements from the tool and the data gathered are relevant to and representative of the aims and objectives of the study (Haynes *et. al,* 1995; Smith, 2010). Such elements include related issues, topic areas and in the instance of close ended questions, response options (Smith, 2010).

Lynn (1985) describes that content validity can be determined via a two stage process. Lynn's procedure was adopted to assess the tool for content validity. Stage one or developmental stage involves the identification of an aim for the instrument followed by the generation of items relating to the construct (study topic) (Smith, 2010). The pool of items generated are refined and assembled into an instrument. Stage one of Lynn validation process was incorporated in the design of the tool through the identification of information from literature suggesting that till now, the tool already has some degree of content validity incorporated.

The second stage of the procedure is the Judgement – quantification stage. This step requires the input of a number of experts to assess (based on their expertise) the items and entire instrument for content validity. The number of experts required depends on how accessible they are to the investigator. Lynn (1985) argues that at least a minimum of three experts are required. A total of six experts specialised in the regulatory and

clinical fields were recruited for the validation process of the proposed tool. The validation panel consisted of one clinical assessor, four regulatory affairs specialists from a competent authority (having senior pharmacist, senior pharmaceutical officer and documentation officer as ranking positions) and one regulatory affairs specialist from a pharmaceutical company.

Each expert was given a sheet (Appendix 2) containing the details of the study to familiarise with the aims and objectives of the study to ensure that judgements are done in the correct context. The sheet contains questions on how relevant each individual item is. Relevance was rated using a four-point rating scale as recommended by Lynn, 1986 (were 4 = very relevant; 3 = relevant but needs minor revision; 2 = Item requires considerable revision to be relevant; 1 = not relevant). The experts were further requested to include any other relevant items which have been potentially omitted from the tools that they can be included (Lynn, 1986).

The four point scale is used in order to quantify content validity via the content validity index (CVI) (Lynn, 1986). It is calculated by the proportion of experts that give a rating of 3 or 4 (Lynn, 1986). A CVI needs to be calculated for both the individual items and the instrument as a whole (Lynn, 1986). The CVI for the instrument is the average of all the content validity indices of all items.

The minimum number of experts that must agree for an item (and the instrument), to ensure content validity, was determined using Table 3.2 which helped to decide if an item should be removed or retained. Since six experts took part in the evaluation process, a CVI value of 0.67 or higher is required for the items and instrument to be

validated for content. The advantage of using such a quantitative system is that it reduces investigator bias when it comes to deciding whether to remove or retain an item. It avoids the need to re-distribute the updated tool (as some validation methods require this) which introduces an element of bias as experts may not be willing to dedicate another intensive session to validate the tools.

Table 2.2. Proportion of Experts (above the line) whose endorsement is required to establish content validity beyond the .05 Level of Significance. (Reproduced from Lynn, M.R. Determination and quantification of content validity. Nursing Research. 1986; 35: 382-5.

Number of Experts	Number of Experts Endorsing Item or Instrument as Content Valid								
	2	3	4	5	6	7	8	9	10
2	1.00								
3	.67	1.00							
4	.50	.75	1.00						
5	.40	.60	.80	1.00					
6	.33	.50	.67	.83	1.00				
7	.29	.43	.57	.71	.86	1.00			
8	.25	.38	.50	.63	.75	.88	1.00		
9	.22	.33	.44	.56	.67	.78	.89	1.00	
10	.20	.30	.40	.50	.60	.70	.80	.90	1.00

Note: The caution over using the standard error of the proportion when $n \leq 10$ (Downie & Heath, 1974) does not apply in this situation because only when $p > q$ is there significance, and any nonunique p [×] q solutions are irrelevant.

2.6 Assessment comparison and data collection

The assessment reports from the EMA and the reviews from the FDA were extracted from the respective websites. The EPAR is divided into different sections and is not available as one whole document for older products. All EPAR related documents were used for the study. The approved product information for the initial approval is part of the EPAR. The most recent product information is available in the EMA website. The product information was sought from the European Commission website under the community registers sections to address for the limitation.[25]

[25] European Commision [Internet]. [cited 2017 Mar 25] Pharmaceuticals - Community Register; Available from URL: http://ec.europa.eu/health/documents/community-register/html/index_en.htm

Similarly, the FDA reviews are divided into sections based on the discipline being evaluated. The related sections (mainly the non-clinical and clinical parts) were used for the study including the original label (the equivalent to the product information in the EEA) as initially approved by the FDA.

2.7 Applicability of the tool for the study

The comparison procedure was conducted by first filling in section 1 and section 6. Section 6 was filled in first as the product information is the result of the assessment by the agency. When any potential differences have been identified in section 6, the other relevant sections of the CCI tool were filled in. This was done to capture the most significant and relevant differences. In the evaluation procedure, since some variations may not have any clinical significance in the evaluation outcome, through the method incorporated, the clinical differences are identified and noted.

The developed CCI tool was used to collect data about all identified products filling it in using the material obtained from the documents extracted from the respective agencies. The processing for comparing data for the indications section of the CCI tool, took place in two phases. Phase one involved comparing the EMA and the FDA approved indication/s from the indication section of the SmPC and the label only. Phase two involved the same process but was extended by further reviewing the other sections of the SmPC and the label. Phase two was done as there could be other references to the use of the product in other sections of the SmPC which may not be present in the indication sections.

2.3 List of Publications and Abstracts

An abstract by Camilleri M, Borg JJ, Sammut Bartolo N, Serracino-Inglott A entitled "A comparison of approved indications between regulatory agencies" was accepted as a poster presentation (Appendix 3. It will be presented at the 2018 American College of Clinical Pharmacy (ACCP) Global Conference on Clinical Pharmacy to be held on October 20-23, 2018, at the Washington State Conference Center, Seattle, Washington, USA**.**

An abstract by Camilleri M, Borg JJ, Sammut Bartolo N, Serracino-Inglott A, entitled "Comparison of post-authorisation requirements between regulatory agencies for medicinal products" was accepted for a poster presentation (Appendix 3. It will be presented at the 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2018 to be held on September 2-6, 2018, in Glasgow, Scotland.

Chapter 3:

RESULTS

3.1 Results Overview

The results are presented in the following manner:

1) Mapping of the European Public Assessment Report (EPAR)
2) Number of cardiology-related medicinal products identified for the study
3) Tool validation
4) Comparison of the evaluations

3.2 Mapping of the European Public Assessment Report (EPAR)

A total of 10 versions of the Day 80 (D80) overview documents (part of the assessment report during Day 80 of the centralised procedure) were used for this part of the study. The D80 documents were used to map the EPAR as the D80 assessment report is the first assessment report that is created during the evaluation procedure and further assessment reports are based on it including the EPAR. Nine versions (2007, 10.09, 04.10, 10.11, 03.13, 04.14, 05.15, 06.16, 10.16) were provided by the European Medicines Agency (EMA) and 1 version, (10.17) was retrieved from the EMA website.

The changes in the D80 overview template are presented in Table 3.1. There was an increase in the number of sections in the overview to include areas for discussions and conclusions starting from version 10.09 onwards. No changes were observed in relation to the non-clinical aspects apart from the introduction of discussion and conclusions. The same applies for the clinical efficacy, the clinical safety and the Risk Management Plan sections. The discussion part of the clinical efficacy section was further sub-divided into a number of sections (version 10.11 onwards). The benefit-risk assessment section of the overview had further sub-sections introduced by incorporating therapeutic context and the effects table as from version 06.16 onwards.

Table 3.1: Changes in the sections of the D80 Overview Template overtime

	D80 Assessment Report Overview Versions									
Criteria	**2007**	**10.09**	**04.10**	**10.11**	**03.13**	**04.14**	**05.15**	**06.16**	**10.16**	**10.17**
Non clinical Aspects: Pharmacology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non clinical Aspects: Pharmacokinetics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non clinical Aspects: Toxicology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non clinical Aspects: Ecotoxicity/environmental risk assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓
Discussion on non-clinical aspects		✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusion on non-clinical aspects		✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical Aspects: Tabular overview of clinical studies		✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical Aspects: Pharmacokinetics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical Aspects: Pharmacodynamics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discussion on clinical pharmacology		✓	✓	✓	✓	✓	✓	✓	✓	✓
Conclusions on clinical pharmacology		✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical efficacy: Dose-response studies and main clinical studies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical efficacy: Clinical studies in special populations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical efficacy: Analysis performed across trials (pooled analyses AND meta-analysis)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical efficacy: Supportive study(ies)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discussion on clinical efficacy		✓	✓	✓	✓	✓	✓	✓		
Discussion on clinical efficacy: Design and conduct of clinical studies				✓	✓	✓	✓	✓	✓	✓
Discussion on clinical efficacy: Efficacy data and additional analyses				✓	✓	✓	✓	✓	✓	✓
Discussion on clinical efficacy: Additional expert consultation									✓	✓
Discussion on clinical efficacy: Assessment of paediatric data on clinical efficacy									✓	✓
Conclusions on clinical efficacy		✓	✓	✓		✓	✓	✓	✓	✓

✓ = presence of the criterion in the D80 AR Overview

Table 3.1 continued in pages 50-52

Table 3.1: Changes in the sections of the D80 Overview Template overtime

	D80 AR Overview Versions									
Criteria	**2007**	**10.09**	**04.10**	**10.11**	**03.13**	**04.14**	**05.15**	**06.16**	**10.16**	**10.17**
Clinical safety: Patient exposure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Serious adverse events and deaths	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Laboratory findings	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Safety in special populations	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Immunological events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Safety related to drug-drug interactions and other interactions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Discontinuation due to AES	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical safety: Post marketing experience										✓
Discussion on clinical safety		✓	✓	✓	✓	✓	✓	✓	✓	✓
Additional expert consultation									✓	✓
Assessment of paediatric data on clinical safety									✓	✓
Conclusion on clinical safety		✓	✓	✓	✓	✓	✓	✓	✓	✓
Pharmacovigilance system	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Risk Management Plan	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discussion on safety specification							✓	✓	✓	✓
Conclusions on the safety specification							✓	✓	✓	✓

✓ = presence of the criterion in the D80 AR Overview

Table 3.1: Changes in the sections of the D80 Overview Template overtime

	D80 AR Overview Versions									
Criteria	**2007**	**10.09**	**04.10**	**10.11**	**03.13**	**04.14**	**05.15**	**06.16**	**10.16**	**10.17**
Orphan medicinal products: Orphan designation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Orphan medicinal products: Similarity									✓	✓
Orphan medicinal products: <Derogation(s) from market exclusivity>									✓	✓
Benefits	✓	✓	✓	✓	✓	✓	✓			
Risks	✓	✓	✓	✓	✓	✓	✓			
Balance	✓	✓	✓	✓	✓	✓	✓			
Benefit risk assessment: Therapeutic Context: Disease or condition								✓	✓	✓
Benefit risk assessment Therapeutic Context: Available therapies and unmet medical need								✓	✓	✓
Benefit risk assessment: Therapeutic Context: Main clinical studies								✓	✓	✓
Benefit risk assessment: Favourable effects			✓	✓	✓	✓	✓	✓	✓	✓
Benefit risk assessment: Uncertainties and limitations about favourable effects		✓	✓	✓	✓	✓	✓	✓	✓	✓
Benefit risk assessment: Unfavourable effects		✓	✓	✓	✓	✓	✓	✓	✓	✓
Benefit risk assessment: Uncertainties and limitations about unfavourable effects			✓	✓	✓	✓	✓	✓	✓	✓
Benefit risk assessment: Effects Table								✓	✓	✓
Benefit risk assessment: Benefit-risk assessment and discussion: Importance of favourable and unfavourable effects		✓	✓	✓	✓	✓	✓	✓	✓	✓
Benefit risk assessment: Balance of benefits and risks			✓	✓	✓	✓	✓	✓	✓	✓

✓ = presence of the criterion in the D80 AR Overview

Table 3.1: Changes in the sections of the D80 Overview Template overtime

	D80 AR Overview Versions									
Criteria	**2007**	**10.09**	**04.10**	**10.11**	**03.13**	**04.14**	**05.15**	**06.16**	**10.16**	**10.17**
Benefit risk assessment: Additional considerations on the benefit-risk balance								✓	✓	✓
Discussion on the benefit-risk assessment		✓	✓	✓	✓	✓	✓			
Conclusion	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ = presence of the criterion in the D80 AR Overview

3.2.1 Analysis of the information included in the D80 Assessment Report (Non-Clinical)

Five versions (2006, 10.09, 04.10, 10.10, 05.15) were provided by the EMA while the latest version (03.16) was extracted from the EMA website. A total of 13 changes were identified when comparing the different versions of the Non-clinical D80 assessment report **(**Table 3.2a-b). All changes, excluding one, involved the addition of information to the assessment report. The standard phrases for the Environment Risk Assessment was the only change that was removed from the assessment report. The greatest number of changes was observed between the 04.10 version to the 10.10 version with 5 changes. The least number of changes took place with the transition from the 10.09 version to the 04.10 version with 2 changes. There was one case were no differences in were identified between 05.15 version and 03.16 version.

3.2.2 Analysis of the information included in the D80 Assessment Report (Clinical)

Eight versions (2006, 10.09, 10.10, 10.11, 03.13, 04.14, 05.15, 03.16) were provided by the EMA while the latest version (10.16) was extracted from the EMA website. Comparing the different versions of the Clinical D80 assessment report, a total of 25 changes were identified **(**Table 3.3a-b). All changes were related to the addition of information to the assessment report template. The greatest number of changes was from the 05.15 version to the 03.16 version with 12 changes. The least number of changes took place with the transition from the 10.10 version to the 11.11 version and with the 11.11 version and 03.13 versions with 2 changes each. There were three cases were no differences were identified which included between 03.13 version and the 04.14 version, 04.14 version and 05.15 version and 03.16 version and 06.16 version.

Table 3.2: Comparison between the different versions of the D80 assessment Report (Non-clinical template)

D80 Assessment Report version comparison	Summary of the differences
Between 2006 and 10.09	Introduction on information related to Paediatric Investigation Plans (PIP) Inclusion of information provided by the Paediatric Committee (PDCO) Introduction of a table for the relevant endpoints of Environment Risk Assessment (ERA)
Between 10.09 and 04.10	Introduction of a table on Absorption data Inclusion of standard phrases for the Environment Risk Assessment (ERA)
Between 04.10 and 10.10	Introduction of clear referencing for mentioned publications Introduction of Assessor's comments Ensuring suitability of information in the Summary of Product Characteristics Removal of standard phrases for Environment Risk Assessment (ERA) Inclusion of minimal standard sentences for the conclusion
Between 10.10 and 05.15	Introduction of implications of non-clinical data for Risk Management Plan (RMP) Introduction of non-clinical comments of possible clinical significance Incorporation of non-clinical findings to be included in the safety specifications
Between 05.15 and 03.16	No differences identified

Table 3.3: Comparison between the different versions of the D80 assessment Report (Clinical template)

D80 Assessment Report version comparison	Summary of the differences
Between 2006 and 10.09	Introduction on Paediatric Investigation Plans (PIP) Including information provided by the Paediatric Committee (PDCO) Addressing pharmacokinetic data in paediatric population Including pharmacodynamic response in paediatric population Introducing discussion on clinical efficacy Introducing safety aspects in paediatric population
Between 10.09 and 10.10	Additional guidance on discussion aspects of the assessment reports Emphasising that clear referencing should take place for mentioned publications Introducing Assessor's comments
Between 10.10 and 10.11	Introducing assessors comments on elderly age groups, condition in the elderly and pharmacokinetics in the elderly Introducing safety information including benefit-risk in elderly population
Between 10.11 and 03.13	Update to the Risk Minimisation Plan with respect to assistance between PRAC and CHMP rapporteur Procedures to be implemented regarding Risk Minimisation Plans
Between 03.13 and 04.14	No differences identified
Between 04.14 and 05.15	No differences identified

Table 3.3 is continued in page 56

Table 3.3: Comparison between the different versions of the D80 assessment Report (Clinical template)

D80 Assessment Report version comparison	Summary of the differences
Between 05.15 and 03.16	Expansion of assessor's comments Introducing statistical methodology like non-compartment models and regression models Evaluation and qualification of models Expansion of population pharmacokinetic analysis and its interpretation Comparison of in silico data with in vivo data Including exposure response or pharmacokinetics/pharmacodynamics analysis with clinical data with respect to interaction and whether there is potential for risk benefit changes Further elaboration on mode of action including mechanistic modelling Elaboration on primary pharmacology Elaboration on the relationship between plasma concentration and effect Inclusion of dose-response study Elaboration on the benefit risk balance Conditions related to post-authorisation efficacy studies
Between 03.16 and 10.16	No differences identified

3.3 Products analysed in the study

Figure 3.1 shows how the products were identified. A total of 922 centrally authorised medicinal products were included in the extracted list of medicinal products from the EMA website. Out of 922 products, 87 were cardiology related medicinal products

identified through the Anatomical Therapeutic Chemical (ATC) code. Fifty-three medicinal products remained after further removing biosimilar and generic products. Twenty-nine medicinal products were identified following the application of the exclusion criteria.

After applying the exclusion criteria, a total of 27 products were identified. During phase two which involved the matching process, there were two products, Reasanz (serelaxin, EMEA/H/C/002817) and Feraccru (ferric maltol, EMEA/H/C/002733) which had to be excluded from the study because the US Food & Drug Administration (FDA) approved medicinal product counterpart could not be identified from the FDA website. Table 3.4 lists the 27 products shortlisted for the study organised according to the active ingredients together with the respective ATC code, agency decision outcome and dates of authorisations.

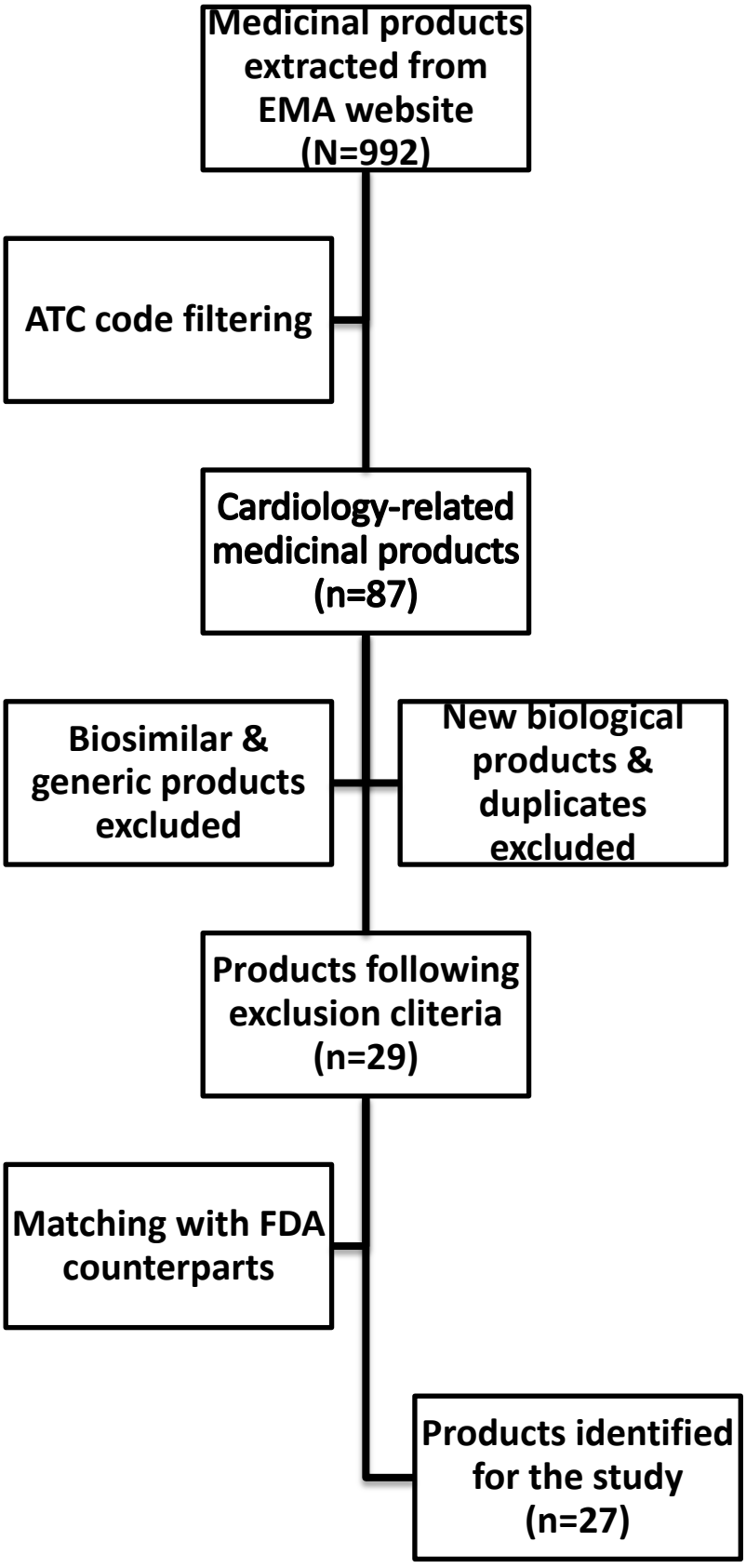

Figure 3.1: Flowchart illustrating the product identification process for the study

Table 3.4: Products identified for the study

Active ingredient/s	ATC code	Product status by the EMA	Product status by the FDA	Date of Authorisation by EC	Date of Authorisation by FDA
aliskiren	C09XA02	Authorised	Authorised	22/08/2007	05/03/2007
apixaban	B01AF02	Authorised	Authorised	18/05/2011	28/12/2012
azilsartan medoxomil	C09CA09	Authorised	Authorised	07/12/2011	25/02/2011
bivalirudin	B01AE06	Authorised	Authorised	20/09/2004	15/12/2000
bosentan monohydrate	C02KX01	Authorised	Authorised	15/05/2002	20/11/2001
cangrelor	B01	Authorised	Authorised	23/03/2015	22/06/2015
clopidogrel hydrogen sulfate	B01AC04	Authorised	Authorised	15/07/1998	17/11/1997
colesevelam	C10AC04	Authorised	Authorised	10/03/2004	26/05/2000
dabigatran etexilate mesilate	B01AE07	Authorised	Authorised	18/03/2008	19/10/2010
dronedarone	C01BD07	Authorised	Authorised	26/11/2009	01/07/2009
edoxaban tosylate	B01	Authorised	Authorised	19/06/2015	08/01/2015
fondaparinux sodium	B01AX05	Authorised	Authorised	21/03/2002	07/12/2001
guanfacine hydrochloride	C02AC02	Authorised	Authorised	17/09/2015	02/09/2009
iloprost	B01AC11	Authorised	Authorised	16/09/2003	29/12/2004
irbesartan	C09CA04	Authorised	Authorised	27/08/1997	13/09/1997
ivabradine hydrochloride	C01EB17	Authorised	Authorised	25/10/2005	15/04/2015
mipomersen sodium	C10AX11	Refused	Authorised	-	29/01/2013
prasugrel	B01AC22	Authorised	Authorised	23/02/2009	10/07/2009
ranolazine	C01EB18	Authorised	Authorised	09/07/2008	27/01/2006
regadenoson	C01EB21	Authorised	Authorised	06/09/2010	10/04/2008
rivaroxaban	B01AF01	Authorised	Authorised	30/09/2008	01/07/2007
sacubitril / valsartan	C09DX04	Authorised	Authorised	19/11/2015	07/07/2015
selexipag	B01AC27	Authorised	Authorised	12/05/2016	21/12/2015
telmisartan	C09CA07	Authorised	Authorised	16/12/1998	10/11/1998
ticagrelor	B01AC24	Authorised	Authorised	03/12/2010	20/07/2011
tolvaptan	C03XA01	Authorised	Authorised	03/08/2009	19/05/2009
vorapaxar sulfate	B01	Authorised	Authorised	19/01/2015	08/05/2014

3.4 Validation of the Collect and Compare Information (CCI) tool

All 6 experts have rated all items in the CCI tool (excluding three) as a 3 and a 4 indicating that they have deemed them as being relevant. A Content validity Index (CVI) value of 1.00 was obtained for the items rated 3 and 4 which is greater than the 0.67 cut-off point (Table 2.3). A CVI of 1.00 suggests that all items that acquired a 3 and a 4 can remain in the CCI tool and should not be removed.

Some experts deemed 3 items as being not relevant. Since in each case only one expert rated these items less than 3, a CVI of 0.83 resulted which is still greater than the 0.67 cut-off point included in Table 2.3 indicating that they can still be retained. The 3 items which obtained a rating lower than 3 are listed in Table 3.5.

Table 3.5: The items deemed to be not relevant by experts in the developed CCI tool.

Date of application submission
Date of CHMP approval
Questions and statements related to the "Pharmacological Class of the Medicinal Product"

Some experts suggested additional changes to the CCI tool which included to:

- Remove "N/A" from the USA column of the proposed indication/s by applicant - this change was recommended since there can be changes in policies over time and the initial proposed indications by the applicant may be included in the documents for some products.
- Include an "Other" section in the approved indication section with the rest of the restrictions - the rationale behind this is that while information on such restrictions have been identified from literature, there may be other restrictions

which have not necessarily been identified so far and that would not be captured. The proposed "other" section would cater for that limitation.

- Change the words "Europe" and "USA" found in section two onwards into "EMA" and "FDA" respectively since the EMA and the FDA are conducting the evaluations.
- Replace the word "information" to "scientific data" - as information can have varying definitions but in view of the aim of the study, scientific data was proposed. "More information" may mean a more detailed description of the clinical studies submitted to the authorities but having more detailed information of the studies may not necessarily mean that more criteria were considered for the decision making process.
- Include of orphan status and whether a Paediatric Investigation Plan has been conducted or waivered. This was included in the "other section" of the CCI tool in section one. These were criteria which were originally overseen and not included in the CCI tool.
- Change the text of "Any scientific advice took place with the respective authority" to "Scientific Advice?" for improved clarity.

3.5 Agreement between authorisations and refusals of medicinal products

Out of the twenty-seven products included in the study, there was one disagreement between the regulatory agencies, which resulted in a refusal by the EMA and an approval by the FDA. The active ingredient concerned was mipomersen sodium (Kynamro) which has the same branded name in both regions. The remaining twenty-six products all acquired a marketing authorisation from both regulatory agencies.

3.5.1 The case of Kynamro

Kynamro containing the active ingredient mipomersen sodium was authorised by the FDA on the 29th January 2013 and refused by the EMA on the 29th May 2013. The date of submission of the medicinal product application to the FDA was on the 29th March 2012 while that to the EMA was on the 28th July 2011. The legal basis for the product for the EMA was an 8(3) application - a complete and independent dossier while the submission type for the FDA was a New Drug Application which are considered as equivalent in terms of the scientific information that is required for the application in the respective territories.

The proposed indication submitted to the FDA was: "*as an adjunct to maximally tolerated lipid lowering medications and diet to reduce low density lipoprotein-cholesterol, apolipoprotein B, total cholesterol, nonhigh density lipoprotein-cholesterol and lipoprotein (a) in patients with homozygous familial hypercholesterolemia*."[26]

Proposed indication to EMA: "*Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apo B, total cholesterol (TC), non-high density lipoprotein-cholesterol (non-HDL-C) and lipoprotein (a) [Lp(a)] in patients with homozygous familial hypercholesterolaemia (HoFH) and in patients with severe heterozygous familial hypercholesterolaemia (severe HeFH).*"[27]

[26] Center for Drug Evaluation and Research [Internet]. [2017 July 14] APPLICATION NUMBER: 203568Orig1s000 ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS; Available from URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf

[27] European Medicines Agency [Internet]. [2017 July 14] Assessment report Kynamro Solution for injection 189mg Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002429/WC500144511.pdf

The refusal by the EMA was based on safety perspective but efficacy issues were also identified. Three main CHMP grounds for refusal provided in the EPAR were:

- The long-term consequences of liver steatosis were of major concern while consequently difficult to monitor in a clinical setting through non-invasive tests.

- Uncertainties remained regarding effects on long-term cardiovascular outcome specifically, the arithmetical imbalance in overall cardiovascular (CV) events, MACE (Major Adverse Cardiovascular Events) and CV hospitalisations. Potential negative effects, in particular inflammatory effects, immunological reactivity, increase in blood pressure and renal toxicity (as shown by proteinuria) may offset the potential beneficial effect.

- The high overall withdrawal rate, even in the restricted population, remained a major concern, harshly limiting the number of patients that may obtain a potential benefit from its effect. Given that withdrawals are mainly due to intolerance, it is unlikely that rates may be improved in a less selected population in standard practice.

The above observations resulted in an overall negative benefit-risk balance despite having no quality issues by the EMA. The FDA evaluation showed a similar conclusion with the main areas of concern being safety issues. The FDA deemed that the identified safety issues can be mitigated through the components in the Risk Evaluations and Mitigation Strategies (REMS). REMS included that only certified health care professionals can specifically prescribe mipomersen and that the medication should be

dispensed from certified pharmacies with evidence or other documentation of safe-use. Further goals in the REMS included the education of prescribers regarding potential risk of hepatotoxicity and the need to monitor patients during treatment and to restrict access to mipomersen to patients with a phenotype consistent with homozygous familial hypercholesterolemia (HoFH).

The FDA review further elaborates that if post-marketing experience in patients with HoFH indicates that mipomersen is well tolerated, a cardiovascular outcomes trial should be considered to document whether the drug reduces the risk for cardiovascular events. Further analysis shows that while the FDA designated the indication as an orphan there is no mention of orphan designation in the EPAR by the EMA.

3.6 Therapeutic indication differences between approved products

Out of the 26 authorised products by both agencies, 18 products had different indications when comparing only the indication section of the label and the Summary of Product Characteristics (SmPC) (Table 3.6). The indications of 26 products were further analysed by using the label and the SmPC as a whole document by reviewing the other sections of the SmPC, 14 products were determined to have different indications (Table 3.7).

Table 3.6: Active ingredients which have been found to have different indication/s when comparing the indication section of the label to the SmPC

aliskiren	guanfacine hydrochloride
apixaban	iloprost
azilsartan medoxomil	ivabradine hydrochloride
bivalirudin	prasugrel
bosentan monohydrate	regadenoson
cangrelor	sacubitril/valsartan
dabigatran etexilate mesilate	selexipag
dronedarone	telmisartan
edoxaban tosylate	tolvaptan

Table 3.7: Active ingredients which have been found to have a different indication/s when comparing the label to the SmPC as a whole document

apixaban	guanfacine hydrochloride
bivalirudin	iloprost
bosentan monohydrate	ivabradine hydrochloride
cangrelor	prasugrel
dabigatran etexilate mesilate	regadenoson
dronedarone	selexipag
edoxaban tosylate	tolvaptan

Telmisartan, azilsartan medoxomil, aliskiren and sacubitril/valsartan were the active ingredients which were removed during the second step of the indication comparison. The reason identified why step 2 was essential was that the EMA left the indications general compared to the FDA approved counterpart for all 4 products. The sections of the SmPC which were essential to make the decision to exclude these 4 products included: 4.2 - Posology and method of administration and 4.4 - Special warnings and precautions for use.

The 14 products which were found to have different approved indications are included in Table 3.8. Table 3.8 includes the approved indications as extracted from both the EMA SmPC and the FDA Label, a small description of the difference between the two

indications (as taken from the developed CCI tool), who made the indication restriction and whether the same clinical trials have been submitted for the same product/active ingredient.

3.6.1 Analysis of differences in the indications

The 14 products (Table 3.8) identified to have different indications between the EMA and the FDA approved counterparts have been classified based on the difference in the indication in accordance to the developed CCI tool into the following categories: restriction based on diseased states (n=5), restrictions related to patient characteristics (n=4), restriction based on severity of the condition (n=3), combination restrictions (n=3), restriction based on previous therapy failure (n=1), restriction of use when alternative therapies are inappropriate (n=1). Different clinical scenario (n=3) was identified where agencies authorised a product for a different clinical setting in view of different efficacy-related clinical studies submitted by the industry.

Both the EMA and the FDA applied restrictions were applicable with the EMA restricting a greater number of indications compared to the FDA (8 vs 4 respectively). The same clinical trials have been presented to both regulatory agencies for all categories except for the different clinical scenario group.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
apixaban	Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.	To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.	Different clinical scenario	N/A	No
bivalirudin	Anticoagulant in patients undergoing percutaneous coronary intervention (PCI)	For use as an anticoagulant in patients in unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). Anguiomax™ is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin	Combination restriction	FDA	Yes
bosentan monohydrate	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in: Primary PAH PAH secondary to scleroderma without significant interstitial pulmonary disease	TRACLEER™ is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening	Disease state, severity of condition	EMA	Yes

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8 is continued in pages 68-74

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
cangrelor	Kengrexal, co-administered with acetylsalicylic acid (ASA), is indicated for the reduction of thrombotic cardiovascular events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) who have not received an oral P2Y12 inhibitor prior to the PCI procedure and in whom oral therapy with P2Y12 inhibitors is not feasible or desirable.	KENGREAL is a P2Y12 platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients in who have not been treated with a P2Y12 platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor	Combination restriction	EMA	Yes
dabigatran etexilate mesilate	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery	PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation	Different clinical scenario	N/A	No

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
dronedarone	MULTAQ is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate	MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrilation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age ;70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter 2:50 mm or left ventricular ejection fraction (LVEF (40%), who are in sinus rhythm or who will be cardioverted	Different clinical scenario, patient characteristics restrictions, disease state restrictions	FDA	No

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
edoxaban tosylate	Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).	To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant	Patient characteristics restrictions, disease state restrictions	EMA	Yes
guanfacine hydrochloride	Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Intuniv must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.	INTUNIV™ is a selective alpha2A-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of INTUNIV™ is based on results of two 8 to 9 weekstudies in children and adolescents (14.1). Maintenance treatment has not been systematically evaluated, and patients who are continued on longer-term treatment require periodic reassessment	Previous therapy failure, alternative therapies inappropriate	EMA	Yes

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
iloprost	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms	Ventavis is indicated for the treatment of pulmonary hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved composite a composite endpoint consisting of exercise tolerance, symptoms, (NYHA Class), and lack of deterioration. Ventavis has not been adequately studied with concomitant use of other approved therapies for pulmonary arterial hypertension.	Severity of condition restriction	EMA	Yes
ivabradine hydrochloride	Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers	Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of betablockers or have a contraindication to beta-blocker use.	Different clinical scenario	N/A	No

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
prasugrel	Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).	Effient is a P2Y'2platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows: Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI)(1.1) Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI	Combination restriction	EMA	Yes
regadenoson	This medicinal product is for diagnostic use only. Rapiscan is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.	Lexiscan is a pharmacological stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.	Patient characteristics restrictions	EMA	Yes

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
selexipag	Uptravi is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease (see section 5.1).	UPTRAVI® is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.	Severity of condition restriction	FDA	Yes

*The indication was taken *vervatim* from the respective SmPC and label.

Table 3.8: Comparison and difference in indications of identified active ingredients

Active ingredient	EMA Approved Indication*	FDA Approved Indication*	Difference	Who effected the restriction?	Same clinical trials?
tolvaptan	Treatment of adult patients with hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH).	SAMSCA is a selective vasopressin V2-receptor antagonist indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [serum sodium < 125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure, cirrhosis, and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) (1). Important Limitations: • Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with SAMSCA (1). It has not been established that SAMSCA provides a symptomatic benefit to patients (1).	Patient characteristics restrictions, disease state restrictions	EMA/FDA	Yes

*The indication was taken *vervatim* from the respective SmPC and label.

3.7 Differences in dosage regimen

From the 22 products analysed (the different clinical scenario group were excluded), 2 products bivalirudin and ranolazine had differences in the authorised dosage regimen. For these two products, there was a difference in the date of approval of about 4 years and 3 years respectively between the two regulatory agencies.

3.8 Contraindications

From the 22 active ingredients (the different clinical scenario group were excluded) a total of 158 contraindications have been identified (Table 3.9). One hundred and five contraindications have been included in the product information by the EMA for all active ingredients while 53 contraindications have been included in the product label for all active ingredients by the FDA.

3.9 Fertility, Pregnancy & Breast-Feeding

From the 25 active ingredients (excluding irbesartan), there were eighteen products were in agreement regarding information for use during pregnancy. There were 7 cases with disagreement in the information for use during pregnancy. One case of disagreement each was found regarding fertility and breast-feeding respectively (Table 3.10).

3.10 Side-effects

Out of 21 products (the different clinical scenario group and irbesartan were excluded), a total of 571 side-effects have been reported in the product information by the EMA (Table 3.11). Four hundred and eighty-two side-effects have been reported in the approved label by the FDA.

Table 3.9: Comparison of the number of contraindications of identified active ingredients

Active Ingredient	Number of CI by EMA	Number of CI FDA
aliskiren	2	0
azilsartan	2	0
bivalirudin	4	2
bosentan	6	4
cangrelor	3	2
clopidogrel	4	2
colesevelam	2	2
dabigatran	7	4
edoxaban	7	4
fondaparinux	4	6
guanfacine	1	1
iloprost	7	0
prasugrel	4	2
ranolazone	5	4
regadenoson	5	2
rivaroxaban	5	2
sacubitril/valsartan	7	4
selexipag	7	0
telimisartan	5	1
ticagrelor	5	3
tolvaptan	8	5
vorapaxar	5	3
Total	**105**	**53**

CI= Contraindications

Table 3.10: Comparison of the information presented for Pregnancy, Fertility & Breast-Feeding

Active Ingredient	Same conclusions? (Pregnancy)	Same conclusions? (Fertility)	Same conclusions? (Breast-Feeding)	Notes
aliskiren	Yes	N/A	N/A	
apixaban	Yes	Yes	Yes	
azilsartan	Yes	N/A	N/A	
bivalirudin	Yes	N/A	Yes	
bosentan	Yes	N/A	Yes	
cangrelor	Yes	Yes	No	EMA: A reversible effect on fertility was observed in male rats treated with the active ingredient cangrelor
clopidogrel	Yes	N/A	Yes	
colesevelam	Yes	N/A	N/A	
dabigatran	Yes	N/A	Yes	
dronedarone	Yes	Yes	Yes	
edoxaban	No	Yes	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus

N/A= No Information available
Irbesartan not included as label was not identified

Table 3.10 is continued in page 78

Table 3.10b: Comparison of the information presented for Pregnancy, Fertility & Breast-Feeding

Active Ingredient	Same conclusions? (Pregnancy)	Same conclusions? (Fertility)	Same conclusions? (Breast-Feeding)	Notes
fondaparinux	Yes	N/A	Yes	
guanfacine	Yes	No	Yes	FDA label states that no toxicity while EMA causes toxicity in both pregnancy and fertility
iloprost	No	N/A	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus
ivabradine	No	N/A	Yes	FDA: No recommendations given;
prasugrel	Yes	Yes	Yes	
ranolazone	Yes	N/A	Yes	
regadenoson	Yes	Yes	Yes	
rivaroxaban	No	N/A	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus
sacubitril/valsartan	No	Yes	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus
selexipag	Yes	Yes	Yes	
telimisartan	No	N/A	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus,
ticagrelor	Yes	Yes	Yes	
tolvaptan	No	N/A	Yes	EMA: Contra-indicated FDA: Only if the potential benefit justifies the potential risk to the fetus
vorapaxar	Yes	Yes	Yes	More information presented by EMA that no studies conducted in humans regarding fertility

N/A= No Information available
Irbesartan not included as label was not identified

Table 3.11: Comparison of the number of side-effects included in the product information and label

Active Ingredient	Number of SE reported by EMA	Number of SE reported by FDA
aliskiren	4	13
azilsartan	9	11
bivalirudin	26	26
bosentan	15	13
cangrelor	43	6
clopidogrel	18	66
colesevelam	9	18
edoxaban	35	11
fondaparinux	26	27
guanfacine	50	36
iloprost	6	19
prasugrel	17	25
ranolazone	65	23
regadenoson	57	12
rivaroxaban	45	23
sacubitril/valsartan	23	10
selexipag	24	15
telimisartan	25	82
ticagrelor	38	18
tolvaptan	18	21
vorapaxar	16	7
Total	**571**	**482**

SE = Side-effects
Irbesartan not included as label was not identified

3.11 Comparison of Post-Authorisation Studies requirements

Table 3.12 shows that in 14 cases post-authorisation studies related to efficacy and safety tend to be required by both regulatory agencies. The European Medicines Agency tends to require more post-authorisation studies compared to the U.S Food and Drug Administration for the same product. The number of studies required may be different while other study requirements may be the same.

Table 3.12: Comparison of post-authorisation studies required by regulatory agencies

Name of product	PAS by EMA needed?	No. of PAS	PAR / PAC by FDA needed?	No. of PAR / PAC	Same?
aliskiren	Yes	4	Yes	3	Yes
azilsartan	Yes	1	Yes	3	No
bivalirudin	No	0	Yes	1	N/A
bosentan	Yes	2	Yes	2	No
cangrelor	Yes	1	No	0	N/A
clopidogrel	No	0	No	0	N/A
colesevelam	Yes	3	No	0	N/A
edoxaban	Yes	6	No	0	N/A
fondaparinux	No	0	Yes	1	N/A
guanfacine	Yes	7	Yes	6	No
iloprost	Yes	1	Yes	0	N/A
irbesartan	No	0	No	0	N/A
prasugrel	Yes	1	Yes	5	No
ranolazone	Yes	13	Yes	1	Yes
regadenoson	Yes	3	Yes	2	Yes
rivaroxaban	Yes	8	Yes	1	Yes
sacubitril/valsartan	Yes	5	Yes	1	No
selexipag	Yes	2	No	0	N/A
telimisartan	Yes	1	No	0	N/A
ticagrelor	Yes	12	No	0	N/A
tolvaptan	Yes	2	Yes	2	Yes
vorapaxar	Yes	1	Yes	1	No

N/A = Not Applicable
PAS = Post-Authorisation Study PAR = Post-Authorisation Recommendation
PAC =Post-Authorisation commitment

Chapter 4:

DISCUSSION

The comparison of medicinal product evaluation is discussed through the mapping of the European Public Assessment Report (EPAR) through the Day 80 (D80) Assessment Report template, the identification of medicinal product to be used for the study, the developed Collect and Compare Information (CCI) tool discussion, comparing the products with different outcomes, comparing products with different indications and comparing the product information. Post authorisation study requirements are discussed.

Changes in the European Public Assessment Report

The mapping of changes of the European Medicines Agency EPAR is particularly beneficial when it comes to the interpretation of results for this study. The information contained in the EPAR is not exhaustive. Some of the information which is considered during the evaluation may not be present in the EPAR, possibly since it does not form part of the document template. There may have been issues in the list of questions identified during the evaluation that may not be relevant for the patient or healthcare professionals and so such information may be left out of the EPAR since the EPAR is intended for the public.

The US Food & drug Administration (FDA) takes a different approach when publishing their evaluations and outcome. All the original documentation is made available to the public and no summary is uploaded with any reference to confidential information is blotted out. In view of this difference in the evaluation publishing, one cannot assume that one agency considers more aspects than the other based on the documents that are freely available.

From the mapping process of the EPAR, there were no additional scientific sections in the non-clinical and clinical sections of the overview. The added contents in the overview were the discussions and conclusions sections. A possible reason why such sections have been included in the report is to improve transparency by the European Medicines Agency (EMA) by including a justification why the product was authorised or refused with the particular conditions. The discussion section establishes a method of identifying the main components of the evaluation while linking the different elements together and how relevant such components are in the therapeutic context. The level of transparency allows a regulator to provide the public confidence and assurance in its processes through the publishing of information (Bonini et. al, 2014).

The discussion section present in the clinical efficacy section of the D80 overview, evolved from one subsection to five subsections to improve comprehensiveness. Another advantage of expanding the discussion section is that it is less likely to cause intra-individual differences in the assessment report. A rapporteur and co-rapporteur are chosen to evaluate and generate an assessment report for each novel product. Each expert would have a different style of writing and reporting which may lead to variations in the details included in the assessment report. The inclusion of structured subsections improves consistency in the reporting of information in the assessment report. A tabular overview of the clinical studies conducted was introduced highlighting all the clinical trials that have been submitted with the dossier. The use of tables to display all the studies involved is a method to ensure better understanding of the material used during the evaluation process.

The section related to benefit-risk had the most changes compared to other changes. Regulatory agencies such as the EMA analyse the benefit-risk balance of a medicinal product qualitatively and through expert opinions with no reference to quantitative methods (Curtin and Schulz, 2011). Such an evaluation in the benefit-risk is subjective. There was a shift from listing the benefits sections, risks sections and balance sections separately to the introduction of the therapeutic context of the benefit-risk balance. Expansion of the therapeutic context facilitates the understanding of the rationale for the decision taken especially since decisions are taken based on the intended use of the product. The expansion of the categories present within the benefit-risk assessment section improves consistency when reporting information.

The D80 guidances were used to identify changes in the content and scientific information that should be included in the assessment report and the EPAR. Analysis of the D80 guidances showed that no information was removed from the different versions and additional sections were included. The information included in the assessment report revolves around changes in regulations. The additional sections identified in the D80 guidances information regarding paediatrics and pharmacovigilance.

The paediatric regulation which came into force in the European Union on 26 January 2007 aimed to encourage the research and development of efficacious and safe paediatric medication and provide more information on their use, addressing the lack of authorisations and approvals of medicines for paediatric use (Turner et. al, 2014; Tomasi et. al, 2017).[28] Companies need to submit a paediatric investigation plan (PIP)

[28] European Medicines Agency [Online]. c2016 [cited 2018 Jan 14] Paediatric Regulation. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp

to the EMA's Paediatric Committee (PDCO) for each and every product, unless a waiver is granted (Tomasi et. al, 2017). The decision by the PDCO regarding the PIP is to be included in the assessment report.

In the pharmacovigilance information, D80 guidances emphasise the link between the non-clinical and clinical parts of the assessment report to the Risk Management Plan (RMP) section. The RMP gives a detailed account of pharmacovigilance activities and interventions intended to recognise, characterise, and manage risks related to a medicinal product (Götsch, 2015). The presence of information related the risks of product contribute to the identification of areas which need to be included in the RMP which ensures a better plan to assess the continued benefit-risk balance of the product.

The non-clinical guidance introduced further add-on information including the addition of tables with the possible intention to make the assessment report more understandable. In the clinical guidance, there is more reference to the paediatric populations as opposed to the non-clinical section which is not surprising considering that the clinical part of the assessment involves human subjects. Information about the elderly populations has been introduced. In 2011, the EMA developed a geriatric medicines strategy with the aim to ensure that the needs of the ageing population in the EU will be met, by taking into account the development and evaluation of new medicines.[29] The needs of the ageing population is achieved through the assurance of high quality medicines which are studied appropriately in the older population during both the pre and post-authorisation stages of the medicinal product life-cycle and through the availability of information for older people on the use of medicines. This additional information

[29] European Medicines Agency [Online]. c2016 [cited 2018 Jan 14] Medicines for older people. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000249.jsp

related to geriatric population may be the result of the EMA commitment to ensure high quality medicine for the elderly population.

The use of the EPAR, to collect information in relation to the evaluation method by the EMA, was justified due to the addition of information observed and no information removed between the D80 versions. The aims of the study were to compare the clinical and safety aspects of the products evaluated by the EMA and the FDA and clinical and safety information are not considered as commercially confidential. Such a conclusion to consider the EPAR as a tool for the study can be compared with a study conducted by Wai Yeen et. al. in 2014. The authors compared the summaries of the assessment reports from different regulatory agencies including the US FDA and the EMA specifically looking at benefit-risk section of the templates. The authors concluded in a similar manner that the templates are similar and differences between these reports are related to formatting differences.

Identification of medicinal products for the study

When the Anatomical, Therapeutic and Chemical (ATC) code is used to identify medicinal products for the study, it may be possible that the selected products would have therapeutic indications not related to the field of cardiology. When such cases arise, it could be in relation to the active ingredients' pharmacology which is related in one way or another to the cardiovascular system. From the sample of products analysed, the product which fits this criteria is Intuniv (guanfacine hydrochloride) which is used in attention deficit hyperactivity disorder (in both Europe and USA) but since the active ingredient is an alpha receptor agonist it falls within the C class of the ATC code classification system and thus was included in the sample of products for study.

Guanfacine has been initially authorised as an antihypertensive agent in the USA in 1986 and could be another reason why it is classified as a C class (Strange, 2008).

Following the filtering process using the ATC code and the exclusion criteria, resulted in a small sample of medicinal products for the study. The small sample is not considered as surprising since the objective of this study was to research on novel medicinal products and one area of specialisation. The overall process of bringing a novel medicinal product to the market is complex, time-consuming and expensive. Typically, the process can take an average of 10 to 12 years to complete and with costs up to €450 million (Tobin & Walsh, 2008). The sample used for the study considered acceptable since it takes considerable time and resources to introduce an innovative product.

During phase three of the study which involved matching with the FDA counterparts and which followed the ATC code filtering and exclusion criteria, two products were excluded from the study since the respective counterpart products were not traced. Reasons could be either because the application for the product was never submitted to the FDA or because the application was submitted to the FDA but the application was withdrawn or rejected.

FDA approval may have not been sought since the pharmaceutical company did not intend to market the product in the American region based on the particular marketing strategy employed (Alqahtani et. al, 2015). If approval was granted by the FDA but was refused or withdrawn, the FDA is not obliged to disclose information on drug applications which are withdrawn or refused prior to the conclusion of the evaluation

process or if refused after the evaluation (Asamoah and Sharfstein, 2010). Lack of transparency on regulatory decisions related to withdrawn or refused products is highly debated and is considered to deserve more future action (Asamoah & Sharfstein, 2010).

Collect and Compare Information Tool

Prior to the commencement of the study, the CCI tool developed for the study was validated using the method described by Lynn (1986) to establish whether the tool addresses the aim of the study and that it is fit for purpose.

The first part of Lynn's method is a Delphi technique where experts scale an item's relevance to the topic. The Delphi method offers some limitations mainly that it is a time consuming method since it incorporates a feedback mechanism whereby experts have to re-review the developed tool (Alumran et. al., 2012). The feedback mechanism was not incorporated into the validation process of the developed tool as the mentioned disadvantages were considered to create bias as experts may not be willing to re-take the validation process or else would not necessarily have the same level of alertness and keenness as the first time.

The main advantage of incorporating Lynn's method is the calculation of the content validity index (CVI). Content validity index is a method to verify whether an item in the proposed tool should be removed or retained. The advantage is that the decision is completely transparent and is not dependant on the decision of the investigator which may introduce bias. The four point Likert-scale was used to quantify content validity as a four point system is needed to calculate the content validity index (Lynn, 1986).

Introducing a five point Likert-scale would not have been beneficial as introducing a neutral point would make it difficult to calculate the CVI. A five point Likert-scale would create confusion amongst the experts as an item cannot be both relevant and not relevant at the same time and would create difficulty during the validation process.

The experts chosen needed to have experience in the field of regulatory affairs to ensure that the tool is validated correctly. Experts were selected from pharmaceutical companies and competent authorities. A number of changes took place following the validation process of the CCI tool but experts did not provide major areas for improvement or areas which have been omitted which is not surprising considering that the tool was developed using criteria from literature. The proposed changes by one or more experts were adopted as these were considered to have valid points and thus promote more towards improving the tool.

Evaluation outcomes between EMA and the FDA

Comparing the degree of agreements between the EMA and FDA from the perspective of evaluation outcomes (approvals and refusals) of medicinal products, there is a high degree of agreement between the two agencies. The current study utilised a very small sample and caution is needed when interpreting such information. It is still reassuring to note that there is an overall agreement from the twenty-seven cardiovascular-related new molecular entities used for the study which suggests that there is a similar degree of data interpretation, analysis and conclusions in this therapeutic field of study by both regulatory agencies.

The only product for which the assessment outcome of the two agencies differed was mipomersen sodium (Kynamro). The product application has been submitted to both the EMA and the FDA within one year from each other, both considered the active ingredient as being a new active ingredient in their respective territory and both applications had similar proposed indications. Both agencies identified similar safety concerns regarding the product. A potential reason for such a difference in the outcome may be related to the classification of the product. The FDA classified the product with an orphan designation while the EMA did not.

In the EU, an orphan designation is given to products intended for the prevention, diagnosis or treatment of life-threatening or chronically/seriously debilitating disorders. An orphan designation is given when the targeted condition of the medicinal product affects not more than five in ten thousand people in the EU or when the incentives provided are likely to ensure the marketing of the product in the Community and would generate sufficient return to justify the necessary investment (Giannuzzi et. al., 2017). In the US, an orphan drug is described as any drug intended to treat a disease or condition that affects less than 200,000 persons in the US (equivalent to 7.5 in 10,000 persons) or in some cases affects more than 200,000 individuals (Giannuzzi et. al., 2017). The definitions of orphan drugs are necessary to understand better the differences. One should notice that while the legislations and policies encouraging the development of such medicines are to some degree similar between the EU and the USA, they are not the same. The eligibilities for orphan designation slightly differ depending between the two based on the respective policies and legislation adopted by each area (Murakami & Narukawa, 2016). One main difference which is potentially relevant in this study with respect to Kynamro is the definition of what is considered as

a rare disease. The definition is mainly based on prevalence and is not universally defined the same in the EU and the USA and depends on the legislation adopted by each region or country (Franco, 2014).

Legislation differences play an important part in the decision making process of a medicinal product. In the case of Kyanmro, the decision to designate a product as an orphan is dependent on the legislation that has to be adopted by the respective agency. Since each agency is obliged to decide the designation based on the prevalence rate as defined in the legislation, the benefit-risk balance of the product can be shifted in either direction because of differences in the legislation and can impact the approval/refusal of the medicinal product.

Tiwari (2015) analysed the number of orphan designations and approvals by both the EMA and the FDA. Starting from the year 2000 (to reflect the date of implementation of EU legislation on orphan drugs). The FDA tended to have more designations and approvals of medication as orphan drugs compared to the EMA. Tiwari (2015) recommend that increased collaboration between agencies should take place to ensure a more streamlined, faster and harmonised process for the designation of orphan status.

The designation of orphan status is considered as a critical finding as the indication and so the medicinal product was approved by one of the two agencies. When one agency approves a product and another agency rejects the same product suggests that large patient groups may be deprived of such a treatment that is available in other territories and the fact that an indication approved by one agency and not by another represents a crucial concern from a public health perspective (Trotta et. al, 2011).

Between 1995 and 2008, twenty percent of oncology-related medicinal products were approved by either the FDA or the EMA, but not both indicating that such a discrepancy in the evaluation outcome like in the case of Kynamro is not an uncommon one (Howie et. al., 2013).

Comparing medicinal products with different indications

Differences in the indications of authorised products as approved by the EMA and the FDA have been identified. Two methods have been used to identify differences in the indication, through the use of the indication section of the product information and through the analysis of the product information as a whole document. The approach was adopted since not all the information regarding the use of the product may be necessarily available in the indications section of the product information. The reader would be required to review other sections of the product information in order to determine further details on the use of the product. Examples identified included products containing telmisartan, azilsartan medoxomil and aliskiren, which initially were considered to have a different indication from the FDA counterpart since the FDA allowed the use of other anti-hypertensives in conjunction with these products but the EMA counterpart no reference to other anti-hypertensives is found in the indication. Further examination of the posology showed that the EMA product could be used with other anti-hypertenives.

All products that have been removed during the second step of the indication comparison, were the result of the EMA including less details in the indication section of the SmPC. While definite conclusions cannot be made in view of the small sample

size of products being analysed and an even smaller number of products being removed from the second step, it can be observed that the approach of the EMA is to keep the indications as simple as possible and to include more details in the relevant sections of the SmPC.

The date of authorisation of the identified four products removed from step two of the indication comparison process, ranged from 1998 to 2015. There is a wide range between the products, indicating that there is no particular period when such a potential approach to keep the indication simple started to take place by the EMA. An alternative reasoning why such an approach took place could be in relation to the targeted condition, which for all four products is related to hypertension. Hypertension is an established condition and a number of products have been authorised to target the condition. It is possible that the system employed by the EMA took place to keep the various products including the identified four products similar to each other to avoid confusion between already authorised products.

It can be concluded that just reviewing the indication section of the SmPC is not sufficient to ensure the indication of a product. It is a must to review other relevant sections in order to ensure proper use of the product. In this sample of products, it was observed that the EMA included less details in the indication section and no product was identified were the FDA did the same. It is most likely related to the small sample of products analysed, which suggests that further research is required by employing a wider range of products and clinical fields to verify whether the FDA employs a similar approach.

It is suggested that when similar studies are conducted, such information regarding the extraction of indication from the SmPC needs to be taken into consideration when analysing differences in the approved indications between different agencies to ensure proper reporting of information. Section 4.2 - Posology and method of administration and section 4.4 - Special warnings and precautions for use, of the SmPC should be considered. Further studies in different fields could potentially identify other sections of the SmPC which can be used apart from those identified during the study.

Differences were observed between the indications approved by the EMA and the FDA which can have a huge impact on clinical practice as a difference in the wording of the indication can result in the inclusion or exclusion of certain patient groups (Trotta et. al., 2011). While both the EMA and the FDA made indication restrictions compared to the other, the EMA approved more products with restrictions compared to the FDA. It is suggested that the EMA may tend to be more conservative in its decision making processes compared to the FDA. Such an observation is in line with Tafuri et. al., (2010) where they analysed the possible use of restrictions by regulators specifically the EMA. Their data suggests that restricting the indications is quite a common practice used by the EMA. The indications proposed by the pharmaceutical industry tend to be wider than those approved by regulators. Following approval, the indications are widened again during subsequent extensions following further data submissions.

Trotta et. al (2011) conducted a similar study comparing the differences in indications between the EMA and the FDA of approved oncology related medicinal products. In the field of oncology, the EMA tended to be more restrictive in 54% of the indications being covered. In 22 of the 28 identified indications, the pivotal studies were the same

and despite the same studies, significant wording differences in the indications were identified. The results observed in the study are similar to Trotta et. al., (2011). The study explored a new therapeutic area contributing to current knowledge as was explored. Another study by Pappas et. al. (2009), focused on differences in approved indications by the EMA and the FDA of antimicrobials and identified both minor and major differences in twelve drugs out of thirteen.

All cases apart from those having a different clinical scenario submitted the same clinical trials to both agencies, yet differences in indications have been identified. In the majority of cases, the restrictions identified have been adopted by the agency to align the indication with the clinical trial conditions through evidence-based data and information. When indications become too specific, there is increased risk of widening the gap between regulators and real clinical practice (Trotta et. al., 2011).

The EMA and the FDA have effected restrictions in the indications for a medicinal product, suggesting that there are other factors and influences involved which effect the indications such as: general medical practice for the condition and re-imbursement procedures which could be different in the different territories.

Four cases were identified that had a different clinical scenario compared to its counterpart meaning that the approved indication by a regulatory agency was totally different from its counterpart. These included: apixaban, dabigatran etexilate mesilate, dronedarone and ivabradine hydrochloride. For example in the USA apixaban is authorised for use in non-valvular atrial fibrillation while in Europe, it is approved for elective hip or knee replacement surgery. The difference in the approved indications

may be attributed to the submission of different clinical trials to support the medicinal product application. A new potential factor which effects an indication is identified i.e. the influence of a pharmaceutical company. The influence of a pharmaceutical company differs from the other factors already identified, as the previous ones were all related to the decisions taken place by the regulatory agencies. It is the pharmaceutical company that submits an application to the regulatory agency and the contents of which is decided by the same company. It is the responsibility of the regulatory agency to verify whether the application is valid and scientifically sound for the targeted indication. The fact that different clinical trials have been submitted to different regulatory agencies suggests that the pharmaceutical company may employ different marketing strategies in different regions and so contributes to discrepancies in the indications.

Apixaban, dabigatran and ivabradine had wide differences in the date of approval compared to their counterpart. The difference was more than a one year difference compared to the counterpart. For ivabradine, there was a ten year difference. It is suggested that pharmaceutical companies may influence the availability of medicines as it is the company that submits the medicinal product application. Potential reasons for differences in the submission of applications could be that the company would like to gather experience about the product evaluation with one regulatory agency first then analyse the situation and proceed with other submissions in other territories. It could be the case that the company would like to gather marketing in one territory and see how the product fairs in practice. Competition by other pharmaceutical companies and differences in availability of products on the market could be the key reason why applications may not be submitted in parallel.

Differences in indications may result in ethical dilemmas by healthcare professionals as they need to abide with the indication as authorised by the respective authority. The indication included in the SmPC and label are legally binding and so the deviation from them and incorporating the indication of another regulatory agency may result in legal repercussions despite the purpose of such a deviation being for the benefit of the patient.

Access to treatment issues in different territories would result because of the decision of the pharmaceutical industry to not submit an application which may have several repercussions. Trotta et. al., (2011) argued that in countries where the product is not approved, there could be pressure by healthcare professionals, patients and support groups on regulatory agencies to introduce a product and such pressure could introduce and lead to biased decisions.

Restrictions of therapeutic indications are a regulatory tool with the intention of identifying the specific patient's population that may benefit the most from the proposed medicinal product (Tafuri et. al., 2010). Restrictions may fuel off-label use and prescribing, and on the long run, may potentially hinder the availability of formally approved indications and the investments in therapeutic innovation in general (Tafuri et. al., 2010). The issue of off-label use is only considered from a regulatory perspective if another country or territory approved the product or indication based on robust data (Trotta et. al., 2011).

Comparing product information between the EMA and the FDA

Differences in the dosage regimen have been observed in this study in only two products. Since two products had differences in the dosage regimen, this indicates that there tends to be more agreement between the regulatory agencies in the dosage regimen compared to indications. It was observed that for both products, bivalirudin and ranolazine there was a gap of over one year between the dates of authorisation between the two regulatory agencies indicating that time lag in the authorisation of a medicinal product may result in differences. It was observed that bivalirudin had a different indication from its counterpart, which may hint that there could be a link between a different indication and different dosage regimen. Ranolazine was not identified to have a different indication, which advocates that further studies would be required.

The EMA tends to include more contraindications than the FDA. In a small amount of cases, the EMA and the FDA agreed with each other. A trend was identified, where the FDA tends not to include the contraindication hypersensitivity to the active substances and excipients. It may be because such a contraindication could be obvious and straightforward. Another noteworthy area is that related to pregnancy and breastfeeding where the EMA tends to include such categories in contraindications. It is rarely observed for products approved by the FDA. There is an overall agreement between the two agencies in the information provided in the respective pregnancy sections. It applies to other areas including fertility and breast-feeding.

Out of the three sections related to pregnancy i.e. fertility, pregnancy and lactation, the pregnancy section had the most discrepancies in the conclusions adopted by the regulatory agencies. The majority of cases being that the EMA would contraindicate

the product use during pregnancy while the FDA would allow its use, only if the potential benefit justifies the potential risk to the foetus. In all the cases the agencies have agreed with the availability or lack of availability of studies related to all three pregnancy related areas. The EMA tends to be more cautious compared to the FDA. The FDA still make cautious choices but impression provides more freedom to healthcare professionals by allowing them to decide whether the medicinal product can be used on a case by case basis to cater for extreme rare cases that may occur. When a contraindication is stated by the EMA, the impression given would be to absolutely never use the product in any circumstance.

The fertility section had the least amount of differences as the EMA did not include such information in a number of cases. Previous templates for the product information did not require such information. For older products such information was not available. For relatively new ones such as Entresto (sacubitril/valsartan), such information is available meaning that for relatively new products and future ones, information on fertility would be available depending on the approval date of the product.

The EMA tends to be more proactive concerning products with potential teratogenic or harmful effects on the foetus. The EMA would include a section for women of child bearing potential indicating that the product may be used in this cohort under the condition that acceptable contraception is used as a cautionary measure. The FDA rarely mentions such a measure.

Regarding the adverse event reporting, it is evident that there are differences in the number of adverse events that are included in the label and the SmPC. The EMA tends

to express more adverse events than the FDA. The products which have been identified to have a different clinical scenario were excluded in this part of the study as a different clinical scenario may vary the frequency and the type of adverse events and would ensure that the side-effects identified are from the same clinical trials. Differences in side-effects may have been observed because the FDA tends to group a number of adverse events while the EMA tends to keep them specific. For example the FDA tends to group the side-effect bleeding into mild, moderate and severe while the EMA includes specific examples of bleeding such as epistaxis, haemorrhage, gingival bleeding. There is though some inconsistency identified in the reporting of side-effects and could be related to changes in the policy of how to report adverse events over time.

Post-authorisation study requirements between the EMA and the FDA

From this study, it was observed that both regulatory agencies required post-authorisation studies for nearly all products. It is important to note that the number of studies required by the two agencies varied, with the EMA tending to require more studies than the FDA. The difference observed during the comparison process maybe because the EMA tends to require missing information, such as information during pregnancy amongst others, while the FDA tends to require information on identified risks. The observation is difficult to fully ascertain, since the assessment reports and reviews are organised in different ways and provide different information.

One limitation of clinical trials during the first registration of the product is that the information on the product is limited especially from a safety perspective. A number of safety concerns may not be captured or fully captured, which introduces concern. The shortening of the clinical development may result in an unclear drug benefit/risk profile,

which would be difficult for regulators and may result in harm to the patient (Tafuri et. al., 2010). The product would require further studies following its approval. Such studies would be beneficial to identify the long term consequences of the product concerned and to identify potential missing information regarding the product which would not be identified during the initial stages of the registration process of the authorisation of the product.

There are cases where the studies requested by the different agencies were the same indicating that there is some alignment between the two. This suggests that there is a difference in how the benefit-risk balance of a given product is assessed by the two regulatory agencies.

Differences in the benefit-risk assessment of medicines between the EMA and the FDA can be attributed to the differences in the number of post-authorisation requirements. Different stakeholders have different perceptions due to different values and priorities which results in different evaluations and conclusions (Mt-Isa et. al., 2014). Difficulty results when multiple data sources are reported as it is very challenging to incorporate such sources due to varying quality, high heterogeneity and different biases (Mt-Isa et. al., 2014). This difficulty in analysing the benefit-risk balance could be why such differences and discrepancies arise. Differences in benefit-risk assessment is seen in a number of studies when in 1999 and 2000, the EMA distributed numerous safety announcements on Orlaam, for the treatment of opiate addiction, due to concerns for cardiac complications. Further studies linking Orlaam to such a side-effect led the EMA to withdraw the drug from the EU market in 2001. In contrast, the FDA maintained the

drug in its market, choosing instead to issue labelling revisions (Davis & Abraham, 2011)

Strengths

1. The centralised procedure was chosen instead of the national or decentralised procedure as a single marketing authorisation is given which is valid for all EU countries as well as Iceland, Liechtenstein, and Norway (European Economic Area countries) (Nagain & Ozama, 2016). The information on the product included in the product information is the same for all countries concerned. A harmonised assessment allows for easier and better comparison with the FDA counterpart since the product is authorised equally and in the same manner throughout the EEA. In the national, decentralised and mutual recognition procedures, the product may be authorised differently with different conditions in different countries making the comparison process more complex and introduces bias. Not all EEA countries may be involved in the evaluation of products authorised through the other routes apart from the centralised procedure. Since information as authorised by the FDA applies to all states it was deemed important to use the centralised route which can be considered as an equivalent to the FDA evaluation process.

2. Analysing products authorised through the centralised route provides the advantage that products evaluated through this route are considered to have a significant innovation and whose authorisation would be in the interest of the public at a European level amongst others. The latter points are criteria considered under the optional scope of the centralised procedure. While cardiovascular drugs do not fall under the compulsory scope of the centralised route, they can fall within the

optional scope especially since the products identified were/are considered novel agents at the time of submission of the application in the EU.

3. The developed validated CCI tool can be applied to other therapeutic areas and to other products which were not included in this study. Widening the therapeutic area and including further products would allow for a better understanding of the differences in the approaches of the respective evaluations.

Limitations & Recommendations

1. A small sample of medicinal products was used for the study. The small sample of medicinal products used makes generalisability difficult but does not mean that the results are not valid and/or robust within the chosen therapeutic field. Information from this kind of study is mainly qualitative and a number of patterns are identified. Any patterns and information identified can still be considered pertinent to add on to existing research. A small sample size may not capture a number of potential, unique and different discrepancies.

2. Emphasis took place on the efficacy and safety aspects of the medicinal to get a holistic approach. An application is also assessed for its quality which was not an aim within the study. Comparing quality aspects may be considered difficult to assess since quality information is considered to be the most confidential of the three aspects. Nevertheless quality information is still available in the respective reviews and can be subject to study. Information available in the public domain related to quality may not be sufficient to allow for a proper comparison.

3. The public assessment report while freely accessible may not include all the required information. Particularly of note, the final decision by the CHMP does not go into detail on what were the determining factors that led to the decision.

4. The study relied on the information available in the reviews published by the FDA and the EPARs published by the EMA. The disadvantage is that there are discrepancies of information which is publically available by the two agencies which may be the result of different structures and laws (Schroll et. al, 2015). The reasons as to why, is that these documents are not necessarily meant for research purposes (Schroll et. al, 2015). A head to head comparison is difficult at times. An example being the proposed indication by the applicant, which at certain periods of time are considered confidential by the FDA (and so are blotted out in the published reviews) but publically available by the EMA.

5. The comparison in the studied evaluations took place during the pre-licensing stage of the product with no reference to the post-licensing stages. There is potential for future research as it would help to get a more complete and holistic picture of how the lifecycles of the products in the different regions are effected. It is particularly important to products which have been identified to have a different clinical scenario. It is suggested that transfers, which are also post-authorisation procedures should be analysed as the transferring of a product from one legal entity to another can potentially affect the availability and access of a product as a different company may employ a different marketing strategy than the previous one. Updates to the marketing authorisations effecting the indications and product information should be studied. Withdrawals should also be considered as some discrepancies have been

found by Makuch and Shi (2014) were a discrepancy of Mylotarg and Thelin have been identified.

6. Comparisons took place between the EMA and the US FDA. A similar study can be replicated including other regulatory agencies such as the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) which is an equivalent regulatory agency, Swissmedic - the Swiss authority responsible for the authorisation and supervision of therapeutic products and Health Canada which reviews medicinal product applications to assess their safety, efficacy and quality.

7. An impact analysis may be conducted to identify how the discrepancies are affecting the use of the product in practice in the different regions. Further studies should be conducted to identify the clinical value of the differences together with the availability of alternative treatments in each health care system (Alqatani et. al, 2015). This recommendation would help to identify whether off-label use of medicinal products is taking place.

Conclusion

1. The European Public Assessment Report (EPAR) can be used to collect information about the evaluation of a medicinal product when such a product has been evaluated by the European Medicines Agency (EMA). There was consistency in the sections of the EPAR over the years.

2. Out of the twenty-seven cardiology-related medicinal products studied, one active ingredient namely mipomersen sodium was identified with a difference in the outcome between the EMA (refused) and the FDA (approved). The FDA designated the indication for the product as an orphan while the EMA did not. Differences in the legislation, related to orphan medicinal products between the EU and the USA may have led to the outcome difference and may be a contributing factor to why discrepancies related to the approvals or rejections of medicinal products may take place.

3. Fourteen out of the twenty-six authorised medicinal products had differences in the approved indications between the EMA and the FDA for the same medicinal product which can potentially affect patients' access to therapeutic options.

4. Four products had a different clinical scenario between the EMA and the FDA approved products as a result of different clinical trials submitted by the pharmaceutical industry. The pharmaceutical industry can also contribute to differences in the approval process.

5. Differences in the approved information for medicinal products by the EMA and the FDA, to be used by health care professionals, have been identified. Differences in the contraindications, pregnancy, lactation and fertility and side-effects have been found which could be the result of different mentality in the reporting of such information.

6. The number of post-authorisation study requirements related to safety and efficacy for the same products were different for all concerned products. The EMA tended to require more studies in most cases compared to the FDA (73 EMA vs 29 FDA).

7. It is recommended that through greater collaboration between the two regulatory agencies together with the pharmaceutical industry, such differences can be overcome and reduced. This is not envisioned to be a hurdle in this current age of globalisation and technology especially since the FDA and the EMA have been in contact to collaborate in other areas.

References

Abraham J, Reed T. Reshaping the carcinogenic risk assessment of medicines: international harmonisation for drug safety, industry/regulator efficiency or both? Social Science & Medicine. 2003;57:195–204.

Agius R. Evolvement of EU Regulations on Innovative Medicines. [Doctorate in Pharmacy Dissertation]. Msida: Department of Pharmacy University of Malta; 2017.

Alqahtani S, Seoane-Vazquez E, Rodriguez-Monguio R and Eguale T. Priority review drugs approved by the FDA and the EMA: time for international regulatory harmonisation of pharmaceuticals? Pharmacoepidemiology and drug safety. 2015;24: 709–715.

Alumrana A, Houa X-A, Hursta C. Validity and reliability of instruments designed to measure factors influencing the overuse of antibiotics. Journal of Infection and Public Health. 2012;5:221—232.

Arif SA, Bilfaqi Z. Drug approval processes: A case study of rivaroxaban. Arch Pharma Pract. 2013;4:186-189.

Asamoah AK, Sharfstein JM. Transparency at the Food and Drug Administration. N Engl J Med. 2010;362:2341–2343.

Avorn J. Two centuries of assessing drug risks. New English Journal of Medicine 2012; 367(3):193–197.

Bellanti F, van Wijk RC, Danhof M, Della Pasqua O. Integration of PKPD relationships into benefit-risk analysis. Br J Clin Pharmacol. 2015 Nov;80(5):979-991.

Berlin RJ. Examination of the Relationship Between Oncology Drug Labeling Revision Frequency and FDA Product Categorization. American Journal of Public Health. 2009 Sept; 99(9):1693-1698.

Berntgen M, Gourvil A, Pavlovic M, Goettsch W, Eichler HG, Kristensen FB. Improving the contribution of regulatory assessment reports to health technology

assessments--a collaboration between the European Medicines Agency and the European network for Health Technology Assessment. Value Health. 2014 Jul;17(5):634-641.

Boucaud-Maitre D, Altman JJ. Do the EMA accelerated assessment procedure and the FDA priority review ensure a therapeutic added value? 2006-2015: a cohort study. Eur J Clin Pharmacol. 2016 Oct;72(10):1275-1281.

Bonini S, Eichler HG, Wathion N, Rasi G. Transparency and the European Medicines Agency--sharing of clinical trial data. N Engl J Med. 2014 Dec 25;371(26):2452-2455.

Branch SK, Agranat I. "New Drug" Designations for New Therapeutic Entities: New Active Substance, New Chemical Entity, New Biological Entity, New Molecular Entity. J Med Chem. 2014 Nov 13;57(21):8729-8765.

Callréus T, Schneider CK. The emergence of regulatory science in pharmaceutical medicine. Pharmaceutical Medicine 2013;27(6):345-351.

Ciociola AA, Cohen LB, Kulkarni P. How drugs are developed and approved by the FDA: current process and future directions. Am J Gastroenterol. 2014 May;109(5):620-623.

Chen F-S and Jiang Z-R. Prediction of drug's Anatomical Therapeutic Chemical (ATC) code by integrating drug–domain network. Journal of Biomedical Informatics. 2015;58: 80–88.

Cohen J, Faden L, Predaris S, Young B. Patient access to pharmaceuticals: an international comparison. Eur J Health Econ. 2007 Sep;8(3):253-266.

Curtin F and Schulz P. Assessing the benefit: risk ratio of a drug--randomized and naturalistic evidence. Dialogues Clin Neurosci. 2011;13(2):183-190.

Davis C & Abraham J. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation. 2011;13(5):413-431.

DeVon HA, Block ME, Moyle-Wright P, Ernst DM, Hayden SJ, Lazzara DJ, et. al. A Psychometric Toolbox for Testing Validity and Reliability. Journal of Nursing Scholarship. 2007;39(2):155-164.

Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory review of novel therapeutics – comparison of three regulatory agencies. N Engl J Med. 2012;366:2284–2293.

Downing NS, Zhang AD, Ross JS. Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011–2015. The new England journal of medicine. 2017;376:1386-1387.

Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov. 2008 Oct;7(10):818-826.

Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, König F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov. 2010 Apr;9(4):277-291.

Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens H, Rowland M, Schneider CK, Bloechl-Daum B. Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response. Nat Rev Drug Discov. 2011 Jul 1;10(7):495-506.

Franco P. Orphan drugs: the regulatory environment. Drug Discov Today. 2013;18(3-4):163–172.

Garrett M. Fostering collaboration between regulatory agencies. Regulatory Rapporteur 2011;8(5).

Genazzani AA, Biggio G, Caputi AP, Tacca MD, Drago F, Fantozzi G et. al. Biosimilar drugs: concerns and opportunities. BioDrugs. 2007;21(6):351-56.

Geigert J. The Challenge of CMC Regulatory Compliance for Biopharmaceuticals and Other Biologics. 2nd ed. New York. Springer; 2013.

Giannuzzi V, Conte R, Landi A, Ottomano SA, Bonifazi D, Baiardi P, Bonifazi F, Ceci A. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. Orphanet J Rare Dis. 2017 Apr 3;12(1):64.

Goodsaid F. Challenges of biomarkers in drug discovery and development. Expert Opin Drug Discov 2012;7(6):457–461.

Götsch S. A shot at demystifying the risk management plan for medical writers. Medical Writing 2015;24(2):72-76.

Haynes S.N., Richard D.C.S., Kubany E.S. Content Validity in Psychological Assessment: A Functional Approach to Concepts and Methods. Psychological Assessment. 1995 Sept;7(3):238 – 247.

Hirako M, McAuslane N, Salek S, Anderson C and Walker S. A comparison of the drug review process at five international regulatory agencies. Drug Information Journal. 2007;41(3):291-308.

Howie LJ, Hirsch BR and Abernethy AP. A Comparison of FDA and EMA Drug Approval: Implications for Drug Development and Cost of Care. Oncology (Williston Park). 2013;27(12):1198-1200.

Johannesen L, Vicente J, Gray RA, Galeotti L, Loring Z, Garnett CE, Florian J, Ugander M, Stockbridge N, Strauss DG. Improving the assessment of heart toxicity for all new drugs through translational regulatory science. Clin Pharmacol Ther. 2014; 95(5):501-508.

Jordan D. An overview of the Common Technical Document (CTD) regulatory dossier. Medical Writing. 2014;23(2):101-105.

Kazi AM, Khalid W. Questionnaire designing and validation. J Pak Med Assoc. 2012 May;62(5):514 – 516.

Kim JH, Scialli AR. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. TOXICOLOGICAL SCIENCES. 2011;122(1):1–6.

Kohler M. Regulatory pathways in the European Union. MAbs. 2011 May-Jun; 3(3): 241–242.

Kurz X. Advancing regulatory science, advancing regulatory practice. Pharmacoepidemiol Drug Saf 2017;26(6):722-726.

Li E, Ramanan S, Green L. Pharmacist substitution of biological products: Issues and considerations. Journal of Managed Care & Specialty Pharmacy. 2015;21(7):532-9.

Lis Y, Roberts MH, Kamble S, J Guo J, Raisch DW. Comparisons of Food and Drug Administration and European Medicines Agency risk management implementation for recent pharmaceutical approvals: report of the International Society for Pharmacoeconomics and Outcomes Research risk benefit management working group. Value Health. 2012;15(8):1108–1118.

Luigetti R, Bachmann P, Cooke E, Salmonson T. Collaboration, not competition: developing new reliance models. WHO Drug Information 2016;30(4):558-566.

Lumpkin MM, Eichler HG, Breckenridge A, Hamburg MA, Lönngren T, Woods K. Advancing the science of medicines regulation: the role of the 21st-century medicines regulator. Clin Pharmacol Ther. 2012 Oct Sept 5;92(4):486-93.

Lynn MR. Determination and quantification of content validity. Nursing Research. 1986;35:382-5.

Makuch RW, Shi R. Comparison of Drug Approvals in Europe Versus the United States: An Analysis of Discrepancies Between Drug Products Reviewed by EMA and FDA. Therapeutic Innovation & Regulatory Science. 2014;48(3):362-366.

Martinalbo J, Bowen D, Camarero J, Chapelin M, Démolis P, Foggi P, Jonsson B, Llinares J, Moreau A, O'Connor D, Oliveira J, Vamvakas S, Pignatti F. Early market access of cancer drugs in the EU. Ann Oncol. 2016 Jan;27(1):96-105.

Mason A, Drummond M, Ramsey S, Campbell J, Raisch D. Comparison of anticancer drug coverage decisions in the United States and United Kingdom: does the evidence support the rhetoric? J Clin Oncol 2010;28:3234–3238.

McAuslane N, Leong J, Liberti L, Walker S. The Benefit-Risk Assessment of Medicines Experience of a Consortium of Medium-Sized Regulatory Authorities. Therapeutic Innovation & Regulatory Science. 2017;51(5):635-644.

Milne CP, Mittra J, Kojima N, Sugiyama D, Awatin J & Simmons G. Prospects for Harmonising Regulatory Science Programs in Europe, Japan, and the United States to Advance Regenerative Medicine. Therapeutic Innovation & Regulatory Science. 2016;50(6):724-733.

Mitra G & Schiff R, Fundamentals of EU Regulatory Affairs, 6th Edition. Regulatory Affairs Professionals Society; 2012.

Mt-Isa S, Hallgreen CE, Wang N, Callréus T, Genov G, Hirsch I, et. al. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiol Drug Saf. 2014 Jul;23(7):667-678.

Murakami M, Narukawa M. Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. Drug Discov Today. 2016;21(4):544–549.

Nagai S, Ozawa K. Regulatory approval pathways for anticancer drugs in Japan, the EU and the US. Int J Hematol. 2016; 104(1):73.

Ohlstein EH. The grand challenges in cardiovascular drug discovery and development. Front. Pharmacol. 2010; 1(125):1-2.

Paine MF. Therapeutic disasters that hastened safety testing of new drugs. Clinical Pharmacology & Therapeutics. 2017;101(4):430-434.

Papathanasiou P, Brassart L, Blake P, Hart A, Whitbread L, Pembrey R, Kieffer J. Transparency in drug regulation: public assessment reports in Europe and Australia. Drug Discov Today. 2016 Nov;21(11):1806-1813.

Pappas G, Ierodiakonou V, Falagas ME. Lost in translation: differences in antimicrobial indication approval policies between the United States and Europe. Clin Ther. 2009 Jul;31(7):1595-603.

Patel M, Miller MA. Impact of regulatory science on global public health. The Kaohsiung Journal of Medical Sciences. 2012;28(7):S5-9.

Rago L, Santaso B. Drug Regulation: History, Present and Future. In: van Boxtel C.J., Santoso B. and Edwards I.R., editors. Drug Benefits and Risks: International Textbook of Clinical Pharmacology. 2nd edition. IOS Press and Uppsala Monitoring Centre; 2008 p. 65-77.

Reggi V. Medicines regulatory harmonisation: international collaboration as a key to improve public health. Med Access. 2017;1(1):e2-e5.

Roberts SA, Allen JD, Sigal EV. Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe. Health Aff (Millwood). 2011;30:1375–1381.

Roden DM, Temple R. The US Food and Drug Administration Cardiorenal Advisory Panel and the Drug Approval Process. Circulation. 2005;111:1697-1702.

Schroll JB, Abdel-Sattar M, Bero. The Food and Drug Administration reports provided more data but were more difficult to use than the European Medicines Agency reports. J Clin Epidemiol. 2015 Jan;68(1):102-7.

Singh J. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Journal of Pharmacology & Pharmacotherapeutics. 2015;6(3):185-187.

Shah RR, Roberts SA, Shah DR. A fresh perspective on comparing the FDA and the CHMP/EMA: Approval of antineoplastic tyrosine kinase inhibitors. Br J Clin Pharmacol. 2013;76(3):396-411.

Smith F. Research Methods in Pharmacy Practice. London: Pharmaceutical Press; 2002.

Smith F. Conducting Your Pharmacy Practice Research Project. 2nd ed. London: Pharmaceutical Press; 2010.

Sifuentes MM, Giuffrida A. Drug Review Differences across the United States and the European Union. Pharmaceut Reg Affairs. 2015;4:e156.

Skerritt J, Cesar de Moura Oliveira J, Arora A, Rasi G, Rys A, O'Mahony P et. al. The International Coalition of Medicines Regulatory Authorities (ICMRA). WHO Drug Information. 2015;29(1):3-6.

Spindler P, Bach KF, Schmiegelow M, Bedlington N, Eichler HG. Innovation of Medical Products: The Evolution of Regulatory Science, Research, and Education. Therapeutic Innovation & Regulatory Science. 2016;50(1):44-48.

Strange BC. Once-daily treatment of ADHD with guanfacine: patient implications. Neuropsychiatr Dis Treat. 2008;4(3):499–506.

Tafuri G, Leufkens HG, Laing R, Trotta F. Therapeutic indications in oncology: emerging features and regulatory dynamics. Eur J Cancer. 2010 Feb;46(3):471-475.

Tafuri G, Stolk P, Trotta F, Putzeist M, Leufkens HG, Laing RO et. al. How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers' views. Annals of Oncology. 2014;25:265–269.

Tiwari J. Navigating through orphan medicinal product regulations in EU and US--similarities and differences. Regul Toxicol Pharmacol. 2015 Feb;71(1):63-67.
Tobin JJ, Walsh G. Medical Product Regulatory Affairs Pharmaceuticals, Diagnostics, Medical Devices. Germany: Wiley-VCH. 2008.

Tomasi PA, Egger GF, Pallidis C, Saint-Raymond A. Enabling Development of Paediatric Medicines in Europe: 10 Years of the EU Paediatric Regulation. Paediatr Drugs. 2017 Dec;19(6):505-513.

Trotta F, Leufkens HG, Schellens HM, Laing R, Tafuri G. Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice. J Clin Oncol 2011;29:2266-2272.

Turner MA, Catapano M, Hirschfeld S, Giaquinto C; Global Research in Paediatrics. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev 2014 Jun;73:2-13.

Pizzuto M. Compliance and medication problems in chronic conditions [MSc Dissertation]. Msida: Department of Pharmacy University of Malta; 2010.

Vogel AM. Hybrid or Mixed Marketing Authorisation Application in the European Union: Not a Trivial Decision in New Development Programs for Established Drugs. Drug Information Journal. 2012;00(0):1-6.

Zineh I, Woodcock J. Clinical Pharmacology and the Catalysis of Regulatory Science: Opportunities for the Advancement of Drug Development and Evaluation. Clinical pharmacology & Therapeutics. 2013; 93(6):515–525.

Zulfikari S, Sučić AF, Meštrović K, Barbarić MP, Mandarić V, Zorić N et. al. Generic Medicines in Croatia--Regulatory Aspects and Statistics. Coll Antropol. 2015 Jun;39(2):363-370.

APPENDICES

APPENDIX 1

Name of Active Ingredient:

	Europe	United States of America
Name of the product		
Marketing Authorisation Holder		
Outcome (Approved/ Rejected)		
Number of indications approved		
Proposed indication/s by applicant		
Approved Indication/s[a]		
Normal/Priority Review		
Number of dosage forms authorised/intended to be authorised		
Current status (Authorised/Withdrawn)		

[a] Is the indication in the EU the same as that of the USA? Y☐N☐

(This should be repeated for each and every indication in the event that more than one indication has been approved. Use the below to appropriately determine this)

If the indication, has either one or more of the following, compared to the other indication, the compared indications are considered different.

a) Restriction of use - defined as when an agency limited the use of the drug to any of the following:
   Disease state ☐
   Previous Therapy Failure (when target not reached or compliance issues developed) ☐
   Alternative Therapies Inappropriate to use ☐
   Monotherapy or combination restrictions ☐ Other _____

b) The product is used in a totally different clinical scenario ☐

If the indication is different and a restriction of use is present, which regulatory agency included more restrictions? EMA ☐ FDA ☐

1) Administrative Information

	Europe	United States of America
Date of submission of the application		
Date of CHMP opinion		N/A
Date of approval/rejection of the product		
Legal basis of the product		
Any scientific advice?		
Has the product been licensed / marketed in another country prior to submission of the application?		

Additional Notes (as applicable):

Note: When “information” is mentioned throughout this document, reference to scientific data is referred.

2) Non-clinical Information

2.1) Pharmacology

2.1.1) Primary Pharmacodynamics

To include relevant information from the EPAR

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐
If Yes, who required a commitment EMA ☐ FDA ☐ Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.1.2) Secondary Pharmacodynamics

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐ Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.1.3) Safety Pharmacology

a) Has all the information presented above been included in the FDA review? Y☐N☐
   i) If, Yes, what factors were considered important (if possible)?
   EMA FDA

   ii) If, No, any possible reason as to why? Y☐N☐
   If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
   i) If Yes, include the additional information

   ii) Why was the additional information included (if available)?

   iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
   If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐
   i) If No, include reasons as to why

   ii) If No, has this effected the final decision to authorise/reject the product?
   Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐
   i) If Yes, who required a commitment EMA ☐ FDA ☐
   Both ☐

   Include the commitment/s and rationale/s
   EMA FDA

2.1.4) Pharmacodynamic Drug Interactions

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2) Pharmacokinetics

2.2.1) Analytical Methods and Validation Reports

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.2) Absorption

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.3) Distribution

a) Has all the information presented above been included in the FDA review? Y☐N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information?? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.4) Metabolism

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.5) Excretion

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.6) Pharmacokinetic Drug interactions (non-clinical)

a) Has all the information presented above been included in the FDA review? Y☐N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.2.7) Other Pharmacological Studies

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3) Toxicology

2.3.1) Single dose toxicity

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.2) Repeat-dose toxicity

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.3) Genotoxicity

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.4) Carcinogenicity

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.5) Reproductive and Developmental Toxicity

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.6) Local Tolerance

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

2.3.7) Other Studies (as applicable)

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3) Clinical Information

3.1) Product Development Rationale

3.1.1) Pharmacological Class of the medicinal product

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.1.2) The targeted indication

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.1.3) Clinical development programme

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

ii) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.2) Biopharmaceutics

Information related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) such as dosage form/strength, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food).

Note: For each parameter mentioned, repeat sections a to d.

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.3) Clinical Pharmacology

3.3.1) Pharmacokinetics

To include information in healthy subjects, patients, and special populations; PK related to intrinsic factors and to extrinsic factors; rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including genetic polymorphism effects and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.

Note: For each parameter mentioned, repeat sections a to d.

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

iii) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.3.2) Pharmacodynamics

To include information regarding the mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favourable and unfavourable pharmacodynamics effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.

Note: For each parameter mentioned, repeat sections a to d.

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.3.3) Other information

To include information on the interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies as applicable.

a) Has all the information presented above been included in the FDA review? Y☐N☐
   i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

   ii) If, No, any possible reason as to why? Y☐N☐
   If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
   i) If Yes, include the additional information

   ii) Why was the additional information included (if available)?

   iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
   If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐
   i) If No, include reasons as to why

   ii) If No, has this effected the final decision to authorise/reject the product?
   Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐
   i) If Yes, who required a commitment EMA ☐ FDA ☐
   Both ☐

   Include the commitment/s and rationale/s

EMA	FDA

3.4) Efficacy

Information regarding the clinical data pertinent to the efficacy of the medicinal product in the intended population. Those studies deemed relevant for evaluation of efficacy should be included, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

For each of the studies, include the following (as applicable):

- Features of the patient populations, including demographic features, disease stage, any other potentially important covariates, patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7), differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing.

- Implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified, validation of any scales used should be included.

- For non-inferiority trials, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).

- Statistical methods and any issues that could affect the interpretation of the study results.

- Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.

- Observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).

- Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

- For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.

- Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.

- The clinical relevance of the magnitude of the observed effects.

- If surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.

- Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

a) Have the same studies been submitted? Y☐N☐
If Yes, refer to point b

Note: For each parameter mentioned, repeat sections b to e.

b) Has all the information presented above been included in the FDA review? Y☐N☐
   i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

   ii) If, No, any possible reason as to why? Y☐N☐
   If Yes, include reasons

c) Was more information presented in the FDA counterpart? Y☐N☐
   i) If Yes, include the additional information

   ii) Why was the additional information included (if available)?

   iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
   If Yes, include the rationale

d) Is there overall agreement in this section between the two reports? Y☐N☐
   i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

e) Where any commitments decided upon (relevant to this section)? Y☐N☐

iv) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5) Safety

3.5.1 Adverse effects characteristic of the pharmacological class and their monitoring.

a) Has all the information presented above been included in the FDA review? Y☐ N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐ Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.2 Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.3 Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use.

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.4 The nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.5 Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.6 Serious adverse events (number and frequency) including those that resulted in discontinuation or dose modification

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.7 Similarities and differences in results among studies, and their effect upon the interpretation of the safety data.

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.8 Differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.9 Relation of adverse events to dose, dose regimen, and treatment duration.

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.10 Long-term safety (E1a)

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.11 Methods to prevent, mitigate, or manage adverse events

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.12 Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues

e) Has all the information presented above been included in the FDA review? Y ☒ N ☐

iii) If, Yes, what factors were considered important (if possible)?

EMA	FDA

iv) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

f) Was more information presented in the FDA counterpart? Y☐N☐

iv) If Yes, include the additional information

v) Why was the additional information included (if available)?

vi) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

g) Is there overall agreement in this section between the two reports? Y☐N☐

iii) If No, include reasons as to why

iv) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

h) Where any commitments decided upon (relevant to this section)? Y☐N☐

ii) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.13 World-wide marketing experience. The following should be briefly discussed:

- **the extent of the world-wide experience,**
- **any new or different safety issues identified,**
- **any regulatory actions related to safety.**

a) Has all the information presented above been included in the FDA review? Y ☒ N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

3.5.14 Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

4) Benefit Risk Balance

a) Has all the information presented above been included in the FDA review? Y☐N ☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

5) Risk Management Plans & Risk Evaluation and Mitigation Strategies

Note: Information on Risk Management Plans for centralised products has been made available in summary form starting from March 2014. RMPs for other centralised products before this date should be also included in the EPAR.

In EMA, RMPs have been introduced in 2005 following new pharmacovigilance regulation

In FDA, REMS have been introduced in 2007 and unlike the EMA counterpart, REMS are not routinely required.

Therefore if either one is not publicly available, comparison cannot be undertaken and this section should be left out.

5.1 Summary regarding the important risks of the medicine and how the risks are managed

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

5.2 Summary of any safety information that is missing and needs to be collected

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

5.3 Any additional measures to ensure safe use that are required as part of the licensing of the medicine

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product? Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

5.4 A list of any planned studies to provide more information on the safety of the medicine

a) Has all the information presented above been included in the FDA review? Y☐N☐

i) If, Yes, what factors were considered important (if possible)?

EMA	FDA

ii) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

iii) Was this additional information considered pertinent to the decision making process compared to the other information? Y☐N☐
If Yes, include the rationale

c) Is there overall agreement in this section between the two reports? Y☐N☐

i) If No, include reasons as to why

ii) If No, has this effected the final decision to authorise/reject the product?
Y☐N☐

d) Where any commitments decided upon (relevant to this section)? Y☐N☐

i) If Yes, who required a commitment EMA ☐ FDA ☐
Both ☐

Include the commitment/s and rationale/s

EMA	FDA

6) Information to Health Care professionals

For this section, the "SmPC (Summary of Product Characteristics) is to be compared with its American counterpart the "Label".

6.1 Posology and method of administration

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐
i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.2 Contraindications

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐
i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.3 Special warnings and precautions for use

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐

i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.4 Interaction with other medicinal products and other forms of interaction

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐

i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.5 Fertility, pregnancy and lactation

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐
i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.6 Effects on ability to drive and use machines

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐
i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐
i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.7 Undesirable effects

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐

i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

6.8 Overdose

EMA	United States of America

a) Has all the information presented above been included in the FDA counterpart?
Y☐N☐

i) If, No, any possible reason as to why? Y☐N☐
If Yes, include reasons

b) Was more information presented in the FDA counterpart? Y☐N☐

i) If Yes, include the additional information

ii) Why was the additional information included (if available)?

APPENDIX 2

To whom it may concern,

I am a University student currently reading for a Doctorate in Pharmacy (PharmD) degree. As part of my postgraduate study, I am currently working on a dissertation entitled 'Assessment of medicinal products: A comparative study between Europe and United States of America'. This study is being done under the supervision of:

Professor Anthony Seraccino Inglott (as supervisor)
Dr. Nicolette Sammut Bartolo (as co-supervisor)

This study aims to compare the evaluations of medicinal products conducted by the regulatory agencies; the European Medicines Agency and the US food and Drug Administration. The information differences and the factors used in the decision making process will be highlighted. A checklist was developed as part of the study to help the investigator collect and compare the information and allows for a better detection of how the decision process took place and identifies what factors were considered.

You are kindly invited to take part in the validation of the developed data collection tool.

Procedure for the study

A checklist was developed to help the investigator collect and compare the required information between assessment reports and reviews. This facilitates the assessment analysis of the decision process took place and what factors were used for the conclusion. The principle of using a checklist ensures that a proper comparison is done by reducing or minimising bias by the investigator. There is also added advantage that it promotes harmonisation, ensures reproducibility and reduces intraindividual variations in the comparison process between one product and another.

The checklist consists of six sections. Section 1 collects administrative information such as legal status, date of submission, date of approval and rejection. Section 2 and section 3 include the essential information regarding the non-clinical and clinical information respectively. Section 4 is an overview of the benefit-risk analysis. Section 5 addresses the risk minimisation plan and risk evaluation and mitigation strategies and section 6 covers the product information.

The content included in sections 2 and 3 reflects the criteria as listed on the "notice to applicants guideline on the content of a dossier[30]" which includes details to applicants on how the backbone of the dossier should be constructed for European applications. Information on section 5 was taken from the "Questions and answers on the risk management plan (RMP) summary"[31] issued by the EMA. Regarding section 6, was created using the information found in the "Quality Review of Documents (QRD) Product Information template" [32] (document which highlights how the product

[30] European Commision [Internet]. [cited 2017 Mar 25] Vol 2: Notice to Applicants Human; Available from URL: https://ec.europa.eu/health/documents/eudralex/vol-2_en

[31] European Medicines Agency [Internet]. [cited 2017 Jul 23] Questions and answers on the risk management plan (RMP) summary; Available from URL: www.ema.europa.eu/docs/en_GB/document_library/Other/.../WC500166101.pdf

[32] European Medicines Agency [Internet]. [cited 2017 Jul 23QRD product-information annotated template (English) version 10; Available from URL:

information should be constructed). The information found on the SmPC was used in the checklist. This section was included as the product information reflect the evaluation conducted by the regulatory agency. The contents in the checklist are therefore standard sections and sub-sections.

Contact Details

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E-mail: matthew.camilleri.10@um.edu.mt

Finally I would like to thank you for your time.

http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf

Content Validity

Please rate the following:

How relevant is the ‘Name of the product’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Marketing Authorisation Holder’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Outcome (Approved/ Rejected)’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Number of indications approved’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Proposed indication/s by applicant’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Approved Indication/s[a]’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Normal/Priority Review’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Number of dosage forms authorised/intended to be authorised’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

Are there any other criteria which in your opinion should be included but weren’t mentioned?
If Yes, kindly include it below

_____

_____

1) Regarding "Administrative Information" section

How relevant is the 'Date of submission of the application' in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the 'Date of CHMP opinion' in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the 'Date of approval/rejection of the product' in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Legal basis of the product’ statement in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the ‘Any scientific advice took place with the respective authority?’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the title ‘Has the product been licensed / marketed in another country prior to submission of the application?’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

How relevant is the title ‘Additional Notes (as applicable):’ in this context?

Not Relevant	Item requires considerable revision to be relevant	Relevant but needs minor revision	Very Relevant
1	2	3	4

If 2 or 3, please state what aspect should be changed.

_____

_____

2) Regarding the rest of the checklist

1 = NOT RELEVANT 2 = ITEM REQUIRES CONIDERABLE REVISION TO BE RELEVANT 3 = RELEVANT BUT NEEDS SOME REVISION 4 = VERY RELEVANT

1) Regarding the 'Primary Pharmacodynamics' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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_____

_____

_____

2) Regarding the 'Secondary Pharmacodynamics' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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_____

3) Regarding the 'Safety Pharmacology' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

_____

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4) Regarding the 'Pharmacodynamic Drug Interactions' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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_____

5) Regarding the 'Analytical Methods and Validation Reports' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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6) Regarding the 'Absorption' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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7) Regarding the 'Distribution' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

_____

_____

_____

8) Regarding the 'Metabolism' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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9) Regarding the 'Excretion' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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10) Regarding the 'Pharmacokinetic Drug interactions (non-clinical)' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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11) Regarding the 'Other Pharmacological Studies' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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12) Regarding the 'Single dose toxicity' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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13) Regarding the 'Repeat-dose toxicity' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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14) Regarding the 'Genotoxicity' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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15) Regarding the 'Carcinogenicity' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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16) Regarding the 'Reproductive and Developmental Toxicity' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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17) Regarding the 'Local Tolerance' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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18) Regarding the 'Other Studies (as applicable)' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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19) Regarding the 'Pharmacological Class of the medicinal product' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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20) Regarding the 'The targeted indication' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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21) Regarding the 'Clinical development programme' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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22) Regarding the 'Biopharmaceutics' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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23) Regarding the 'Pharmacokinetics' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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24) Regarding the 'Pharmacodynamics' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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25) Regarding the 'Other information' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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26) Regarding the 'Efficacy' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question e)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question e) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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27) Regarding the 'Adverse effects characteristic of the pharmacological class and their monitoring' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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28) Regarding the 'Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation)' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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29) Regarding the 'Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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30) Regarding the 'The nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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31) Regarding the 'Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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32) Regarding the 'Serious adverse events (number and frequency) including those that resulted in discontinuation or dose modification' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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33) Regarding the 'Similarities and differences in results among studies, and their effect upon the interpretation of the safety data' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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34) Regarding the 'Differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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35) Regarding the 'Relation of adverse events to dose, dose regimen, and treatment duration' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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36) Regarding the 'Long-term safety (E1a)' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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38) Regarding the 'Methods to prevent, mitigate, or manage adverse events' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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39) Regarding the 'Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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40) Regarding the 'World-wide marketing experience. The following should be briefly discussed: the extent of the world-wide experience, any new or different safety issues identified, any regulatory actions related to safety' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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41) Regarding the 'Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5)' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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42) Regarding the 'Benefit Risk Balance' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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43) Regarding the 'Summary regarding the important risks of the medicine and how the risks are managed' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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44) Regarding the 'Summary of any safety information that is missing and needs to be collected' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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45) Regarding the 'Any additional measures to ensure safe use that are required as part of the licensing of the medicine' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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46) Regarding the 'A list of any planned studies to provide more information on the safety of the medicine' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) iii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement c) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question c) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question d) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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47) Regarding the 'Posology and method of administration' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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48) Regarding the 'Contraindications' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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49) Regarding the 'Special warnings and precautions for use' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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50) Regarding the 'Interaction with other medicinal products and other forms of interaction' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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51) Regarding the 'Fertility, pregnancy and lactation' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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52) Regarding the 'Effects on ability to drive and use machines' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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53) Regarding the 'Undesirable effects' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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54) Regarding the 'Overdose' section, how relevant is:

Question a)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question a) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b)	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Statement b) i	**1** ☐	**2** ☐	**3** ☐	**4** ☐
Question b) ii	**1** ☐	**2** ☐	**3** ☐	**4** ☐

If 2 or 3, in any of the above, please state what aspect should be changed.

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Appendix 3:

Publications

A comparison of approved indications between regulatory agencies

Matthew Camilleri, John Joseph Borg, Nicolette Sammut Bartolo, Anthony Serracino-Inglott

Introduction

Medicinal products are allowed on the market following approval by autonomous regulatory agencies which are tasked with their evaluation. Differences in evaluation practices during the registration of medicinal products are found in Europe and the United States of America which may lead to discrepancies in clinical guidelines, pricing policies, and drug use.

Research question

Are there differences in the authorised drug indication/s between the European Medicines Agency (EMA) and the US Food & Drug Administration (FDA) using new molecular entity cardiology-related medicinal products as models?

Study Design

Retrospective observational review study.

Method

All cardiology-related medicinal products assessed by the EMA were identified using the Anatomical Therapeutic Chemical (ATC) code and cross-matched with the FDA counterparts using active ingredients, branded names and authorisation holder details. The assessment reports from the EMA, the reviews from the FDA and initial product information for each identified drug were obtained. A tool was developed and validated to compare the differences between authorised indications.

Results

Twenty-six products with a marketing authorisation from both agencies were identified. A total of fourteen products were found to have different indications when comparing the label to the Summary of Product Characteristics (SmPC). Differences in the indications have been categorised according to the following restrictions: disease states (n=5), patient characteristics (n=4), different clinical scenario (n=3), severity of the condition (n=3), combination (n=3), previous therapy failure (n=1), inappropriate alternative therapies (n=1). Reasons for such restrictions have been mainly attributed to alignment with the conducted clinical trials. Both agencies have been found to restrict indications.

Conclusions

Differences in approved indications exist between the EMA and the FDA. Pharmaceutical companies also contribute to discrepancies based on marketing strategies employed during submission of applications. Regulatory collaboration between agencies is deemed essential to ensure a harmonised approach to the use of medications.

Comparison of post-authorisation requirements between regulatory agencies for medicinal products

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Background information: Information submitted during the initial registration phase of medicinal products may not be sufficient to fully assess the benefit-risk balance of the product. Post-authorisation studies for new medicinal products are often requested by regulatory agencies to address this limitation and better assess the product.

Purpose: To compare the post-authorisation actions requested by the European Medicines Agency (EMA) and the U.S Food and Drug Administration (FDA) using cardiovascular-related medicinal products as models

Method: Medicinal products assessed by the EMA were identified and matched with the FDA counterparts. The assessment reports from the EMA and the reviews from the FDA were obtained for each product. Post-authorisation requirements from both agencies were extracted and compared. . Clinical and safety requirements were considered.

Results: Twenty-two products having the same clinical context in the indication were identified. For all products, seventy-three post-authorisation studies were required by the EMA while twenty-nine post-authorisation requirements or commitments were needed by the FDA. Two products did not require further studies from both agencies. In eight cases there were discrepancies in the required studies. In four cases there were common requirements.

Conclusion: Differences in post-authorisation requirements exist between the EMA and the FDA approved products. Regulatory collaboration between agencies is deemed essential to ensure a harmonised approach in this respect. Further studies using other therapeutic areas are recommended in order to further assess the extent of such differences.

Topic area: Regulatory sciences