

Benefit-Risk Assessment of Human Medicines within the Drug Approval Process – A Comparison of EMA's and FDA's Approach

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Abbreviations

ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
AR	Assessment Report
BLA	Biologic License Application
BRAT Framework	Benefit Risk Action Team Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CIRS	Center for Innovation in Regulatory Science
COBRA	Consortium of Benefit-Risk Assessment
CTD	Common Technical Document
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal Growth Factor Receptor
EPAR	European Public Assessment Report
EWG	Expert Working Group
FY	Fiscal Year
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
IoM	Institute of Medicine
MaPP	Manuals of Policies and Procedures
MCDCA	Multi Criteria Decision Analysis
NCA	National Competent Authority
NDA	New Drug Application
NME	New Molecular Entity
NSCLC	Non-Small Cell Lung Carcinoma

Abbreviations

ORR	Objective Response Rate
PBC	Primary Biliary Cirrhosis
PDUFA	Prescription Drug User Fee Act
PFS	Progression Free Survival
PhRMA	Pharmaceutical Research Manufacturers of America
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium
PROTECT BR	PROTECT Benefit-Risk Group
RMP	Risk Management Plan
R/R CLL	Relapsed or Refractory Chronic Lymphocytic Leukaemia
SAG	Scientific Advisory Group
SMEs	Micro, small and medium-sized enterprises
SmPC	Summary of medicinal Product Characteristics
TKI	Tyrosine Kinase Inhibitor
UDCA	Ursodeoxycholic Acid
UMBRA	Unified Methodology for Benefit-Risk Assessment
USPI	United States Package Information
WP	Work Package

1. Introduction

The assessment of a medicinal product, which evaluates the product's benefits and risks is at the heart of drug approval decisions (1). Within the European Union the marketing authorisation is supposed to be refused if the benefit-risk balance of the drug is not considered to be favourable, or if therapeutic efficacy is insufficiently substantiated (2). In the United States drugs have to be effective and safe to receive approval (3), whereby safe means that the benefits outweigh the risks (4).

The thalidomide disaster in the 1960's was a key driver for the establishment of modern regulatory systems, and paved the way for the introduction of benefit-risk (B/R) assessment in the drug approval process (5). However, it is a phenomenon of the past decade that regulatory authorities, pharmaceutical industry and academia have turned their focus on methods to facilitate the B/R assessment of medicines (1).

In 1998 the Council for International Organizations of Medical Sciences (CIOMS) expressed concerns about the lack of generally agreed procedures for evaluating the B/R balance of a drug (6).

Furthermore, in recent years there have been some highly publicised cases where major safety issues emerged in the post marketing phase. One example is Vioxx which was withdrawn from the market as it caused cardiovascular problems (7). Such incidents have sparked increased risk awareness among patients and risk aversion among regulators (8).

Headlines such as *'Europe has not learned a thing from the Tamiflu scandal'* (9), or *'The FDA is basically approving everything'* (10) demonstrate on the one hand a large public interest in decisions made by regulatory authorities and contest on the other hand the reliability of these important authorities. The performance of regulators has become subject to close scrutiny and the demand for more structured and transparent approaches for regulatory decision making has evolved (8).

This thesis focuses on the B/R initiatives of the *'two dominant players in the drug development arena'* (11, p.17), the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). The intention is to compare EMA's and FDA's B/R assessment approaches. Section 2 starts with the challenges of B/R assessment and outlines current B/R initiatives. Section 3 includes a description of EMA's B/R initiatives, while Section 4 presents FDA's B/R efforts. In Section 5 EMA's and FDA's B/R initiatives are compared. Section 6 analyses how the authorities communicate their decisions in the respective assessment reports of six selected drugs and which uncertainties are present at the time of approval. Section 7 covers the implications of the B/R initiatives on the industry sector. Section 8, finally, concludes and discusses the findings of this thesis.

2. The Challenges of Benefit-Risk Assessment and Current Initiatives

2.1 The Challenges of Benefit-Risk Assessment in the Drug Review Process

The B/R assessment of human medicines implies the review of two dimensions, i.e. the benefits and the risks. The dimension of benefits is mainly determined by the therapeutic efficacy, e.g. improvement of a disease, while the dimension of risks comprises the safety profile of a drug, including identified adverse drug reactions and the inherent risk for not yet identified adverse reactions (12).

To determine the B/R balance regulators have to investigate a vast amount of data, including quality, safety, and efficacy data (13). The safety of a drug is tested in preclinical and clinical trials while the efficacy is mainly examined in phase II and III clinical trials (14).

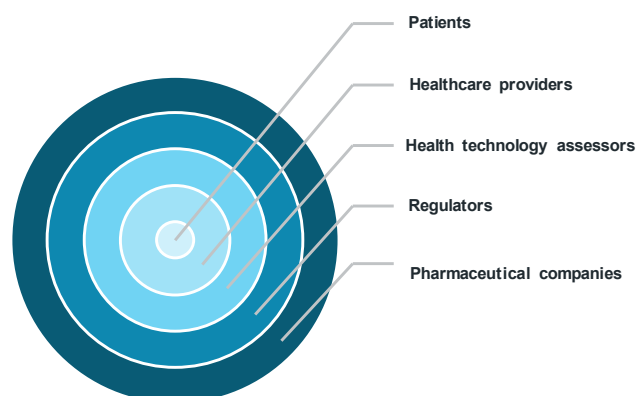
A critical concern for the B/R assessment of human medicines is that not all benefit and risk aspects can be measured within clinical trials. This is corroborated by the fact that rare adverse events are commonly not identified in Phase III clinical trials (15). On the benefit side, indirect measures, such as biomarkers or laboratory measures, are often used as replacement or surrogates for clinically significant endpoints (16). A crucial question is whether these surrogates reliably predict clinically meaningful benefit.

Furthermore, the clinical trial situation per se creates an artificial environment since trial subjects are more often investigated and questioned by medical doctors than patients in the healthcare routine. In addition, trial subjects usually do not exactly represent the broad patient population that receives the drug in the healthcare routine (17).

Simplified and shortened, reviewers have to consider multiple sources of uncertainty, even though a drug has run through a comprehensive program of clinical trials. According to Janet Woodcock¹, uncertainty is central in the drug review process and it is impossible to know everything there is to know about a drug when the FDA must conclude on a positive or negative B/R balance (18). The regulators' dilemma encompasses the decision whether the drug receives market access or not despite these uncertainties.

The regulators' decision to approve a drug or not has far-reaching implications for other stakeholders, in particular for patients. Furthermore, not only regulators decide about the benefits and risks of a drug, but there are other decision-makers like health technology assessors. Figure 1 presents the stakeholders and decision-makers for whom the evaluation of the benefits and the risks of a drug is fundamental.

¹ Director, Center for Drug Evaluation and Research (CDER), FDA

Figure 1: Stakeholders and Decision-Makers

Source: IMI PROTECT, Perspective on Benefit-Risk Decision-Making in Vaccinology Conference, 24 June 2014 (19)

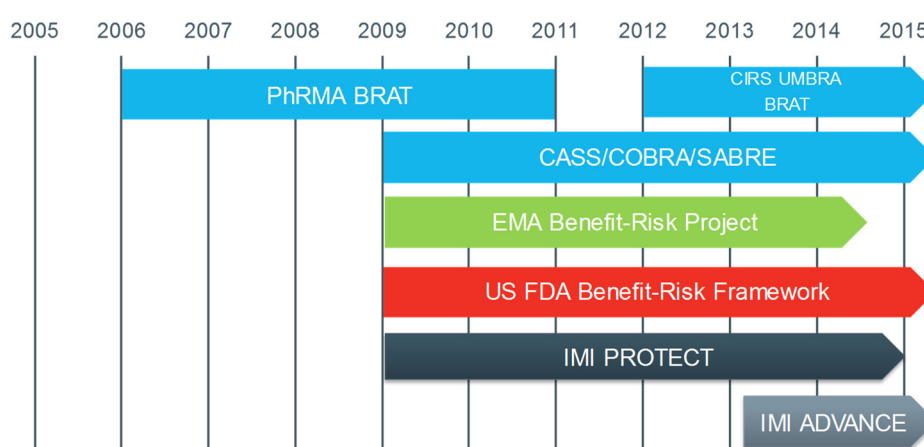
The central group of stakeholders are patients which expect effective and safe treatments and want to decide for themselves whether to take a drug or not. If a drug is not approved, patients do not have the option to decide.

Healthcare providers want the best treatment for their patients and make decisions based on treatment guidelines. Health technology assessors focus on the cost-effectiveness of a drug. Regulators consider the B/R balance of a drug to individuals and public health and decide whether the drug receives approval or not. Pharmaceutical companies decide to scrap or further develop a drug candidate and for which licenses to apply (19). In conclusion, the assessment of the B/R balance of a drug is crucial for all stakeholders and all these stakeholders evaluate the benefits and risks from different perspectives.

2.2 Overview - Current Benefit-Risk Initiatives

Regulators, industry and academia have developed various approaches, ranging from descriptive textual to decision-analytic, quantitative models, to facilitate the B/R assessment of medicines. All these approaches share common goals, namely to assist the B/R analysis and to improve the communication of decisions. Figure 2 shows a summary of the main B/R initiatives. Although these approaches share common goals, there are some differences between the methods and a unified internationally agreed method has not yet been established.

Figure 2: Summary of the Main B/R Initiatives



Modified from Pignatti et al., Structured Frameworks to Increase the Transparency of the Assessment of Benefits and Risk of medicines: Current Status and Possible Future Directions, Nov. 2015 (1).

Abbreviations:

PhRMA BRAT: Pharmaceutical Research Manufacturers of America Benefit Risk Action Team

CIRS: Center for Innovation in Regulatory Science, UMRA: Unified Methodology for Benefit-Risk Assessment

CASS: Taskforce representing regulators from Australia, Canada, Singapore and Switzerland

COBRA: Consortium of Benefit-Risk Assessment, SABRE: Southeast Asia Benefit-Risk Evaluation

IMI PROTECT: Innovative Medicines Initiative Pharmacoeconomic Research on Outcomes of Therapeutics by a European Consortium

IMI ADVANCE: IMI Accelerated Development of Vaccine Benefit-Risk Collaboration in Europe

The Benefit Risk Action Team (BRAT) framework was developed by the Pharmaceutical Research Manufacturers of America (PhRMA) and traces its origin to 2005. It is mainly a structured six-step approach including tabular and graphical displays to aid the interpretation of outcomes.

The Center for Innovation in Regulatory Science (CIRS), founded in 2001, has worked closely with international regulatory groups to investigate B/R analysis methods. One of those groups is the Consortium of Benefit-Risk Assessment (COBRA) representing

regulators from Australia, Canada, Singapore and Switzerland. These regulators exchanged review reports and developed the COBRA Benefit-Risk Template.

Regulatory authorities from Chinese Taipei, China, Indonesia, Malaysia, Singapore and the Philippines have been working with the CIRS to test a summary version of the COBRA framework.

Recognising a high degree of consistency across several frameworks the CIRS generated the Unified Methodology for Benefit-Risk Assessment (UMBRA), an eight-step framework that combines common elements of existing frameworks (1).

The Innovative Medicines Initiative (IMI) Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project was a collaborative European project including regulators, industry representatives and academics. IMI PROTECT comprised several work packages (WPs), one of which, WP 5 focussed on the integration and representation of B/R data. Since the IMI PROTECT project was coordinated by the EMA (20) the project will be described in Section 3 'EMA's Initiatives to the B/R Assessment of Human Medicines'. FDA's B/R framework is presented in Section 4 'FDA's Initiatives to the B/R Assessment of Human Medicines'.

The IMI ADVANCE project aims to develop and examine methods in order to establish a B/R framework for vaccines (21).

3. EMA's Initiatives to the Benefit-Risk Assessment of Human Medicines

3.1 Background and Introduction

EMA's efforts to investigate methods for the B/R assessment of human medicines started in 2006. The Committee for Medicinal Products for Human Use (CHMP) established a working group on B/R assessment that evaluated the current drug review process and several methods of B/R assessment described in the literature. In March 2008, the working group's conclusions were published in a reflection paper².

The working group inferred that expert judgement has been and remains the fundamental basis of B/R assessment; furthermore, quantitative methods will not replace qualitative evaluation of the benefit-risk ratio. Nevertheless, quantitative methods could be useful as they may lead to a structured discussion between reviewers. The reflection paper concluded with two main recommendations, i.e. to further research the methodology of B/R assessment and to revise the current B/R assessment section of the CHMP assessment report templates. Accordingly, a proposal for modification was provided including a structured list of benefit and risk criteria (22). The remainder of this chapter describes EMA's Benefit-Risk Methodology Project, the revision of the CHMP assessment report templates, the IMI PROTECT project, and finally discusses the outcomes of EMA's B/R efforts.

3.2 EMA's Benefit-Risk Methodology Project

Following the recommendation of the CHMP working group on B/R assessment, the EMA started its Benefit-Risk Methodology Project in 2009 with the aim to investigate methods that can improve transparency, consistency, and communication of B/R decisions (23). The recommendation to further research methodologies was also implemented in EMA's Roadmap to 2015³ (24).

A project team including decision theorists, regulators, and psychologists, under the guidance of Lawrence Phillips⁴ was constituted to detect methods that would suit (23) the complex organisation of the EMA (seven scientific committees and experts from various working parties and related groups) (25). The National Competent Authorities (NCAs) of France, Germany (Paul-Ehrlich Institut), the Netherlands, Spain, Sweden, and the UK volunteered to participate in the project (26), which consisted of five consecutive work packages (Table 1). The first four work packages formed a research phase with the aim to

² *Reflection Paper on Benefit-Risk Assessment Methods In The Context Of The Evaluation Of Marketing Authorisation Applications Of Medicinal Products For Human Use*, see (22)

³ One of the strategic areas identified in EMA's Roadmap to 2015 was to facilitate the access of medicines through reinforcing the benefit-risk balance assessment model.

⁴ Professor of Operational Research at the London School of Economics

develop and test tools and methods of B/R assessment, whereas the fifth work package was intended for training and initial implementation (27).

Table 1: The Five Work Packages of EMA's Benefit-Risk Methodology Project

- | | |
|----|--|
| 1. | Description of current practice of B/R assessment for centralised procedures in the EU |
| 2. | Applicability of current tools and processes for regulatory B/R assessment |
| 3. | Field tests of the most appropriate tools |
| 4. | Development of a toolkit for B/R assessment |
| 5. | Pilot and training |

Source: EMA, Benefit-Risk Methodology Project (27)

Current Practice of B/R Assessment

The first step of EMA's project was to detect how the centralised drug approval process has been realised within each of the participating agencies. This step was important since potential methods for B/R assessment must be adaptable to the current practice within the EU regulatory network. Between June and September 2009, members of the project team visited participating agencies and interviewed staff members with a key role in the regulatory decision making process.

One of the main findings of work package 1 is that licensing decisions have been made intuitively based on expert judgement without using a systematic approach. Either an accountable senior assessor or a group of assessors have been responsible to judge the B/R balance, after extensive analysis of the data and discussion among experts.

Another crucial observation is that interviewees had divergent views on the meaning of benefits and risks. Many interviewees experienced difficulties to define the meaning of a *benefit* or a *risk* precisely, in particular, defining a risk was challenging (26).

Consequently, the four-fold frame was invented which differs between favourable and unfavourable effects and the uncertainties regarding these effects (Table 2). The terms of the four-fold frame have been implemented in the CHMP Day 80 assessment report: overview and list of questions guidance.

Table 2: The Four-Fold Frame for Separating the Elements of B/R Assessment

Favourable effects	Uncertainty of favourable effects
Unfavourable effects	Uncertainty of unfavourable effects

Source: EMA, Benefit-Risk Methodology Project: Work Package 2 Report (28)

Furthermore, the project team established working definitions for the terms benefit and risk which are described in Table 3.

Table 3: Definitions for Benefits and Risks	
Favourable effects (benefits or clinical benefits)	any beneficial effects for the target population which are related to the product
Unfavourable effects (risks, harms, known and unknown hazards)	any detrimental effects that can be associated with the product or that should be considered for their undesirable effect on patients' or public health, or the environment
Uncertainties (surrounding both types of effects)	originate from variation, unsettled issues, methodological flaws, limitations of the data set, and important sources of bias

Source: EMA, Benefit-Risk Methodology Project: Work Package 2 Report (28)

Applicability of Current Tools for B/R Assessment

After acquiring an understanding of the current practice of B/R assessment, the next step of the project was to identify methods that could be valuable for regulatory decision making. During work package 2, the project team reviewed B/R assessment methods that appeared in scientific literature and appraised their usefulness to regulators.

A central finding of work package 2 is that any quantitative approach requires a qualitative framework within which the approach can be sufficiently developed. A qualitative framework serves to frame the decision context and to structure the problem. The project team appraised the ProACT-URL framework as a valuable tool to guide the B/R evaluation process (28).

ProACT-URL is an acronym for Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk and Linked decisions. ProACT was developed by Hammond et al. (29) and applied to decision making in health care by Hunink et al. (30). It is a generic framework which is generally suitable to evaluate problems with multiple criteria (31). To address specific topics within the B/R assessment of medicines, the framework has been adapted to drug decision making. Table 4 shows the steps of the extended ProACT-URL framework for the B/R assessment of medicines. The framework can be combined with quantitative modeling.

Table 4: A Summary of the ProACT-URL Framework as Adapted to Regulatory Use

Problem	<ol style="list-style-type: none"> Determine the nature of the problem and its context <ul style="list-style-type: none"> Consider among others indication, the therapeutic area and disease epidemiology, the severity of condition and if there is an unmet medical need What is to be decided and by whom? Frame the problem <ul style="list-style-type: none"> Is this a problem of uncertainty, or of multiple conflicting objectives, or some combination of the two, or something else?
Objectives	<ol style="list-style-type: none"> Identify objectives (e.g. to maximise the benefits and minimise the risks) Select favourable and unfavourable effects and define criteria (e.g. study endpoints) for these effects → Create an Effects Tree
Alternatives	<ol style="list-style-type: none"> Identify the options that should be evaluated against the criteria <ul style="list-style-type: none"> The options are the drug under evaluation and its comparator(s) (e.g. placebo or active comparator)
Consequences	<ol style="list-style-type: none"> Describe how the alternatives perform for each of the criteria <ul style="list-style-type: none"> Report the favourable and unfavourable effects for each alternative (e.g. drug and placebo) separately → Use an Effects Table
Trade-offs	<ol style="list-style-type: none"> Evaluate the balance between favourable and unfavourable effects <ul style="list-style-type: none"> Is the benefit risk balance positive or negative and what is the rationale for the judgement? Quantitative models like MCDA could be used
Uncertainty	<ol style="list-style-type: none"> Describe the uncertainties of favourable and unfavourable effects Consider how the B/R balance is affected by uncertainty
Risk	<ol style="list-style-type: none"> Consider the relative importance of the decision makers risk attitude <ul style="list-style-type: none"> Which factors influence the decision makers risk attitude? (e.g. orphan drug status, unmet medical need, risk management plan) Describe how this affected the balance reported in step 9
Linked decisions	<ol style="list-style-type: none"> Compare this decision with past/future decisions and consider the consistency of the decisions

Modified from: EMA, Benefit-Risk Methodology Project: Work Package 4 Report (32)

With regard to quantitative modelling, Multi-Criteria Decision Analysis (MCDA) was found particularly useful to represent the B/R balance numerically (28). The field tests of work package 3, as well as the case studies of the IMI PROTECT project (described in Section 3.4) are based on MCDA, therefore the steps of this modelling process are explained in more detail in Table 5. The first three steps of MCDA modelling are comparable to the Problem, Objectives, Alternatives and Consequences steps of the ProACT-URL framework. Scoring and weighting are the special steps within the MCDA process that require assessors to assign numerical weights to favourable and unfavourable effects.

Table 5: The Steps of the MCDA Process within the B/R Assessment of a New Drug

1. **Establish the decision context:** The purpose and context of the decision should be defined.
2. **Identify the options:** Within the B/R assessment of new drugs, the drug and its comparators represent the options.
3. **Identify objectives and criteria:** Usually, the objective is to maximise the benefits and minimise the risks. With respect to the criteria, the benefits and risks that significantly influence the B/R balance should be selected. Value trees are useful to demonstrate the effects.
4. **'Scoring':** The intention of scoring is to achieve for each criterion a preference scale. This means that each favourable and unfavourable effect has to be converted into a preference value on a 0 to 100 scale, e.g. the absence of an adverse reaction scores 100 (most preferred) while the presence of the specific adverse reaction in 5% of treated patients scores 0 (least preferred). It is important to understand that only differences in the scores can be compared, not ratios of the scores themselves. Differences in the scores indicate differences in preference. The conversion is established by a value function (a linear or non-linear translation).
5. **'Weighting':** The purpose of weighting is to ensure that the units of the preference values are equated. The former step, scoring leads to a relative scale for each effect, but assessors may assign different values for each scale difference. To equate preference values, assessors have to compare the swings in preference on the 0 to 100 scale for all the effects. This process is called swing weighting. For each effect assessors have to consider how big the scale difference is and how much they care about that difference. This process inevitably requires judgment. Within the MCDA model, weights represent trade-offs, which means that assessors have to identify the largest swing that matters and assign this swing a weight of 100. Then the other swings are compared to 100 and assigned appropriate weights.
6. **Combine the weights and scores for each option:** Within this step the weights are normalised and the preference values for each option are multiplied with the weights on each criterion.
7. **Examine the results:** The results show how the different treatment options score within this model. Graphical representation is possible to demonstrate the results.
8. **Sensitivity analysis:** This step explores if different weights or preferences affect the obtained results, i.e. the ordering of the treatment options. Sensitivity analysis helps to assess the robustness of the results (33).

Based on: Benefit-Risk Assessment Model for Medicines: Developing a Structured Approach to Decision Making (33)

Field Tests

As part of work package 3, five NCAs were engaged in field testing the most relevant models. In each agency between four and six clinical assessors or experts participated in an one-day workshop to generate a benefit-risk model of the drug and its comparator(s). Each agency selected a drug that was currently under review by the CHMP.

During the preparation of the field-tests it became obvious that a MCDA model might be valuable for the B/R assessment of medicines since such models enable comparisons of

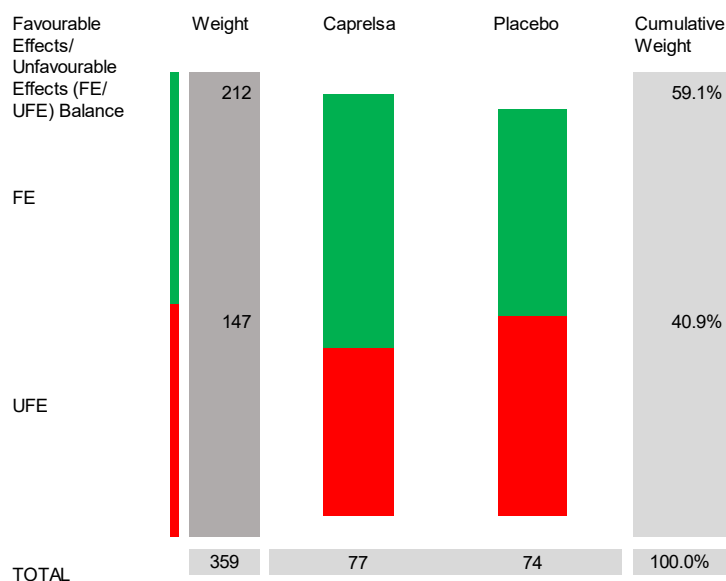
dissimilar favourable and unfavourable effects, e.g. percentage of responders versus QTc prolongation. For each field test the PrOACT-URL framework was utilised as a general structure to guide the process. To define the objectives, Effects Trees were created that demonstrated key favourable and unfavourable effects. Subsequently, Effects Tables were prepared to provide criteria definitions of the effects, the units, as well as upper and lower limits of the effects (34). Table 6 provides a brief description of the format and content of an Effects Table (35).

Table 6: The Format and Content of an Effects Table						
Effect	Description	Unit	Treatment	Control (e.g. Placebo)	Strength of evidence/ uncertainties	References
Acronym or short identifier of the effect.	Short definition of the effect. Further description could be included as footnotes.	Unit for measurement for each effect, e.g mmHg.	Summary of the key effects for the drug under assessment and comparators. The Effects Table includes separate columns for each treatment group.		Description of major uncertainties or limitation for each effect.	Optional column. Should be used for complex issues to refer to specific data
Favourable and unfavourable effects						

Source: EMA, Guidance Document on the Content of the Co-Rapporteur Day 80 Critical Assessment Report, Overview and list of questions, 2015 (35)

Specialised MCDA software enabled participants to represent the BRB numerically. First, each favourable and unfavourable effect was converted into a preference value on a 0 to 100 scale. Subsequently, the units for the preference values were equated through swing weighting. This method requires assessors to judge the clinical relevance of scale differences. Finally, weighted effects can be summed. Following these steps graphical displays were created to illustrate the overall B/R balance.

In this context, the Added-Value Bar Graph proved to be useful to demonstrate the B/R balance. Figure 3 presents a hypothetical example of the Added-Value Bar Graph in the case of Caprelsa. This stacked bar graph shows the final results of the assessment with the overall score for the alternatives (Caprelsa and placebo) given just below each bar graph. Longer green bars imply more benefit while longer red bars indicate less risk. The overall weighted score for Caprelsa and placebo, 77 and 74 respectively, demonstrate that Caprelsa is the preferred option, since the higher the score the 'better' is the B/R balance. The *Weight* column shows the sums of the weights on the favourable and the unfavourable effects, 212 and 147 respectively; whereas the *Cumulative Weight* column illustrates those same weights in relative terms (32).

Figure 3: Added Value Bar for Caprelsa

Source: EMA's Benefit-Risk Methodology Project, Work Package 4 Report (32)

To detect how the balance changed, if different input data or altered judgements about clinical relevance were used, participants performed sensitivity analysis. This type of analysis appeared to be useful to investigate uncertainties and different views on the importance of a criterion.

In summary, the field tests demonstrated that the collective application of three processes, i.e. the ProACT-URL framework, the workshop approach and decision-analytic modelling could indeed support regulatory decision-making. Feedback from participants indicated that this type of methodology can test different perspectives and helps to understand how far uncertainties influence the B/R balance. One of the main conclusions of work package 3 was to adopt the ProACT-URL framework as an adjunct to current CHMP processes. However, the project team also noticed that quantitative modelling is not necessary for every new drug application but rather for complex B/R decisions (34).

Development of a Toolkit for B/R Assessment

The objective of work package 4 was to establish a methodology or a set of tools supporting the B/R assessment of human medicines, based on previous findings. Four tools have been proposed as a result of the project: a generic decision-making approach, i.e. the PrOACT-URL framework, a tabulated summary specifying the key effects, namely the Effects Table, MCDA modelling, and graphical displays.

Recognising that quantitative modelling might be superfluous in more simple cases, the project team suggested a graduated methodology. First, the PrOACT-URL framework should generally be applied to guide the drug review process. This framework could be created irrespective of any quantitative model. Step 6 of the framework recommends creating an Effects Table to represent the key contributors to the B/R assessment in a common and concise format. Secondly, a simple MCDA model could be developed with no special software other than Microsoft Excel. Finally, a full MCDA model would be a valuable tool for more complex or contentious cases, for instance when the B/R balance is marginal or in case of diverse conflicting attributes. The use of specialised MCDA software would enable assessors to create graphical displays and to conduct sensitivity analysis (32).

Pilot and Training

Within work package 5 an Effects Table pilot phase was initiated involving ongoing procedures for initial marketing authorisations. The Effects Tables were completed by the rapporteur/assessors and circulated to the CHMP. Participating rapporteurs assessed the Effects Table as a valuable tool that improves transparency and supports the communication with other committees and the public. Accordingly, a crucial recommendation of work package 5 was to incorporate the Effects Table in the B/R assessment section of the CHMP assessment reports (36).

As of 2015, the Effects Table has been incorporated in the benefit-risk section of the European Public Assessment Reports (EPARs) for new drug applications and guidance is applicable for regulators how to complete the Table (35).

3.3 Revision of the CHMP Assessment Report Templates

In 2008, the CHMP working group on B/R assessment recommended to revise the B/R assessment section of the CHMP assessment report templates (22). These templates should be used by the rapporteur to prepare the assessment report for a new drug (37). In this context, the Day 80/150/180 Overview templates cover the B/R assessment of a new drug. The rapporteur firstly uses the template at day 80 and updates it within the drug approval process (38).

Since 2008 the Overview templates and respective guidance documents have been repeatedly revised (35), (39). The structure and content of the revised templates reflect the proposed modifications from the CHMP working group and the findings from EMA's Benefit-Risk Methodology Project.

A comparison between the B/R assessment sections of the EPARs of two drugs, i.e. Votrient (40) and Ocaliva (41), demonstrates the modifications (Table 7).

Table 7: Structure of the B/R Sections in the EPARs of Votrient and Ocalvia	
Votrient , EMA Approval: 14/06/2010 Overall conclusions, risk / benefit assessment and recommendation	Ocaliva , EMA Approval: 12/12/2016 Benefit – risk balance
Quality	—
Non-clinical pharmacology and toxicology	—
—	<u>Therapeutic context</u> <ul style="list-style-type: none"> • Disease or condition • Available therapies and unmet medical need • Main clinical studies
Efficacy	Favourable effects
—	Uncertainty and limitations about favourable effects
Safety	Unfavourable effects
—	Uncertainty and limitations about unfavourable effects
—	Effects Table
Risk – benefit assessment	<u>Benefit – risk assessment and discussion</u> <ul style="list-style-type: none"> • Importance about favourable and unfavourable effects • Balance of benefits and risks • Additional considerations on the benefit-risk balance
Recommendation	Conclusion

Based on the respective EPARs of Votrient (40) and Ocaliva (41)

Votrient was approved in 2010, whereas Ocaliva was authorised in 2016. It becomes apparent that quality, as well as non-clinical pharmacology and toxicology aspects are no longer included in the B/R assessment sections of the EPARs, unless these aspects significantly influence the B/R balance. Furthermore, the terms *benefit* and *risk* have been replaced with four separate items, namely favourable effects, uncertainties about favourable effects, unfavourable effects, and uncertainties about unfavourable effects. Contrary to Votrient, the EPAR of Ocaliva includes therapeutic context considerations, the Effects Table, and a detailed discussion of the B/R balance.

Chapter 6 of this thesis compares the B/R section of EPARs with those of FDA's Medical Reviews for selected drugs; therefore, the following paragraph summarises the recommendations of the current CHMP assessment report overview guidance⁵ regarding the B/R assessment section.

Within the B/R assessment of a drug, EMA's reviewers have to consider the therapeutic context which embraces the disease to be treated or prevented, available therapies and the main clinical studies. This serves the purpose to frame the B/R assessment and to further justify the risk attitude.

Furthermore, the key favourable and unfavourable effects, as well as their uncertainties should be described. Key favourable effects are for instance primary or secondary efficacy endpoints that are considered clinically relevant. Key unfavourable effects are not necessarily based on clinical safety endpoints but also on other safety issues, e.g. pharmacodynamic interactions or non-clinical safety concerns. It is essential to note that the key unfavourable effects are not inevitably the most common ones.

The Effects Table provides an overview of the effects and uncertainties and should first appear in the Rapporteur's Day 80 Report, should then be merged at Day 120 List of Questions and kept updated until the CHMP Day 210 Report. Finally, the Effects Table should be implemented in the EPAR.

The next step is to discuss the importance of favourable and unfavourable effects, as well as the B/R balance. The purpose is to put the observed effects in relation to the therapeutic context and to assess the impact of uncertainty on the B/R balance. Reviewers have to address the following question:

- *'Do the favourable effects outweigh the unfavourable effects given the current state of knowledge, uncertainties and limitations?'* (39, p.48)

⁵ Guidance document on the content of the <Co-> Rapporteur day <60*><80> critical assessment report, Overview and list of questions, revised in 2016, see (39)

Reviewer may also use quantitative approaches to determine the B/R ratio. However, no single method has been established that fits every B/R assessment and further experience is necessary, according to the guidance.

Where appropriate, regulators have to describe regulatory options for approval, e.g. conditional marketing authorisation, or recommended studies. Finally, regulators have to conclude whether the B/R balance of the drug is positive or negative (39).

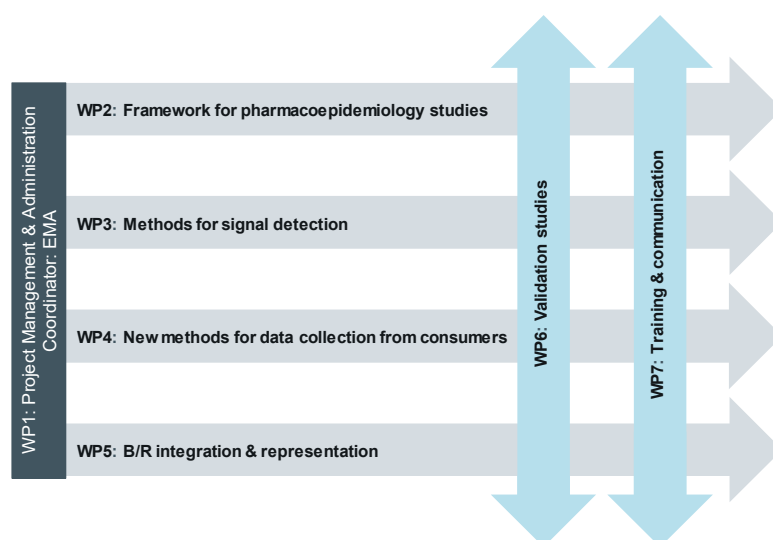
In conclusion, the current CHMP assessment report overview guidance includes a detailed description of the aspects that should be considered within the B/R assessment of a drug. It includes considerations on the therapeutic context, the uncertainties surrounding the effects, the Effects Table, and finally a comprehensive discussion of the B/R balance.

3.4 IMI PROTECT

IMI PROTECT was a collaborative European project coordinated by the EMA. PROTECT included a multi-national consortium of 34 partners including academics, regulators, micro, small and medium-sized enterprises (SMEs) and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies (20). The EMA developed PROTECT with the purpose to enhance the monitoring of benefit-risk of medicines in Europe as a response to IMI's call to address limitations of currently used methods in pharmacovigilance and pharmacoepidemiology.

The project took place from September 2009 to June 2015 (42) and comprised one managerial and six scientific Work Packages (WPs) (Figure 4).

Figure 4: The Work Packages of the IMI PROTECT Project



Modified from IMI PROTECT Communication, Strategy and Plan, 2009 (20)

Within IMI PROTECT various innovative tools and methods were developed, tested, and validated to improve data collection directly from consumers of medicines, to enhance early and proactive signal detection, to assess and disseminate methodological standards for pharmacoepidemiology studies, and to establish methods for continuous B-R monitoring (20), (42).

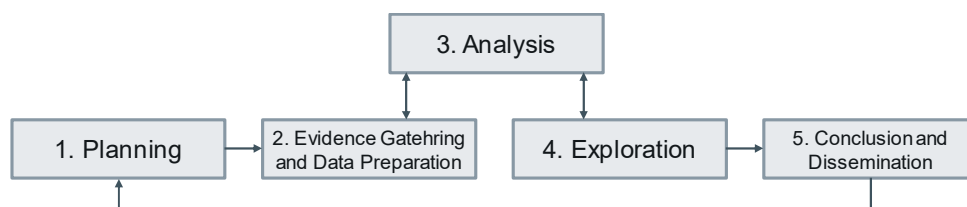
WP 5 of PROTECT focused on the integration and visual representation of benefit and risk data. Following a comprehensive literature review⁶, a set of methodologies and visualisation techniques to establish the B/R balance were tested in 'real-life' case studies⁷. As a result of the case studies, the PROTECT Benefit-risk group (BR) developed various

⁶ 49 methodologies were reviewed and 13 of these methodologies were field-tested.

⁷ The case studies were based on real-world scenarios involving medicines with a marginal B/R balance.

practical recommendations for B/R assessment methods. These recommendations are arranged around the five stages of a generic B/R Roadmap (Figure 5).

Figure 5 : IMI PROTECT Benefit-Risk Assessment Roadmap and Recommendations



Source: Hughes et al., Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations (43)

Planning: The purpose and context, as well as critical issues of the B/R assessment should be defined and documented as a reference for updates and future analysis. The PROTECT BR appraised the ProACT-URL and BRAT framework as useful tools to describe contextual aspects of the B/R assessment. A table template, e.g. the Effects Table, should be prepared to represent the relevant benefit and risk data.

Evidence Gathering and Data Preparation: Assessors should review all available data and decide which sources of evidence to use for the analysis. Visualisation techniques, like structured and color-coded tables were found useful to transfer relevant data into suitable formats.

Analysis: The purpose of this stage is to quantify the magnitude of benefits and risks. Quantitative models are recommended for complex evaluations, while simple descriptive frameworks suffice for more obvious assessments. When using a quantitative approach, value preferences should be expressed through appropriate bar graphs, e.g. the Difference Display (Figure 8).

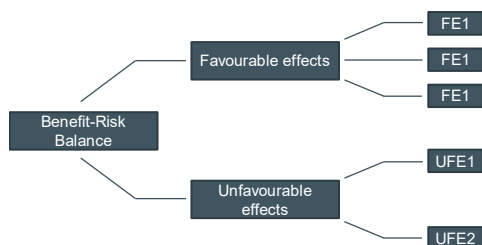
Exploration: Assessors should evaluate the robustness and sensitivity of the results considering uncertainties and risk minimisation measures. Sensitivity analysis is recommended for this stage of the assessment.

Conclusions and dissemination: Considering all the information in the previous four stages, assessors should conclude on the B/R balance and communicate the decision explicitly with a transparent audit trail. The selection of visual aids for communicating the B/R balance should depend on the technical knowledge of the audience (44).

The PROTECT Benefit-risk roadmap provides an overarching view of B/R assessments. Within each stage the PROTECT BR appraised the usefulness of specific methodologies and visualisation methods. The descriptive frameworks ProACT-URL and BRAT are recommended to guide the decision making process. Furthermore, two visual representations, the Effects Table and the Value Tree were evaluated as particularly useful for every B/R assessment. These tools demonstrate those benefits and risks that strongly

influence the B/R balance. The Value Tree (Figure 6) clusters the benefits and risks into smaller groups while the Effects Table (Table 6) lists numerical values for the effects.

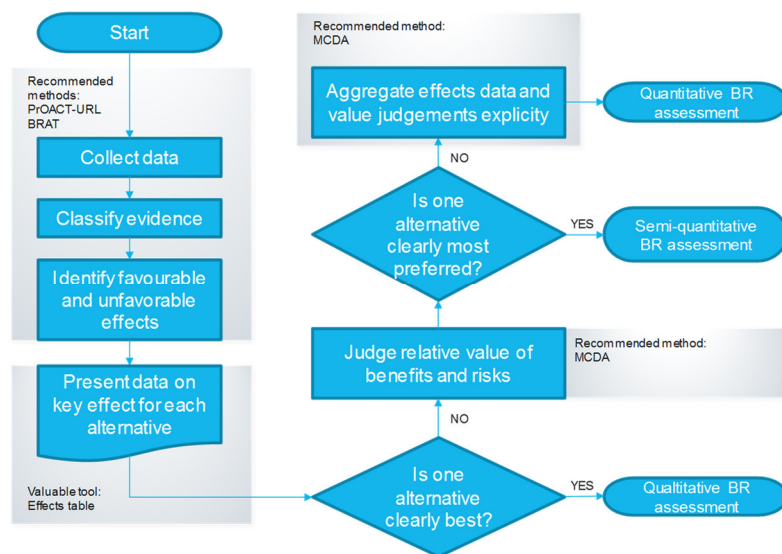
Figure 6: Simplified Value Tree



Modified from Hughes et al., Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations (43)

According to the PROTECT BR, the Effects Table is an important milestone as it includes all the objective information of a B/R assessment. This table may clearly demonstrate whether one treatment is superior to its comparators. For more complex assessments quantitative methods might be helpful. Figure 7 illustrates when to apply quantitative methods. In this context, quantitative modelling means to assign preferences to the treatment effects. A semi-quantitative B/R assessment includes ranking of the treatment effects while a fully quantitative model further requires explicit utilities (43).

Figure 7: The Possible Ways within a B/R Assessment

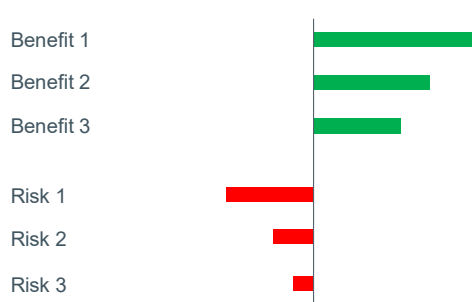


Modified from Hughes et al., Recommendations for Benefit-Risk Assessment Methodologies and Visual Representations (43)

Bar charts, particularly in the form of the Difference Display are recommended to communicate the decision to different stakeholders, such as patients, physicians or the general public. Figure 9 shows a simplified Difference Display for two treatment options. This bar graph is based on MCDA and illustrates the extent and direction of difference between two treatment options. The green bars indicate that the first option (drug 1) performs better, while the red bars show that the second option (drug 2) scores better.

Figure 8: Difference Display

Drug 1 versus Drug 2



Modified from IMI PROTECT Benefit-Risk Group, Recommendations Report (44)

In summary, WP 5 resulted in a practical guidance with recommendations for which assessments and how to apply certain methodologies and visualisation techniques (44). The recommendations regarding B/R methods have been divided into the following four IMI PROTECT outputs:

- Methodologies for B/R evaluation (output 14)
- Methodologies for graphical representation (output 15)
- Final tools for graphical B/R representation (output 16)
- Recommendations on methodologies for B/R integration and representation (output 17).

Overall, PROTECT has yielded a significant amount of scientific research and more than 20 outputs. A panel within the EMA was established to investigate whether these outputs were mature enough to be implemented in regulatory or clinical practice. Several PROTECT outcomes have already been implemented, e.g. the use of the Summary of medicinal Product Characteristics (SmPC) Adverse Drug Reaction (ADR) database to flag listed adverse events in the electronic Reaction Monitoring Reports. Other outputs need further research work to be translated into outcomes with long-term improvement on regulatory practices.

In order to assess the impact and feasibility of PROTECT outputs a survey was conducted with participants of the Final PROTECT Symposium⁸ and additional panels of EMA staff members. Within this survey, the impact of an output refers to a change on public health. To estimate the impact on public health respondents had to consider the specific output's impact on regulatory activities, processes, behaviors, and the acceptability of the specific output by stakeholders. Regarding the feasibility of an output respondents had to reflect the degree of scientific development, the speed of potential implementation of the output, as well as the impact on IT and human resources.

This survey revealed a clear difference between regulators⁹ and other stakeholders (industry and academic representatives) regarding the four main outputs of the B/R assessment. In contrast to other respondents, regulators did not consider the B/R outputs ready for implementation. In this context, the impact on IT, human, and other resources, as well as timelines were identified among all respondents as the major concerns affecting the feasibility of implementation. Furthermore, industry and academic representatives rated the impact of B/R outputs very high, whereas regulators evaluated the impact of these outputs as moderate. The feasibility of the B/R assessment outputs was similarly assessed among both responder groups as moderate.

In conclusion, PROTECT WP 5 has confirmed the added value of formal and structured B/R assessment methods to facilitate clear and transparent decision-making. The PROTECT BR has not developed a one-size-fits-all approach as the selection of a single approach or combination of methods depends on the complexity of the assessment. The experience of the case studies has been distilled into a practical guide with recommendations how to apply various classes of methodologies and visualisation techniques

Considering the impact and implementation of these B/R recommendations the survey demonstrated a sharp difference between regulators and other participants. In contrast to industry and academic representatives, regulators did not evaluate the B/R outputs as ready for implementation. According to EMA's report on PROTECT's outcomes *'This difference may reflect some of the respondents' willingness for these outputs to have an impact'* (42, p.39).

⁸ The Final Protect Symposium was organised at the EMA on 18-20 February 2015 to present and discuss the main results of PROTECT to a broad audience, including pharmaceutical industry, academia, regulatory authorities and patient representatives.

⁹ Regulators from the EMA or NCAs

3.5 Discussion of The Results and Future Considerations

The main objective of EMA's Benefit-Risk Methodology Project was to research methodologies that can improve transparency, communication and consistency of benefit-risk decisions and to develop a toolkit for B/R assessment methods (23). As a result, the project team proposed a stepwise approach within the PrOACT-URL framework that includes the Effects Table, a tabular display of the key effects and their uncertainties. Furthermore, the project team concluded that quantitative modelling is valuable for more complex benefit-risk decisions but not necessary for every new drug application. The project has neither identified for which cases quantitative approaches would be appropriate, nor has it addressed the question of how much modelling – simple or complex – would be helpful for regulators (32).

It is essential to note, that the members of EMA's scientific committees do not agree but rather debate about the usefulness of quantitative modelling. Critics describe quantitative modelling as resource intensive, highly subjective, and unnecessary. Quantitative approaches are labelled as a 'black box' that may obscure the expert judgement. Proponents, on the contrary, emphasise that minimal training is necessary to apply quantitative approaches, since these methods can be easily understood. In addition, quantitative models would enable an explicit benefit-risk dialogue (1).

This discussion shows that further research is necessary before implementing quantitative models. In this context, Hans-Georg Eichler¹⁰ concluded *'that the implementation of a simple qualitative benefit-risk decision-making tool within agencies, such as the EMA effects table [...] is key in order that regulators may explore and familiarise themselves with these tools before agreeing to the use of more complex models'* (45, p.21). This is consistent with Francesco Pignattis¹¹ statement that the implementation of MCDA modelling requires substantial training and poses some practical challenges; therefore, the use of the Effects Table would be the logical first step in incorporating a benefit-risk methodology within the drug evaluation process (45).

Apart from the debate about quantitative approaches, the findings of the Benefit-Risk Methodology Project have also contributed to the revision of the CHMP assessment report Overview templates. The revised version differs greatly in terms of content and structure to former templates. The proposals of the CHMP working group on B/R assessment and the findings from EMA's Benefit-Risk Methodology Project have been implemented. The revised guidance provides a detailed description of the therapeutic context, of the key favourable

¹⁰ Senior Medical Officer, EMA

¹¹ Head of Section Oncology, Haematology and Diagnostics, EMA

and unfavourable effects, of the uncertainties surrounding those effects, and finally a comprehensive discussion of the B/R balance (39).

EMA's Benefit-Risk Methodology Project and WP 5 of the IMI PROTECT project followed a similar approach; existing methodologies were reviewed and evaluated via case studies.

The experience gained from WP 5 of IMI PROTECT has been outlined in a practical guidance when and how to apply B/R methodologies and visualisation techniques. Indeed, PROTECT WP 5 has resulted in comprehensive recommendations on the use of B/R methods (44), nevertheless, these B/R outputs have not yet been implemented in regulatory practice and it seems that some regulators are not convinced to implement such models. (42). The question whether such methodologies become an integral part in EMA's B/R assessment of medicines remains unanswered at present.

4. FDA's Initiatives to the Benefit-Risk Assessment of Human Medicines

4.1 Background and Introduction

In 2006, the Institute of Medicine (IoM) recommended that the Center for Drug Evaluation and Research (CDER) within the FDA should establish a systematic approach to the B/R assessment of medicines (46).

In addition, some FDA stakeholders have argued that FDA's B/R assessment of human medicines could be improved with regard to clarity and transparency. In the course of a new product approval the FDA publishes the relevant documents, including Medical Reviews, to communicate the rationale of a regulatory decision. In fact, it may be difficult to understand these documents for a broad audience with varying backgrounds. Furthermore, some stakeholders have demanded for more formalised and quantitative methods to B/R assessment; while others have expressed scepticism regarding quantitative approaches.

Consequently, the FDA started an initiative in 2009 to investigate more systematic approaches for the B/R assessment and communication in the context of the human drug review process. This initiative was driven by CDER's leadership's request to be more explicit and consistent in explaining the reasoning behind benefit-risk decisions (17).

As part of the reauthorisation of the Prescription Drug User Fee Act¹² (PDUFA) V related to fiscal years 2013-2017, the FDA made certain commitments to enhance the framework for B/R assessment. These commitments are specified in Section X of the PDUFA Goals Document, titled *Enhancing Benefit-Risk Assessment in Regulatory Decision making*. The commitments include the publication of a Five Year Plan, that describes FDA's approach to incorporate a structured B/R assessment in the drug review process (48).

The remainder of this chapter covers the development and the structure, as well as the implementation of FDA's Benefit-Risk framework in regulatory practice. Finally, the results of FDA's approach to B/R assessment will be discussed.

4.2 FDA's Approach to Developing a Benefit-Risk Framework

The FDA started its initiative by defining certain principles or requirements for a benefit-risk framework. Accordingly, the framework must be established within applicable legal, regulatory and policy limits and should be appropriate throughout the lifecycle of a drug. Furthermore, the framework should enable to identify critical issues and focus the discussion on those issues. Eventually, a benefit-risk framework should integrate into existing review processes.

¹² PDUFA is a law, enacted in 1992 by the United States Congress, which enables the FDA to collect user fees from pharmaceutical companies. Those funds are destined for FDA's approval activities. PDUFA must be reauthorised every five years and the FDA is required to fulfil performance goals, that are specific to the Fiscal Years (47).

The next step within the development of a benefit-risk framework was to investigate previous regulatory decisions to ascertain the general approach and structure for B/R assessment that is already present at the FDA. The intention was to outline FDA's thinking during a drug review process. This analysis of past decisions was supported by decision science, and drug regulatory expertise including an advisory group of senior management in CDER. The focus has been primarily on challenging B/R assessments, as it is particularly important and demanding to be explicit about the rationale behind a complex benefit-risk decision. As part of this analysis, interviews were conducted with reviewers who were involved in the specific benefit-risk decision.

This analysis demonstrated that review considerations could be classified and grouped into several areas. On the one hand, therapeutic area considerations on the other hand, drug-specific factors have to be taken into account during the drug review process. Consequently, the FDA elaborated a five-step qualitative Benefit-Risk framework (Table 8) that encompasses the following key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management.

Table 8: FDA's Benefit-Risk Framework		
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

Source: FDA, Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making, PDUFA V Plan 2013, (17)

The first two decision factors, Analysis of Condition and Current Treatment Options define the context of the decision or the therapeutic area considerations. The information found here describes the current state of knowledge of the condition and an evaluation of applicable therapies. The additional decision factors, Benefit, Risk and Risk Management, demonstrate the product-specific area of the framework. These decision factors include the

evaluation of the efficacy and safety data from clinical trials, as well as potential efforts to mitigate risk.

Within each of these decision factors, reviewers have to consider the evidence and uncertainties based on the available information, and subsequently, have to draw conclusions and reasons from that evidence and uncertainties (17). During B/R assessment of medicines, reviewers have to address the following questions:

- What is the evidence from the available information?
- Where are the uncertainties? What is left unknown?
- What conclusions can be generated from that evidence?
- What are the implications for the decision (49)?

Ultimately, reviewers have to integrate and outline the information of each of the decision factors into the final row of the framework, the Benefit-Risk Summary Assessment. This summary should clearly communicate FDA's reasoning behind a regulatory decision. The summary should include conclusions from each decision factor and important differences of opinion among the review team and how they were resolved.

In fact, FDA's Benefit-Risk framework reflects the dynamic nature of B/R assessment during a drug's lifecycle, since the whole framework can be updated, as soon as new information becomes available.

In 2012, the FDA started piloting its framework in the drug review process using six new molecular entity (NME) New Drug Applications (NDAs) or Biologic License Applications (BLA). The framework has served as a template to guide reviewers which kind of data to consider during the drug review process. Question based prompts were developed to direct reviewers' completion of the framework and to elicit the critical information of the B/R assessment. The pilot demonstrated that the framework efficiently describes key considerations of B/R assessment in a concise format. A crucial finding of the pilot is that the framework should be incorporated into the existing drug review process, instead of representing an added layer (17). Accordingly, the next section covers the implementation of the framework in PDUFA V.

4.3 Benefit-Risk Framework Implementation in PDUFA V

FDA's PDUFA V commitments comprised the revision of the CDER Clinical Review¹³ Templates as well as the revision of the corresponding Manuals of Policies and Procedures (MaPP) and equivalent Center for Biologics Evaluation and Research (CBER) documents in order to integrate a structured B/R assessment in the human drug review process (48). The FDA determined a staged implementation of the Benefit-Risk framework in the human drug review process, starting during FY 2014 and 2015 with NME NDAs and BLAs. This gradual implementation should enable a continued refinement of the framework (17).

In March 2015, the FDA started applying a revised template for Clinical Reviews that includes the Benefit-Risk framework as part of the Executive Summary section (1). However, the currently available online corresponding manual, MaPP 6010.3Rev.1¹⁴ that covers the review of a NDA or BLA has been effective since December 2010 and does not include FDA's B/R framework (50). This could be due to the fact that the revision of the manual is still under development.

4.4 Discussion of the Results and Future Considerations

From the analysis of previous regulatory decisions, the FDA came to the conclusion that a structured qualitative approach best fits its drug-regulatory decision-making process. It is crucial to note that the FDA rejected quantitative decision modelling approaches for the B/R assessment of medicines. According to the FDA, assigning numerical weights to benefit and risk considerations involves subjective judgements that *'would be much less transparent, if not obscured, to those who wish to understand a regulator's thinking'* (17, p.4). In addition, quantitative decision modelling would be most appropriate for binary decisions, however, most decisions are far more complex and nuanced. The FDA concluded that the reliance on a complex model would make the entire process more difficult to understand. Nevertheless, the FDA has been well aware that quantitative assessments definitely support qualitative judgement. However, not the entire drug review process should be based on quantitative decision modelling.

Accordingly, the FDA adopted a qualitative five-step Benefit-Risk framework. These steps refer to the five key areas to be discussed during the drug review process, namely the Analysis of Condition, Current Treatment Options, Benefit, Risk and Risk Management.

The FDA determined that the purpose of its framework is to provide a standardised, predictable and accessible form, which explains the rationale behind a regulatory decision to the public. Hence, FDA's framework should represent a communication tool, while also

¹³ The Clinical Review or Medical Review serve to document the evaluation of a new drug. The Clinical Review template outlines the content and structure of the Clinical Review, that FDA's reviewer have to describe within the evaluation process (50).

¹⁴ MaPP 6010.3Rev.1: Good Review Practice: Clinical Review Template (50)

documenting the decision as reference for further regulatory decisions. A second and equally important purpose of FDA's framework is to serve as a decision support tool during the drug review process. By clearly articulating FDA's key considerations (i.e. relevant facts, uncertainties and main areas of judgment) the framework for B/R assessment should inform and clarify the regulatory discussion (17).

According to Theresa Mullin¹⁵ the framework has the potential to improve the predictability and consistency of decision-making through a standardised structure. Furthermore, transparency of regulatory decision-making can be improved as the framework clearly outlines the evidence and uncertainties and articulates the judgement behind a decision (51).

In terms of future considerations, the FDA has to elaborate guidance how to complement its framework during B/R assessment of a new drug since the revision of the manual for the Clinical Reviews is still outstanding.

¹⁵ Director, Office of Planning and Informatics, FDA, CDER

5. Comparison of EMA's and FDA's Initiatives

The FDA and the EMA, have recognised the need for a more structured and transparent B/R assessment within the drug-review process (17),(22). Furthermore, both authorities are required by legal or regulatory provisions to implement a structured B/R assessment approach. As part of the reauthorisation of the PDUFA V, the FDA made certain commitments to enhance the benefit-risk framework (48); while EMA's Roadmap to 2015 determined that the reinforcement of the benefit-risk assessment model is one of the strategic areas, to be focused on through a set of priority activities (24).

Consequently, both authorities were investing substantial resources in the evaluation of B/R assessment methods. The EMA started its Benefit Risk Methodology Project in 2009 with the aim to investigate methods that improve transparency, consistency and communication of benefit-risk decisions (23). The FDA initiated its efforts to explore more systematic approaches to B/R assessment and communication as part of the human drug review process also in 2009 (17). In fact, the efforts of both regulatory agencies share common goals, i.e. to enhance the quality of regulatory B/R assessments, to switch from implicit to explicit decision-making, to make B/R assessments more predictable, and finally to increase public confidence in B/R decisions (17), (23). However, the initiatives resulted in different approaches.

The FDA decided that a qualitative approach, the five-step FDA Benefit-Risk framework, would be the best solution for regulatory decision-making. According to Patrick Frey¹⁶, FDA's framework reflects the reality that B/R assessment is a qualitative exercise based on the quantification of various data. Furthermore, reducing complex considerations into a single scale would not capture the nuanced assessments in FDA decisions, and quantitative analysis would risk obscuring subjective expert judgement (45). Thus, the FDA adopted a qualitative framework and rejected quantitative decision modelling approaches for the B/R assessment of medicines.

The FDA Benefit-Risk framework was developed through extensive analysis and review of previous regulatory decisions. Key review disciplines were interviewed to gain an understanding of FDA's thinking during the decision-making process. As a result of this analysis, five key decision factors were identified which are included in FDA's B/R framework. In 2015 the FDA started to use the framework for the review of NME NDAs and BLAs (17).

EMA's Benefit-Risk Methodology Project, on the contrary, resulted in a graduated methodology. The use of a generic framework, the ProACT-URL was recommended to guide the B/R assessment process. It is mainly a qualitative approach that frames the

¹⁶ Director, Office of Planning and Analysis, FDA, CDER

problem and structures the drug review process. The PrOACT-URL includes a tabular display, the Effects Table, that demonstrates the key favourable and unfavourable effects as well as any uncertainties that are considered as influencing the B/R balance (32). In 2015, the Effects Table has been implemented in the B/R section of the EPARs (35). Furthermore, as a result of EMA's initiatives, decision-analytic models, based on MCDA that express the B/R ratio in quantitative terms were proposed for more complex or contentious B/R assessments (32).

The most obvious difference between the two authorities is that the FDA clearly rejects quantitative models for the B/R assessment of medicines, whereas the members of the EMA scientific committees have been divided over the usefulness of such models. It is an open question whether the EMA will implement quantitative models into the drug review process in the future. This is corroborated by the fact that the outputs of IMI PROTECT WP 5 regarding methodologies for B/R evaluation and graphical representations have not yet been implemented within EMA's regulatory practice (42).

Another disparity is that FDA's initiative resulted in one tool, the five-step FDA framework, while the EMA proposed a graduated methodology. Furthermore, the implementation or the actual use of the proposed tools within the drug review process differs. Regarding EMA's stepwise approach only the Effects Table has been implemented in the Day 80 assessment report overview guidance. Even though the project team proposed endorsing the PrOACT-URL framework as an adjunct to current CHMP processes, this framework is not included in the Day 80 assessment report guidance. If the CHMP utilises this framework for decision making, then the completed PrOACT-URL for the respective drugs should be published to ensure transparency. FDA's framework has been incorporated in the Executive Summary of the Clinical Reviews, however, the corresponding manual has not yet been revised. The CHMP assessment report Overview guidance, on the contrary has been repeatedly revised since the recommendation of the CHMP working group on B/R assessment in 2008 and currently entails a structured discussion of the B/R assessment including guidance how to generate the Effects Table.

Considering the evolution of the proposed tools, the FDA developed its framework from the analysis of previous regulatory decisions, while the EMA additionally field-tested quantitative methods that appeared in scientific literature.

6. Comparison of FDA's and EMA's B/R Assessment of Selected Medicines

6.1 Background

One of the main objectives of EMA's and FDA's B/R initiatives was to improve the communication of regulatory decisions (17), (23). FDA's and EMA's efforts have resulted in major changes regarding the B/R sections of the publicly available assessment reports which are the means for documenting the assessment and the rationale behind a B/R decision.

As a consequence of FDA's efforts, FDA's Benefit-Risk framework has been implemented for NME NDAs and BLAs in the Executive Summary of the Medical Reviews to explain its B/R assessment (1). The EMA describes its decision in the Benefit-Risk Balance section of the EPARs. As a result of EMA's B/R initiatives, the B/R section of the CHMP assessment report overview guidance has been revised to include a comprehensive and structured B/R evaluation (39).

A crucial finding of the B/R initiatives was that efficiently communicating regulatory decisions requires to differentiate between the facts and the uncertainties regarding the effects of a drug. Reviewers of both authorities have to detect and investigate sources of uncertainty in a regulatory application. The CHMP assessment report overview guidance recommends to clearly describe the uncertainties surrounding favourable and unfavourable effects, and to evaluate the impact of these uncertainties (39); while FDA's Benefit-Risk framework differs between evidence and uncertainties and the conclusions of these aspects (17).

6.2 Objective

The intention of this comparison is to investigate qualitative differences between FDA's Benefit-Risk framework as an integral part of the Medical Reviews and EMA's Benefit-Risk Balance section of the EPARs. The comparison aims to identify insights into how and what type of information each authority communicates in their B/R assessments. The purpose is to detect differences in the way each agency assesses and explains the relevant information and to examine the impact of these differences on a marketing authorisation to be explicit on the approved indication of a medicinal product.

In addition, this analysis intends to illustrate the types of complex uncertainties that reviewers must consider when determining the B/R balance based on clinical evidence. Apart from the intention to conceptualise uncertainties, this analysis should investigate if the authorities describe identical uncertainties and if there are differences in the way each authority assesses the impact of these uncertainties on the B/R balance.

6.3 Methods

Within this analysis the B/R sections of the EPARs and FDA's Medical Reviews of six selected drugs were investigated. Furthermore, the indications of the European SmPC and the US Label were compared. The EPARs and SmPCs as well as the Medical Reviews and Labels were retrieved online from the EMA and FDA website. Table 9 shows the selected medicinal products which were chosen according to the following criteria:

- For each drug, the EPAR had to include an Effects Table and the Medical Review the FDA Benefit-Risk framework as integral part of the B/R assessment section. This criterion was established to assure that the results of EMA's B/R Methodology Project as well as the results of FDA's Structured Approach to B/R Assessment were implemented in the respective B/R assessment sections.
- The difference in time between the submission dates¹⁷ of the marketing authorisation application should be less than three months, to ensure that the authorities refer to comparable study results.
- Drugs were also selected according to their therapeutic class. To investigate a diversity of B/R assessments, drugs with different therapeutic classes or indications were preferred.

Table 9: Selected Drugs within the Analysis

Coagadex, a plasma-derived blood coagulation factor X concentrate (factor X deficiency)
Ninlaro (ixazomib), an oral proteasome inhibitor (multiple myeloma)
Ocaliva (obeticholic acid), a farnesonid X receptor agonist (biliary cirrhosis)
Praxbind (idarucizumab), a humanized monoclonal antibody fragment reversal agent for the anticoagulant effect of dabigatran
Tagrisso (osimertinib), a protein kinase inhibitor, (non-small cell lung carcinoma)
Venclycto (EU) / Venclexta (US) (venetoclax), a b-cell lymphoma-2 (Bcl-2) protein inhibitor (chronic b-cell leukemia)

¹⁷ The date when the applicant submits its application for approval to the authorities.

Inspired by the method of Jay Bordoloi et al¹⁸. (52) a standardised data collection tool was developed to compare EMA's and FDA's B/R assessment as well as the approved indication for each product. The criteria to analyse the B/R sections were elaborated based on FDA's Five-Year Plan (17) and on EMA's guidance for the CHMP assessment reports (39). The analysis focused on the main factors, described in the above-mentioned documents, that should be considered within the drug approval process, and to convey regulatory decisions, i.e. the therapeutic context, the benefits, the risks, the uncertainties, the need for future studies, and finally the B/R balance.

To be more explicit, data collection focused on eight sections and each section had predefined criteria to detect whether a remarkable difference exist. The criteria listed in Table 10 were utilised to consistently investigate each section for all drugs. If at least one of the listed criteria varied, then the respective section was considered remarkably different. Questions were developed to decide whether the criteria differ (see in Section 6.4: Results). The sections 1-7 refer to the B/R assessment sections in the EPAR and Medical Review, whereas section 8 is related to the SmPC and the Label.

Table 10: Sections and Criteria to analyse EMA's and FDA's B/R Assessment and the Approved Indications	
1.	Therapeutic context (disease or condition / current treatment options)
2.	Benefits (selection of benefits / description of benefits)
3.	Uncertainties related to benefits (choice of uncertainties / description of these uncertainties)
4.	Risks (identified risks / presentation of the risks)
5.	Uncertainties related to risks (choice of uncertainties / description of these uncertainties)
6.	B/R balance (selection of concerns / conclusion)
7.	Post-marketing requirements (obligation or not / choice of recommended studies)
8.	Indication (population / disease state)

¹⁸ Jay Bordoloi et al. compared the product information in the US Package Insert to the product information provided in the EU SmPC.

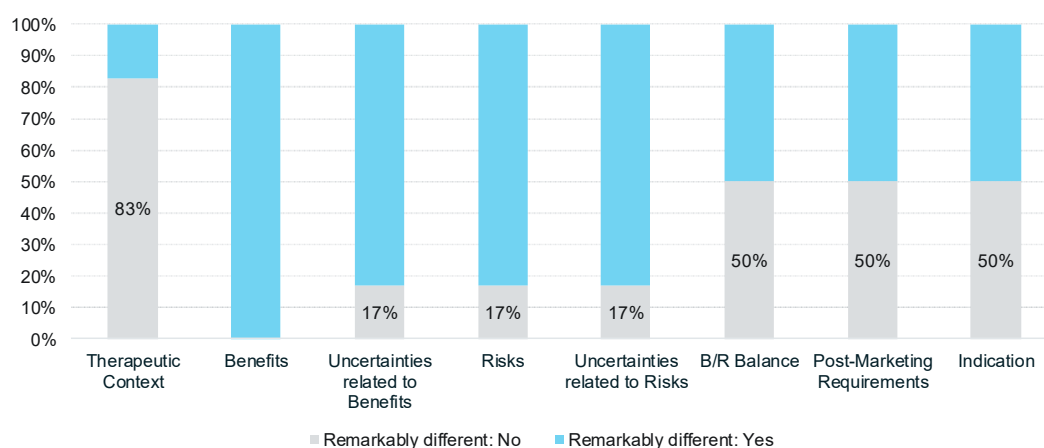
6.4 Results

The results section is divided into two parts. The first part focuses on the differences between EMA's and FDA's B/R assessments as well as on the approved indications. The second part entails an overview of the central review issues, i.e. the main uncertainties and a summary of the comparison for each selected drug. Annexes I-VI contain the comparison for each drug in more detail.

Part I - Differences between the B/R Sections and the Approved Indications

Figure 9 demonstrates the percentage of remarkable differences between the investigated sections of the assessment reports and the product information. Table 11 shows the data collection for each section and each drug. The clearest areas, where remarkable differences existed, were the sections: benefits, uncertainties related to benefits, risks, and uncertainties related to risks. In the following, the differences for each section are explained.

Figure 9: Percentage of Remarkable Differences between the Investigated Sections of the Assessment Reports and the Product Information



The 'Therapeutic context' section was remarkably different for one drug (Tagrisso), due to the fact that this drug received orphan drug status only in the US. However, the B/R section of EMA's EPAR entailed solely for Ocaliva a detailed description of the therapeutic context. This could be due to the fact that the EPAR of Ocaliva is based on the current guideline for the Day 80 assessment reports, whereas the EPARs of the other drugs are based on the former guideline that does not include therapeutic context considerations within the B/R section of the EPAR (35).

Regarding the 'Benefits', all six drugs (100%) were remarkably different in this section because the authorities partly mentioned different benefits or described the results of the clinical trials in a dissimilar way (e.g. different percent values for primary endpoints).

The section 'Uncertainties related to benefits' was remarkably different for five drugs (83%). This difference results from the fact that for three drugs (Ninlaro, Tagrisso, Venclyxto/Venclexta) the EMA identified uncertainties surrounding benefits that were not mentioned by the FDA. For the other two drugs (Coagadex, Praxbind), the EMA described the uncertainties regarding benefits more explicitly compared to the FDA.

With respect to the risks, the authorities detected identical major safety concerns for all drugs. Nevertheless, the 'Risks' section was remarkably different for five drugs (83%) because each authority mentioned other risks apart from the major safety concerns or the presentation of the safety data varied¹⁹.

The section 'Uncertainties related to risks' was remarkably different for four drugs (67%). However, it is important to note that the authorities were concerned for all drugs about identical major uncertainties surrounding risks (e.g. limited safety database) that influence the B/R balance significantly. The remarkable difference is caused by the fact that each authority reported different uncertainties in addition to the major uncertainties surrounding risks or described the uncertainties differently²⁰.

Regarding the 'B/R balance' section, there was a remarkable difference for three drugs (50%). For all the selected drugs the B/R balance was positive. However, the authorities discussed different issues or uncertainties to establish the B/R balance for three drugs. To be more explicit, the EMA considered uncertainties that were not explicitly examined by the FDA. In the case of Ninlaro, the EMA discussed the magnitude of the treatment effect, in the cases of Tagrisso and Venclyxto/Venclexta the EMA appraised the benefits for specific subpopulations.

The post-marketing requirements section was remarkably different for three drugs (50%). For two drugs (Ninlaro, Venclyxto) the EMA obligated the applicant to complete studies that were not required by the FDA. For one drug (Coagadex) the FDA required a registry study that was not demanded by the EMA.

The indication section was remarkably different for three (50%) drugs. For these drugs (Coagadex, Tagrisso, Venclyxton/ Venclexta) the SmPC includes a broader defined indication compared to the Label.

In conclusion, the information provided in the B/R sections of EMA's and FDA's assessments reports differed notably. These differences are mainly caused by the fact that the authorities described the effects or uncertainties differently or reported other additionally relevant effects or uncertainties.

¹⁹ For instance, in the case of Tagrisso, the B/R section of EMA's EPAR entails a description of the incidences of adverse events; while FDA's framework provides rather an evaluation of the safety profile comparing the expected toxicities with the de facto detected adverse events.

²⁰ For instance, in the case of Ocaliva, the FDA referred to non-clinical data, contrarily to the EMA

Table 11: Data Collection For Each Drug		Coagadex	Ninlaro	Ocaliva	Praxbind	Tagrisso	Venclyxto/ Venclexta
<u>Therapeutic context (disease or condition/ current treatment options)</u>							
<ul style="list-style-type: none"> Do the authorities estimate the incidence (e.g. orphan disease) and severity (e.g. life-threatening) of the disease similarly? Do the authorities describe current treatment options similarly (e.g. unmet medical need)? 		✓ ✓	✓ ✓	✓ ✓	✓ ✓	✗ ✓	✓ ✓
<u>Benefits (selection of benefits/ description of benefits)</u>							
<ul style="list-style-type: none"> Do the authorities report identical benefits (e.g. results of clinical trials)? Do the authorities describe the benefits in a similar manner (e.g. percent values of primary outcomes)? 		✗ ✗	✗ ✗	✗ ✗	✗ ✗	✗ ✗	✗ ✗
<u>Uncertainties related to benefits (choice of uncertainties / description of these uncertainties)</u>							
<ul style="list-style-type: none"> Do the authorities identify the same uncertainties related to benefits? Do the authorities describe these uncertainties in a comparable manner (e.g. explicitly, understandable)? 		✓ ✗	✗ ✗	✓ ✓	✗ ✗	✗ ✗	✗ ✗
<u>Risks (identified risks/ presentation of the risks)</u>							
<ul style="list-style-type: none"> Do the authorities describe identical risks? Is the presentation of the data regarding risks comparable? 		✓ ✗	✗ ✗	✓ ✓	✗ ✗	✗ ✗	✗ ✗
<u>Uncertainties related to risks (choice of uncertainties / description of these uncertainties)</u>							
<ul style="list-style-type: none"> Do the authorities report identical uncertainties related to risks? Do the authorities describe the uncertainties in a comparable manner (e.g. explicitly, understandable)? 		✓ ✓	✓ ✓	✓ ✗	✗ ✗	✗ ✗	✗ ✗
<u>B/R balance (Selection of concerns / Conclusion)</u>							
<ul style="list-style-type: none"> Do the authorities discuss identical issues or concerns to establish the B/R balance? Do the authorities come to the same conclusion (positive or negative B/R balance)²¹? 		✓ ✓	✗ ✓	✓ ✓	✓ ✓	✗ ✓	✗ ✓
<u>Post-marketing requirements (obligation or not/ choice of recommended studies)</u>							
<ul style="list-style-type: none"> Do both authorities require post-authorisation measures? Are identical post-marketing measures (e.g. clinical trial) required to confirm efficacy or safety of the drug? 		✗ ✗	✗ ✗	✓ ✓	✓ ✓	✓ ✓	✓ ✗
<u>Indication (population / disease state)</u>							
<ul style="list-style-type: none"> Is the approved indication comparable regarding population and disease state? 		✗	✓	✓	✓	✗	✗
		✓ yes; ✗ no					

²¹ This criterion is exclusively related to the overall B/R balance, to be explicit, if the benefits outweigh the risks or not. It covers not if the B/R balance is positive or negative for specific populations. This will be covered by the 'Indication' section.

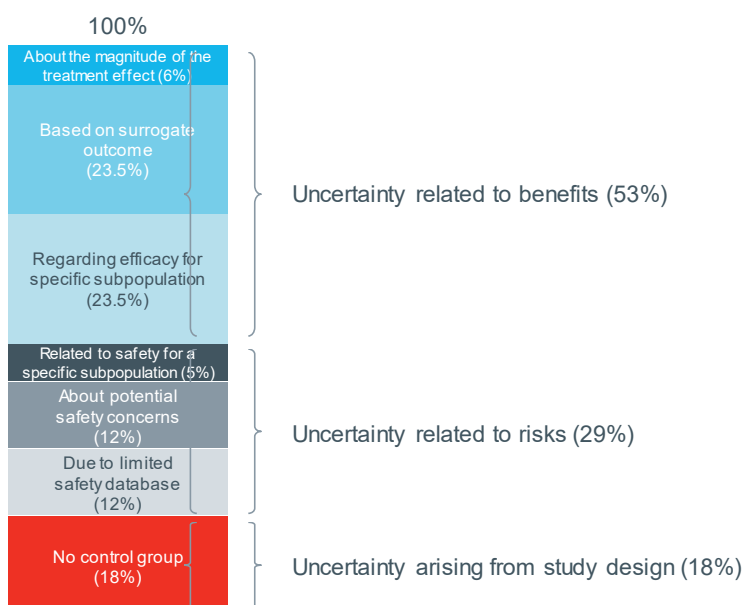
Part II – The Central Review Issues and a Summary of the Comparison for each Drug

The B/R assessment of the selected drugs was informed by an extensive body of evidence and multiple sources of uncertainty. Table 12 shows the central review issues or the major uncertainties for each drug that reviewers had to consider during the B/R assessment.

Table 12: Summary of Major Uncertainties in the B/R Assessment for Each Drug		
Drug	Uncertainties	Classification of uncertainties
Coagadex	<ul style="list-style-type: none"> Insufficient data in patients with severe FX deficiency undergoing major surgery. 	<ul style="list-style-type: none"> Uncertainty regarding efficacy for specific subpopulation.
	<ul style="list-style-type: none"> Uncertainty related to the benefits for paediatric patients. 	<ul style="list-style-type: none"> Uncertainty regarding efficacy for specific subpopulation.
	<ul style="list-style-type: none"> Due to the limited safety database it was not possible to clearly define the risks, in particular hypersensitivity reactions, thromboembolic events and the formation of inhibitors. 	<ul style="list-style-type: none"> Uncertainty about potential safety concerns (that occurred with other treatments).
Ninlaro	<ul style="list-style-type: none"> Uncertainty about the magnitude of the treatment effect (improvement in Progression-free survival (PFS)). 	<ul style="list-style-type: none"> Uncertainty about the efficacy of the medicinal product.
Ocaliva	<ul style="list-style-type: none"> Alkaline phosphatase (ALP) reduction as a surrogate to predict clinical benefit. 	<ul style="list-style-type: none"> Uncertainty regarding clinical benefit (based on surrogate outcome).
	<ul style="list-style-type: none"> Lack of data in patients with a more advanced disease. 	<ul style="list-style-type: none"> Uncertainty related to efficacy and safety for a specific subpopulation.
	<ul style="list-style-type: none"> Uncertainties surrounding risks are related to lipid disorders and liver injury. 	<ul style="list-style-type: none"> Uncertainty about potential safety concerns.
Praxbind	<ul style="list-style-type: none"> Reversal of elevated anticoagulation tests as a surrogate for clinical efficacy. 	<ul style="list-style-type: none"> Uncertainty regarding clinical benefit (based on surrogate outcome).
	<ul style="list-style-type: none"> Small safety database. 	<ul style="list-style-type: none"> Uncertainty regarding the safety profile due to limited safety database.
	<ul style="list-style-type: none"> Design of the studies (no control group). 	<ul style="list-style-type: none"> Uncertainty arising from the study design.
Tagrisso	<ul style="list-style-type: none"> Design of the studies (no control group) 	<ul style="list-style-type: none"> Uncertainty arising from the study design
	<ul style="list-style-type: none"> Objective response rate (ORR) as a surrogate for clinical benefit. 	<ul style="list-style-type: none"> Uncertainty regarding clinical benefit (based on surrogate outcome).
	<ul style="list-style-type: none"> Small safety database. 	<ul style="list-style-type: none"> Uncertainty regarding the safety profile due to limited safety database.
Venclyxto / Venclexta	<ul style="list-style-type: none"> ORR as a surrogate for clinical benefit. 	<ul style="list-style-type: none"> Uncertainty regarding clinical benefit (based on surrogate outcome).
	<ul style="list-style-type: none"> Single arm trials (no control group) 	<ul style="list-style-type: none"> Uncertainty arising from study design.
	<ul style="list-style-type: none"> Uncertainty related to benefits for patients who do not have 17p del/ TP53 mutation. 	<ul style="list-style-type: none"> Uncertainty regarding efficacy for specific subpopulation.

Figure 10 illustrates the percentage of identified uncertainties for all drugs related to risks, to benefits and to the study design. In this analysis, the most common identified uncertainties were related to the beneficial effects, followed by uncertainties related to risks. Overall, uncertainty regarding clinical benefit due to the use of a surrogate outcome and uncertainty related to efficacy for specific subpopulations were the most frequently detected uncertainties.

Figure 10: The Main Identified Uncertainties of the Sample Group



Note: Sample group includes Coagadex, Ninlaro, Ocaliva, Praxbind, Tagrisso, Venclyxto/Venclexta

The remainder of this chapter comprises a summary of the comparisons for each selected drug (Annexes I-VI). The summaries for each drug entail a brief description of the therapeutic context, followed by an explanation of the central review issues and a comparison of FDA's and EMA's approach to manage these issues or uncertainties.

1.Coagadex

Coagadex (Annex I) is indicated for the treatment of Hereditary FX deficiency, a rare and life-threatening bleeding disorder with a lack of specific therapy. The European Commission and the FDA designated Coagadex as an orphan medicinal product. Clinical trials demonstrated that Coagadex was effective in treating acute bleeds and for perioperative management of bleeding. Nevertheless, the EMA and the FDA²² discussed several uncertainties within their B/R assessment sections of Coagadex.

²² Within this analysis, the terms 'EMA' and 'FDA' are used as synonyms for the reviewers of the CHMP or CDER/CBER who were involved in the B/R assessment of the specific drugs.

Due to the rarity of the disease, the safety database was limited (18 subjects) and even if clinical trials did not give rise to concern, there were a few potential safety concerns (i.e. hypersensitivity reactions, thromboembolic events and the formation of inhibitors). The ability to clearly define the risks was limited because of the small study size. However, both authorities accepted this situation, and these uncertainties were addressed in the warnings and precautions section of the SmPC and the Label, respectively.

Apart from the uncertainties surrounding risks, both authorities focused also on uncertainties related to benefits. The crucial uncertainty was whether the expected favourable effects apply also to paediatric patients and to patients with severe or moderate FX deficiency undergoing major surgery. Both authorities considered these uncertainties and came to different conclusions. The FDA decided that a broad perioperative indication was not approvable and recommended a registry study to obtain additional data for patients with moderate or severe FX deficiency undergoing major surgery. As a result, the indication in the US Package Information (USPI) determines a limitation of use for this specific subpopulation. Furthermore, the USPI indication excludes children younger than 12 years of age.

Contrarily to the FDA, the European Commission approved Coagadex also for patients with severe FX deficiency undergoing major surgery. Additionally, according to the indication in the SmPC, paediatric patients are not explicitly excluded, however, section 4.2 of the SmPC states that the safety and efficacy in children less than 12 years of age have not been established (53), (54), (55), (56).

In summary, both authorities discussed identical uncertainties during the B/R assessment of Coagadex and came to different conclusions that become apparent in the approved indications. As a result, the European SmPC entails a broader defined indication compared to the US Label.

2. Ninlaro

Ninlaro (ixazomib) (Annex II) is an oral proteasome inhibitor indicated for the treatment of multiple myeloma. The European Commission and the FDA granted orphan designation for the treatment of multiple myeloma, a life-threatening disease.

EMA's and FDA's B/R assessment of Ninlaro vary significantly. This is mainly due to the fact that the CHMP was concerned about the magnitude of the treatment effect. In November 2015, the FDA granted traditional approval, whereas the EMA recommended a conditional marketing authorisation and the European Commission followed this recommendation in November 2016. The CHMP opinion was based on a majority decision. Furthermore, six months ago in May 2016, the CHMP proposed to refuse the marketing authorisation due to concerns about the evidence of efficacy. The central issue was that the

first interim analysis of the pivotal trial has shown a 6 months improvement in progression-free survival (PFS) that was considered clinically meaningful and significant; however, according to the CHMP, the statistical approach was not as rigorous as expected since a second interim analysis demonstrated a reduced difference in effect between the study arms. This second analysis represented a major concern for the CHMP, particularly in an application based on a single pivotal trial, where data is expected to be especially compelling.

The applicant proposed restricting the use of Ninlaro to patients with poor prognosis, who have been treated with at least two prior treatments. However, the CHMP decided that data in these subgroups were not compelling enough and that no clear scientific rationale would explain a greater efficacy in these higher risk groups. Following the CHMP proposal to refuse the marketing authorisation, the applicant provided detailed grounds for re-examination of the refusal. Subsequently, a scientific advisory group (SAG) was convened to discuss the CHMP grounds for refusal with regard to the applicant's response. The SAG decided unanimously that the efficacy data based on the primary PFS analysis and the favourable toxicity profile establish a definitely positive benefit-risk balance. The SAG acknowledged that the size of the effect, demonstrated in the primary analysis, might be overestimated and that this uncertainty has to be considered during the B/R assessment; nevertheless, this uncertainty would not be enough to diminish the conclusions about a demonstrated beneficial effect. The CHMP considered the views of the SAG and re-examined its initial opinion. Finally, the CHMP concluded by majority decision that the B/R balance of Ninlaro is favourable and recommended the granting of a conditional marketing authorisation that is contingent upon verification of efficacy data established through several post-authorisation measures.

The crucial difference between EMA's and FDA's B/R assessment of Ninlaro is that the FDA was not concerned about the magnitude of the benefit; while the EMA strongly doubted the level of efficacy evidence. This difference resulted in noticeably distinct B/R assessments. Regarding the results of the second analysis that represented a major review issue for the CHMP, the CDER mentioned that a non-inferential evaluation would have somewhat abated the improvement in PFS; however, clinically meaningful benefit would still remain. Thus, it seems that the CDER was not concerned about uncertainties surrounding the treatment effect and the Benefit-Risk Summary Assessment of FDA's framework for Ninlaro does not include an extensive discussion about the demonstrated benefit. It seems that the decision to grant a traditional approval for Ninlaro was a logical step for the FDA without substantial concerns. The CHMP on the contrary, was concerned about uncertainties regarding the efficacy data. The B/R balance was extensively discussed

and finally the CHMP recommended a conditional approval that requires the applicant to conduct various post-authorisation measures (58), (59), (60).

The comparison of EMA's and FDA's B/R assessment of Ninlaro demonstrates that despite having the same data reviewers are concerned about different facts and may have different priorities.

3.Ocaliva

Ocaliva (Annex III) is a modified bile acid indicated for the treatment of primary biliary cirrhosis (PBC), a rare and life-threatening liver disease resulting in death without adequate treatment. The European Commission and the FDA designated Ocaliva as an orphan medicinal product. Both, the EMA and the FDA identified an unmet clinical need in patients with PBC who are intolerant or have an inadequate response to Ursodeoxycholic acid (UDCA), the only approved medicine to treat patients with PBC.

The central review issue of Ocaliva was that the demonstrated beneficial effect was based on changes in biochemical parameters. Indeed, Ocaliva treatment has led to relevant alkaline phosphatase (ALP) reductions; the critical issue was if reduction in ALP is reasonably likely to predict clinical benefit. Both, the EMA and the FDA discussed this uncertainty explicitly and concluded that despite limited clinical data there would be adequate evidence to support that a reduction in ALP correlates with clinical outcomes.

Regarding the safety profile of Ocaliva, both, the EMA and the FDA concluded that albeit several uncertainties, the safety profile appeared to be overall well tolerated and for most part manageable with supportive medications or dose reductions. Remaining uncertainties surrounding risks were mainly related to lipid disorders and liver injury. These uncertainties were addressed in the post-marketing requirements.

Finally, the CHMP recommended a conditional approval for Ocaliva and the European Commission followed this recommendation. The FDA granted accelerated approval for Ocaliva. These approvals are contingent upon the completion of several post-marketing requirements or measures to confirm the efficacy and safety of Ocaliva (61), (62), (63),(64).

The review of Ocaliva particularly illustrates the complexity and the difficulty of benefit-risk decisions. Reviewers have to make decisions despite several uncertainties. In the case of Ocaliva, the central review issue was the acceptability of a biochemical parameter being used as a surrogate for clinical benefit. On the one hand there is the risk that the reduction in ALP does not correlate with clinical benefit and patients exposed to Ocaliva could experience adverse reactions. On the other hand, if ALP does predict clinical outcome and the drug is not approved, then an effective treatment would have been denied to patients.

4. Praxbind

Praxbind (refer to Annex IV) presents a specific reversal agent for dabigatran as it neutralises dabigatran's anticoagulant effect. Both, the EMA and the FDA acknowledged the therapeutic importance of such a reversal agent for patients receiving dabigatran who experience bleeding or require invasive procedure.

The effect of Praxbind was demonstrated in phase I studies in healthy subjects, supported by an ongoing phase III trial in patients. The reversal of elevated anticoagulation tests was used as a surrogate for clinical efficacy. The effect of Praxbind on clinical outcomes such as mortality or morbidity remained uncertain since there was no control group to assess whether the administration of Praxbind impacts mortality rates. Such a control group would not have been ethical according to the FDA. Furthermore, the assessment of clinical outcomes was confounded by the underlying clinical situation (e.g. trauma). In the phase III trial, 26 patients died (from 123 treated patients), however, the mortality rate was not unexpected and these patients presumably died due to their underlying serious medical conditions.

The main uncertainty surrounding the risks of Praxbind was the limited safety database. Additionally, the safety data was mainly derived from healthy subjects instead of patients typically treated with dabigatran. Nevertheless, both the EMA and the FDA concluded that Praxbind appears to have an acceptable safety profile. Both authorities required the completion of the ongoing phase III trial to further confirm the efficacy and safety of Praxbind. However, the FDA required the results of the study as an obligation of the accelerated approval of Praxbind; while the EMA recommended a full marketing authorisation and required the completion of the study as part of the Risk Management Plan (RMP) (65), (66), (67).

In conclusion, the EMA and the FDA were concerned about identical major uncertainties, i.e. the effect on Praxbind on clinical outcomes and the limited safety database.

5. Tagrisso

Tagrisso (Annex V) is a Tyrosine Kinase Inhibitor (TKI) indicated for the treatment of non-small cell lung carcinoma (NSCLC) in patients who have a specific mutation, i.e. the epidermal growth factor (EGFR) T790M mutation. NSCLC represents the majority of all lung cancers; about 10% of NSCLC patients have EGFR mutations and they are primarily treated with EGFR TKIs. Within the first year of treatment, the patients will eventually develop treatment resistant disease. The majority of these treatment resistant patients have EGFR T790 mutations. Tagrisso is indicated for these patients harboring the T790 'gatekeeper' mutation. The EMA and the FDA identified an unmet medical need for this life-threatening

disease (68), (69). However, it seems that only the FDA granted Tagrisso an orphan drug designation (70).

The central concern in the review of Tagrisso was the design of the studies. The major obstacle was the absence of a control group. Both authorities determined that the clinical benefit of Tagrisso had to be further established in adequate and well-controlled trials. Compared to the FDA, the EMA identified several further uncertainties related to benefits and described those explicitly. In particular, the EMA discussed an uncertainty related to the treatment effect in a subgroup, to be specific in patients who have not been treated previously with TKIs. The assessment of this uncertainty is particularly important as it has an impact on the approved indications. The CHMP proposed to approve Tagrisso with a broader defined indication including patients who have not previously been treated with TKIs, whereas the FDA restricted the use of Tagrisso to patients who have progressed on or after TKI therapy.

With respect to the toxicity of Tagrisso, both authorities ascertained that due to the limited size of the safety database it was not possible to clearly define the risks. However, the tolerability seemed to be adequate and manageable. Finally, the EMA proposed a conditional marketing authorisation and the FDA granted an accelerated approval for Tagrisso. Both approvals are contingent upon the results of a phase III study.

In conclusion, the main difference between FDA's and CHMP's B/R assessment of Tagrisso lies in the fact that the CHMP discussed study results for a specific subpopulation, i.e. patients who have not previously been treated with TKIs. The FDA, on the contrary did not mention this subpopulation in the Benefit-Risk framework for Tagrisso (68), (69). As a result, the European Commission approved Tagrisso also as first line treatment (71). The FDA in contrast, approved Tagrisso as second line therapy, excluding patients who have not previously been treated with a TKI (72).

6.Venclyxto (EU)/ Venclexta (US)

Venclyxto/ Venclexta Annex VI is a Bcl-2 protein inhibitor indicated for the treatment of relapsed or refractory chronic lymphocytic leukaemia (R/R CLL), a rare and life-threatening disease. Specific genetic mutations (i.e. 17p gene deletion/ TP53 mutation) present ultra-high risk poor prognostic factors for patients with CLL. The European Commission and the FDA designated Venclyxto/ Venclexta orphan drug status.

The efficacy of Venclyxto/ Venclexta was assessed in single arm trials. The objective response rate (ORR) was used as a surrogate endpoint. Despite the lack of comparative data both authorities concluded that clinically meaningful benefits were demonstrated in patients with R/R CLL harbouring the specific mutation. In contrast to the FDA, the EMA referred also to study results for patients who did not have the specific mutation.

Furthermore, the EMA discussed whether the presence of this mutation affects the activity of venetoclax. Finally, the EMA came to the conclusion that the B/R balance is also favourable for this small subpopulation (patients without specific mutation). The FDA, on the contrary, does neither describe any study results nor any uncertainty related to benefits for this subpopulation.

Regarding the risks, except for tumour lysis syndrome (TLS) and neutropenia no major safety concerns were identified. Nevertheless, due to the lack of controlled data it was difficult to clearly define the safety profile. The underlying disease was a strong confounding factor during the assessment of the observed events (73), (74). Finally, the FDA granted accelerated approval (75) and the European Commission conditional approval (76). Both authorities required the completion of a post-authorisation safety study to further establish the safety profile. Contrarily to the FDA, the EMA required also the results of a further study, particularly to confirm the B/R balance for patients without the specific mutation(73), (75).

In conclusion, FDA's and EMA's B/R assessment for Venclyxto/ Venclexta are notably different. This is mainly due to the fact that the EMA included study results for patients irrespective of the specific mutations, whereas the FDA excluded patients who do not have the genetic changes. This dissimilarity becomes apparent in the approved indications. Compared to the FDA, the CHMP proposed to approve a broader defined indication, including patients without the genetic mutations and the European Commission followed this proposal (77), (78).

6.5 Discussion of the Results and Conclusion

First of all, this analysis demonstrated the complexity and difficulty of approval decisions. The B/R assessment of the selected drugs was informed by an extensive body of evidence and multiple sources of uncertainty. The case of Ocaliva particularly illustrates the regulator's dilemma. For this drug, the central review issue was, whether a biochemical parameter is a reliable surrogate to predict clinical benefit. In fact, drugs without clinical benefit should not be approved. But what is a regulator supposed to do when the clinical effect is not clearly demonstrated? Should the regulator approve the drug and take the risk that patients could experience adverse reactions without improvement of the disease? Or should the regulator refuse the marketing authorisation, and thus deny a possible effective treatment to patients?

For all selected drugs, the uncertainties presented the central review issues that complicated the approval decisions. In this analysis, the most common identified uncertainty was related to the beneficial effects. This is mainly due to the fact that the clinical benefit was demonstrated by the evaluation of surrogate outcomes. Furthermore, in the cases of three drugs, uncertainties regarding the benefits for specific subpopulations were identified. The most obvious differences between the B/R assessments in EMA's EPAR and FDA's Benefit-Risk framework was also related to the uncertainties surrounding benefits.

In the case of Ninlaro, the EMA extensively discussed the magnitude of the treatment effect and initially proposed to refuse the marketing authorisation before the CHMP finally recommended to approve the drug. The FDA, on the contrary, was not concerned about the clinical benefit and approved Ninlaro already one year earlier than the European Commission.

In the cases of Coagadex, Tagrisso and Venclyxto/Venclexta, the SmPCs entail a broader defined indication, including specific subpopulations, compared to the Labels. This is mainly due to the fact that the EMA discussed the uncertainties related to the beneficial effects for these specific subpopulations extensively and finally concluded that the B/R balance is also positive for these subpopulations, contrarily to the FDA.

Furthermore, this analysis demonstrated that the information provided in the B/R sections of EMA's and FDA's assessment reports varied significantly. The clearest areas where remarkable differences existed between the B/R sections were: benefits, uncertainties related to benefits, risks, and uncertainties related to risks.

These differences are mainly caused by the fact that the authorities described the effects or uncertainties differently or reported other additional relevant effects or uncertainties. Considering the variety of data that regulators have to investigate in a marketing authorisation application it seems plausible that the assessment reports entail to some extent different data. However, for several drugs, it was difficult to differ between the key

benefits and risks that significantly influence the B/R balance. A quantitative approach based on MCDA could support to precisely define the key effects.

In conclusion, FDA's Benefit-Risk framework provided a clear and easily accessible presentation of the data. Nevertheless, FDA's frameworks for the selected drugs differed in terms of length and comprehensiveness. In the case of Praxbind the Benefit-Risk Summary Assessment of FDA's framework entailed information that was not mentioned in the rows of the key decision factors. Furthermore, in the case of Coagadex, FDA's framework includes only a brief summary of the data without a clear assessment of the uncertainties; whereas, FDA's framework for Ocaliva comprises a detailed and comprehensive description of the key decision factors. Indeed, more complex or difficult B/R assessments require a more detailed description of the relevant data. Notwithstanding, efficiently communicating regulatory decisions involves being explicit about the uncertainties and in the case of Coagadex the FDA did not explicitly explain the impact of the uncertainties on the B/R balance.

The Benefit-Risk Assessment sections of EMA's EPAR were generally comprehensive and detailed. For each drug the uncertainties were clearly and understandably discussed. Furthermore, it was easy to differentiate between the effects and the uncertainties since EMA's B/R section is structured into different parts provided with a heading. Even though, FDA's framework, differs between 'Evidence and Uncertainties' and 'Conclusions and Reasons', it was more difficult to distinguish uncertainties from effects.

6.6 Limitations

Limitations of this analysis arise from the small sample size and the use of a standardised, but not validated data collection tool. Thus, further investigation with a larger sample size could provide more information about differences between the B/R sections of EMA's EPAR and FDA's Medical Review. Furthermore, this analysis mainly focused on the B/R sections of the respective assessment reports, that represent only a small part of the whole assessment report. Other sections of the assessment reports or other documents have not been investigated. In addition, these sections may not represent discussions or differences of opinion between reviewers.

7. Implications for the Industry – ICH Revisions to B/R Assessment

The B/R assessment of medicines is the fundamental basis of regulatory decision-making both for sponsors and regulators. It is for this reason that the B/R assessment of medicines is not only a crucial topic for regulatory authorities but also for the pharmaceutical industry. The fact that two of the most global relevant regulatory authorities, the FDA and the EMA have turned their focus on B/R assessment methods suggested that changes could be anticipated in the way sponsors have to submit their B/R information in an approval application (11).

In order to receive a marketing authorisation for a drug, applicants have to submit an application dossier to the regulatory authorities. The International Conference on Harmonisation (ICH) Common Technical Document (CTD) is an internationally agreed format for the preparation of such applications (13). According to the ICH guideline M4E, sponsors are requested to describe their conclusions on the benefits and risks of a medicinal product in the Clinical Overview of Module 2, to be more explicit in Section 2.5.6 of the CTD (79).

In 2014, the ICH set up an Expert Working Group (EWG) to revise the above-mentioned B/R section of the ICH guideline M4E (R1). The purpose was to provide more specificity regarding the format and structure of B/R information and to harmonise the presentation of this information in regulatory submissions. The former guideline, ICH M4E (R1) provides general guidance, however, no further structure is recommended that supports industry in completing their B/R assessment.

As a result, regulators were confronted with different approaches taken by applicants, ranging from unstructured to structured qualitative, as well as quantitative methods. The revision of the ICH M4E (R1) guideline should establish a standardised presentation of B/R assessment information in submissions (80). On the one hand a standardised structure of the B/R information should assist regulators to understand the applicant's perspective, and on the other hand the revised guideline should support applicants to better comprehend what is important to a regulator's B/R decision (81).

Currently, the revised guideline ICH M4E (R2) has reached step 5 of the formal ICH procedure and will be implemented within the ICH regulatory bodies (82).

Compared to the former guideline M4E(R1), the revised guideline M4E(R2) describes the requirements for the B/R assessment far more detailed. Table 13 shows the differences between the guidelines regarding the content and structure of an applicant's B/R assessment in an application dossier. The former guideline determines a brief analysis of the benefits and risks, whereas the revised guideline recommends a clearly explained B/R assessment divided into several sections (79), (83).

Table 13: The CTD Efficacy Guideline (ICH M4E) – Clinical Overview: Comparison of B/R Requirements	
ICH M4E (R1) M 2.5.6	ICH M4E (R2) M 2.5.6.1 – 2.5.6.5
<ul style="list-style-type: none"> • Issued 2012 • A very brief analysis of benefits and risks, that identifies the most important conclusions and issues, (including efficacy, significant safety findings, dose-response relationships). • 2.5.6 Benefits and Risks Conclusions 	<ul style="list-style-type: none"> • Current step 5: Implementation • A succinct, integrated, and clearly explained benefit-risk assessment of the medicinal product for its intended use that includes the following sections: <ul style="list-style-type: none"> • 2.5.6 Benefits and Risks Conclusions <ul style="list-style-type: none"> • 2.5.6.1 Therapeutic Context • 2.5.6.2 Benefits • 2.5.6.3 Risks • 2.5.6.4 Benefit- Risk Assessment • 2.5.6.5 Appendix

Modified from: ICH Revisions for Benefit-Risk Assessment. Regulatory Rapporteur (11)

The revised guideline entails therapeutic context considerations including a description of the disease and current treatment options. Key benefits and risks should then be summarised. Furthermore, strengths, limitations and uncertainties of the benefit and risk information should be discussed. Finally, the Benefit-Risk Assessment section should provide the applicants' conclusion on the B/R assessment of the medicinal product. In this section, also key aspects of risk management should be included.

With regard to B/R assessment methods, the revised guideline states that a descriptive approach which clearly explains the interpretation of the data would generally be appropriate. The revised guideline does not prescribe a particular approach. Applicants may use methods to express the B/R assessment quantitatively, however, before using such a method, applicants should assess its utility, its complexity, and whether the method facilitates the interpretation of the results. If the applicant applies a benefit-risk methodology, detailed description of the methodology should be submitted in an appendix (79).

In conclusion, the ICH approach includes the main factors that drive the decision which are also described in the CHMP assessment report overview guidance and in FDA's B/R framework. Furthermore, the revised guideline seems to reflect FDA's view that a qualitative approach is most appropriate for B/R assessments. However, the revised guideline does not entirely exclude quantitative approaches; applicants may use such methods to assess and describe the B/R balance but only after having evaluated the usefulness of the specific method.

8. Discussion

Over the past decade a rising amount of discussion has focused on the B/R assessment of medicines and resulted in various B/R approaches developed by regulatory authorities, industry and academia. A unified methodology has not yet been established and the fact that regulators dissent over the usefulness of quantitative models complicates among others the implementation of a uniform methodology.

The intention of this thesis is to compare EMA's and FDA's approaches to the B/R assessment of human medicines within the drug approval process. The FDA has rejected quantitative approaches and adopted instead a qualitative approach, the FDA five-step Benefit-Risk framework. The EMA, on the contrary, proposed a stepwise approach including the use of quantitative models for more intricate decisions. However, it seems that regulators within the EMA still disagree about the practicality of quantitative models. The IMI PROTECT project has resulted in comprehensive recommendations on the use of various methodologies and visualisation techniques, though such methods have not yet been implemented in EMA's regulatory practice. In this context, the question rises whether more research is necessary to incorporate such B/R methodologies in the European drug review process or whether such methods are not suitable to be implemented within EMA's daily regulatory practice. Although EMA's report on PROTECT's outcomes revealed that several European regulators may not be willing to implement such models, it is too early to draw any firm conclusions as EMA's survey included only a small number of European regulators, and therefore, the results of the survey do not represent the view of the EMA as a whole. Furthermore, EMA's report on PROTECT's outcomes was published only recently, in September 2016. Hence, it remains unclear whether the EMA will incorporate B/R methodologies and graphical representations within the B/R assessment process in the future.

The analysis of FDA's and EMA's B/R assessments of selected drugs demonstrates that such assessments are complex and challenging. Most notably, the uncertainties represent central review issues that significantly impede decision-making. Furthermore, it is particularly difficult to verbalise why the benefits of a drug outweigh the risks and how far uncertainties influence the B/R balance. At present, both authorities explain the rationale behind approval decisions in a descriptive manner. Even though FDA's B/R framework and the CHMP assessment report overview guidance determine similar key decision factors, the discussion of the B/R balance may differ greatly. The fact that different reviewers interpret the same evidence differently suggests that B/R assessments are based on subjective judgements. The regulators' challenge lies in being explicit about subjective judgments. Regulators have a responsibility to convey approval decisions in a clear and understandable form to ensure transparency and accountability.

The intention of B/R methodologies, irrespective of quantitative or qualitative, is to support the analysis and communication of regulatory decisions. Qualitative methods are particularly suitable to frame the decision, to structure the decision making process and to provide the 'big picture' of the decision. Furthermore, quantitative models based on MCDA could support regulators to define the key aspects that primarily influence the B/R balance more precisely and explicitly.

However, there remains a crucial problem which cannot be resolved by B/R frameworks, neither by qualitative nor by quantitative methods. Such methods do not enable regulators to be explicit about 'unknown unknowns'. Within the drug approval process the 'unknown unknowns' represent the missing information that regulators or other stakeholders are not aware of at the time of approval. According to Janet Woodcock, the 'unknown unknowns' have historically caused some of the biggest safety controversies (18).

Indeed, safety issues that arise in the post-market phase when the drug is applied outside the restricted clinical trial population undermine public confidence in decisions made by regulatory authorities. Structured B/R methods cannot prevent tragic events and criticism but they can contribute to a more transparent and auditable decision-making process. According to Baruch Fischhoff²³, a better method does not lead to fewer conflicts, but to better conflicts and a more constructive discussion (84).

In conclusion, B/R assessments of medicines are subjective, based on expert judgment and objective facts. B/R methodologies, irrespective whether qualitative or quantitative cannot replace human judgement, however, such methods add clarity and transparency about subjective evaluations. The FDA has adopted a qualitative approach, whereas EMA's B/R initiatives resulted in a graduated methodology. Furthermore, several organisations have developed various frameworks of differing complexity. The implementation of a consistent approach is hampered by the lack of a one-size-fits all B/R assessment approach. In fact, B/R methodologies are valuable tools to improve the analysis and communication of B/R assessments, nevertheless weighing the benefits against the risks remains a challenging process which requires assessments and finally, decisions on individual basis.

²³ Howard Heinz University Professor, Member of the Institute of Medicine, past President of the Society for Judgment and Decision Making and the Society for Risk Analysis, and former chair of FDA's Risk Communication Advisory Committee

Glossary

Term	Definition
Added value graph	A graph that demonstrates the benefit-risk balance of a drug and its comparator(s) in quantitative terms. This graph includes a bar for each of the alternatives, e.g. drug under assessment and placebo. Each bar is divided into segments, the favourable and the unfavourable effects. This stacked bar graph is based on MCDA and provides an overall comparison of the options.
BRAT Framework	A descriptive framework structured into six steps: define the decision context, identify outcomes, identify and extract source data, customise the framework, assess outcome importance, display and interpret key benefit-risk metrics.
Difference Display	A bar graph that demonstrates the differences between two treatment groups in terms of benefit and risk scores. This bar graph is based on MCDA and clearly shows for each criterion (i.e. favourable or unfavourable effect) whether the drug or its comparator performs better.
Effects Table	A chart that illustrates the key aspects within the B/R assessment of a drug. This chart represents the benefits and risks of a drug and a control group and includes limitations or uncertainties of the effects for the drug. Effects Tables were used in EMA's Benefit Risk Methodology project and in the IMI PROTECT project.
Effects Tree or Value Tree	A decision support tool that demonstrates important facts of a decision in a tree-like graph. Within the B/R assessment of a drug this tool serves to illustrate the benefits and risks of a drug that have a significant impact on the B/R balance.
FDA Benefit-Risk Framework	A qualitative framework that describes and structures the key aspects of a drug's B/R assessment in a table. The table includes five decision factors (analysis of condition, current treatment options, benefit, risk, risk management) and a row for the summary of the assessment. Facts and uncertainties are separated from conclusions within the table.
Multi criteria decision analysis	Encompasses a collection of methods that could be applied for complex decisions with different options and multiple criteria. Such methods quantify the performance of two or more alternatives on specified criteria. Within the B/R assessment of a drug, the different options are the drug under evaluation and its comparator(s) (e.g. placebo), while the criteria refer to the benefits and risks. Assessors have to judge the performance of the drug and its comparators on the favourable and unfavourable effects according to their clinical relevance. To establish a common unit of a preference value all effects are weighted. Those weighted effects can then be summed to establish the overall benefit-risk balance for each drug in quantitative terms. Visual representations like the Added value bar help to demonstrate the B/R balance.
PrOACT-URL	A framework that is not specific to the B/R assessment of medicines but suitable to evaluate problems with multiple criteria. PrOACT-URL serves to frame the decision and guide the decision-making process. It consists of eight steps: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions. It is mainly a qualitative framework but can be combined with quantitative models, e.g. MCDA. Within EMA's Benefit-Risk Methodology project and the IMI PROTECT project, this framework was used in case studies.
Qualitative benefit risk assessment approaches	A method that structures the B/R assessment or frames the problem in a descriptive manner. An example for a qualitative B/R assessment approach for a drug is the FDA Benefit-Risk framework.

Quantitative benefit risk assessment approaches	An approach that enables decision-makers to assign numerical weights to benefits and risks in order to quantitatively express the B/R balance of a drug. The intention of such methods is to transfer expert judgment into values in order to put benefits and risks on the same scale. Several quantitative approaches within the B/R assessment of drugs are based on MCDA. However, there are various quantitative models of differing complexity.
Sensitivity analysis	A technique to evaluate to how far different values or uncertainties influence a decision. Sensitivity analysis investigates the robustness of a decision. Within the B/R assessment of a drug sensitivity analysis helps to explore to what extent the B/R balance changes if the value of the input data is changed, e.g. the value of a specific risk like QTc prolongation. Sensitivity analysis is one of the steps within the MCDA process.
UMBRA	The intention of the UMBRA framework is to incorporate common features of existing frameworks into a unified methodology. This framework helps to establish the decision context, identify and assess the benefits and risks and to interpret the results. It consist of the following eight steps: decision context, building the value tree, refining the value tree, relative importance of benefits and risks, evaluating the options, evaluating uncertainty, concise representation of results (visualisation), expert judgement and communication.

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Annex I: Comparison of EMA's and FDA's B/R Assessment of Coagadex				
Coagadex, a Plasma-Derived Blood Coagulation Factor X Concentrate, Factor X Deficiency				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR²⁴	FDA's Clinical Review²⁵	Comparison of EPAR and Clinical Review	
Approval date	16/03/2016	20/10/2015	5 months	
Submission date	06/05/2015	27/04/2015	~ 1 week	
Review classification	<ul style="list-style-type: none"> Orphan designation 	<ul style="list-style-type: none"> Orphan designation 		
Disease or condition	<ul style="list-style-type: none"> Detailed description of FX deficiency and current treatment options under section: Scientific discussion→2.1 Introduction. 	<ul style="list-style-type: none"> Hereditary FX deficiency is a rare, but potentially life-threatening bleeding disorder caused by inherited lack of coagulation factor X. The clinical manifestations include haemorrhage into the skin, muscles, or soft tissues, menorrhagia, excessive bleeding following surgery or trauma and cerebral haemorrhage. The objectives of treatment are to effectively control bleeding during acute bleeding episodes (on-demand treatment) and in the surgical setting (perioperative management). 	<ul style="list-style-type: none"> Both authorities describe hereditary factor X deficiency as a rare and potentially life-threatening disease. 	
Current treatment options	<ul style="list-style-type: none"> Patients are currently treated with coagulation factor compounds such as FFP or prothrombin complex concentrates. Dosing is difficult. Potential complications are thrombosis and embolism. 	<ul style="list-style-type: none"> Currently, there are no approved purified FX concentrate replacement therapies. Current treatment regimens (FFP and PCC) are not labelled with the specific FX content. Possible adverse reactions are thrombosis and transfusion related acute lung injury. 	<ul style="list-style-type: none"> Both authorities enumerate disadvantages of current treatment options and draw the same conclusion: There is a lack of specific therapy to treat hereditary FX deficiency. 	
Benefits	<ul style="list-style-type: none"> In the pivotal study, Ten01, Coagadex was able to satisfactorily treat bleeding events in subjects with severe (14) or moderate (2) hereditary FX deficiency. <ul style="list-style-type: none"> Of the 187 treated bleeds, nearly all (98.4%) were considered a treatment success. 	<ul style="list-style-type: none"> Of the 208 bleeds treated with Coagadex, greater than 90% were treated effectively. Coagadex was used for perioperative management for seven surgical procedures, incl. four major surgeries that were performed in two subjects with mild FX deficiency and three 	<ul style="list-style-type: none"> Both authorities report the results of the pivotal clinical trials. Compared to the CBER, the CHMP describes the benefits in more detail. 	

²⁴ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003855/WC500204191.pdf

²⁵ <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM472311.pdf>

Coagadex	EMA's EPAR	FDA' Clinical Review	Comparison of EPAR and Clinical Review
Cont. benefits	<ul style="list-style-type: none"> ○ In addition, the overall efficacy in three minor surgeries undertaken in this trial was rated as excellent by investigators. • Four major surgeries undertaken in two subjects in trial Ten03 demonstrated that blood loss during and after these procedures was less than expected or as expected under FX coverage. <ul style="list-style-type: none"> → These results underline that Coagadex acts as a functional blood coagulation factor X in the blood of the recipient and is able to correct symptoms of FX deficiency. • Two patients with recurring bleeding events used routine FX infusions as a long-term prophylactic treatment also this was a protocol deviation. <ul style="list-style-type: none"> ○ Available data indicate that it was effective in both patients and reduced the bleeding rate meaningfully. • Description of data that supports the usefulness of FX for short-term prophylaxis. 	<p>minor surgeries in three subjects with moderate or severe disease. One minor surgery was considered a failure by FDA's clinical reviewer as a result of postsurgical bleeding.</p> <ul style="list-style-type: none"> • In conclusion: <ul style="list-style-type: none"> ○ Results of trial Ten01 demonstrate that Coagadex is effective in treating acute bleeds ○ Data from Ten01 and Ten03 demonstrate that Coagadex is effective for perioperative management of bleeding. • Description of further benefits in section 11.2 <i>Risk-Benefit Summary and Assessment</i>. 	<ul style="list-style-type: none"> • For instance, the CHMP describes available data regarding long-term and short-term prophylaxis of bleeding. • However, both authorities draw the same conclusion: Coagadex is effective in treating acute bleeds and for perioperative management of bleeding.
Uncertainty in terms of benefits	<ul style="list-style-type: none"> • The final efficacy assessment in surgery is influenced by missing data regarding major surgery in patients with severe FX deficiency. <ul style="list-style-type: none"> ○ However, it is expected that Coagadex will also provide sufficient protection for this subpopulation undergoing major surgery. ○ Including dosing regimens for all severity grades will provide appropriate guidance to clinicians. ○ The applicant has an agreement with the FDA to provide additional data on three additional patients with moderate to severe FX deficiency undergoing major surgical procedures. • Although the final study report from study Ten02 on PK and clinical data in paediatric patients is still outstanding, preliminary data demonstrate that Coagadex would have comparable effects in paediatric patients younger than twelve years of age. 	<ul style="list-style-type: none"> • The Benefit-Risk framework for Coagadex does not include uncertainties regarding benefits. The following uncertainty is described in section 11.3 <i>Discussion of Regulatory Options</i>: <ul style="list-style-type: none"> • Insufficient data in patients with severe FX deficiency undergoing major surgery. <ul style="list-style-type: none"> ○ Therefore, a broad postoperative indication was not approvable. ○ Additional data is needed. ○ These data should be obtained from a registry study. • Furthermore, this section entails four regulatory options that includes or excludes children <12 years of age in the indication. 	<ul style="list-style-type: none"> • The FDA and the EMA describe the same important uncertainty related to benefits, i.e. insufficient data regarding major surgery in patients with severe FX deficiency. • This uncertainty has an impact on the approved indications. • According to the FDA, a broad postoperative indication was not approvable. The FDA excludes a perioperative indication in patients with moderate to severe disease. • The CHMP, on the contrary proposes to approve Coagadex also for perioperative management of patients with moderate or severe disease. • Furthermore, the CHMP clearly describes an uncertainty regarding the benefits for paediatric patients, with the conclusion that Coagadex would have comparable effects in children <12y

Coagadex	EMA's EPAR	FDA's Clinical Review	Comparison of EPAR and Clinical Review
Cont. uncertainty in terms of benefits			<ul style="list-style-type: none"> The FDA does not explicitly describe this uncertainty, but mentions several regulatory options for approval. According to the USPI Coagadex is not approved for paediatric patients.
Risks	<ul style="list-style-type: none"> Only a small proportion (3%) of observed TEAE were assessed as related to Coagadex. Related adverse events (infusion site reactions, fatigue and back pain) were of mild or moderate severity and manageable. The nature and frequency of all AEs reported do not give rise to concern and did not reveal unexpected safety signals. 	<ul style="list-style-type: none"> All the evidence indicates that Coagadex was well tolerated. 	<ul style="list-style-type: none"> The FDA and the EMA conclude that the safety profile appears to be acceptable. However, compared to the FDA, the EMA briefly describes the adverse reactions.
Uncertainty regarding risks	<ul style="list-style-type: none"> The available safety database of 18 unique subjects is very small, but taking into account the rarity of the disease, it is acceptable. A high and variable percentage of aggregates in the final drug product could potentially cause tolerability problems or the formation of inhibitors that were not captured during these small trials (with reference to the RMP) Information will be collected at post-marketing phase. 	<ul style="list-style-type: none"> The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of FX inhibitors. <ul style="list-style-type: none"> There were no reports of FX inhibitors or confirmed thromboembolic events. The ability to clearly define these risks is limited by the study size. 	<ul style="list-style-type: none"> The CHMP and the FDA identify the same main uncertainty related to risks and identical potential safety concerns: <ul style="list-style-type: none"> Due to the limited safety database (18 unique subjects) the ability to clearly define the risks is limited Potential safety concerns are tolerability problems, thromboembolic events, and the formation of inhibitors
Benefit-risk balance	<ul style="list-style-type: none"> Brief summary of the therapeutic context. The favourable effects of Coagadex are considered to outweigh the observed unfavourable effects, which were generally benign and did not negatively impact the patients' ability and willingness to continue treatment with Coagadex. Two patients even initiated regular prophylactic infusions once weekly in order to stave off bleeding events. These favourable effects are expected to apply also to patients younger than 12 years of age, in patients with severe or moderate FX deficiency undergoing 	<ul style="list-style-type: none"> Succinct summary of the therapeutic context Description of the safety data: <ul style="list-style-type: none"> The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of FX inhibitors The ability to clearly define these risks is limited by the study size However, of the 18 subjects treated with Coagadex, no subjects were positive for FX inhibitors or had a reported thromboembolic event. There were no reports of anaphylaxis 	<ul style="list-style-type: none"> The EMA and the FDA discuss the same issues during the review of Coagadex: <ul style="list-style-type: none"> Due to the rarity of the disease, the safety database is limited (18 subjects). Even if the clinical trials did not give rise to concern, there are a few potential safety concerns (i.e. hypersensitivity reactions, thromboembolic events and the formation of inhibitors). Due to the limited safety database, rare events cannot be expected to be captured. However, both the EMA and the FDA accept this situation since FX deficiency is a rare disease.

Coagadex	EMA's EPAR	FDA's Clinical Review	Comparison of EPAR and Clinical Review
<p>Cont. benefit-risk balance</p>	<p>major surgery and for preventative therapy.</p> <ul style="list-style-type: none"> From a clinical point of view FX was shown to be safe and efficacious product. Coagadex will present the only specific therapy for patients with hereditary FX deficiency. Discussion on the B/R balance: <ul style="list-style-type: none"> The efficacy of Coagadex for the treatment of bleeding episodes and prophylaxis in minor surgery in subjects 12 years of age or older is considered established. Data from two patients initiating long-term prophylaxis underline the usefulness for long-term prevention of bleeds. In addition, the applicant has adequately addressed open issues with regard to short-term preventative treatment and major surgery in patients with severe FX deficiency. Preliminary data Ten02 (paediatric trial) support an extrapolation of the beneficial effects to the paediatric population. Summary of the safety profile with the conclusion that rare events cannot be expected to be captured during the clinical development programme. Recommendation: The CHMP considers by consensus that the B/R balance of Coagadex is favourable and therefore, recommends the granting of the MA. 	<ul style="list-style-type: none"> Description of the benefits: <ul style="list-style-type: none"> The clinical response to Coagadex for on-demand treatment and control of bleeds was good or excellent for 99% of 187 bleeds. Coagadex was considered effective in controlling bleeding in 4 subjects who underwent 6 surgical procedures. Data from Ten01 and Ten03 demonstrate that the proposed dosing for the treatment of acute bleeds and for perioperative management of major surgical procedures in subjects with mild disease are appropriate. If approved, Coagadex would be the first purified plasma-derived FX product approved in the U.S. Approval would fulfill an unmet medical need. Discussion of regulatory options: As a result of insufficient data in subjects with the highest risk for postoperative bleeding (i.e. subjects with moderate or severe FX deficiency) a broad perioperative indication was not approvable. In order to support a perioperative indication in patients with moderate to severe disease, the FDA advised the company that additional data is needed. 	<ul style="list-style-type: none"> The central uncertainties are related to benefits. The crucial question is if the expected favourable effects apply also to paediatric patients and in patients with severe or moderate FX deficiency undergoing major surgery. The CHMP considers these uncertainties and concludes that the favourable effects are expected to apply also in this subpopulations. The FDA, on the contrary, discusses several regulatory options related to the indication for Coagadex, and finally restricts the indication.

Coagadex	EMA's EPAR	FDA' Clinical Review	Comparison of EPAR and Clinical Review
Post-market requirements	-	<ul style="list-style-type: none"> The applicant is required to evaluate the safety and efficacy of Coagadex for perioperative management in patients with moderate to severe hereditary Factor deficiency undergoing major surgical procedures in Study TEN06, a post-marketing registry study of perioperative management of moderate to severe hereditary factor X deficient patients receiving Coagadex (human factor X concentrate) for major surgical procedures²⁶. 	<ul style="list-style-type: none"> Contrarily to the EMA, the FDA recommends a registry study to obtain additional data (for patients with severe FX deficiency undergoing major surgery).
2. Comparison of the European SmPC and the US Prescribing Information (PI)			
Coagadex	European SmPC ²⁷	USPI ²⁸	Comparison oSmPC and USPI
Indication	<ul style="list-style-type: none"> Coagadex is indicated for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary factor X deficiency. 	<ul style="list-style-type: none"> Coagadex is indicated in adults and children (aged 12 years and above) for: <ul style="list-style-type: none"> On-demand treatment and control of bleeding episodes Perioperative management of bleeding in major surgery in patients with mild hereditary FX deficiency. Limitation of Use: Perioperative management of bleeding in major surgery in patients with moderate and severe FX deficiency has not been studied 	<ul style="list-style-type: none"> The indication of Coagadex in the SmPC is broader defined compared to the USPI. The USPI excludes patients younger than 12 years of age and patients with severe FX deficiency undergoing major surgery. According to the indication of the SmPC, pediatric patients are not explicitly excluded, nevertheless, section 4.2 of the SmPC states that the safety and efficacy of Coagadex in children less than 12 years of age have not yet been established.

²⁶ <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM468124.pdf>

²⁷ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003855/WC500204189.pdf

²⁸ <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM468127.pdf>

Annex II: Comparison of EMA's and FDA's B/R Assessment of Ninlaro				
Ninlaro, Ixazomib, Multiple Myeloma				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR²⁹	FDA' Medical Review³⁰	Comparison of EPAR and Medical Review	
Approval date	21/11/2016	20/11/2015	~ 1 year	
Submission date	30/07/2015	10/07/2015	~ 3 weeks	
Review classification	<ul style="list-style-type: none"> Orphan drug designation. Conditional approval. 	<ul style="list-style-type: none"> Orphan drug designation³¹. 		
Disease or condition	<ul style="list-style-type: none"> Brief description of multiple myeloma (MM) in section Scientific Discussion → 2.1 Introduction. 	<ul style="list-style-type: none"> Multiple myeloma is not a curable disease and is associated with morbidity and mortality. The typical course of multiple myeloma is shortened periods of disease inactivity with the disease becoming unresponsive to treatment. Relapsed multiple myeloma is a progressive and fatal disease. 	<ul style="list-style-type: none"> Both authorities describe MM as a life-threatening disease. The European Commission and the FDA granted orphan designation for the treatment of MM. 	
Current treatment options	<ul style="list-style-type: none"> Succinct description of current treatment options in section Scientific Discussion → 2.1 Introduction. 	<ul style="list-style-type: none"> Current treatment options are not curative. Current treatments have toxicities that may limit use in certain patients. Effective therapy for MM, with different safety profiles, are necessary to provide options to patients. 	<ul style="list-style-type: none"> The EMA enumerates current treatment options without describing the benefits and risks of these available options in section 2.1 of the EPAR. The FDA, on the contrary, clearly states in the Benefit-Risk framework of Ninlaro that the use of current treatments is limited due to toxicities, and therefore, effective therapies with different safety profiles are required. Nevertheless, both authorities acknowledge that there is an unmet medical need for patients with MM who received at least one prior therapy. 	

²⁹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003844/WC500217623.pdf

³⁰ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000MedR.pdf

³¹ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000Approv.pdf

Ninlaro	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Benefits	<ul style="list-style-type: none"> In pivotal trial, the ixazomib triplet regimen had a 35% improvement in the primary endpoint PFS compared to placebo regimen and reached a statistically significant difference (HR 0.742). PFS in all subgroup populations was in favour of ixazomib regimen (HR<1). Overall survival (OS) favours the ixazomib regimen (median OS not reached in either arm). The ixazomib regimen delayed the time to disease progression by approximately 6 months. Duration of response to treatment is longer with ixazomib regimen. The supportive data from the China Continuation Study provided a statistical and clinically significant effect in terms of PFS. 	<ul style="list-style-type: none"> In a double-blind, randomized, placebo-controlled trial, ixazomib demonstrated an improvement of progression free survival of 4.1 to 5.9 months when added to lenalidomide and dexamethasone. No improvement in overall survival has been demonstrated. 	<ul style="list-style-type: none"> Compared to the FDA, the EMA describes the results from the pivotal trial in more detail. The FDA states solely the improvement of PFS, whereas the EMA refers also to the duration of response and supportive data from the China Continuation Study.
Uncertainty in terms of benefits	<ul style="list-style-type: none"> Updated efficacy data from a second interim analysis representing the most up-to date data, showed a reduced difference between arms in the overall ITT population for PFS, response rates and time to progression compared to previous analysis. Although higher effects were observed in the subgroup of patients with at least 2 prior therapies, this observation is not supported by appropriate adjustments for multiplicity and lacks convincing biological and clinical plausibility. Uncertainty about the magnitude of the treatment effect (improvement of PFS). The efficacy evaluation is primarily based on assessment of PFS and requires verification of the effect on overall survival. <ul style="list-style-type: none"> The median OS is not yet evaluable and the data is considered immature. 	<p style="text-align: center;">-</p>	<ul style="list-style-type: none"> The crucial difference between the authorities is that the FDA appears to be convinced that the data from the single pivotal study are sufficient to demonstrate a relevant benefit for Ninlaro; while the EMA is concerned about the magnitude of the treatment effect (gain in PFS). EMA's concerns refer to updated efficacy data from a second interim analysis that demonstrated a reduced difference in effect between the ixazomib arm and the placebo arm. <ul style="list-style-type: none"> The reduced difference relates to PFS, response rates, and time to progression. The hazard ratio for the updated analysis was 0.818, while the previously reported was 0.742. The FDA comments on this second analysis in the summary assessment of the framework (see in row: B/R balance)

Ninlaro	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Risks	<ul style="list-style-type: none"> • Listing of the most frequently reported adverse reactions. • More detailed description of thrombocytopenia, gastrointestinal toxicity and peripheral neuropathy. <p>→ Overall, ixazomib has significantly lower toxicity and more favourable safety profile that is superior to that of available treatment options.</p>	<ul style="list-style-type: none"> • Enumeration of treatment emergent adverse events that were increased with the addition of ixazomib <p>→ The overall safety profile is acceptable to the patient population.</p>	<ul style="list-style-type: none"> • Compared to the FDA, the EMA describes the risks in more detail, particularly for the events thrombocytopenia, gastrointestinal toxicity and peripheral neuropathy. • However, both authorities conclude that the safety profile is acceptable and there are no major concerns.
Uncertainty regarding risks	<ul style="list-style-type: none"> • There are no important uncertainties in the knowledge of unfavourable effects. 	–	<ul style="list-style-type: none"> • Neither the FDA, nor the EMA describes any uncertainties related to risks.
B/R Balance	<ul style="list-style-type: none"> • Concise description of the identified favourable and unfavourable effects. • Considerations to the benefit-risk balance: <ul style="list-style-type: none"> ◦ The delay in disease progression is clinically relevant. ◦ The possible uncertainty about the magnitude of the effect seems acceptable given the favourable toxicity profile and considering that ixazomib is an oral medication. ◦ The benefit risk balance for ixazomib is considered positive, albeit the efficacy evidence is not as comprehensive as normally required. • Recommendations following re-examination: <ul style="list-style-type: none"> ◦ The CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the B/R balance of Ninlaro was favourable and recommended the granting of the conditional MA. 	<ul style="list-style-type: none"> • Brief summary of ixazomib's pharmacological mechanism of action, the disease, and current treatment options. • Description of the benefits: <ul style="list-style-type: none"> ◦ PFS was 14.7 months in the placebo arm to 20.6 months in the ixazomib arm. ◦ The stratified hazard ratio was 0.74. ◦ The improvement in PFS is abated somewhat with a subsequent non-inferential evaluation, however, there remains clinically meaningful benefit. ◦ Ixazomib is an oral medication. • Summary of ixazomib's safety profile. • Conclusion: <ul style="list-style-type: none"> ◦ Ixazomib adds an additional treatment option with a different safety profile to current treatment options. ◦ The recommendation is traditional approval. 	<ul style="list-style-type: none"> • Considering ixazomib's benefit and risks, the FDA concludes that the primary efficacy benefit demonstrated substantial evidence of efficacy and that the risks are acceptable and do not outweigh the benefit. <ul style="list-style-type: none"> ◦ It is interesting to note that the FDA mentions a 'non-inferential evaluation' which has somewhat abated the improvement in PFS. However, the FDA does not attach importance to that second analysis and seems to be still convinced that there remains clinically meaningful benefit. • The EMA, on the contrary, discusses the benefit-risk balance with focus on the uncertainty regarding the magnitude of the effect. <ul style="list-style-type: none"> ◦ CHMP's opinion related to the favourable B/R balance of Ninlaro was concluded by majority decision. ◦ The CHMP recommends to grant a conditional approval. ◦ A report of divergent positions is appended to the EPAR of Ninlaro.

Ninlaro	EMA's EPAR	FDA' Medical Review	Comparison of EPAR and Medical Review
Post-market requirements	<ul style="list-style-type: none"> • Obligation to conduct a post-authorisation efficacy study (PAES) to provide a report on overall survival from the phase 3, randomized, double-blind study. • As a specific obligation of the conditional marketing authorisation, the MAH shall complete: <ul style="list-style-type: none"> ◦ A phase 3, randomized, study in patients with relapsed and/or refractory MM. ◦ A phase 3, randomized study in patients with newly diagnosed MM. ◦ A phase 3 randomized study of maintenance therapy in patients with MM following autologous stem cell transplant. ◦ A global prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in MM patients. 	<ul style="list-style-type: none"> • There are no post marketing requirements or post marketing commitments. 	<ul style="list-style-type: none"> • On the contrary to the FDA, the EMA requires various phase 3 trials and one observational study to provide comprehensive evidence of efficacy.
2. Comparison of the European SmPC and the US Label			
Ninlaro	European SmPC ³²	US Label ³³	Comparison of the SmPC and the Label
Indication	Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.	Ninlaro is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.	<ul style="list-style-type: none"> • There are no differences in the approved indications.

³² http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003844/WC500217620.pdf

³³ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208462bl.pdf

Annex III: Comparison of EMA's and FDA's B/R Assessment of Ocaliva				
Ocaliva, obeticholic acid, Biliary Liver Cirrhosis				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR³⁴	FDA's Medical Review³⁵	Comparison of EPAR and Medical review	
Approval date	12/12/2016	25/07/2016	~ 4.5 months	
Submission date	08/06/2015	27/06/2015	~ 3 weeks	
Review classification	<ul style="list-style-type: none"> Orphan drug designation Conditional approval 	<ul style="list-style-type: none"> Orphan drug designation Accelerated approval 		
Disease or condition	<ul style="list-style-type: none"> Primary biliary cirrhosis (PBC) is a rare, serious, life-threatening liver disease characterised by cholestasis with progressive impairment of bile flow in the liver. <ul style="list-style-type: none"> Hepatocellular injury results in a local inflammatory response and leads to secretion of alkaline phosphatase (ALP). In patients with an inadequate response to therapy, the disease frequently progresses to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant. 	<ul style="list-style-type: none"> PBC is a slowly progressive, serious and rare liver disease characterised by inflammatory destruction of interlobular and septal bile ducts. <ul style="list-style-type: none"> PBC predominantly affects women with a typical age of onset 40-60 years. Exact pathogenesis is unknown but thought to occur in genetically predisposed patients in the presence of environmental triggers. Patients eventually progress to liver cirrhosis, liver failure, hepatocellular cancer and death or liver transplant. 	<ul style="list-style-type: none"> Both authorities describe PBC as a rare, serious and life-threatening disease that results in liver transplant or death without adequate treatment. 	
Current treatment options	<ul style="list-style-type: none"> Ursodeoxycholic acid (UDCA) is currently the only approved medicine to treat PBC. <ul style="list-style-type: none"> UDCA improves biochemical indices, such as ALP and bilirubin, and delays histological progression. Studies provided strong evidence that UDCA increases progression-free survival. However, up to 50% of UDCA-treated patients either fail to respond or have a suboptimal. 	<ul style="list-style-type: none"> UDCA is the only medical treatment available. <ul style="list-style-type: none"> Overall, UDCA has a good safety profile. Non-cirrhotic PBC patients who achieve a biochemical response with UDCA have survival comparable to that of a healthy population. However, about 40% achieve inadequate response with UDCA and a small percentage (<5%) do not tolerate UDCA. 	<ul style="list-style-type: none"> The authorities recognise that there are limited therapeutic options (UDCA or liver transplant) for patients with PBC. Both authorities summarise the benefits and risks of currently available therapeutic options and conclude that there is an unmet clinical need in patients with PBC who are intolerant or have an inadequate response to UDCA. 	

³⁴ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004093/WC500218422.pdf

³⁵ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000MedR.pdf

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
Cont. Current treatment options	<p>response. A small subset of PBC patients is unable to tolerate UDCA.</p> <ul style="list-style-type: none"> Liver transplantation can improve survival and pruritus in patients but is a complex, time-consuming operation with various risks. <ul style="list-style-type: none"> The disease can recur in a significant percentage of patients receiving liver transplants. 	<ul style="list-style-type: none"> Patients who do not respond to UDCA require liver transplantation if eligible or succumb to death. <ul style="list-style-type: none"> Even with liver transplantation, PBC recurrences are noted. 	
Benefits	<ul style="list-style-type: none"> Short description of the single pivotal study in section: 3.1.3 Main clinical studies. Results from the study at month 12 showed that a higher percentage of patients in the fixed Ocaliva (OCA) 10mg group (47%) and of patients in the OCA titration group (46%) achieved the primary endpoint³⁶, compared to placebo; thus demonstrating superiority compared to placebo. Treatment effect on the primary composite endpoint was supported by additional efficacy analyses performed in the completer and efficacy evaluable populations. Mean, absolute and percentage change from baseline to 6 and 12 months in ALP, conjugated bilirubin, GGT, ALT, and AST showed statistically significant differences over placebo for both OCA treatment groups for most of the endpoints. Responder analyses showed a higher percentage of patients in both OCA treatment groups achieved the ALP reduction, compared to placebo, at both time points, 6 and 12 months. At 12 months approximately one third of patients in both OCA treatment groups achieved an ALP reduction of > 40%, compared with 1% in the placebo group. 	<ul style="list-style-type: none"> Brief summary of the trials (one phase III trial, two phase II trials), incl. the number of enrolled patients. Phase III results are as follows: At month 12, a total of 46% and 47% patients on OCA titration and OCA 10mg arm respectively achieved reduction in ALP < 1.67 × ULN and at least ≥15% reduction in ALP, and these were statistically significant relative to placebo. Out of the 18 patients who had elevated ALP and total bilirubin (TB) at baseline, 1 out of 4 patients in the titration arm, 2 out of 7 patients in the OCA 10mg and none out of 7 patients in the placebo arm achieved the composite endpoint. The ALP reduction response is durable as seen in the long-term safety extension trial in data submitted to a cutoff point off up to 30 months. The Global PBC study group published results by conducting retrospective analysis and found ALP and TB, as a composite endpoint, prognosticates death and liver transplantation. FDA conducted additional analyses of the Global PBC data and identified a subset of patients that matched the trial population. Thresholds were identified to designate patients 	<ul style="list-style-type: none"> Both authorities report the same results with respect to the primary endpoint from the pivotal phase III trial. Apart from the phase III trial results, each agency emphasises distinct benefits or describes the benefits in a different manner. For instance, the FDA mentions the results of the Global PBC study group. Based on these results, the FDA identified new thresholds to designate patients as responders. The FDA derived thresholds lead to better C-Statistics and Hazard Ratio. It seems that the FDA describes the benefits in more detail; whereas the EMA appears to be more focused on the key benefits.

³⁶ The primary endpoint is defined as the proportion of patients with ALP < 1.67 × upper limit(s) of normal (ULN) and at least ≥15% reduction in ALP, and a total bilirubin ≤ ULN at month 12)

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
Cont. Benefits	<ul style="list-style-type: none"> In the monotherapy study, after 12 weeks of treatment, the mean percent change from baseline in ALP was – 44.5% and – 37.6% for the 10mg and 50mg OCA groups, respectively, in comparison to a 0.4% increase in the placebo group. Results from Phase II trials are consistent with those of the pivotal study, which add robustness to the evidence provided. 	<p>as responders. For the FDA derived thresholds, the C-statistics and Hazard ratio were better compared to the pre-specified thresholds.</p> <ul style="list-style-type: none"> The secondary endpoints were TB, GGT, AST and ALT. <ul style="list-style-type: none"> For a few patients treated with OCA total bilirubin was reduced. A statistical significant number of patients treated with OCA achieved GGT reduction, and aminotransferases reduction (ALT, AST). 	
Uncertainty in terms of benefits	<ul style="list-style-type: none"> The choice of a biochemical surrogate challenges the interpretation of study results regarding clinical benefit (although it is acknowledged that using long-term hard endpoints is largely unfeasible in a phase III trial in PBC patients). <ul style="list-style-type: none"> The main uncertainty concerns to what extent changes in laboratory parameters correlate with clinical liver outcomes. The results from the primary composite endpoint are mainly driven by changes in ALP, since the majority of patients entered with normal bilirubin values. Despite that about one third of patients in OCA treated groups achieved an ALP reduction > 40% at 12 months, only few patients achieved normalised ALP levels. ALP normalisation with UDCA relays to better prognosis; it is unknown if the same can be extrapolated to OCA results. Nevertheless, based on the experience gained with UDCA, OCA treatment resulted in changes in laboratory parameters that are indicative of a potential clinically relevant benefit. Other important uncertainties: lack of data in patients with advanced stage disease and limited long-term data. 	<ul style="list-style-type: none"> An Advisory Committee (AC) meeting was held to query whether ALP was an appropriate surrogate that is reasonably likely to predict clinical benefit. <ul style="list-style-type: none"> The AC members voted unanimously in favour of OCA approval on the surrogate basis of ALP reduction. Based on the biological plausibility of ALP as a surrogate in PBC, the AC considered ALP as a diagnostic biomarker. The phase III trial enrolled 90% of patients with early stage disease. The remaining 10% of patients had moderately advanced disease; therefore, data are limited. There are no data in advanced liver disease patients or in patients with decompensated cirrhosis. <ul style="list-style-type: none"> The benefits and risks in this population with OCA use are unknown. The confirmatory trial is ongoing and until the results are analysed the clinical benefit outcomes of ALP to support its use as a surrogate are yet to be established. 	<ul style="list-style-type: none"> The EMA lists all the uncertainties surrounding favourable effects in section 3.3 'Uncertainties and limitations about favourable effects' of the EPAR. The FDA, on the contrary, describes the uncertainties in terms of benefits on different places in the Benefit-Risk framework. Several uncertainties can be found in the <i>Conclusions</i> and <i>Reasons</i> column of the <i>Benefit</i> row. Apart from minor differences, both authorities are concerned about the same uncertainties surrounding benefits: <ul style="list-style-type: none"> Is ALP reduction an appropriate surrogate to predict clinical benefit? Lack of data in patients with a more advanced stage of the disease and no information about patients with decompensated disease. Lack of long-term data.

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
Risks	<ul style="list-style-type: none"> The most commonly reported adverse reactions were pruritus and fatigue. <ul style="list-style-type: none"> Pruritus was the most reported TEAE across all treatment groups. The majority of pruritus occurred within the first month of treatment and tended to resolve over time. Pruritus was included as important identified risk in the RMP and guidance on management and dose adjustment for severe pruritus was included into the SmPC. AR leading to discontinuation were 1% in the Ocaliva Titration group and 11% in the OCA 10mg group. 	<ul style="list-style-type: none"> Dose dependent increase in pruritus as well as severe pruritus, and in the incidence of fatigue was observed. There were 7 discontinuations due to pruritus in OCA 10mg arm and 1 in OCA titration arm compared to zero in the placebo arm. Pruritus and fatigue appear to be worsened in some patients taking OCA and could limit use in some patients. Drug-Drug interactions were limited. There were no major/serious safety concerns (i.e. death or life-threatening adverse events). 	<ul style="list-style-type: none"> Both authorities are focused on identical adverse events, namely pruritus and fatigue The FDA describes that pruritus and fatigue could limit use in some patients; while the EMA includes pruritus as important identified risk in the RMP
Uncertainty regarding risks	<ul style="list-style-type: none"> Representation of patients with more advanced disease and/or various degree of liver impairment was scarce. At present no information is available in patients with decompensated disease. Hepatic effects related with disease progression seemed to be numerically higher in OCA treated patients. <ul style="list-style-type: none"> The SmPC advises to monitor patients for elevation in liver enzymes and liver related AEs. None of the clinical hepatic AEs at doses \leq 10mg were considered related to the study drug. The hepatic-related events may be due to disease progression. It is acknowledged by the CHMP that there is insufficient support to conclude on a causal association between liver injury and OCA at the proposed clinical doses. Therefore, liver injury was qualified as an important potential risk in the RMP. <ul style="list-style-type: none"> The occurrence of liver injury should further be investigated in the confirmatory studies that 	<ul style="list-style-type: none"> OCA can result in liver injury at high exposures as seen in nonclinical and in early phase trials with higher doses. <ul style="list-style-type: none"> Nonclinical data indicated that OCA can induce liver injury at high doses (OCA 100mg). In the healthy human trials liver biochemical abnormalities were noted at OCA 100mg dose.; at doses of 25 and 50mg higher rates of hepatic decompensation events were observed. OCA undergoes enterohepatic circulation and its conjugates have a very long half-life. OCA 10mg once a day administration leads to very high OCA systemic and liver exposures in patients with moderately advanced and advanced disease. These high exposures could cause an increased risk of hepatic injury. There is a lack of data in patients with advanced cirrhosis. 	<ul style="list-style-type: none"> Both authorities are concerned that OCA could induce liver injury, especially in patients with advanced stage disease. Contrarily to the EMA, the FDA refers also to non-clinical data to describe the risk of liver injury. Apart from the uncertainty regarding liver injury, both authorities describe lipid disorders or dose-dependent HDLc reductions as an important uncertainty regarding the risk for cardiovascular events. On the contrary to the EMA, the FDA states that ALP may be an inadequate marker for patients with advanced disease. (The question is if this uncertainty belongs rather to the uncertainties surrounding benefits).

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
Cont. uncertainty regarding risks	<p>should be performed in patients with more advanced stages of the disease.</p> <ul style="list-style-type: none"> The SmPC has been revised to include details regarding serious hepatic events to help healthcare professionals manage their patients appropriately. Additionally, dosage recommendations for patients with moderate to severe hepatic impairment have been included. Lipid disorders were also reported in patients treated with OCA. <ul style="list-style-type: none"> Lipid disorders are commonly seen in PBC patients. A clear pattern could not be identified and these changes did not seem to be associated with the occurrence of cardio vascular (CV) AEs. Further characterisation of the long-term safety of OCA with respect to changes in lipid levels will become available by means of the conditions of the marketing authorisation. 	<ul style="list-style-type: none"> Patients with impaired hepatic function can have much higher exposures and a reduced dose has been recommended for these patients. Additional data is needed in patients with hepatic impairment. ALP may be a better marker of progression of disease and response to treatment in early phases of PBC. <ul style="list-style-type: none"> As the disease progresses the ALP levels may gradually decrease as bilirubin increases making it an inadequate marker for trials in patients with advanced disease. Dose dependent HDLc reductions were seen. Reduction in HDLc may occur over time and may increase the risk for cardiovascular events. Data of longer duration of OCA use are required to understand the implications of cardiovascular events with HDLc lowering. 	
B/R Balance	<ul style="list-style-type: none"> Description of the therapeutic context with the conclusion that there is an unmet medical need for patients who are intolerant or do not respond to UDCA treatment. Overall the beneficial effect of OCA is currently based on changes in biochemical parameters. OCA treatment has demonstrated relevant ALP reductions. Although very limited clinical data are currently available sufficient correlation has been established between ALP levels and liver outcomes from previous clinical experience with UDCA. Available data are sufficiently indicative of a clinically relevant benefit in the treatment of PBC in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. 	<ul style="list-style-type: none"> Approval of OCA for treatment of PBC is recommended. The approvability of this application relied upon the acceptability of the surrogate endpoint of reduction in ALP to be reasonably likely to predict clinical benefit. Description of the therapeutic context with the conclusion that there is an unmet medical need in patients who do not respond or are intolerant to UDCA. Given the long duration for clinical outcome trials to show clinical benefit, it is reasonable to consider accelerated approval of OCA for PBC using a surrogate endpoint. Description of the phase III trial, the primary and secondary endpoints. The overall OCA profile is safe. 	<ul style="list-style-type: none"> Both authorities define the therapeutic context and emphasise the unmet medical need for patients who are intolerant or do not respond to UDCA. Both authorities describe the benefits and risks of Ocaliva and identify several uncertainties that should be addressed by post-authorisation measures/ requirements. The most important issue related to the benefit-risk assessment of Ocaliva is that the beneficial effect is based on changes in biochemical parameters. OCA treatment has led to relevant ALP reductions; the crucial question is if reduction in ALP is reasonably likely to predict clinical benefit.

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
<p>Cont. B/R balance</p>	<ul style="list-style-type: none"> It remains to be demonstrated by the post-authorisation follow-up within this conditional marketing authorisation, if the biochemical parameter correlates with clinical outcome data. The safety profile appeared to be overall well tolerated and for most part manageable with supportive treatments and /or dose adjustments. In particular, the lack of direct clinical evidence showing the extent of efficacy and safety also in the long-term treatment and in more advanced liver diseases stages will be addressed within the condition of the MA. This is considered acceptable due to the lack of treatment options in this second line indication of a severely debilitating disease. <p>→ The B/R balance of Ocaliva for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA is considered to be positive in the context of this conditional marketing authorisation.</p>	<ul style="list-style-type: none"> Detailed summary of the risks, with focus on pruritus, fatigue, HDLc reductions, and liver injury. The acceptability of ALP being used as a surrogate for accelerated approval in this application was the central review issue. ALP is a non-specific enzyme and ALP can come from different sources, incl. bone, liver, and intestines. To address this issue, the Applicant submitted the analyses of the PBC Study group data that demonstrated that ALP is reasonably likely to predict clinical outcomes. Another uncertainty remains whether ALP can predict outcomes in advanced stages disease. There is always a potential risk with accelerated approval if the surrogate in question, ALP reduction, does not in actuality predict clinical outcomes, as patients would be exposed to the drug, and have the potential to experience AR, as well as the potential for financial costs of ineffective treatment. However, if ALP does predict outcomes in early stage disease, then the patients will benefit from OCA treatment, resulting in increased treatment options for patients who are intolerant to UDCA. There is adequate evidence to support that a reduction of ALP is reasonably likely to predict clinical benefit; however, until the phase 4, confirmatory trial is completed the validity of ALP as a surrogate is unknown. In addition, there are no data on OCA in advanced stage disease or in patients with decompensated cirrhosis. The applicant has agreed to a PMR to assess PK safety and efficacy in advanced stage disease patients. 	<ul style="list-style-type: none"> Both authorities discuss this uncertainty and conclude that despite limited clinical data there is adequate evidence to support that a reduction of ALP correlates with clinical outcomes. Both authorities define the safety profile of OCA and assume that despite several uncertainties, particularly in patients with more advanced stage disease, the safety profile appeared to be overall well tolerated and for most part manageable with supportive medications or dose reductions. Remaining uncertainties surrounding risks are related to lipid disorders and liver injury. The risk of liver injury is especially important for patients with more advanced stage disease. These uncertainties are addressed in the post-marketing requirements. Both authorities determine that the B/R balance is positive.

Ocaliva	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical review
<p>Post-market requirements</p>	<ul style="list-style-type: none"> As a specific obligation of the conditional marketing authorisation, in order to confirm the efficacy and safety of Ocaliva, the MAH shall complete: <ul style="list-style-type: none"> The Interventional study 747-302: <p>A confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints.</p> <p>→ Rationale: to investigate the effect of Ocaliva on clinical outcomes in subjects with PBC</p> The interventional study 747-401: <p>A double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment.</p> <p>→ Rationale: to investigate the uncertainties related to the lack of data in a population with more advanced liver disease</p> 	<ul style="list-style-type: none"> Accelerated approval requirements: <ul style="list-style-type: none"> PMR # 3057-1: <p>A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of Ocaliva in patients with PBC with Child-Pugh Classes B and C hepatic impairment, including Child-Pugh Class C patients with varying levels of Model for End-Stage Liver Disease scores. The applicant may conduct this as a stand-alone trial or in a subset of patients in the confirmatory trial.</p> PMR # 3057-2: <p>A randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of Ocaliva used as monotherapy in patients with PBC who are intolerant or non-responsive to UDCA. Enroll patients of all stages of PBC, by the Rotterdam criteria. The applicant may conduct this as a stand-alone trial or in a subset of patients in the confirmatory trial.</p> PMR # 3057-3: <p>A randomized, double-blind, placebo-controlled trial to verify and describe that Ocaliva induced reductions in ALP or TB are associated with improvements in the composite clinical endpoint of progression of cirrhosis, death, transplant, decompensation events and hepatocellular cancer. The ongoing trial (747-302) should be revised to include patients across the spectrum of stages of PBC, including patients with early, moderately advanced and advanced PBC, and should be powered to demonstrate benefit in each stage.</p> 	<ul style="list-style-type: none"> Both authorities require the results of the ongoing pivotal trial (747-302) to further establish the effect of Ocaliva on clinical outcomes. Furthermore, both authorities require efficacy and safety data for patients with more advanced stage disease. Compared to the EMA, the FDA clearly determines which patients (e.g. Child-Pugh Class C patients with varying levels of Model for End Stage Liver Disease) should be included and that safety and efficacy data of Ocaliva monotherapy should be submitted.

2. Comparison of the European SmPC and the US Label			
Ocaliva	European SmPC ³⁷	US Label ³⁸	Comparison of the SmPC and the Label
Indication	<ul style="list-style-type: none"> Ocaliva is indicated for the treatment of: <ul style="list-style-type: none"> Primary biliary cholangitis in combination of ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. 	<ul style="list-style-type: none"> Ocaliva is indicated for the treatment of: <ul style="list-style-type: none"> Primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. 	<ul style="list-style-type: none"> There is no difference between the approved indications.

³⁷ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004093/WC500218418.pdf

³⁸ http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207999s000lbl.pdf

Annex IV: Comparison of EMA's and FDA's B/R assessment of Praxbind				
Praxbind, Idarucizumab, Hemorrhage				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR³⁹	FDA's Medical Review⁴⁰	Comparison of EPAR and Medical Review	
Approval date	20/11/2015	16/10/2015	~ 1 months	
Submission date	02/03/2015	19/02/2015	~ 2 weeks	
Review classification		Accelerated Approval		
Disease or condition	<ul style="list-style-type: none"> Brief description of the therapeutic context in section: Scientific discussion→2.1 Introduction Idarucizumab (Ida) is being developed as a specific reversal agent for dabigatran. Ida neutralizes dabigatran's anticoagulant effect due to its very high affinity for dabigatran. With the increasing use of novel oral anticoagulants such as dabigatran, patients with life-threatening or uncontrolled bleeding can benefit from additional options that could be used in emergency situations in order to reverse the anticoagulant effects of these drugs. 	<ul style="list-style-type: none"> As with all anticoagulants, patients treated with dabigatran, may be at increased risk for bleeding. Studies demonstrated that Ida is able to reverse the pharmacodynamics anticoagulant effect of dabigatran. Reversal of the anticoagulant effect of dabigatran is an important clinical benefit in order to decrease the risk of bleeding in patients who may require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. 	<ul style="list-style-type: none"> Both authorities briefly describe the therapeutic context and the therapeutic importance of the drug. Both authorities acknowledge the clinical benefit of Ida for patients treated with dabigatran who require invasive procedure or experience uncontrolled bleeding. 	
Current treatment options	<ul style="list-style-type: none"> Neither the section 'Scientific discussion' nor the section 'Benefit-Risk Balance' entails a description of available therapies. 	<ul style="list-style-type: none"> Currently there are no approved therapies for the reversal of the anticoagulant effect of dabigatran. Description of recommendations and management approaches for patients who bleed while receiving dabigatran with the conclusion that no optimal treatment is available. 	<ul style="list-style-type: none"> The EMA does not describe available treatment options. This is due to the fact that there are no approved therapies reversing the anticoagulant effect of dabigatran. The FDA lists recommendations and management approaches that could be considered for patients who are treated with dabigatran and experience bleedings. 	

³⁹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003986/WC500197465.pdf

⁴⁰ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761025Orig1s000MedR.pdf

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Benefits	<ul style="list-style-type: none"> The effect of Ida in reversing the anticoagulant effect of dabigatran has been shown in three pharmacokinetic PK/ pharmacodynamics PD studies in 283 healthy subjects. <ul style="list-style-type: none"> The subjects were pre-treated with dabigatran in supratherapeutic doses for 3.5 days. Subsequent administration Ida reversed markers of dabigatran anticoagulant activity to levels similar to those seen before treatment with dabigatran. Full reversal was observed in subjects receiving Ida doses of 1g or more and was evident in young and elderly subjects, in subjects with normal renal function as well as subjects with mild or moderate renal impairment. The reversal of the anticoagulant effect was rapid and sustained. The results of the second interim analysis of the ongoing case series clinical study in patients treated with dabigatran who were in actual need of rapid reversal of the anticoagulant activity largely confirmed the results of the PK/PD studies in healthy subjects with regards to reversed markers of dabigatran activity. <ul style="list-style-type: none"> However, the variability of this reversal was larger than in the PK/PD studies. Restart of the anticoagulant treatment with dabigatran after a bleeding event and Ida administration could be initiated already 24 hours after last Ida dose. Ida administration did not interfere with routine emergency patient management in case of bleeding. Ida administration alone had no effect on coagulation parameters. 	<ul style="list-style-type: none"> Two clinical pharmacology studies demonstrate that Ida decreases the pharmacodynamics anticoagulant effect of dabigatran in normal healthy volunteers, pre-treated with dabigatran. Additional support for these results comes from one ongoing phase III study. <ul style="list-style-type: none"> To date 123 of 300 patients have been enrolled. The study has been conducted in patients who are being treated with dabigatran and require reversal of the dabigatran pharmacodynamics effect since they need emergency surgery or have life-threatening or uncontrolled bleeding. 	<ul style="list-style-type: none"> Both authorities describe the effects of Ida in healthy subjects. However, the EMA refers to three PK/PD studies, whereas the FDA relates to two clinical pharmacology studies. Furthermore, both authorities report that the ongoing phase III trial (in patients treated with dabigatran who required rapid reversal of the anticoagulant effect) supports the previous detected study results. Compared to the FDA, the EMA describes the results of the studies in more detail.

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Uncertainty in terms of benefits	<ul style="list-style-type: none"> For all the presented subpopulations regarding sex, age, underlying disease and race, the numbers of assessed subjects were still too small to draw final conclusions regarding possible differences in the beneficial effects. The effect of Ida on reduction in mortality or morbidity (most notable bleeding complications) remained uncertain. The ongoing phase III study was not powered nor designed to detect a difference between standard of care plus Ida versus standard of care alone. <ul style="list-style-type: none"> However, this uncertainty was considered to be acceptable in view of the results of the non-clinical studies and since the PD biomarkers used in the PK/PD studies were considered to be good surrogates for efficacy. The results of the second interim analysis of the ongoing phase III trial supported the view that reversal of elevated anticoagulation tests in dabigatran-treated patients was a surrogate for clinical efficacy. However, the clinical benefit of this reversal was depending very much on the individual patient clinical situation, disease and bleeding severity or location of the bleeding. Some patients may present with very high dabigatran exposure (e.g. patients with suicidal intention); in such situations a repeated dose may be appropriate. Very limited data in patients with severe renal impairment. 	<ul style="list-style-type: none"> The A decrease in the risk of bleeding is difficult to assess. <ul style="list-style-type: none"> In many cases, bleeding is not visible and cannot be readily measured, e.g. in patients with intracranial haemorrhage. Other clinical outcomes such as mortality are also significantly confounded by the severity of the underlying clinical situation (e.g. trauma or complications of surgery). A control group to compare outcomes would not be ethical to determine whether mortality rates are impacted by administration of Ida. 	<ul style="list-style-type: none"> Both authorities ascertain that it is difficult to determine the effect of Ida on clinical outcomes (such as mortality) due to the lack of a control group and confounders like the underlying clinical situation. Compared to the FDA, the EMA discusses this uncertainty and concludes that it is acceptable to use the reversal of elevated anticoagulation tests as a surrogate for clinical efficacy. The CHMP detects also an uncertainty regarding possible differences in the beneficial effects for subpopulations (e.g. sex, age, underlying disease), and for patients with severe renal impairment. In conclusion, the EMA describes the uncertainties more explicitly.

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
<p>Risks</p>	<ul style="list-style-type: none"> In patients with hereditary fructose intolerance (HFI), the risk of Ida must be weighed against the benefit, since one target dose of the drug includes a high amount of sorbitol and these patients could suffer from undesirable effects including death. Brief summary of the safety data from the placebo-controlled PD/PP trials: <ul style="list-style-type: none"> There were few adverse events. Ida was not associated with any serious or severe adverse events. For some events a causal relationship with Ida was considered by the CHMP, but it was not confirmed. A dose-dependent, transient proteinuria was observed. Concise description of the safety data from the ongoing phase III trial. <ul style="list-style-type: none"> Mild symptoms of potential hypersensitivity were reported for which a causal relationship to Ida could not be established. 5 patients experienced thrombotic events; this was most likely not a direct effect of Ida, but was caused by the lack of anticoagulant treatment. Anti-Ida antibodies were detected in subjects treated with placebo and Ida, and some had pre-existing antibodies. However, titers were generally low, and there were no suggestions that anti-Ida antibodies diminished the efficacy to a clinically relevant degree. 	<ul style="list-style-type: none"> Data from the two studies in healthy volunteers demonstrated no discontinuations due to AE or serious AE. The observed AE were of mild or moderate severity. In 123 patients treated with Ida (in the ongoing phase III study) adverse events appeared to be unrelated to treatment. <ul style="list-style-type: none"> In this study 26 patients died due to their underlying serious medical conditions. The mortality rate was not unexpected in a high-risk population with life-threatening events. Two patients developed thrombotic events, these occurred 9 and 13 days after treatment with Ida and in the absence of any antithrombotic treatment. 	<ul style="list-style-type: none"> To describe the safety data, both authorities refer to the studies in healthy volunteers and to the ongoing phase III trial. Nevertheless, the authorities highlight distinct risks or describe the risks in a different manner. For instance, the FDA briefly discusses the mortality rate in the ongoing phase III trial, while the EMA is concerned about the risks for patients with HFI. Both authorities report on thrombotic events that occurred in the absence of antithrombotic treatment during the phase III trial. The EMA describes the observed events in more detail with the conclusion that a causal relationship could not be established.

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Uncertainty regarding risks	<ul style="list-style-type: none"> The main uncertainty in the knowledge about unfavourable effects was the limited safety database rather than the results themselves. Safety data from placebo-controlled trials were solely derived from healthy subjects except for relatively few patients with renal impairment, and not from a population, typical of that treated with dabigatran, i.e. old frail patients with many comorbidities. Safety data from placebo-controlled studies were supported by interim data from the ongoing phase III trial (open-label, uncontrolled). There was uncertainty about the safety and tolerability in patients with renal impairment (as stated in the beneficial effects section). <ul style="list-style-type: none"> This uncertainty is important since a large proportion of the target population has some degree of renal impairment; patients with major bleedings are likely to suffer from acute renal impairment, and Ida elimination is dependent on renal function. 	<ul style="list-style-type: none"> The safety database is relatively small. <ul style="list-style-type: none"> The phase III trial is ongoing (123 patients have been treated out of a planned 300 patients to be enrolled). 	<ul style="list-style-type: none"> Both authorities are concerned about the small safety database. On the contrary to the FDA, the EMA ascertains that the safety data were mainly derived from healthy subjects instead of patients typical treated with dabigatran. Furthermore, the EMA amplifies uncertainty about the safety and tolerability in patients with renal impairment.
Benefit-risk balance	<ul style="list-style-type: none"> In 3 PK/PD Phase I studies in healthy volunteers and results of the interim analysis of the ongoing phase III study, 5g of Ida reversed the anticoagulant effect of dabigatran. <ul style="list-style-type: none"> This was shown with coagulation tests. The reversal of the anticoagulant effect of dabigatran was demonstrated in a still limited population of 123 patients. Brief summary of the safety data: <ul style="list-style-type: none"> The clinical events observed among the patients studied were often life-threatening and a high mortality rate was expected. There was no indication of a pro-thrombotic effect of Ida. 	<ul style="list-style-type: none"> In two studies in normal healthy volunteers, reversal of the dabigatran pharmacodynamics effect was observed within 30minutes of the administration of idarucizumab Brief description of the administered doses, including the doses for patients with renal failure In an interim analysis of the ongoing phase III study, idarucizumab was able to reverse the pharmacodynamics effect of dabigatran <ul style="list-style-type: none"> The reversal of elevated anticoagulation tests in dabigatran treated patients is a surrogate for clinical efficacy Concise summary of the safety data from the studies in healthy volunteers (adverse events (AE) observed were of mild-moderate severity, no discontinuations due to AEs, no SAEs) 	<ul style="list-style-type: none"> It is interesting to note that FDA's <i>Benefit-Risk Summary and Assessment</i> entails more detailed information, especially regarding dose recommendations, than the following rows (key decision factors) of the framework Both authorities report that the results from the studies in healthy volunteers and the ongoing phase III trial demonstrated the reversal of the anticoagulant effect of dabigatran Furthermore, both authorities ascertain that the clinical efficacy was demonstrated by a surrogate, the reversal of elevated anticoagulation tests Each authority defines the safety profile of Ida and concludes that Ida appears to be safe

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
<p>Cont. benefit-risk balance</p>	<ul style="list-style-type: none"> ○ There is no evidence of worsening of the renal function when this drug was given to patients with renal impairment, although number of patients were too small to draw final conclusions. ○ Ida was considered to have an acceptable safety profile. However, conclusions regarding the safety profile were hampered by the small population of patients treated so far and the underlying morbidity of these patients. • There is a high unmet medical need for patients on direct anticoagulants and having uncontrolled bleeding or before emergency surgery/urgent procedures. • Discussion of the Benefit-risk balance: <ul style="list-style-type: none"> ○ The data assessed supported that Ida in subjects exposed to dabigatran lead to rapid reversal of the anticoagulant effect. ○ The preliminary results of the ongoing phase III study support the results of the PK/PD data in healthy volunteers and confirm that the reversal of prolonged clotting times in dabigatran treated patients could be a surrogate of clinical efficacy. ○ However, the clinical benefit for this reversal depends very much on the clinical status of the individual patient. ○ The applicant has to complete the ongoing phase III study and submit the results to further confirm the efficacy and safety of this medicinal product. ○ No adverse events were reported in studies where a causal relationship to Ida was evident. <p>→In conclusion: The efficacy of idarucizumab was supported by the presented data in healthy volunteers as well as in patients. The favourable effects of complete reversal of the anticoagulant effect of dabigatran in combination with a supportive safety profile lead the CHMP to the conclusion on a positive benefit-risk balance.</p>	<ul style="list-style-type: none"> • Succinct description of the safety data from the ongoing phase III study: <ul style="list-style-type: none"> ○ Adverse events appeared to be unrelated to treatment. ○ 26 patients died; mortality rate was not unexpected in a high-risk population. ○ Two patients developed thrombotic events. ○ No evidence that idarucizumab worsens renal function when given to patients with renal impairment. • Discussion of the results: <ul style="list-style-type: none"> ○ The clinical outcome, i.e. a decrease in the risk of bleeding, is difficult to assess since bleeding is not visible and cannot be readily measured. ○ Other clinical outcomes such as mortality are also confounded by the underlying clinical situation. ○ A control group to compare outcomes would not be ethical whether mortality rates are impacted by the administration of the drug. ○ Definition of the target population and the incidence of the conditions, with the conclusion that idarucizumab is not intended for patients with minor bleeding or when standard supportive care is sufficient. <p>→In summary, 5g of idarucizumab appears to be safe and effective in the reversal of dabigatran anticoagulant effect in the target population. The sponsor should complete the ongoing phase III study to support the approval of idarucizumab in this indication.</p>	<ul style="list-style-type: none"> • Both authorities discuss the difficulties during the benefit-risk assessment of idarucizumab and come to the same conclusion that the overall benefit-risk balance is positive. • However, the CHMP proposed a full MA; whereas, the FDA granted an accelerated approval

Praxbind	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Post-market requirements	<ul style="list-style-type: none"> The results of the ongoing phase III study (Trial 1321.3) will be submitted as per pharmacovigilance plan agreed in the RMP and should permit for further confirmation of the efficacy of Ida. 	<u>Accelerated approval requirement:</u> <ul style="list-style-type: none"> Completion of the phase III trial, (trial 1321.3). 	<ul style="list-style-type: none"> Both authorities require the results of the ongoing phase III study. However, the FDA requires the completion of the study as part of the accelerated approval of Praxbind; while the CHMP recommends a full MA.
2. Comparison of EMA's SmPC and FDA's Label			
Praxbind	European SmPC ⁴¹	US Label ⁴²	Comparison of the SmPC and the Label
Indication	<p>Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:</p> <ul style="list-style-type: none"> For emergency surgery/urgent procedures In life-threatening or uncontrolled bleeding 	<p>Praxbind is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed:</p> <ul style="list-style-type: none"> For emergency surgery/urgent procedures In life-threatening or uncontrolled bleeding 	<ul style="list-style-type: none"> The approved indications are identical

⁴¹ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003986/WC500197462.pdf

⁴² http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf

Annex V: Comparison of EMA's and FDA's B/R Assessment of Tagrisso				
Tagrisso, Osimertinib, Non-Small Cell Lung Carcinoma				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR ⁴³	FDA's Clinical Review ⁴⁴	Comparison of EMA and FDA	
Approval date	02/02/2016	13/11/2015	~ 3 months	
Submission date	05/06/2015	06/05/2015	~ 1 months	
Review classification	<ul style="list-style-type: none"> Conditional approval 	<ul style="list-style-type: none"> Accelerated approval⁴⁵ Orphan designation⁴⁵ 		
Disease or condition	<ul style="list-style-type: none"> Detailed description of the disease and available therapies in section: <i>Scientific discussion</i> → 2.1 <i>Introduction</i>. Lung cancer is the most common cause of death from cancer worldwide. Non-small cell lung cancer (NSCLC) represents about 80-90% of all lung cancers. In recent years, studies have identified the presence of EGFR mutations in about 10% of patients with lung cancer in the EEA. The first choice treatment for patients with activating mutations in EGFR are EGFR tyrosine kinase inhibitors (TKIs), which offer objective response rates (ORRs) of 60-70% and median PFS of 9 to 14 months. Despite these good initial response rates, the patients will eventually develop treatment resistant disease after 9-14 months. 	<ul style="list-style-type: none"> Lung cancer is the leading cause of cancer death worldwide. The majority of these cases are non-small cell lung cancer (NSCLC). EGFR mutations are present in about 10% of metastatic NSCLC patients in the US. First-line treatment for these patients is primarily EGFR TKIs with ORR of 60-70% and median PFS of 9 to 14 months. Patients typically develop treatment resistant disease within the first year of treatment. In about 60% of patients, the mechanism of resistance involves development of EGFR T790M mutations. 	<ul style="list-style-type: none"> Both authorities describe lung cancer as the leading cause of cancer death worldwide. Furthermore, NSCLC represents the majority of all lung cancers. About 10% of NSCLC patients have EGFR mutations. These patients are primarily treated with EGFR TKIs. Within the first year of treatment, the patients will eventually develop treatment resistant disease. About 60% of these treatment resistant patients have EGFR T 790M mutations. In conclusion: The agencies agree on the severity and the incidence of metastatic EGFR T790M mutation positive NSCLC. However, only the FDA granted an orphan designation for Tagrisso. 	
Current treatment options	<ul style="list-style-type: none"> Many agents and combinations have tried to overcome the acquired resistance to EGFR TKIs, but response rates were quite limited. 	<ul style="list-style-type: none"> There are no effective treatment options for metastatic EGFR/T790M positive NSCLC patients. 	<ul style="list-style-type: none"> Both authorities describe current treatment options and identify an unmet medical need for patients with metastatic EGFR/T790M positive NSCLC. 	

⁴³ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004124/WC500202024.pdf

⁴⁴ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208065Orig1s000MedR.pdf

⁴⁵ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/208065Orig1s000Ltr.pdf

Tagrisso	EMA's EPAR	FDA's Clinical Review	Comparison of EMA and FDA
Cont. Current treatment options	<p>→ Currently there is no approved targeted therapy for the T790 'gatekeeper' mutation.</p>	<ul style="list-style-type: none"> Standard chemotherapy is the usual regimen which is associated with marginal benefit and with a wide range of toxicities. 	
Benefits	<ul style="list-style-type: none"> Pooled results from two phase II studies demonstrated an objective response rate (ORR) of around 66% (as assessed by a Blinded Independent Central Review Committee (BICR)). The median duration of the response (DOR) according to the BICR has not been achieved yet. <ul style="list-style-type: none"> However, data from investigator assessment provide a median DOR of 8.5 months. Secondary variables (incl. tumour shrinkage) support the efficacy of osimertinib. These results are supported by those obtained in the AURA phase I study, where the median DOR was 9.7 months in the subset of 37 patients receiving 80mg osimertinib, as assessed by BICR. 	<ul style="list-style-type: none"> The efficacy of osimertinib was shown in two single arm trials (AURA extension and AURA2) with ORR of 57.2% and 61.0% in patients with metastatic EGFR/T790M positive NSCLC. Supportive evidence from the phase I portion of AURA (AURA phase 1) demonstrated ORR of 50.8% and DOR of 12.4 months in 63% patients with metastatic EGFR/T790M positive NSCLC. 	<ul style="list-style-type: none"> Both authorities refer to the results from identical studies, i.e. two phase II trials (AURA extension and AURA2) and one phase I trial (AURA phase I). Nevertheless, the authorities describe the benefits in a different manner, for instance, the authorities report dissimilar percent values for the primary efficacy endpoint (ORR) or the secondary outcome variable (DoR).
Uncertainty in terms of benefits	<ul style="list-style-type: none"> The design of the studies could be considered the most important uncertainty, as there was no control group. <ul style="list-style-type: none"> Therefore, it is difficult to draw firm conclusions on the added benefit from treatment. Despite ORR is a commonly used endpoint in oncology studies, its use is usually limited to exploratory studies, since it is not able to reliably estimate the ultimate benefit for patients in terms of life expectancy. <ul style="list-style-type: none"> Furthermore, data in terms of PFS and OS are too immature to reflect the real benefit of osimertinib. DOR has not yet been totally estimated in the main studies. <ul style="list-style-type: none"> Moreover, it is very likely that mechanisms of resistance are developed by the tumour, decreasing the activity of osimertinib and leading to the failure of treatment. 	<ul style="list-style-type: none"> Osimertinib meets efficacy standards for accelerated approval based on demonstration of durable ORR of large magnitude in two single arm trials. Traditional approval for osimertinib requires confirmation of clinical benefit in adequate and well controlled trials, which can be randomized if the condition of equipoise exists. 	<ul style="list-style-type: none"> The FDA determines that osimertinib meets efficacy standards for accelerated approval; therefore, the clinical benefit has to be further established in adequate and well-controlled trials. Apart from the uncertainty regarding the studies to demonstrate clinical benefit, the FDA does not describe any other uncertainties in terms of benefits. The EMA, on the contrary, identifies several uncertainties surrounding benefits, and describes these uncertainties explicitly According to the EMA, the most crucial uncertainty is the design of the studies since there was no control group. Furthermore, the primary efficacy outcome, ORR, would not be able to reliably estimate the ultimate benefit for patients in terms of life expectancy. In addition, the duration of response has not yet been

Tagrisso	EMA's EPAR	FDA's Clinical Review	Comparison of EMA and FDA
Cont. uncertainty in terms of benefits	<ul style="list-style-type: none"> The subgroup analyses reveal differences in ORRs between patients with different EGFR mutations and also between patients of Asian and non-Asian ethnicity. There are no data in patients with the T790 mutation, who have not been treated previously with TKIs. <ul style="list-style-type: none"> However, the expected benefit of osimertinib should not be related to previous treatment. An ongoing study will explore the efficacy of osimertinib in first-line. 		<p>completely established and it is assumable that the tumour develops mechanisms of resistance.</p> <ul style="list-style-type: none"> Moreover, the EMA describes an uncertainty regarding the effect in a subgroup, to be specific in patients who have not been treated with TKIs. This uncertainty has an impact on the approved indications. The CHMP proposes to approve osimertinib with a broader defined indication (including patients harbouring the T790M in the absence of previous exposure to TKIs). The FDA clearly determines that Tagrisso is indicated in patients who have progressed on or after TKI therapy.
Risks	<ul style="list-style-type: none"> According to the phase II studies, the administration of osimertinib is mainly characterised by the following AEs: diarrhea (42.3%), rash (23.8%), dry skin (23.1%) and paronychia (17.5%). Description of: <ul style="list-style-type: none"> the incidence of adverse events (AEs) Grade ≥ 3 the incidence of AE Grade 4 the incidence of possibly related AEs Grade ≥ 3 the most frequent AEs Grade ≥ 3 fatal AEs / the most common/ possibly related the incidence of SAEs / related SAEs the incidence of AEs of special interest (AESIs), interstitial lung disease (ILD)/pneumonitis and the QT interval prolongation. 	<ul style="list-style-type: none"> Brief description of the safety database: <ul style="list-style-type: none"> The safety database was considered adequate in terms of size, exposure, duration of treatment and disease characteristics. Median duration of exposure was 4.4 months in the primary database but increased to 7 months with the 90-day safety update, which was reviewed extensively. This was considered adequate by the reviewer for an accelerated approval with longer follow-up to be submitted with confirmatory trials. The most frequently-observed AEs were consistent with expected toxicities based on preclinical data, previous clinical experience and class effects of other EGFR TKIs. <ul style="list-style-type: none"> These included diarrhoea and rash. The most important rare but serious identified AE that was thought to be the cause of 4 treatment-related deaths on study was ILD. <ul style="list-style-type: none"> This is a known class effect of anti-EGFR TKIs. 	<ul style="list-style-type: none"> The authorities describe the risks of osimertinib differently. The EMA provides a detailed description of the incidences of the AEs; while the FDA rather evaluates the safety profile of osimertinib comparing the expected toxicities with the de facto detected adverse events. On the contrary to the EMA, the FDA compares the safety profile of osimertinib with other TKIs, and finally, concludes that it compares favourably to the profile of other approved EGFR TKIs.

Tagrisso	EMA's EPAR	FDAs' Clinical Review	Comparison of EMA and FDA
Cont. Risks		<ul style="list-style-type: none"> Another important identified AE was QTc prolongation, also a known class effect of EGFR TKIs. 	
Uncertainty regarding risks	<ul style="list-style-type: none"> The most important uncertainties related to toxicity are the size of the safety database and the few data in the long run. Again the lack of comparator hampers to appraise the actual safety profile. Severe skin reactions, diarrhea, ocular toxicity and hepatotoxicity have been reported for similar TKI. <ul style="list-style-type: none"> A few cases were seen for osimertinib, however, this could be due to the limitations of the safety database. So, at the present time, these events are considered relevant potential safety concerns. Uncertainty regarding drug-drug interactions Available data in very elderly patients (>75 years old) is limited and considered relevant missing information. Hepatic impairment might be expected to lead to increased exposure. <ul style="list-style-type: none"> A clinical study investigating the impact of mild and moderate hepatic impairment on osimertinib pharmacokinetics is currently ongoing. No clear risk factors have been identified in the ongoing investigations into ILD events. It is not certain what effect osimertinib will have in patients with cardiac abnormalities in rhythm and conduction (since these patients were excluded from the studies). 	<ul style="list-style-type: none"> There is little uncertainty regarding the estimated incidence of: <ul style="list-style-type: none"> common toxicity ILD QTc prolongation. However, ongoing experience with the drug in phase III trials and in real-world usage will ultimately be needed to confirm the toxicity profile, the ILD incidence and to uncover more cases of arrhythmic events. Exposure for this drug was limited to a relatively small patient population in a research setting. <ul style="list-style-type: none"> Potential safety concerns could emerge in the post-market setting when there is wider clinical exposure. Data will be available once phase III data is submitted by the sponsor to support traditional approval. There is likely to be little off-label use of osimertinib as there is targeted activity of this drug only in a specific subpopulation of lung cancer patients. 	<ul style="list-style-type: none"> Both authorities agree that safety data are limited due to the study design. Apart from the uncertainty surrounding risks related to the study design, the FDA mentions off-label use as an uncertainty. In contrast to the FDA, the EMA enumerates several further uncertainties. The EMA reports uncertainties regarding drug-drug interactions, regarding data in very elderly patients and in patients with hepatic impairment. Furthermore, the CHMP is concerned about missing data of potential safety concerns, incl. severe skin reactions, diarrhoea, ocular toxicity and hepatotoxicity. In conclusion: The EMA describes the uncertainties related to risks in more detail; while the FDA provides a rather general statement that ongoing experience with the drug is required to confirm the safety profile.
Benefit-risk balance	<ul style="list-style-type: none"> Brief discussion of the obtained favourable result (ORR) with a special emphasis on a potential over-estimation of the response rate. <ul style="list-style-type: none"> Even assuming that the response rate could be overestimated, thus tumour responses associated with osimertinib treatment are 	<ul style="list-style-type: none"> Based on demonstration of durable ORR of large magnitude and an acceptable safety profile in two single-arm trials, the reviewers recommend granting accelerated approval. Concise description of the disease Summary of the study results related to efficacy 	<ul style="list-style-type: none"> The FDA grants an accelerated approval and the CHMP recommends a conditional approval for osimertinib. Both authorities require the results of the phase III study to further confirm the efficacy and safety of osimertinib.

Tagrisso	EMA's EPAR	FDA's Clinical Review	Comparison of EMA and FDA
<p>Cont. benefit-risk balance</p>	<p>expected to be superior to the different alternatives.</p> <ul style="list-style-type: none"> • Succinct summary of the safety profile, coming to the conclusion that despite the limited database the safety profile is considered overall acceptable. • Weighing the benefits against the risks: <ul style="list-style-type: none"> ◦ Despite the remaining uncertainties on the true magnitude of the benefit, the observed benefits are considered to outweigh the expected risks associated with osimertinib in the initially claimed indication that is restricted to patients with locally advanced or metastatic EGFR T790M positive NSCLC who have progressed on or after EGFR TKI therapy. ◦ Furthermore, benefits are considered to outweigh risks also in the small subset of patients with EGFR T790M positive NSCLC <u>not previously exposed to EGFR TKIs</u>. • In conclusion, data available are not considered sufficiently comprehensive to grant a full MA, however, they are of sufficient relevance in the context of a life-threatening disease where an unmet medical need exists. <p>→ Therefore, a conditional approval is supported</p>	<ul style="list-style-type: none"> • Description of the safety data with the conclusion that ongoing experience with the drug in phase III trials and in real world usage would be necessary to confirm the toxicity profile. Furthermore, warnings and precautions on the osimertinib label will address ILD, QTc prolongation, and embryo-fetal toxicity. • Risk management recommendations include several PMRs including a clinical efficacy study which will provide phase III confirmatory data on safety and efficacy. 	<ul style="list-style-type: none"> • Both authorities summarise the benefits and risks. • Compared to the FDA, the EMA mentions the uncertain magnitude of the obtained benefit (ORR) and discusses a potential overestimation. • On the contrary to the FDA, the EMA considers also the B/R balance for the small subset of patients with EGFR T790M positive NSCLC who were not previously treated with EGFR TKIs. Finally, the CHMP proposes to approve osimertinib also for this small subset of patients
<p>Post-market requirements</p>	<ul style="list-style-type: none"> • The specific obligation to complete post-marketing authorisation measures for the conditional applicant has to complete the phase III study AURA 3, in order to further confirm safety and efficacy of osimertinib. 	<ul style="list-style-type: none"> • According to the accelerated approval PMR, the applicant has to submit the study results of the phase III, open label, randomized study (AURA3). • Furthermore, the applicant is required to complete 4 drug-drug interaction studies and 1 hepatic impairment study. 	<ul style="list-style-type: none"> • To further confirm the efficacy and safety of osimertinib, both authorities require the completion of the phase 3 study (AURA3). • The drug-drug interaction study and the hepatic impairment study is included in EMA's RMP.

2. Comparison of EMA's SmPC and FDA's Label			
Tagrisso	European SmPC ⁴⁶	FDA's Label ⁴⁷	Comparison of SmPC and Label
Indication	<p>Tagrisso is indicated for the treatment of:</p> <ul style="list-style-type: none"> Adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC). 	<p>Tagrisso is indicated for the treatment of:</p> <ul style="list-style-type: none"> Patients with metastatic epidermal growth factor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) <u>who have progressed on or after TKI therapy.</u> 	<ul style="list-style-type: none"> The approved indications are different. According to the SmPC, Tagrisso is also indicated for the small subset of patients with EGFR T790M mutation positive NSCLC who have not previously been treated with TKI medications.

⁴⁶ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004124/WC500202022.pdf

⁴⁷ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf

Annex VI: Comparison of EMA's and FDA's B/R Assessment of Venclexta/Venclyxto				
Venclyxto (EU) / Venclexta (US), Venetoclax, Lymphocytic, Chronic, B-cell Leukemia				
1. Comparison of the Benefit-Risk Assessment Sections of EMA's EPAR and FDA's Medical Review				
	EMA's EPAR⁴⁸	FDA's Medical Review⁴⁹	Comparison of EPAR and Medical Review	
Approval date	05/12/2016	04/11/2016	~ 1 month	
Submission date	13/11/2015	29/10/2015	~ 2 weeks	
Review classification	<ul style="list-style-type: none"> Orphan drug designation Conditional approval 	<ul style="list-style-type: none"> Orphan drug designation Accelerated approval 		
Disease or condition	<ul style="list-style-type: none"> Detailed description of relapsed or refractory chronic lymphocytic leukaemia (R/R CLL) in section: Scientific discussion→2.1 Introduction. Approximately 5% - 10% of patients with early stage CLL have a 17p del and/or TP53 mutation; this rate increases with treatment lines up to 40% in advanced refractory CLL. Approximately 80% of CLL patients with a 17p del also have a mutation in TP53; sole TP53 mutations in the absence of 17p del have been reported to occur in about 4 to 5% of patients. 	<ul style="list-style-type: none"> Relapsed or refractory CLL with 17p deletion is serious, life threatening, and rare in frequency. The median duration of survival for patients with 17p del is poor. 		<ul style="list-style-type: none"> Both authorities describe R/R CLL as a serious, life-threatening and rare disease. Additionally, the 17p gene deletion is an ultra-high risk poor prognostic factor that is more common in patients with relapsed or refractory disease.
Current treatment options	<ul style="list-style-type: none"> Summary of current treatment options in section; Scientific discussion→2.1 Introduction. 	<ul style="list-style-type: none"> Detailed description of current treatment options in section: Therapeutic Context→2.2 Analysis of Current Treatment Options. FDA- approved therapies for the treatment of patients with R/R CLL include combination chemo-immunotherapy, ibrutinib, idelalisib with rituximab, and ofatumumab. The only FDA-approved therapy for the treatment of patients with 17p deleted CLL is ibrutinib. 		<ul style="list-style-type: none"> Both authorities define the risks and benefits of available therapies and draw the same conclusion: despite several new approvals for relapsed or refractory CLL, current treatments are not curative. Furthermore, the response rate in patients with 17p deletion are lower and the available therapies for this subgroup are much more limited. There is an unmet medical need for patients with R/R CLL harbouring the 17p deletion.

⁴⁸ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004106/WC500218804.pdf

⁴⁹ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208573Orig1s000MedR.pdf

Venetoclax	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Benefits	<ul style="list-style-type: none"> Updated results from study M 13-982 showed an overall response rate (ORR) of 82.4% in the safety expansion cohort, and 74.8% in the main cohort; 77.2% in both cohorts with complete response (CR) of 15.7%. Description of results from study M14-032 (venetoclax in patients with CLL who were refractory or intolerant to treatment with either ibrutinib or idelalisib). <ul style="list-style-type: none"> Status with respect to del17p/TP53 did not affect response rates. Updated data from the dose-escalation phase I trial, M 12-175 show an ORR of 82%. Current estimate for progression-free survival (PFS) at 24 months is 62%. Median durations of exposure in the studies M13-982 and M12-175 are sufficiently long for a reasonably precise estimate of benefit. 	<ul style="list-style-type: none"> The phase 2 trial, M 13-982, was venetoclax for the treatment of patients with R/R CLL harbouring the 17p deletion. The trial included 107 patients and 106 patients had 17p del. <ul style="list-style-type: none"> The ORR in 106 patients was 80.2% with a CR of 7.5%. The phase I, dose-escalation trial, M12-175 was venetoclax for the treatment of RR CLL. This trial was designed to evaluate the safety of venetoclax. <ul style="list-style-type: none"> The trial was not powered to evaluate efficacy, and all efficacy evaluations were considered exploratory. 	<ul style="list-style-type: none"> Each authority describes the results from the phase II, single arm trial, M 13-982. <ul style="list-style-type: none"> However, compared to the EMA, the FDA removed one patient without 17p deletion from the analysis, so that only patients with 17p deletion were included. Another difference between the two authorities is that the EMA refers to the 'updated results' compared to the FDA. Both authorities mention trial M12-175, however only the EMA describes the results of this dose escalation trial. On the contrary to the FDA, the EMA states the results of study M14-032. In conclusion, the FDA considers only study results for patients with 17p del; whereas the EMA describes also study results for patients with R/R CLL irrespective of 17p del.
Uncertainty in terms of benefits	<ul style="list-style-type: none"> Although the anti-tumour activity of venetoclax in B-cell receptor pathway inhibitor (BCRi) refractory patients independent of 17p del was acknowledged, the non-comparative and limited data due to the low number of subjects and limited follow-up time in this population represents an uncertainty. <ul style="list-style-type: none"> The patient population in this study is more heterogeneous. Very few patients have been treated > 2y and PFS and OS data are still immature. <p>→ Therefore, additional efficacy data would be needed as confirmatory and will be provided from the expanded study M14-032.</p>		<ul style="list-style-type: none"> The <i>Benefit</i> column of FDA's framework does not include any uncertainties surrounding benefits. Whereas, the EMA determines an uncertainty regarding the efficacy for BCRi refractory patients independent of 17p del mutation. Due to the fact that the FDA does not describe study results for patients who do not have the 17p del, it is not unexpected that the FDA does not state any uncertainties regarding benefits for this subpopulation.

Venetoclax	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
Risks	<ul style="list-style-type: none"> The main safety concern was the risk of tumour lysis syndrome (TLS), especially at the initiation of treatment. <ul style="list-style-type: none"> Protocol amendments followed that included a slow ramp-up dosing during the first five weeks. Dose reductions were undertaken in a total of about 10% mainly for neutropenia, and thrombocytopenia, but also for diarrhoea. Infectious events were very common and altogether there were about 20% of infectious events classified as SAEs (mainly pneumonia). Adverse events with a reasonable possibility of being related to venetoclax that occurred in ≥10% of subjects in the all 400mg Analysis set were: neutropenia, nausea, diarrhoea, fatigue, thrombocytopenia and anaemia. 	<ul style="list-style-type: none"> Generally, the pattern of adverse reactions reflects events expected for a heavily pre-treated elderly population with R/R CLL. No major safety concerns were identified except for the on-target events of tumour lysis syndrome and neutropenia. <ul style="list-style-type: none"> The risk assessment and prophylaxis of TLS was modified in two major protocol amendments. The dosing regimen for venetoclax was adjusted to include a ramp-up phase. The risk of neutropenia is significant both from underlying CLL and from treatment with venetoclax. <ul style="list-style-type: none"> Neutropenia is usually manageable with standard of care treatments. Importantly, no correlation was found between neutropenia and infections. Drug-drug interactions were seen with CYP3A4 inducers and inhibitors and P-gp inhibitors. 	<ul style="list-style-type: none"> Both authorities identify the risk of tumour lysis syndrome as a major safety concern that can be managed by a ramp-up dosing and other measures. Furthermore, both authorities classify neutropenia as an important risk. The FDA states the risk of drug-drug interactions; whereas the EMA lists adverse events with a reasonably possibility of being related to venetoclax treatment. Additionally, the EMA reports that infectious events were very common as expected in the treatment of CLL. The FDA concludes that apart from the identified safety concerns (neutropenia and TLS) the general pattern of adverse reactions would reflect expected events. In conclusion, both authorities identify identical major safety concerns (TLS and neutropenia).
Uncertainty regarding risks	<ul style="list-style-type: none"> Assessment of the safety profile of venetoclax is compromised by the lack of controlled data, as manifestations of CLL include cytopenias, infectious events, etc. The incidence of Richter's syndrome appears somewhat high compared with historical data. Richter's transformation should be considered an important potential risk. Data on long term safety and on the development of resistance for venetoclax is limited. 	<ul style="list-style-type: none"> All safety information to date has been from single-arm trials, so contribution of the underlying disease is difficult to determine. Venetoclax is metabolised by the liver, and a very limited number of patients with moderate hepatic impairment were treated with venetoclax. There is an increased risk of TLS in patients with renal impairment. 	<ul style="list-style-type: none"> Both authorities draw the same conclusion: the ability to define the safety profile is limited due to the lack of comparative data. Apart from that conclusion, each authority highlights other uncertainties related to risks. <ul style="list-style-type: none"> The FDA identifies an uncertainty regarding the risks for patients with hepatic impairment. The EMA describes Richter's symptom as an important potential risk. Furthermore, limited data on long term safety and the development for resistance of venetoclax pose uncertainties related to risks.

Venetoclax	EMA's EPAR	FDA's Medical Review	Comparison of EPAR and Medical Review
B/R Balance	<ul style="list-style-type: none"> Explanation why no randomised comparative studies were undertaken and why the single arm studies demonstrated clinically meaningful benefits of venetoclax treatment. Description of the important and serious risk of TLS and the risks of infections. Discussion if the presence of the specific mutations or prior therapy affects the activity of venetoclax. Conclusion: <ul style="list-style-type: none"> As there are differences in the safety profiles comparing venetoclax with the BCRi (idelalisib and ibrutinib) and possible anticipated differences in tolerance, the defined use of venetoclax in patients with CLL in the presence of 17p deletion who are unsuitable for or have failed a B-cell receptor pathway inhibitor is clinically meaningful. Furthermore, the following indication is supported: Venclyxto monotherapy is indicated for the treatment of CLL in the absence of 17p deletion in adult patients who have failed both chemoimmunotherapy and B-Cell receptor pathway inhibitor. 	<ul style="list-style-type: none"> Short summary of the therapeutic context. Description of the results of the single-arm, phase 2 trial, M13-982. Report of the safety profile including the main safety concerns (TLS and neutropenia) and the measures to mitigate the risk. Conclusion: The efficacy of venetoclax for the treatment of patients with R/R CLL with the 17p deletion is supported based on a surrogate endpoint of ORR. As such, it represents an improvement over available therapies. The safety is acceptable with rigorous management of the risk of TLS which are addressed through appropriate labelling. 	<ul style="list-style-type: none"> The FDA summarises the results from the trials and explains why venetoclax is eligible for accelerated approval. The EMA, on the contrary, explains why it is hardly feasible to conduct randomised comparative studies in patients with R/R CLL and discusses, if venetoclax is eligible for the proposed indications. <ul style="list-style-type: none"> →Finally, the authorities determine a positive B/R balance. Nevertheless, the SmPC entails a different indication compared to the Label (see comparison of SmPC and Label)
Post-market requirements	<p>Obligation to complete post-authorisation measures:</p> <ul style="list-style-type: none"> PASS: The results of the MURANO study should be submitted in order to confirm the overall safety profile and investigate the risk of Richter's syndrome/secondary malignancies, Specific obligation to complete post-authorisation measures for the conditional MA: <ul style="list-style-type: none"> The results of study M14-032 should be submitted to further confirm the efficacy and safety of venetoclax. <ul style="list-style-type: none"> Additional 60patients will be enrolled, this will enable confirmation of benefit-risk in the target population for the second part of the indication. 	<p>The following Post-Marketing Requirements are planned for this application:</p> <ul style="list-style-type: none"> Confirmatory Trial entitled MURANO: Conduct a randomized, phase 3 trial comparing venetoclax and rituximab versus bendamustine and rituximab in patients with relapsed or refractory CLL (including 17p del). Drug-drug interaction Study with a P-gp substrate: To investigate the effect of single dose venetoclax on the pharmacokinetics of a P-gp substrate. Hepatic Impairment Study: To evaluate the pharmacokinetics of venetoclax in subjects with varying degree of hepatic impairment. 	<ul style="list-style-type: none"> Both authorities require the results of the MURANO study. The FDA requires a hepatic impairment study and a drug-drug interaction study. These studies are also included in EMA's RMP for venetoclax. As an obligation of the Conditional Approval, the EMA requires the results of study M14-032.

2. Comparison of the European SmPC and the US Label			
Venclyxto/ Venclexta	European SmPC ⁵⁰	US Label ⁵¹	Comparison of SmPC and Label
Indication	<ul style="list-style-type: none"> Venclyxto monotherapy is indicated for the treatment of: <ul style="list-style-type: none"> Chronic lymphocytic leukemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemimmunotherapy and a B-cell receptor pathway inhibitor. 	<ul style="list-style-type: none"> Venclexta is indicated for the treatment of: <ul style="list-style-type: none"> Patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. 	<ul style="list-style-type: none"> The first part of the SmPC's indication is comparable to the indication of the Label, however there are some differences. <ul style="list-style-type: none"> According to the SmPC, the drug is approved for patients harbouring the specific mutations who are <u>unsuitable</u> for or have failed a BCRi. The Label includes patients <u>who have received</u> at least one prior therapy. According to the SmPC the prior therapy has to be a BCRi. However, the difference lies in the wording, since the only FDA approved therapy for patients with 17p deleted CLL is ibrutinib, that belongs to the BCRi. The SmPC includes also patients with TP53 mutation. The second part of the SmPC's indication refers to patients without the genetic mutations. The Label does not include this subpopulation in the indication.

⁵⁰ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004106/WC500218800.pdf

⁵¹ http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

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