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**Running Title: Moving towards a Question-centric approach for regulatory
decision-making in the context of drug assessment**

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Abstract

The most intuitive question for market access for medicinal products is the benefit/risk (B/R) balance. The B/R assessment can conceptually be divided into sub-questions related to establishing efficacy and safety. There are additional layers to the B/R ratio for medical products, including questions related to dose selection, clinical and non-clinical pharmacology, and drug quality. Explicitly stating the actual questions and how they contribute to the overall B/R provides a structure that helps better informed cross-domain discussions.

There is currently no systematic approach in the regulatory setting to assess and establish the acceptability of alternative methods and data sources. In most cases, the medicinal product sponsors tend to prioritise traditional data types and methods, which are well accepted by regulators for inclusion in regulatory submissions. This, in addition to the absence of rigour in the use and validation of new data types and methods, and the limited training of assessors in related fields can lead to increased regulatory scepticism toward new data types and methods. A data-knowledge backbone is needed to mitigate the uncertainty in efficacy and safety characterisation.

This white paper discusses the value of explicitly redefining and restructuring the regulatory scientific decision-making around the scientific question to be addressed. The ecosystem proposed is based on three pillars: (a) a repository connecting questions, data, and methods; (b) the development and validation of high-quality standards for data and methods; (c) credibility assessment. The ecosystem is applied to four use-cases for illustration. The need for training and regulatory guidance is also discussed.

1. Introduction

The current regulatory assessment and decision-making process is sequential and compartmentalised in three well-established domains (quality, nonclinical or clinical) based on traditional data types, with limited integration. There are well-established methods for each domain with related acceptability criteria.

In the EU regulatory system, different regulatory procedures are in place for interacting with drug sponsors at the European Medicine Agency (EMA) and at National Competent Authorities (NCA) levels. These include Innovation Task Force (ITF) meetings, Scientific Advice (SA), qualification advice (QA), qualification opinion, (QO), Market Authorization Authorizations (MAA), variations, referrals, signals, Periodic safety update report single assessments (PSUSA), Periodic benefit-risk evaluation report (PBRER), and renewals. At the EMA, depending of the aim of each procedure, the type of product, and the targeted population, different committees are involved, namely the Committee for Medicinal Products for Human Use (CHMP), the Committee for Advanced Therapies (CAT), the Committee for Orphan Products (COMP), the Pharmacovigilance Risk Assessment Committee (PRAC) and working parties (Scientific advice Working Party (SAWP), Modelling and Simulation Working Party (MSWP), Biostatistics Working Party (BSWP)). For ITF briefing meetings, QAs and SAs, drug sponsors request regulatory advice on different aspects of their development programs. Advice are related to, and discussed separately for quality, nonclinical, clinical pharmacology, dose selection, clinical efficacy and safety. For QO, MAA, and post-marketing procedures, the regulators receive a request from a sponsor and need to issue an opinion either on the adequacy of data and methods used to establish efficacy, safety and a favourable benefit/risk balance.

The current regulatory standards and guidance documents are mostly related to more traditional studies, historical data types and related analytical methods. This is illustrated by the fact that the International Council for Harmonisation of technical requirements for pharmaceuticals (ICH) guidelines are organised into quality, safety, efficacy, and multidisciplinary (QSEM) domains. Likewise, EMA guidance documents and training are also compartmentalised around the same domains.

This white paper will discuss the value of explicitly redefining and restructuring the regulatory scientific decision-making around the scientific question to be addressed. This is the so-called “Question-centric

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approach” which expands the V&V40 (Verification & Validation) approach proposed for medical devices and applied by regulators to also include when modelling and simulation is used to support drug development [1]. This will conceptually improve the way in which evidence (including data and analytical methods) is assessed by regulators for final decision-making. The implementation will permit a clear shift from the current partitioned and sequential evidence generation and regulatory assessment to a more integrated approach centred on the drug development question and offer the possibility to combine different types of data in an integrated assessment approach. Of note currently, regulatory assessment is mostly limited to three types of data: quality, non-clinical and clinical in the electronic Common Technical Document (eCTD) modules 3, 4 and 5, respectively [2] (see figure 1) . These different data types are separately assessed as part of the different regulatory procedures.

This new model will open up more possibilities for the acceptability of alternative data types and analytical methods, provided that their relevance in addressing the question of interest is demonstrated.

The need for a repository of the key drug development questions, their related sub-questions and ramifications, as well as the way they connect to related data and methods will be discussed. This repository would support regulatory assessors and drug sponsors in finding relevant information on previous use cases of similar methods or similar questions by querying the repository. The repository would also provide a new model for knowledge sharing on regulatory assessment, by introducing transparency on all relevant scientific questions and (innovative) methods used to answer scientific questions. The repository would thus complement the existing regulatory structures, increase transparency, and pose a powerful engine for learning and consistency across procedures and medicinal products.

The need for regulatory guidance will also be discussed, in particular on cases where new/alternative data types (including RWD) are used, and/or cases where advanced methods (including in silico approaches) are used to address relevant drug development questions. There is currently no specific guidance on alternative data types and innovative analytical methods and their use to support regulatory decision-making. The newly adopted ICH Model Informed Drug Development (MIDD) guideline will be the first to be explicitly dedicated to the use of computational modelling and simulation

in drug development. Currently, alternative data types and methods included in regulatory submissions are assessed on a case-by-case basis. At the EMA, a qualification opinion is requested for new methods and biomarkers, when used for high regulatory impact applications, i.e., when alternative data types and innovative analytical methods are proposed to replace a (traditional) clinical study [3].

With regards to data quality standards, different standards exist, tailored to the usual data types and specific to the regulatory application. The FDA has developed a data standard named cDISC [4] for the submission of patient level clinical data and the ICH recommends the eCTD format for submission of reports of drug development for MAA [5].

The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) standard can be cited for observational data [6]. In the context of standard development, this white paper will discuss an expansion of the credibility approach, initially proposed for model-informed medical devices development, to objectivise the assessment of new methods/data in the context of regulatory submission related to drugs and drug-device combinations.

In the proposed model, the credibility-based assessment framework will be introduced into the regulatory workflow in a unique manner, to structure and standardise the evaluation method and the data attributes. This approach permits identifying the key decision points when the different methods and data sources are used, taking into account the knowledge on the specific phenomena/system of interest evolves through the life cycle of a medicinal product. This approach allows for continued learning for both regulators and drug sponsors to ensure the necessary level of rigour of evidence at key stages of drug development.

We will illustrate the proposed framework using five use-cases: paediatric drug development, orphan medicines development, drug efficacy, cardiac safety assessment and use of real-world data to inform regulatory decision making.

2. The Concept of the Question-Centric approach

The question-centric approach is designed to be an integrated model for regulatory decision-making centred around drug development questions: this will constitute a transparent ecosystem for drug assessment that will facilitate the adoption of alternative data types and innovative analytical methods.

The overall concept of the question-centric approach is illustrated in Figure 2 where an example is given on a drug development question: “Question A - What is the effect size of the medicinal product X in population Y?”.

In Figure 2 three different methods are presented: (1) a randomized controlled trial (RCT) on clinical efficacy vs (2) a single arm clinical trial (SAT) with real-world data as the external control arm versus (3) a computational modelling and simulation approach with an agent-based model coupled to a virtual (in silico) trial. For the three approaches, the regulatory impact of the method(s) would be high, as the standard requirement (for a new drug entity) would be to conduct two independent, prospective, double blind and fully powered clinical trials. The data types/sources will vary depending on the approach taken, and so will the contexts of use, the acceptability criteria, the technical implementation, credibility factors, uncertainty quantification and the final contribution to the answer to Question A. For each of the approaches, the assessment process of understanding the validity of the results that a method provides (in this case the answer to Question A), relies heavily on subject matter/domain expertise. Not only do sub-questions, such as disease status and concomitant treatments related to the representability of the patient population, become important, but also the pharmacology and toxicology of the drug, as well as the quality of the drug substance and its formulation, can impact the outcomes of the trials and must be taken into account.

For the RCT, Dataset 1 would be the efficacy results generated from conducting the trial. The context of use would be that the data from that one fully powered RCT will constitute the only source of evidence to confirm the relevant treatment effect of drug X in patient population Y with no further data collection planned. The acceptability criteria will include the prospective nature of the study, the blinding, prespecified statistical analyses with a stringent p-value and adequate characterisation of the estimand. There exist international (ICH) and European guidelines to support drug assessments based on RCT [12-14].

For the SAT coupled to RWD, Dataset 2 and 3 would be the data collected in the single arm and the already existing RWD, respectively. The RWD could be collected from EHRs or other observational data sources (e.g., registries). The acceptability criteria would also be prespecified in the protocol. As

part of these criteria, the SAT endpoints, the requirement for RWD attributes and quality as well as the role of the external arm can be defined.

Lastly, when an *in silico* approach is taken, the context of use should precisely define not only the objectives and implementation approach, but also the data sources for model building and evaluation and the methods used for creation of virtual populations. The datasets used to generate the quantitative model describing the phenomena/system of interest would come from a variety of different sources. Further, a series of datasets would normally be used to calibrate and validate the predictive ability of the model. While the output of the *in silico* trial (the synthetic data), here denoted by Dataset 4, is an important piece of the evidence, this dataset would not be evaluated as self-standing in the manner that Datasets 1 and 2 would be. The acceptability criteria for the quantitative model would be prespecified in the modelling analysis plan. Such criteria include the technical performance of the model (verification), the performance of the model to predict the behaviour of the phenomena of interest (validation) and the relevance of the activities (applicability).

It is important to have an objective and standardised means to compare reliability of the different answers obtained from alternative methods, in order to permit their use in regulatory decision-making. This general approach can be applied to safety characterisation or extended to include quality, nonclinical and clinical data domains.

Another concept important for the question-centric approach is the attributes framework. In the question-centric approach we will use the general term “attributes” to describe important properties or features of the phenomena that are being investigated. The framework will provide a workflow that will structure the process of identifying and managing the quality, non-clinical and clinical particulars. The framework provides a workflow that will allow explicit identification of potential critical sources of variability and uncertainty in the field(s) relevant to the related question and corresponding answer.

The underpinning assumption of the question-centric approach is that the full potential of alternative (new) data types and innovative methods can only be realised when appropriate tools for contextualising their credibility exist and are used by regulators. It is assumed that, given a functioning and transparent

ecosystem, where underlying scientific questions and the strengths and limitations of both traditional/well-established and innovative data sources and methods are well-understood, the latter data sources and (in silico) methods will prove their usefulness.

Fundamental to this approach is the availability of a workspace (data platform) that allows the confluence of all relevant data types (submitted regulatory data and external data) which is integrated, curated and connected to a computational platform that can efficiently manage the workflows for such an interactive, question-based approach (see figure 3).

The ecosystem proposed by the question-centric approach will be based on three pillars: (a) a repository connecting questions, data and methods; (b) the development and validation of high-quality standards for data and methods; (c) credibility assessment. As part of the question-centric approach, the ecosystem will be set up and applied to five use-cases in four different types of applications.

a. Repository of drug development questions

To support the question-centric approach, a repository of key scientific questions relevant to drug development should be established. The scope will be to deliver, thanks to data-driven interrogation of different data sources (e.g. eHealth data, registries, study reports, etc. applying standards and advanced analytics) structured data (including digital twins), implement analyses, assess methods' performances, and benchmark alternative methods for identified questions.

The repository should include:

- descriptions of the different data sources and types (and related quality) used to answer a specific question,
- related contexts of use,
- analytical methods,
- acceptability criteria to assess the credibility of the method(s) used for the particular question.

A hierarchical structure should be developed to support the entry of questions. This is needed to

differentiate the key drug development questions from the sublayers of specific questions related to aspects such as methods, data sources and particularities of the medicinal product and the patient population. An attributes framework is also needed as described below in section 6. The standardised entry of questions and methods, and the development of the prototype will be dependent on it.

Importantly, in addition to the literature, clinical trials, e-Health and real-world data, and/or pharmaceutical industry internal data, a retrospective review of representative regulatory procedures could be conducted to ensure that the hierarchical structure is fit-for-purpose for all regulatory submissions across therapeutic areas, types of medicinal products, regulatory procedures and across the life-cycle of the medicinal products. As part of this review, retrospective searches can be performed in regulatory submissions and related assessment reports: the concerned questions, related methods and data sources will be extracted, with all such information populating the repository. All submissions (including innovative methods) to the EMA through the different regulatory procedures (ITF, SA, PIP, QA, QO, MAA, variations, signals, referrals, PBRER, PSUSA, PSUR, renewals etc.) can be reviewed. The learning documents developed by the various EMA committees and Working Parties could also be analysed. In addition, a prospective study to collect submissions of innovative methods can also be planned and conducted as part of the question-centric approach in agreement with the EMA and the NCAs.

The structured retrospective review of the different data sources (literature, clinical trials, e-Health and real-world data, Pharmaceutical industry internal data, and regulatory submissions) will support the development of the hierarchy of questions, that will identify the principal question and the related sub-questions. All relevant findings would be used for the expansion and update of the repository.

The repository can subsequently undergo an automation process. There is currently an unmet need for automated overarching tools for data searching, formatting, integration, and analysis to support the regulatory work. Ideally, well-designed platform relying on advanced methods such as artificial intelligence (AI)/machine learning (ML)-based methods could offer a great potential to this regard, thanks to scientist-supervised automation of the relevant aspects of regulatory assessment work.

b. Standards to assess the credibility of (a) method(s)

The risk-informed analysis approach based on credibility assessment, initially proposed for model-informed medical devices and drug development, can be expanded to objectivise the assessment of new methods/data in the context of regulatory submission related to drugs and drug-device combinations. The credibility-based assessment framework will then be introduced into the regulatory workflow in a unique manner, to structure and standardise the evaluation method and the data attributes. As stated above, the results of credibility assessment will constitute one of the features of the repository for each combination of question, data and methods, given the context of use.

The risk-informed analysis approach has recently been expanded to models used for drug and combined drug-device products [15, 16]. In one of the papers, it was demonstrated that the approach is consistent with recommendations in the European Medicines Agency's (EMA) Guidelines on Physiologically Based Pharmacokinetic (PBPK) Modelling and the ICH and EMA guidelines on paediatric extrapolation [17-19]. Pilots have been conducted at EMA and within NCA such as the Belgian Federal agency for medicines and health products and the Norwegian Medicines Agency where the credibility framework was successfully applied to empirical and mechanistic models in the context of drug development [20]. The question-centric approach will expand the approach to other data-driven methods and innovative tools (e.g. AI, Bayesian statistical models, etc.) and to alternative data types used to answer questions related to medicinal product development. To comply with the recommendations in the initial standards and subsequent papers, the question-centric approach will include a description of the context of use (COU) for each method used to address a specific question. This will be written as a short and concise description of the aims of the method, the data used for implementing and validating the approach, as well as additional evidence that supports the decision (answer to the specific question).

As part of the communication of the risks associated with the methodological choice, the risk-informed analysis approach also explicitly describes the regulatory impact of the concerned method. The regulatory impact will describe the influence the method used will have on the final decision (given the available data), as well as how the proposed method compares with currently established methods for answering the question(s) of interest. If the method is intended to replace a clinical study or other

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established methods of answering the question, which often would represent a request for extrapolation, this should be clearly described. The next step is to outline the decision's consequence. The decision's consequence is defined as the significance of an adverse outcome resulting from an incorrect decision. In regulatory submission for medicinal products, this generally relates to the risk to the patient in case the method, the modelling predictions or assumptions lead to erroneous regulatory decisions. One aspect of such risks relates to patients either being over- or underexposed to the drug, but other adverse events or risks can also be relevant depending on the question of interest.

Credibility activities should include verification and validation as well as assessment of applicability [16, 20]. The framework will use credibility factors to describe how rigorous each activity need to be. This way, the credibility framework provides a structure to the process of model assessment.

The goals of verification activities is to identify and remove errors in the source code and numerical algorithms of the computational software [21]. Specific activities on code verification will include software quality assurance and numerical code certification. To verify calculations, activities to estimate the discretisation and the numerical solver errors and to identify use errors will be launched. The goals of the validation activities will be to assess the adequacy of the model in representing the phenomena/system of interest and to understand how to improve the model or perform further validation activities if needed. Credibility activities will include assessment of the structure of the model, its input parameters and related uncertainties. Activities will also be performed to describe the quality and the adequacy of observed data sets for validation purposes.

Uncertainty quantification (UQ) can be described as the process of quantifying and managing uncertainty in computational model predictions of the behaviour of real-world phenomena/systems. UQ aims to address how the various sources of error and uncertainty feed into uncertainty in the model-based prediction of the outcome measures (often called quantities of interest) [22]. As described, common sources of uncertainty relevant for computational models include uncertainties in the parameters and structure of the models and uncertainties in the observed data used to calibrate or validate those models. Once potential sources of uncertainty are identified, simulations will be performed to predict their impact on the variability of the outcome measures. The probability distributions or ranges

of uncertainty of the source data should also be defined as well as the uncertainties propagated through the model. Structural identifiability should also be characterised. If parameter estimates are used to inform about treatment effects, optimal design strategies, or other critical decisions, then it is essential that the parameters are uniquely identifiable.

Different tools exist for assessing the comparability of the model predictions (outputs) with available data on the phenomena (observed data). In the pharmacometrics domain, visual tools (so called Visual Predictive Checks, VPCs) are often used for this comparison, which represents a lower grade rigour of thoroughness into this credibility factor.

c. Standards for data quality

To develop a data quality framework a set of standards are required to specify the use of standardised definitions for the identification and description of requirements on data generation. Together with the question centric approach, an attributes framework will standardise the manner which the quality, non-clinical and clinical particulars are identified and described (annotated). Three standards should be developed for tailored credibility assessment. Standards will be developed for the quality of:

- data searching,
- structuring/formatting,
- data analysis (including data curation and interpretation).

This will be to facilitate the reliable exchange of data used to answer drug development questions in a robust and consistent manner. Data quality standards are needed for the following data types and sources: (non)clinical trials, synthetic data, digital twins, scientific literature, healthcare data, drug and disease repositories, previous regulatory submissions, healthcare record data and patient report outcomes (PROs). Standards will also be proposed for model types not covered by existing solutions, such as PBPK, Quantitative systems pharmacology (QSP), agent-based models and AI. Each of these data types and models are represented in the use cases included in the project. This will permit validation

of the newly proposed standards and ensure their feasibility. It should also be noted that the link between data and methods to be used for their analysis to inform regulatory decision-making will be preserved.

To develop the standards for data quality a structured review of relevant standards and technical solutions needs to be conducted. The new standards should be built on the existing frameworks and solutions (e.g., standards on the identification of medicinal products (IDMP), as well as solutions within the European health data space). Recommendation for specific data sources/types will be given as appropriate. Additional standards will be proposed for data types and methods not covered by existing standards. Care will be taken to ensure that the data are presented in an acceptable format, consistent with the attribute framework and with the FAIR (Findability, Accessibility, Interoperability, and Reuse) principles [9], given the data space, the question to be addressed and the concerned analytical methods.

d. The attributes framework

The attributes framework is a workflow that will structure the process of identifying and managing the quality, non-clinical and clinical particulars, and their related uncertainty. This approach permits identifying the key decision points when the different methods and data sources are used, as the knowledge on the specific phenomena/system of interest evolves through the product life cycle.

This approach allows for continued learning for both regulators and drug sponsors to ensure the necessary level of rigour of evidence at key stages of drug development. As a consequence, methods suitable for answering specific questions will be derived, which allow the move towards standardisation (matching Q&As). Such a framework will provide a workflow that will structure the process of identifying and managing the quality, non-clinical and clinical particulars that lead to requirements on data generation to answer (and submit data) on the related drug development questions. An approach already exists for this in the quality domain [23], which will inform the standards for quality attributes, while the approach will be extended into the non-clinical and clinical domains. The workflow will allow explicit identification of potential critical sources of variability and uncertainty in the field(s) relevant to the concerned question and related answer. The distinction, systems, relationships and perspectives (DSRP) principles for describing real world phenomena as systems [24], will be applied in combination

with the hierarchy of drug development questions and subject matter expertise on regulatory assessment to provide standards for how to describe the relevant phenomena/system and identify and describe attributes of potential importance. The attributes framework is intended to function as a common standard (“an umbrella”) that will support the assessment process. The outcome (product) of following the workflow of the attributes framework will be an explicit description of the quality, non-clinical and clinical particulars, which can support a shared understanding of both which questions to be addressed as well as any implications on which methods can be used to address the questions at different stages of development. As such, this “product” can function as a qualitative tool that reflects the current knowledge level and can dynamically reflect the evolving knowledge, i.e. reflect the decrease in the epistemic uncertainty. The knowledge gained by developing the attributes framework is intended to provide guidance on annotations needed to identify the relevant and the critical attributes for the questions of interest and for submitting raw data, synthetic data and analysis results to the regulatory authorities.

3. Regulatory guidance documents

The current regulatory standards and guidance documents are mostly related to more traditional studies, historical data types and related analytical methods. This is illustrated by the fact that the International Council for Harmonisation of technical requirements for pharmaceuticals (ICH) guidelines are organised into quality, safety, efficacy, and multidisciplinary (QSEM) domains. Likewise, EMA guidance documents and training are also compartmentalised around the same domains.

There are currently no EMA regulatory guidance documents relevant to new methods such as AI/ML or in silico trials. For data attributes standards, they are closely linked to the analytical methods and the specific application. Guidance is therefore needed for cases where alternative data types are analysed by advanced methods to address relevant drug development questions.

There is currently no specific guidance on alternative data types and methods and their use to support regulatory decision-making. The newly adopted ICH Model Informed Drug Development (MIDD) M15 guideline will be the first to be explicitly dedicated to computational modelling and simulation in drug development.[25]

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Currently, the alternative data types and methods are assessed on a case-by-case basis, when included in regulatory submissions. At EMA, a qualification opinion is requested for new methods and biomarkers, when used for high regulatory impact applications, i.e., when alternative data types or innovative methods are proposed to replace a (traditional) clinical study [7]. The criteria for these qualification opinions for alternative data and methods are not always transparent and might depend on the assessment team's expertise. Of note there is currently a very limited number of submissions related to new methods and alternative data types with successful regulatory outcomes.

As regards data quality standards, different standards exist, tailored to the concerned data types and specific to the regulatory application. The FDA has developed a data standard named cDISK [8] for submission of patient level clinical data and the ICH recommends the eCTD format for submission of reports of drug development for MAA [9]. The OMOP CMD standard can be cited for observational data [10].

There are no regulatory standards for the alternative data types and innovative methods applicable to drug development.

4. Training

In the EU regulatory network, training for assessors is available within the EMA and NCA networks via the EU-Network training centre (EU-NTC) channel. Moreover, training and workshops on key topics are organized by the EMA for drug sponsors. Most of the available trainings concern traditional data types and domains as well as commonly used analytical methods.

There is currently an unmet need for training packages and workshops dedicated to increase awareness among assessors and drug developers on the technical and scientific aspects of innovative methods, their credibility assessment as well as the contextualisation of traditional and innovative methods in relevant application areas. This should be set as a high priority for the regulatory bodies.

5. Use-cases

Five end-to-end use-cases are described below to illustrate the value and outline the question-centred

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approach. They are related to (1) paediatric drug development drug, (2) drug cardiac safety assessment, (3) efficacy assessment and (4) rare disease drug development and (5) use of real-world data. We will discuss how, in each of the use-cases the repository can be used to better define the question, the context of use, the relevant data types and sources, and the related analytical methods. The value of implementing data quality standards, attributes framework and the assessment of credibility will also be discussed as well as the potential to generate packages for high quality regulatory submissions.

a. Paediatric and rare diseases drug development

Drug development in small population including (children and rare disease) is more challenging than in adults due to practical and ethical limitations in collecting experimental evidence (mostly data from randomized controlled trials) in this groups of patients. Current requirements for the approval of medicines for children are based primarily on a slowly progressing evidence generation model that assumes, in many cases, prior clinical experience in adult subjects. Likewise, the data included in the registration packages for rare diseases is most often more limited than for more common diseases, due to feasibility issues and difficulties to enrolment of patient in the clinical studies. Alternative approaches are often suggested for evidence generation to establish the efficacy and safety of medicinal products in children rare disease. Among the numerous conditions for which medical needs remain unmet, the following case-studies can be cited: chelating agents in transfusion-dependent haemoglobinopathies, sirolimus as first-line therapy for the treatment of autoimmune cytopenia in paediatric subjects, metformin for the treatment of tuberous sclerosis complex (TSC)-related epilepsy in children and anti-retrovirals/antimalarials as treatment of inborn errors of immunity or primary immunodeficiency disorder.

To support the use of the question-centric approach in these cases, key drug development questions need to be identified. The repository can be implemented as part of the clinical (repurposing) development plan to identify relevant data sources, refine the questions, determine the contexts of use and the related analytical methods. The available data from existing repositories (e.g. The EPTRI repository (ref) and the Rare Disease Cures Accelerator - Data and Analytics Platform (RDCA-DAP) (ref) for paediatric

and rare diseases, respectively) can be explored for this purpose, in addition to literature and regulatory submissions.

An attributes framework can be developed for each case. It is anticipated that the analytical methods to be used for clinical evaluation will include quantitative systems pharmacology, model-informed extrapolation, clinical trial simulations and integrated summaries of safety and efficacy to assess the overall B/R profile using data visualization and dynamic data interrogation tools, in which historical and real-world data will be evaluated in the target paediatric population. There is a potential value to interrogate the repository for alternative data & innovative methods used in the context of model-informed paediatric drug development. Subsequently, the identified relevant data can be scrutinized against the standards developed for data searching, data formatting and data analysis. The attributes framework can be applied, and the credibility assessment can be implemented on the identified cases, that will be evaluated and, if necessary, updated to reflect the compliance of the cases with standards. Simulation tools developed can be applied to benchmark the different approaches from the identified cases. By benchmarking approaches that rely on alternative data & innovate methods against more traditional approaches the aim would be establishing the applicability for alternative data & innovate methods in the context of model-based paediatric drug development.

The proposed use-cases can provide data packages for EMA qualification opinion(s) and /or scientific advice(s) related to paediatric drug development and repurposing. This can also permit to implement a simplified clinical development plan ensuring faster, efficient marketing authorisation approval. The proposed development plan, including a proof-of-concept study, where appropriate, would be assessed as part of a Paediatric Investigation Plan (PIP), through a close interaction with the EMA.

b. Assessment of drug cardiac toxicity

There is a regulatory requirement for sponsors of non-pro-arrhythmic drugs concerning the assessment of the potential of their drug to delay cardiac repolarization. This assessment should include testing the effects of new agents on the QT/QTc interval as well as the collection of cardiovascular adverse events (ref: ICH E14). The question-centric approach can be used to establish how far back in the 'hierarchy'

of *in silico*, *in vitro*, *in vivo* and clinical models it is possible to confidently predict the presence or absence of the delayed repolarisation hazard. An attributes framework can be developed for this purpose. This focus on hazard identification “before QT” can be used to minimise both clinical QTc assessments and large animal *in vivo* QT assessments. The hazard is sometimes associated with a metabolite molecule rather than the parent; in these cases, emerging *in silico* models will be used. The use case will examine situations where the hazard is likely to be from either or both parent and metabolite.

In those cases where the hazard is present the focus shifts to risk assessment – the probability that proarrhythmia will occur in specific populations or patients. Based on exposure and ion channel effects interacting with heart rate and disease state the risk can be placed into higher or lower risk categories. In the use case this will expand the integrative outputs “beyond QT” and will also use active tension to illustrate the trade-off between proarrhythmia risk and contractile function. The question-centric approach would then be related to hazard identification for delayed cardiac repolarisation and the assessment of proarrhythmic risk for those molecules with a positive hazard identification.

A number of historical products in oncology can be compared in terms of cardiovascular safety using QTc and other ECG parameters. Oncology can be considered as a use-case indication as heart disease and cancer have significant commonalities including risk factors (e.g. age) and genetic components. A method can be developed to evaluate both these historical patient level and aggregate level data and how best to combine them for safety assessment and benchmarking.

An alternative method, model-based meta-analysis (MBMA) can also be considered. It will incorporate parametric models based on literature data (synthetic data) and patient-level data. It will quantify the effect of treatment, time, and patient population characteristics on the safety outcomes. It can include compound/trial-level covariate relationships on the dose-concentration- safety response models to account for compound/trial differences in patient populations (e.g. covariates such as age, race, and comorbidities). It also allows for simultaneous modelling of multiple endpoints and can therefore link concentration, and biomarkers to clinical endpoints (e.g. safety). It can provide indirect comparisons and simulations of head-to-head trials but uses longitudinal dose-response models for individual compound or compound classes. It can also be used for simulations of trials and trial success predictions.

An aggregated comparator databases can be created by compiling information from multiple data sources to collate information for MBMA of C-QTc and Dose-PK-ECG assessment for a number of oncology indications.

The credibility assessment can also be implemented for translational quantitative systems pharmacology/ toxicology models as a method to predict drug-induced cardiac toxicity, integrating preclinical in vitro and in vivo safety data, PBPK models of exposure at the cardiac site of action, multi-scale computational models of cardiac (patho)physiology and real-life patient outcomes.

These innovative methods are good candidates for regulatory submissions to EMA, including QA and QO procedures. They would be compared to thorough QT interval (TQT) clinical study in humans and concentration-QTc analysis in early clinical studies, which are considered the standard approaches for establishment of cardiac safety of drugs.

c. Assessment of drug efficacy and vaccines relative effectiveness

The question-centric approach automated repository will be used to identify and refine the questions related to establishing drug efficacy or vaccine relative effectiveness and link those to relevant data types/sources and contexts of use. The question could be related to the effect size of vaccines or therapeutics. The therapeutic monoclonal antibodies and vaccines against SARS-CoV-2 can be taken as illustrative cases. An attribute framework can be developed, with an emphasis on the different features that potentially could be relevant for the answer to the initial question. In silico approaches fed by in vitro and e-Health data (variants of SARS-CoV-2, viral load, interleukins levels (IL-1, IL-6, IL-12, IL-10, IFN-gamma, type I IFNs), level of CD8, CD4 and FoxP3 lymphocytes and specific anti-SARS-CoV-2 IgG.) can be benchmarked against more traditional statistical methods based on analyses of (fully powered) Phase 2/3 clinical studies. In silico trial platform such as the UISS-SARS-CoV-2 would be good candidate for this exercise.

The standards to be developed can be used to characterize the data quality and also context of use and acceptability criteria for UISS-SARS-CoV-2 to answer the initial question, as part of the credibility assessment of UISS-SARS-CoV-2, for example. Thus, the available data to inform the model structure

and parameters, as well as to validate model predictions will play an important role during the credibility assessment. Data from laboratory initiated clinical trials evaluating the immunological response following SARS-CoV-2 infection and after vaccine administration can be used to validate the predictions by the *in silico* platform.

If validated, the *in silico* platform can be endorsed by the regulators as part of a qualification opinion procedure.

d. Use of real-world (EHR) data

Compared to the traditional means of health-related data collection, which provide a limited snapshot of a person's health and symptoms, continuous remote assessment through wearables provides a deeper understanding of disease variability, which is likely to be an important factor to treatment response.

Data from videos captured in the home setting allows assessment of ambulation, providing a more continuous, rather than snapshot, view of ability. For example, Aparito have collected and analysed movement data from videos of study participants completing clinical assessments such as the Timed Up & Go and SARAhome, and specific tasks such as walking, turning and upper-limb movement. Pose estimation software is used to extract data on body position and movement, from videos. Such software provides a confidence value associated with point location, allowing filtering of data. Video data provides opportunity to consider several areas in which standardisation is required, and the differing approaches in each case.

Wearable devices can collect health-data on a 24/7 basis remotely as patients go through their daily routines at home and work or school, and is a data parameter that can be uploaded via Aparito's Atom5™ app.

Based on the question-centric approach repository, the relevant drug development questions to be addressed by the app can be identified, together with the related context of use and analytical method. Each of the steps of credibility assessment can then be implemented and a framework developed for the identification of relevant data sources and the development of curated databases with specific biosignals data that are accurately labelled by outcome and tailored to each use.

The repository can be used to structure, annotate, and standardise the wearable data and provide data mapping tools to electronic data capture databases. AI/Machine-learning can allow for the development of decision support tools based on the acquired data from the wearable devices.

This can lead a package for EMA endorsement via EMA ITF-meeting and qualification advice/opinion procedures.

6. Conclusion and Recommendation

The current regulatory standards and guidance documents are mostly related to more traditional studies, historical data types and related analytical methods. Box 2: Unmet need for Standards and Regulatory guidance documents

There is currently an unmet need for standards and attribute framework to support regulatory assessment of new methods and data types.

The question-centric approach will introduce an integrated model for regulatory decision-making centred on the drug development questions.

For the first time, the regulatory scientific decision-making will be explicitly redefined and restructured around the scientific question to be addressed. This approach expands the V&V40 approach proposed for medical devices and applied by regulators to the use of modelling and simulation to support drug development [5]. This will conceptually improve the manner evidence (including data and analytical methods) is assessed by regulators for final decision-making. The implementation of question-centric approach will permit a clear shift from the current partitioned and sequential evidence generation and regulatory assessment (mostly limited to three types of data: quality, non-clinical and clinical eCTD modules 3, 4 and 5, respectively [6]) to a more integrated approach centred on the drug development question and offering the possibility to combine different types of data in an integrated assessment approach. This new model will open more possibilities for acceptability of alternative data types and analytical methods, provided that their relevance to address the question of interest is demonstrated.

The three standards identified as to be urgently developed for tailored credibility assessment are the ones for data searching, structuring/formatting, and analysis, respectively. This will permit to develop a high-

level framework applicable across questions, contexts of use, data sources and methods as well as more granular criteria applicable to specific questions, and related data types (including real world data (RWD) and synthetic data), and methods (including modelling and simulation and AI). Structuring and documenting the process allows for explicit sharing of current knowledge on the real-world phenomena/system with all stakeholders. This is a key prerequisite for shared understanding and agreement on the needs for the uncertainty quantification (UQ) as well as for setting the requirements on the range of attributes/features that need to be investigated in clinical studies or in real-world data sources.

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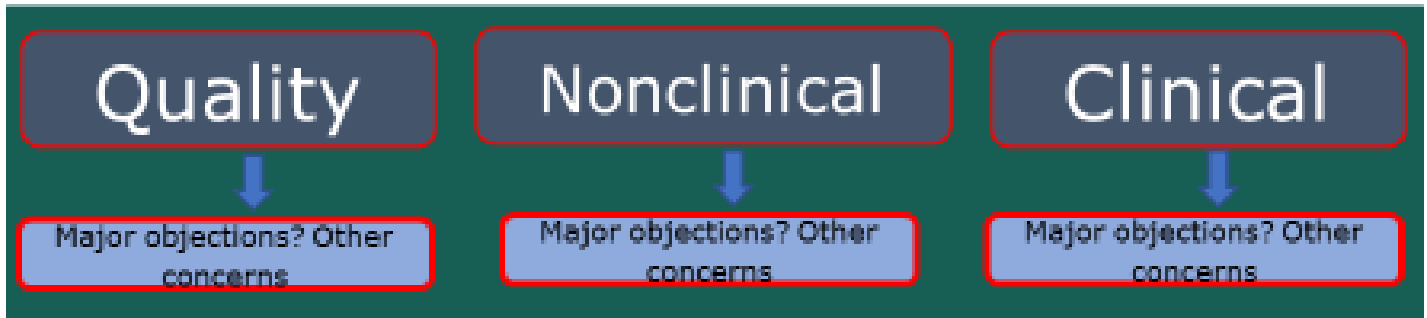
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Figure Legends

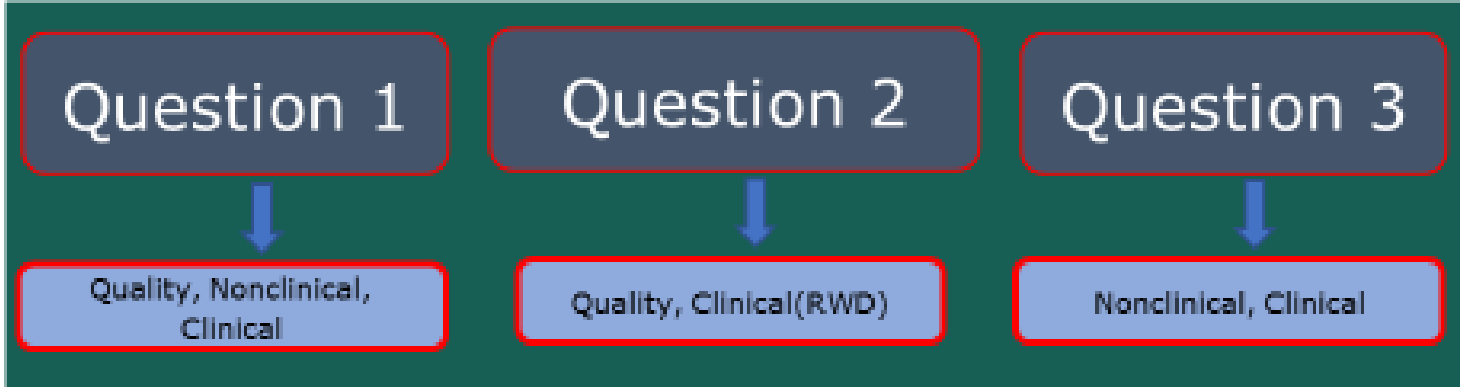
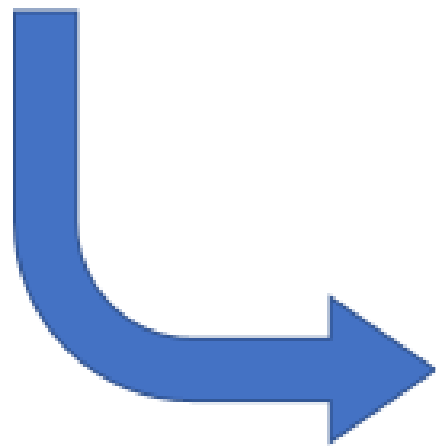
Figure 1. Schematic representation of the shift in mindset from the current regulatory assessment approach, segmented toward data types to a more integrated approach, centered on the Questions and based on knowledge building.

Figure 2. Illustration of regulatory decision making based on the question-centric approach. For addressing a question related to characterization of the effect size 3 different approaches can be proposed: a randomized controlled trial (RCT), a single arm trial + real-world evidence, or a model-based (in silico) approach: Their assessment can be streamlined using a risk-based analysis. This will allow benchmarking of these methods and related results.

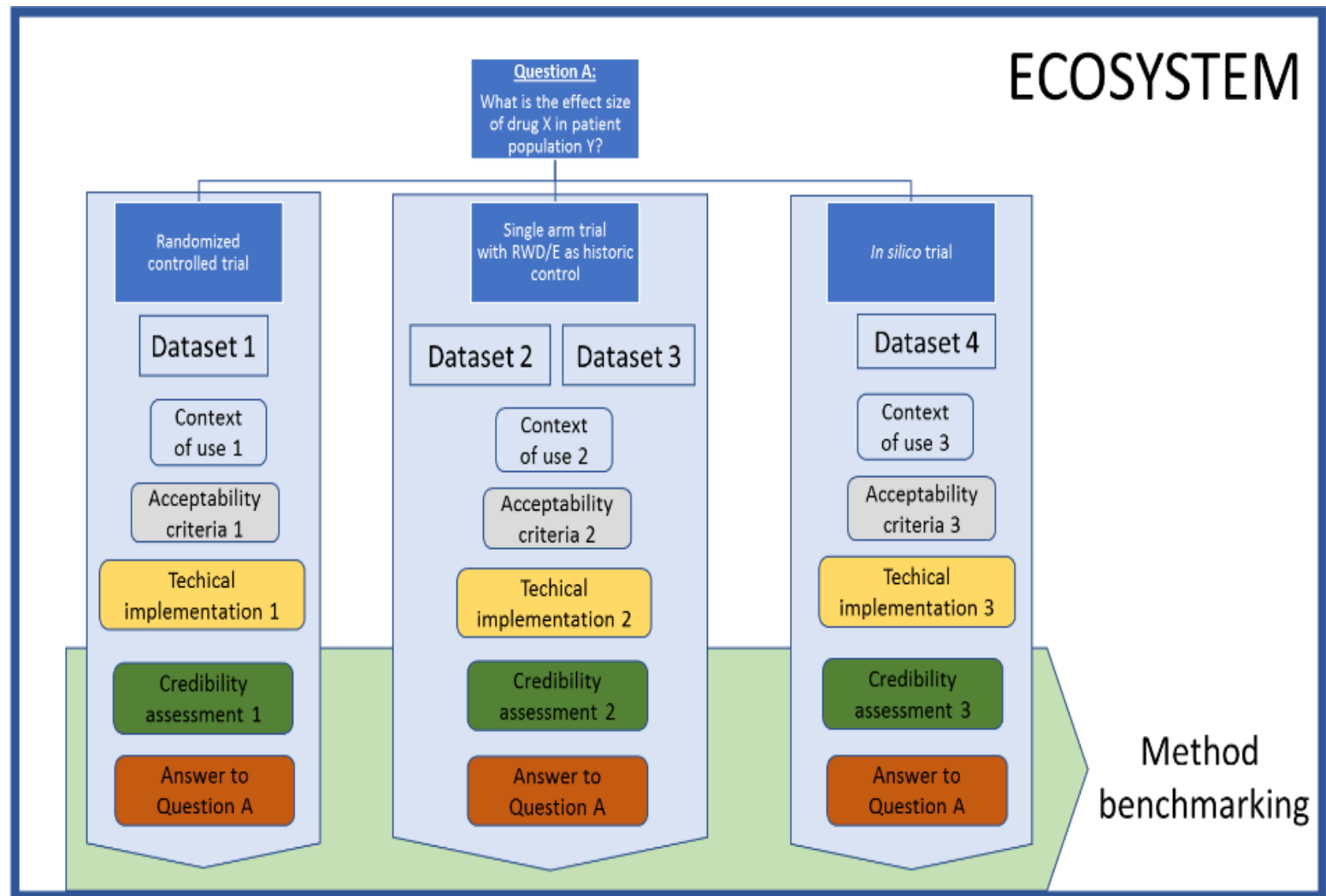
Figure 3. Schematic representation of the implementation of the question-centric approach. Different steps include, data searching, data formatting, interrogation of relevant data sources, data analysis and benchmarking of the approaches (if applicable) to inform the final regulatory decision-making.



Qualitative benefice/ risk assessment

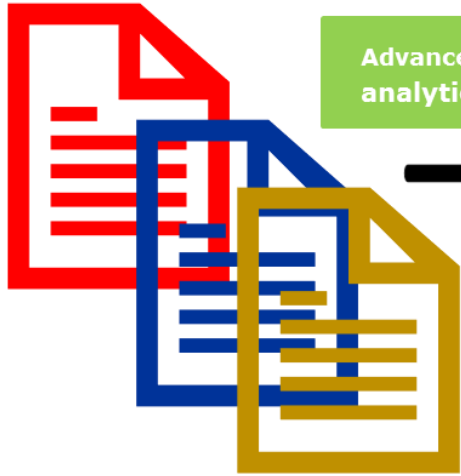


Quantitative benefice/ risk assessment



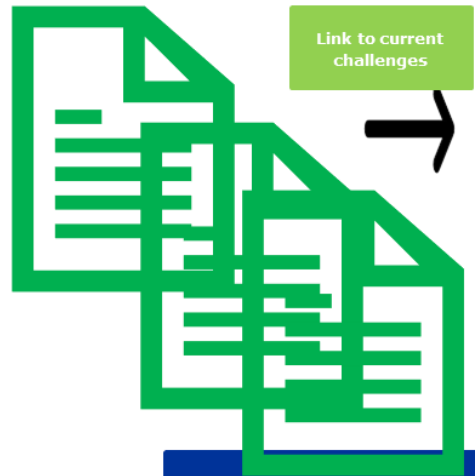
Original Data from root sources

Augmented, searchable, FAIR, and ready for use data



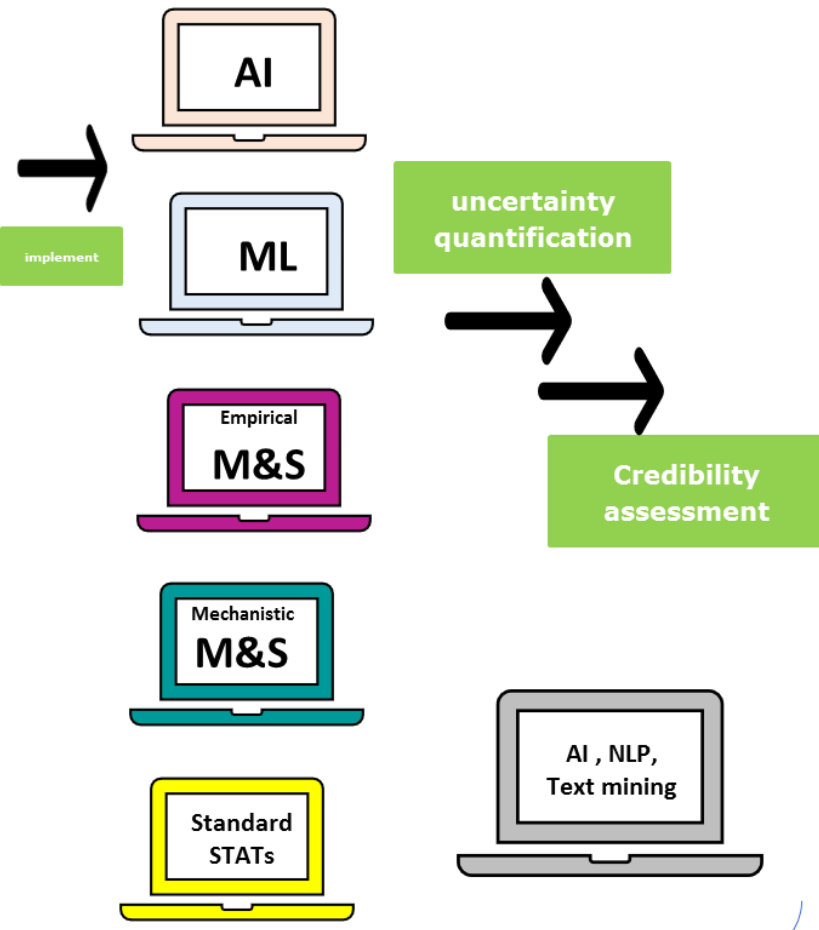
Advanced analytics

Link to current challenges



Regulatory/HTA Questions

(Innovative and traditional) Analysis Methods



Optimised Regulatory/HTA Decision-making

Adoption of optimised innovative methods

Method benchmarking for specific regulatory questions

Unstructured data (in primary data sources)



Structured data (in a repository)

Training and Guidance for regulators, academia and industry