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Regulatory / PV / Medical Devices Working Group

Brussels, 12 February 2020

Welcome/ Next Events

Agenda

- **Welcome / next events**
- **Priorities 2020**
  - Focus groups – composition and topic leads
- **EMA Regulatory Science Strategy 2025**
  - Follow up on the EMA stakeholder meeting (Lucia D'Apote, Amgen)
- **Pharmacovigilance**
  - Current topics of interest. (Wendy Huisman, Seattle Genetics)
- **Promoting RWE for regulatory purposes**
  - Innovative approach for regulatory decision making (Jill Morell, Biomarin)
- **Medical Devices**
  - Latest update on the activities of the Medical Device Coordination Group (MDCG) and working groups (Jörg Plessl, Norgine)
  - Status of designated Notified Bodies; Policy update
  - EMA Meeting on Drug-device combination products
- **AOB / End of meeting**

Next events

- 25 February 2020: Gene and Cell Therapies Working Group
- **26 February 2020**: **Members Meeting**, Brussels
- 05 March 2020: OMP Working Group Meeting, Brussels
- 10 March 2020: Pricing & Reimbursement / Market Access Working Group, Brussels
- 19 May 2020: Regulatory & Medical Devices Working Group Meeting, Brussels
- **17 June 2020**: **Members Meeting**, Brussels
- 10 September: Regulatory & Medical Devices Working Group Meeting, Brussels
- 14 October 2020: Members Meeting, Brussels
- 8 December 2020: Regulatory & Medical Devices Working Group Meeting, TC

Priorities 2020

Priorities 2020

Regulatory / Medical Device / Pharmacovigilance Working Group

The focus of this EUCOPE working group is an overarching approach on **any regulatory aspect in drug / device development**.

The core target is to voice EUCOPE members‘ (specifically SME’s) interests **towards decision making regulatory bodies** (EMA, HMA, NCA, CMDh) and other stakeholders.

Priorities of core topics for 2020 have been identified and positions will be developed in **dedicated focus groups**, lead by team members.

Additional topics may be addressed ad hoc and on demand.

Due to resource limits, some topics will only be kept for information.

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Commissioner for Health and Food Safety

Mission letter to Stella Kyriakides

1. s**upply** of **affordable medicines** to meet its needs
2. new regulatory framework on **medical devices**
3. potential of **e-health** to provide high-quality healthcare and reduce inequalities, creation of a **European Health Data Space**
4. European One Health Action Plan against **Antimicrobial Resistance**
5. prioritise communication on **vaccination**
6. E**urope's Beating Cancer Plan**

EC Beating Cancer Plan

Regulatory impact and EMA contribution

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Ref. Ares(2020)693786 - 04/02/2020

European Commission

ROADMAP	
TITLE OF THE INITIATIVE	Europe's Beating Cancer Plan
LEAD DG – RESPONSIBLE UNIT	DG SANTE C4: Health determinants and international relations
LIKELY TYPE OF INITIATIVE	Communication and accompanying Staff Working Document(s)
INDICATIVE PLANNING	*Q4 2020*
ADDITIONAL INFORMATION	*DG SANTE Public Health*

Speech by President von der Leyen at the Europe's Beating Cancer Plan conference, 4 Febr 2020 World Cancer Day

„Technology can be a lifesaver for thousands of people."

SME specific approach

EC dedicated SME strategy

*"...strengthening the **backbone of our economy**: our SMEs. They represent 99% of all businesses and account for 85% of new jobs created in the last five years. They are our **innovators and entrepreneurs**. They provide **vocational training to our young people**. They represent everything that is good in our economy.*

*We need more young and nimble innovators with **breakthrough technologies**, like this generation's tech giants were only a decade ago.*

*I want to make it easier for small businesses to become large innovators. We must continue **developing the growth finance market for the innovative companies** of the future."*

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Drug Discovery Today • Volume 23, Number 10 • October 2018

ELSEVIER

Marketing authorisation applications submitted to the European Medicines Agency by small and medium-sized enterprises: an analysis of major objections and their impact on outcomes

Nadia Amaouche[1], Hélène Casaert Salomé[1], Olivier Collignon[1,2], Mariana Roldao Santos[3] and Constantinos Ziogas[1]

[1] European Medicines Agency, 30 Churchill Place, Canary Wharf, London E14 5EU, UK
[2] Luxembourg Institute of Health, 1A rue Thomas Edison, L1445 Strassen, Luxembourg
[3] United Nations Development Programme, 1, Klovsky Uzviz Str., Kyiv 01021, Ukraine

Small and medium-sized enterprises (SMEs) are an important source of innovative medicines. Compared with their larger counterparts, they experience challenges as a result of insufficient human and financial resources that can hamper drug development and regulatory compliance. This analysis reviews the profile of major objections raised in marketing authorisation applications for medicines for human use submitted by SMEs to the European Medicines Agency (EMA) between 2011 and 2015 and their impact on the outcome of applications. It showed that SMEs experience challenges in the quality (e.g. manufacturing process validation and control and/or characterisation data of drug substance or drug product) and clinical sections of marketing authorisation applications (e.g. analysis or robustness of pivotal data or selection of submitted studies, study design issues and marginal or no clinical relevant efficacy), with deficiencies in demonstrating clinical efficacy representing the major eventual hurdles to authorisation.

HMA-EMA joint Big Data Taskforce (BDTF)*

Data **A**nalysis and **R**eal **W**orld **I**nterrogation **N**etwork - **DARWIN**

* BDTF reviewd landscape in 2017 and published phase I report Q1 2019, 10 priorities published Q4 2019

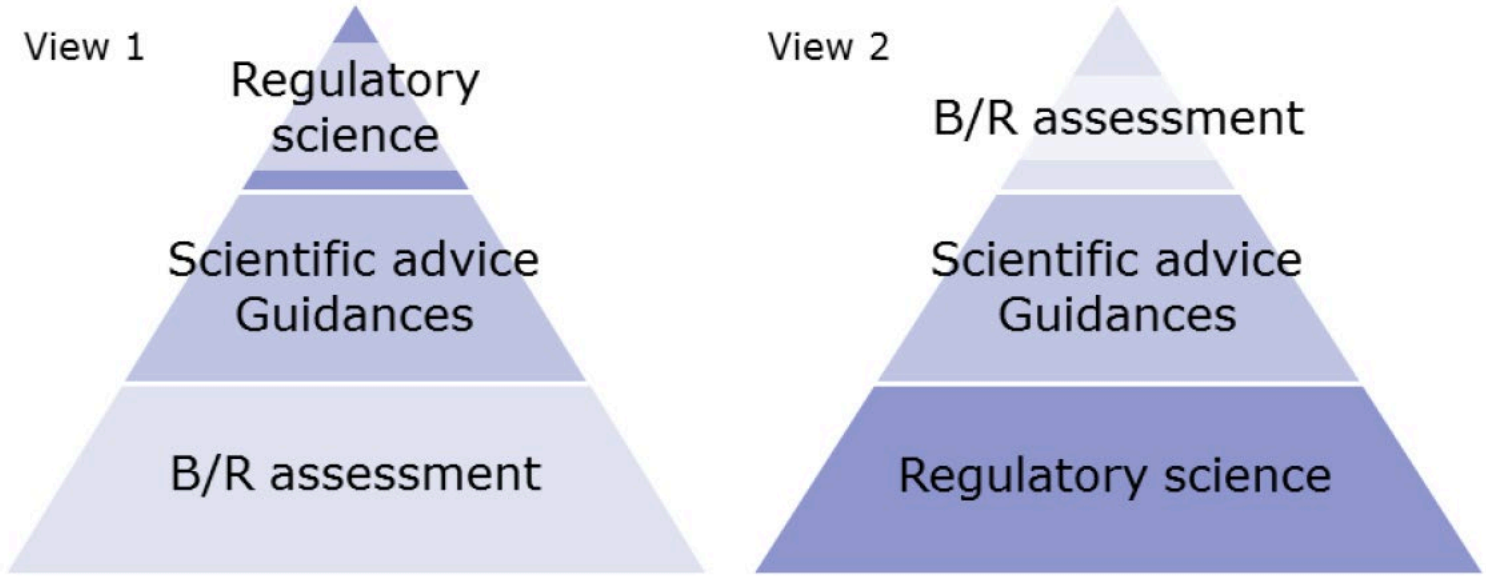
- Deliver a sustainable platform to access and analyze health care data from across the EU
- Establish a data quality framework (DQF) to support trust of patients and HCP
- Modernize IT infrastructure
- **Darwin** Data Analysis and Real World Interrogation Network

„Big data includes real word data such as e-Heatlh records, registry data and claims data, pooled clinical trials data, datasets from spontaneously reported suspected adverse drug reaction reports, and genomics, proteomics and metabolomics datasets. Big data are generally large, accumulating rapidly incorporate multiple types and forms and are of varying value and quality."

The role of Regulatory Science at the EMA

Legislation follows science, not the other way round

„To underpin it‘s mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems.“



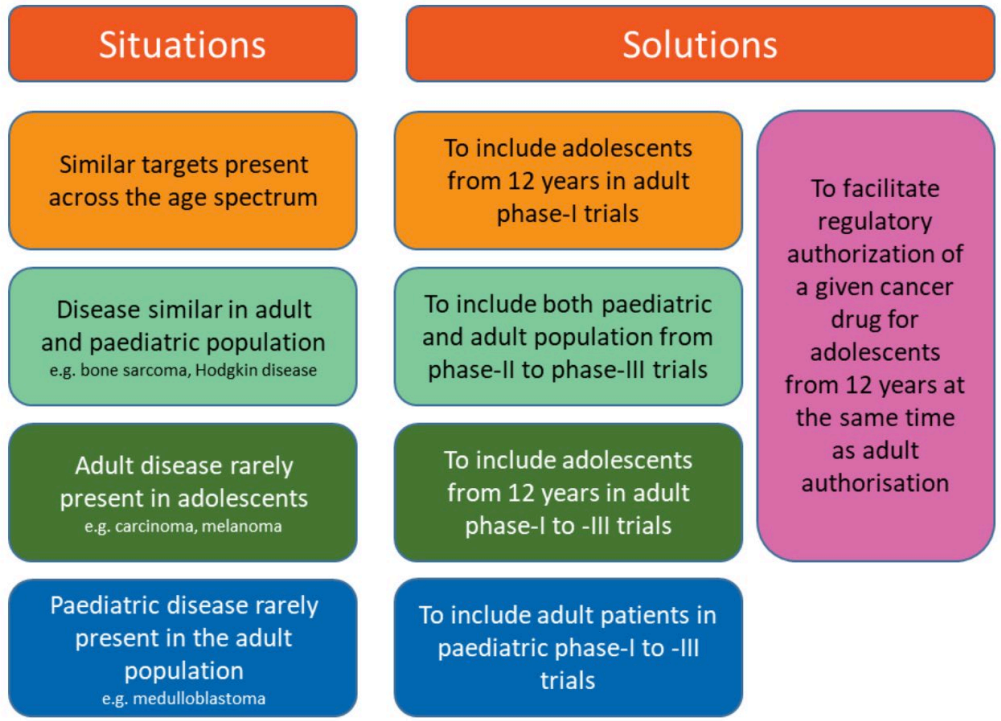
Paediatrics / Young adults

Medicines for Children and Rare Diseases

ACCELERATE
INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

Project Accelerate:

- Fostering Age Inclusive Research (FAIR) Trials for Adolescents & Young Adults
- six-point approach in order to improve access for adolescents to new anti-cancer drugs and to make the drug development process more efficient.



https://www.accelerate-platform.org/fair-trials/what-you-can-do/industry/

Latest EMA / HMA / CMDh topics

- Industry Stakeholder scientific/technical meeting on Nitrosamines – 20 February 2020
- EMA consultation: Reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders – comments by 17 April 2020
- Brexit – transition
- Corona Virus letter from EMA
- CMDh best practise quide on multi-lingual packaging

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Priorities 2020

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TOP 1 Research & Development / Regulatory Science

- **Digital technology** in medicine development programs – BDTF
- Reflection on perspectives for **scientific advice** (incl. joint EMA+HTA)
- Regulatory challenges for **ATMPs** incl. combined ATMPs
- **Paediatrics** - improvement of handling PIP applications - cancer
- **Patient** focused drug development
- Promoting **RWE** for regulatory purposes and down-stream decision making
- Foster **global** regulatory convergence and harmonisation

Priorities 2020

Regulatory / Medical Device / Pharmacovigilance Working Group

TOP 2 Implementation of the MDR & IVDR

- Regulation of **drug-device combinations (DDC)** within the EMA remit and alignment with Notified Bodies (NBs)
- Engagement in several **MDCG** working groups at EC level
- Functioning of the **EUDAMED** and **UDI** implementation on global standards
- Challenges for Companion Diagnostics (**CDx**), **biomarkers** and **Omics**

Priorities 2020

Regulatory / Medical Device / Pharmacovigilance Working Group

TOP 3 Implementation of the Clinical Trial Regulation (CTR) and the Clinical Trial Information System (CTIS)

- Practical regulatory considerations in alignment with other legal provisions
- Innovative clinical trial approaches (RWE)
- Master protocol and complex trials (to add from Lucia)
- Prepare for implementation of CTIS expected in June 2021

Priorities 2020

Regulatory / Medical Device / Pharmacovigilance Working Group

TOP 4 Vigilance – PV and medical device

- EU focussed approach in alignment with the ICH

Additional topics

- **ISO IDMP / SPOR** and **telematics** (in the loop for information)
- **Personalized / precision medicine – biomarkers** (partly in R&D)
- **Antimicrobial Resistance AMR** – incentives to support the development of new antibiotics
- **Early Access Tools** and compassionate use (on demand)
- Regulatory flexibility for **OMPs** (on demand and alignment OMP group)
- **Serialisation** – monitoring of safety features
- **Brexit** implications on Regulatory Affairs and supply chain
- Regulatory Challenges for Drug Repurposing (alignment P&R WG)

Focus Groups - draft

Composition and topic leads

Topic	Topic lead	Team
RSS 2025: Focus on **scientific advice** incl. HTA	Lucia	Andrea, Joao, Laura, Jill
Digital technology in medicine development programs	Joao	Cécile, Emmanuel, next to Joao
Regulatory challenges for **ATMPs** incl. combined ATMPs	Andrea	Nasir, Christian, Laura, Jill ,Laid
Drug – device combinations (**DDC**)	Lars	Jörg, Mats, Laid, nexto to Joao, Jill, Kristen
Paediatrics - improvement of handling PIP applications	Cécile	Jill, Lucia, Trine, Laura, Joao, (link to OMPs), Budhesh
Pharmacovigilance, signal detection, upcoming issues	Wendy	Gilead (Joe?), Alexion (colleagues from Joao)
Promoting **RWE** for regulatory purposes / DARWIN	Lucia	Jill, Andrea, Laid, Nassir, Laura,
Implementation of the **MDR / IVDR**	Jörg	Lucia, Emmanuel, Otsuka, next to Joao, Jill,
Clinical Trials **CTR / CTIS**	Roberta?	Roberta (Gilead), Florin (CSL),

EMA Regulatory Science Strategy 2025

(Lucia D'Apote, Amgen)

EMA Regulatory Science (RSS) to 2025

EUROPEAN MEDICINES AGENCY

EMA Regulatory Science to 2025

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

#RegScience2025

EMA Regulatory Science Strategy

Five strategic goals

Strategic goal 1
To catalyse the integration of science and technology in drug development.

Strategic goal 2
To drive collaborative evidence generation to improve the scientific quality of evaluations.

Strategic goal 3
To advance patient-centred access to medicines in partnership with healthcare systems.

Strategic goal 4
To address emerging health threats and availability/therapeutic challenges.

Strategic goal 5
To enable and leverage research and innovation in regulatory science.

Follow Up on the EMA Stakeholder Meeting

EMA Regulatory Science Strategy to 2025
Post-consultation Stakeholders Workshop

Human Workshop - Participants' Brief

18 – 19 November 2019

European Medicines Agency
Amsterdam, The Netherlands

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SCIENCE MEDICINES HEALTH

Integrated evaluation pathway for assessment of MDs, IVDs and borderline products

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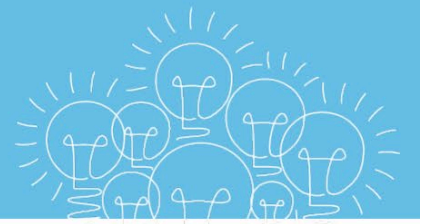
Regulatory requirements and guidance development



- A clear outline of the roles and responsibilities of Notified Bodies and National Competent Authorities/EMA is essential. Therefore, the process for interaction between EMA/National Competent Authorities and NBs as well as the timing of the various assessments should be defined in a procedural guideline
  - Mechanism for integrated MAA/NB review process of a drug combined with medical device, or an in vitro diagnostic
  - Clarification of how information and assessment of a CDx will be shared with EMA/NCAs during the drug approval process
  - Considerations regarding information from the device, or in vitro diagnostic to be included in the Risk Management Plan

Regulatory Science and Innovation Programme for Europe (ReScIPE)

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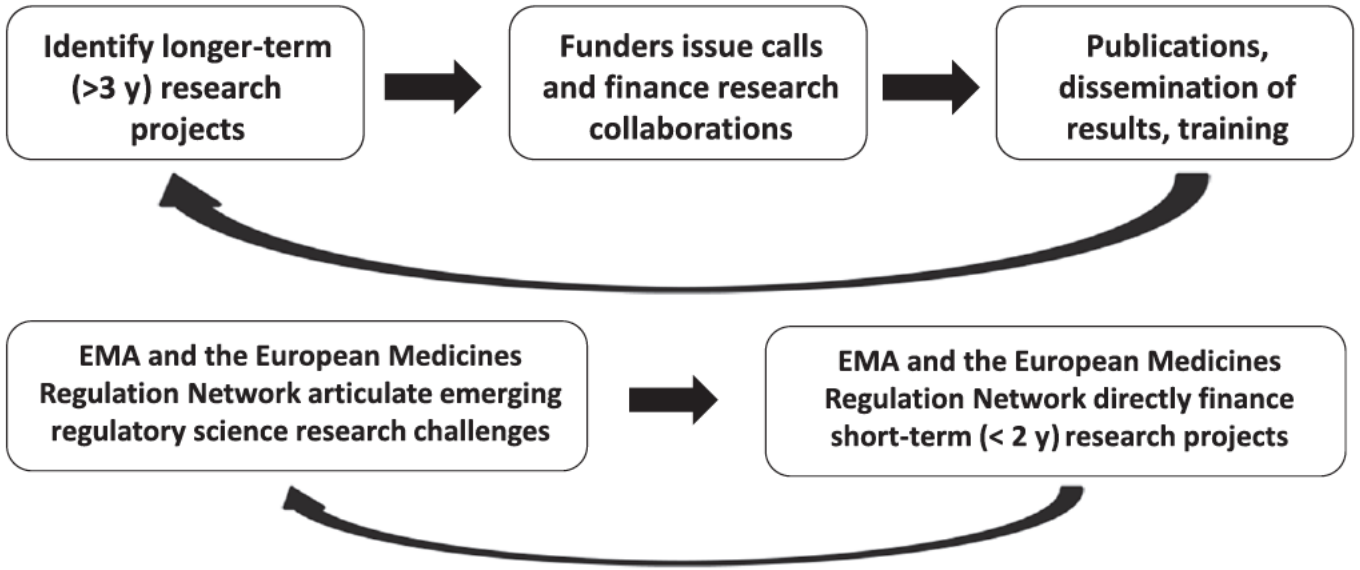
Received: 21 May 2019 | Revised: 12 August 2019 | Accepted: 14 August 2019
DOI: 10.1111/bcp.14099

EMA GUIDELINES SERIES

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Regulatory Science and Innovation Programme for Europe (ReScIPE): A proposed model

Philip A. Hines[1,2] | Richard H. Guy[1,4,5] | Angela Brand[2,3] | Anthony J. Humphreys[1] | Marisa Papaluca-Amati[1]



Pharmacovigilance (Wendy Huisman, Seattle Genetics)

PHARMACOVIGILANCE

Wendy Huisman

EU QPPV

SeattleGenetics®

Seattle Genetics

- Global biotechnology company that discovers, develops, and commercializes transformative therapies targeting cancer to make a meaningful difference in people's lives.
- Commercial products
  - ADCETRIS® (brentuximab vedotin) and PADCEV™ (enfortumab vedotin-ejfv). ADCETRIS is approved for certain types of CD30-expressing lymphomas, and PADCEV is approved to treat certain types of metastatic urothelial cancer.
- Under EMA evaluation
  - MAA for tucatinib is validated, HER2-positive breast cancer
- Headquartered in Bothell, Washington, with offices in California, Switzerland, and the European Union

Wendy Huisman

- Contract EU QPPV for Seattle Genetics
- 25 years experience in PV / QPPV in Pharma and consultancy

- 13 years chair of the Medicines for Europe PV working group

PV environment - Topics of interest

- Clinical trial Regulation EU No 536/2014
  - Will not be applicable yet in 2020. Timing of its application depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit. The Regulation becomes applicable six months after the European Commission publishes a notice of this confirmation. The start of the audit is now planned for December 2020.

- E2B(R3)
  - From 30 June 2022, it will be mandatory to report side effects to EudraVigilance using a data format based on international standards set by the International Organization for Standardization (ISO). This will help increase the data quality and analytical capabilities in EudraVigilance.

PV environment - Topics of interest

- Signal detection pilot
  - Extended to end of 2021.
  - Monitoring for active substances on list as on EMA website.
- GVP

Draft GVP chapters and annexes for public consultation

Draft guideline on good pharmacovigilance practices: Product- or population-specific considerations III: Pregnant and breastfeeding women (PDF/475.52 KB)

Draft: consultation open

First published: 11/12/2019
Consultation dates: 11/12/2019 to 28/02/2020
EMA/653036/2019

PV environment - Topics of interest

- ICH

E2D(R1) EWG Post Approval Safety Data Management: Definition and Standards for Expedited Reporting

This topic was endorsed by the ICH Assembly in June 2019.

The E2D(R1) EWG is working on the revision of the of the E2D Guideline "Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting" with a view to clarifying the management of post-approval safety information from new or increasingly used data sources including the need to adapt definitions and standards.

Rapporteur: Ms. Vicki Edwards (EFPIA)

Status: *Step 1*

Endorsed Documents

- E2D(R1) Concept Paper
- E2D(R1) Business Plan

Expert list

Is there a need for a PV working group?

- Advantages
  - Together you achieve more
  - Benchmarking helps you improve and increases knowledge
- Disadvantages
  - Time
- Commitment
- Separate PV calls?


SeattleGenetics®

Promoting RWE for regulatory purposes (Jill Morell, BioMarin)

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Promoting RWE for Regulatory Purposes

Innovative Approach for Regulatory Decisions Making

- RWE from observational studies is well accepted for satisfying post approval safety monitoring requirements
- Examples of approvals utilizing RWE in support of efficacy, mainly in rare disease/oncology space
- Increasing global acceptability of the potential for RWE to support regulatory decision-making
- As frameworks, guidance and methodologies for RWE develop the use will become more common
- The challenge: HTA/payer acceptability?

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Promoting RWE for Regulatory Purposes

Innovative Approach for Regulatory Decisions Making

- How aligned are regulators currently?
- Where has RWE been used?
- Where are regulators going?
- Expectations for the future

- Perspectives of a rare disease developer

How aligned are regulators currently?

Heading in the same direction

EU	US	ROW
EMA Regulatory Science Strategy • Promote use of high-quality real-world data (RWD) in decision making **Guidance** Post-authorisation efficacy studies Discussion paper on registries for regulatory purposes	**21st Century Cures Act** • Draft guidance on RWE by December 2021 • Framework for evaluating RWE (new indication/post-approval study requirements)	**China** Guideline on Using Real-World Evidence to Support Drug Research & Development and Evaluation (draft)
EMA Big Data Taskforce • Deliver a sustainable platform to access and analyse healthcare data **(D**ata **A**nalysis and **R**eal **W**orld **I**nterrogation **N**etwork -**DARWIN).** • Establish an EU framework for data quality and representativeness; develop guidelines	**Guidance:** Rare Diseases: Natural History Studies for Drug Development Guidance for Industry Guidelines for the Use of Electronic Health Record Data in Clinical Research	**Japan** Proposed a new ICH topic on technical requirements for more efficient use of RWD for post-marketing epidemiological research

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How aligned are regulators currently?

Definitions of RWD and RWE from some key international regulatory authorities

	Real World Data (RWD)	Real World Evidence (RWE)
FDA (US)	Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources	Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD
EMA (Europe)	Health care related data that is collected outside of randomized clinical trials	Evidence coming from registries, electronic health records and insurance data
PMDA (Japan)	Data that is electronically generated and stored by medical institutions	*No official definition has been issued at this time*
NMPA (China)	All kinds of data related to patients health status and/or diagnosis and treatment and health care collected on a routine basis. *Only RWD that meet the suitability requirements can produce RWE*	Clinical evidence about the use and potential benefits or risks of medical products, obtained through the analysis of suitable RWD, including evidence obtained through interventional studies including retrospective or prospective observational studies or pragmatic clinical trials

Where has RWE been used?

Historical Control/Natural History

Product/Indication	Approval	RWE
Bavencio Merkel cell carcinoma	FDA and EU 2017	Single arm OL, P2 study Historical control that met enrolment criteria: benchmark of NH from EHR and German patient registry
Zolgensma spinal muscular atrophy	FDA 2019	2 OL, non-randomized studies. Prospective observational cohort study to contextualize a single-arm efficacy trial
Brineura CLN2 disease	EMA and FDA 2017	Single arm, OL dose escalation study. Best matched patients from natural history registry.
Strensiq perinatal/infantile- and juvenile-onset hypophosphatasia	(FDA and EU 2015)	2 single arm, OL, P2 studies. Retrospective medical record review of natural history at academic HPP centres.
Xuriden hereditary oroticaciduria.	(FDA 2015)	Single arm trial (n=4) and literature review of available patients treated with uridine (n=19)

Andre, ED. Trial designs using real-world data: The changing landscape of the regulatory approval process *Pharmacoepidemiol Drug Saf*. 2019;1–12.

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Where has RWE been used?

Historical Control/Natural History

Product/Indication	Approval	RWE
Yescarta R/R DLBCL	EMA 2018	Single arm OL, P2 study (ORR endpoint) Retrospective patient level pooled analysis of two Phase III RCTs and two observational studies to contextualise the P2 study results
Kymriah R/R DLBCL	EMA 2018	Single arm OL, P2 study (ORR endpoint) Efficacy results compared against three external data sets (SCHOLAR-1, the CORAL extension study, PIX301) to contextualise the results of the single arm trial

Cave et al 2019. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe.

Where has RWE been used?

Pragmatic trial, label expansion (new population/subgroups), post-marketing efficacy evaluation

Product/Indication	Approval	RWE
Invega Sustenna Schizophrenia- label expansion	FDA 2018	Trial in real world clinical practice, flexible treatment interventions, active comparators, relaxed exclusion criteria (high risk patients).
Bevacizumab Metastatic squamous NSCLC	China 2018	Initial approval in combination with carboplatin/paclitaxel. Label expansion based on retrospectively analysed patient data from 3 hospitals using bevacizumab with a combination of platinum-based chemotherapy.
Bevacizumab	China 2018	Real-world studies provided data in different patient subgroups such as those with EGFR mutations or brain metastases
Unnamed Cardiovascular drug	China	Multi-regional trials supported approval ex-China but included small number in Chinese subgroup. Prospective, observational, PM real-world study comparing treatment+SOC vs SOC alone.

Andre, ED. Trial designs using real-world data: The changing landscape of the regulatory approval process *Pharmacoepidemiol Drug Saf*. 2019;1–12;

NMPA

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How aligned are regulators currently?

Common Themes

- **Whether the RWD are fit for use (*Data Quality*)**
  - Data should be selected based on their suitability to address specific regulatory question.
  - The strength of RWE depends on the clinical study methodology and the reliability (data accrual and data quality control (data assurance)
    - Methodological challenges: observational data are not collected with research as principle purpose; issues: missing data, bias and confounding.
      - *FDA hesitant over RWE from observational studies supporting efficacy*
  - Relevance of the RWD.
- **Evaluation of RWE (*Methodology*)**
  - Whether the RWE can support the clinical questions that need to be answered
  - Reliability and validity of the evidence generated through RWD
    - *Whether desired RWE can be obtained from existing RWD through scientific study design, rigorous organization and implementation and **reasonable statistical analysis.***

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RWD for Regulatory Decision Making

Challenges and Possible Solutions for Europe

"Defining the exact evidentiary standards of such RWE *a priori* is challenging as necessary standards will vary depending on the context within which the question is asked.

Given the broad range of regulatory use cases, it seems clear that a one-size-fits-all approach will not be sufficient; a hybrid approach to evidence generation will be required, depending on the question being asked and the context in which the derived evidence will be used, and early planning of the strengths and limitations of the possible approaches is required."

Cave et al 2019. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe.

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Where are regulators going?

EMA	FDA
EMA Regulatory Science Strategy: First steps • **Identify use-cases for RWD ie use cases that clinical trials can't fully address** (compelling business case for RWD for product safety) • Deliver sustainable access to existing RWD (aim to optimize data collection and use) • Create a public inventory of existing data sources (**incl. quality and representativeness metrics)** • **Establish a RWD framework, principles for use, standards, acceptance** • **Initiate a patient-led RWD pilot using a rare disease**	**FDA planned guidance:** • How to assess the reliability and relevance of RWD from medical claims, EHRs, registry data and international EHC data used to generate RWE • Considerations for design of clinical trials with pragmatic design elements • recruitment/enrollment, facilitating interventions, and approaches to assessing outcomes. **FDA potential guidance:** • Use of RWD to generate external control arms for non-randomized, single-arm trials • Potential gaps in RWD sources and strategies to address them
Big Data Taskforce: • DARWIN, • **EU framework for data quality/representativeness**	

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Expectations for the future

Extract from China Guidance (NMPA)

- **Real-World Evidence Supporting Drug Regulatory Decisions**
  - Efficacy and safety evidence for the registration/marketing of new drugs
  - Evidence for changing leaflets of approved drugs
    - New indications, subgroups, paediatrics
  - Evidence for post-marketing requirements or re-evaluation
  - Other uses of real-world evidence for regulatory decision making
    - Guiding the design of clinical studies
      - RWE can provide valid reference for inclusion and exclusion criteria, parameters for sample size estimation, and determination of non-inferiority margins
    - Accurately identifying the target population
      - Using real-world information such as omics data, public gene bank information, and related clinical data in population cohorts,
      - RWE from data mining techniques (eg machine learning) could identify population for targeted therapies.
- **Basics of Real-World Research Design**
  - Pragmatic clinical trials
  - Single-arm trial using RWD as external control
  - Observational studies

Real-World Research Design

Pragmatic clinical trials

- Encepp
  - A study comparing several health interventions among a randomised, diverse population representing clinical practice, and measuring a broad range of health outcomes' (IMI GetReal Glossary)
  - Focused on evaluating benefits and risks of treatments in patient populations and settings that are more representative of routine clinical practice.
  - To ensure generalisability, pragmatic trials should represent the patients to whom the treatment will be applied, inclusion criteria would be broad (e.g. allowing co-morbidity, co-medication, wider age range), the follow-up minimized and allow for treatment switching etc.
  - Monitoring safety in a phase III real-world effectiveness trial: use of novel methodology in the Salford Lung Study
- Impact of biases and confounders can make the statistical analysis complicated; study design and sample size can be much larger than a regular RCT design
  - Randomization reduces the impact and biases of the confounders
- Scientific guidance on post-authorisation efficacy studies
  - Randomised (including pragmatic trials, non-randomized trials (including observational studies)

➢ Complex innovative trial design

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Real-World Research Design

Single-arm trial using RWD as external control

- When a parallel assignment control arm is unethical or not feasible and usually when the effect size is expected to be large
  - Rare disease, small patient numbers; for some life-threatening major diseases without effective treatment
- Types of external control
  - Historical external controls
    - RWD previously obtained are used as controls,
    - Consider impact of different historical periods on the comparability in disease definition, diagnosis, classification, natural history and usable treatment
  - Parallel controls
    - Patient registry data concurrently obtained with the single-arm trials are used as controls.
    - Consider the impact of comparability of target populations for RW; for data of patients receiving other interventions, whether sufficient covariances are available to support correct and sufficient statistical analysis
- Appropriate methods for statistical analysis:
  - Propensity Scores (PS) method and Virtual Matched Control method. Fourthly,
  - Sensitivity analysis and quantitative analysis of biases should be fully used to evaluate the impact of known or measured confounders or unknown or unobservable confounders and model hypotheses on analytical results.

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Real-World Research Design

Observational studies

- Closest to the real-world
  - Notable limitations are the existence of various biases, data quality is difficult to guarantee, and known or measured or unknown or unobservable confounders are difficult to identify.
  - *Retrospective observational study:*
    - The study identifies the population and determines the exposure/treatment from historical data
  - *Prospective observational study*,
    - Population of interest is identified at study start and exposure/treatment and outcome data are collected from that point forward.
- RWE from observational study data to support regulatory decisions depends on:
  - Data characteristics
    - Data sources/quality, study populations, collection of data of exposure and related endpoints, consistency of records, data curation process, description of missing data, etc.
  - Study design and analysis
    - Whether ppropriate positive controls are set, whether variability of potential unmeasured or unmeasurable confounders and potential measurement results are considered, whether the analytical methods are rigorous and transparent and comply with regulatory requirements
  - Robustness of results
    - sensitivity analyses, qualitative analysis of biases and predeterimined statistical methods
- The key technique for analyzing RWD from observational studies is causal inference

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Perspectives of a rare disease developer

Ensuring stakeholder acceptability of RWD/RWE

- Required standards to produce RWE that is acceptable for regulatory decision-making have not yet been fully defined
- **Whether the RWD are fit for use (*Data Quality*)**
  - Registries
    - EMA draft registry guidance
    - Qualification procedure eg. EBMT
    - No suitable registry for regulatory/HTA purposes in many rare conditions
  - Electronic medical record-enabled trials
    - Endpoints in rare disease space are often not conducive to capture in EMR
    - Some potential (US) for EMR for PASS
  - ➢ Drive RWD quality by designing a study to answer the question
- **Evaluation of RWE (*Methodology*)**
  - ➢ **Need agreed methodology across stakeholders**

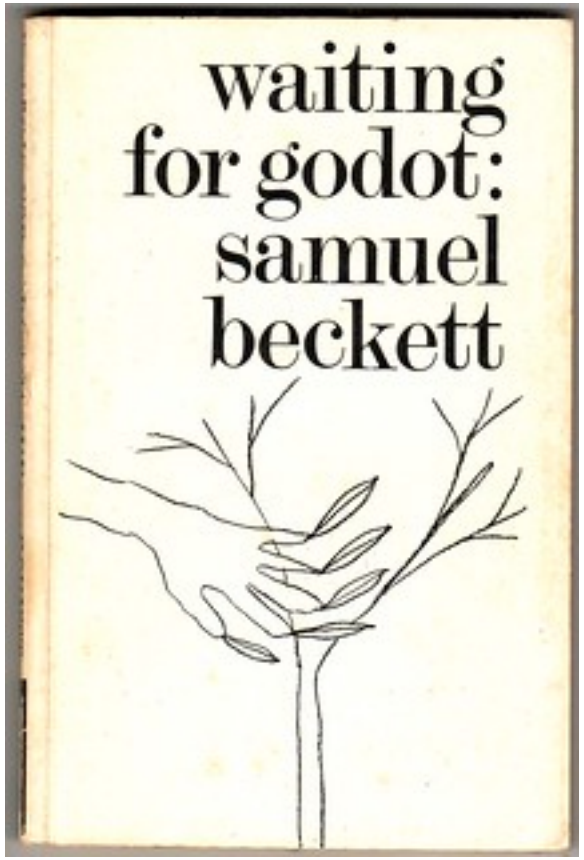
Medical Devices – latest updates

MDCG Working Groups with EUCOPE representation

- Borderline and Classification Working Group (B&C)
- Unique Device Identification Working Group (UDI)
- New Technologies

Borderline and Classification Working Group (BCWG)

- Last meeting on 4th December
  - Status update on consultation on MEDDEV guidelines
  - Update on functioning of the Helsinki procedure
  - Consultation on ancillary medicinal products and TSE susceptible animal tissues
- MEDDEV 2.1/3 rev. 3 - final draft expected already last December…
- MEDDEV and 2.4/1 rev. 9 - yet to receive first draft…
- Helsinki procedure will be updated in line with MDR, no major changes expected, waiting for new process…
- EUCOPE provided comments on the consultation for MEDDEV 2.1/3 rev. 3 and the consultation procedure
- Workshop between regulators and stakeholders expected to discuss impact of new guidelines on existing products – date TBC…
- Ongoing Helsinki request on classification of vaginal products containing lactic acid – EUCOPE to provide comments by 29th March 2020



UDI WG Updates

Future UDI database in EUDAMED

- The Commission informed that EUDAMED database will **not** be fully functional by May 2020, Go-Live has been postponed by two years (May 2022).
- Delay will only impact what related to the setup of EUDAMED but not to the rest of aspects as for example the UDI. Assignment to the products of the Basic UDI and UDI must continue (UDI assignment and UDI *Labelling won't be affected by the delay of EUDAMED)

  (*:*From EUCOPE we still need to clarify this point with the Commission on labelling)*
- Point raised from an industry stakeholders on the need to have a clear guidance from the Member States with respect to the timelines to register the devices and to avoid differences between MS.
- The Commission states that is working towards this objective, to have an identical approach through the different MS.
- With respect to the timing for this work, this will be started at the earliest being the MDCG involved to create a guidance for this.
- EC is in discussion with MS in order to give to this legal certainty

UDI WG Updates

Future UDI database in EUDAMED

- Q&A session with designated UDI Issuing Entities
  - As per Commission Implementing Decision (EU) 2019/939 of 6th June 2019
  - To designate issuing entities to operate a system for the assignment of Unique Device Identifiers (UDIs) in the field of medical devices
    - GS1 AISBL
    - Health Industry Business Communications Council (HIBCC)
    - ICCBBA (EU and USA)
    - Informationsstelle für Arzneispezialitäten — IFA GmbH
  - Proposal for participation of Issuing Entities in WG meetings for aligment with group discussions
- Discussions on draft guidance “Considerations on the control of the Manufacturer’s Quality Management System (QMS)”
  - Guidance document to promote a common approach to the implementation of the UDI obligations as an essential part of an organisation’s Quality Management System as required by MDR Article 10(9h) and IVDR Article 10(8h).
  - Working on its finalization for further adoption
  - Looking for endorsement in next MDCG meeting (11-12 March)

UDI WG Updates

Future UDI database in EUDAMED

- Contact lenses/spectacles: Rules for assignment – Discussion on approach
  - The Group is working in order to reduce the number of UDI-DI for this type of products due to the high number of different references that can be generated due to their particularities.
  - Some initiatives actioned from the contact lens manufacturers association to make a change in the standard lenses but this could impact aspects related to PV. For the prescription lenses (were more variability is expected) it is proposed to make groups of references reducing in this way the number of references.
  - The above could result in the reduction of around 5000-7000 for a sole UDI. Also for the contact lenses it is estimated a high reduction in the UDI-DI to assign.
  - This raises the concern on the fact that too much grouping / reducing of the numbers could result on a loss of traceability which is the main objective of the MDR.

- Working on draft Guidance clarifying specific UDI-Triggers
  - Guidance intended to provide a clarification on the notion of Basic UDI-DI, its use in relevant documentation and the factors triggering UDI-DI changes. It is an amendment to the Guidance MDCG 2018-1 v2 "Basic UDI-DI and changes to UDI-DI‘’
  - Changes of UDI-DI: A new UDI—DI shall be required whenever there is a change that could lead to misidentification of the device and/or ambiguity in its traceability (e.g change of name or trade name, device version or model, labelled as single use, packaged sterile, need for sterilization before use, quantity of devices provided in a package, critical warnings or contra-indications (e.g. containing latex or DEHP), CMR/Endocrine disruptors)
  - Aim is for this new guidance to be presented for endorsement in the next UDI WG on 17th February

UDI WG Updates

Future UDI database in EUDAMED

- Discussion on differences in the US-EU UDI systems
  - MedTech Europe presented a document in the WG for discussion
  - Aim of this work is to look for a single and globally harmonised identification system of Medical Devices
- Working on minor revisions of Implant Card guidance MDCG 2019-8:
  - To provide guidance for Member States, concerned industry and other stakeholders on a blueprint of an implant card (IC) required by the MDR (Article 18, Regulation (EU) 2017/745)
  - Main objectives of the implant card:
    - Enable the patient to identify and get access to other information related to the implanted device (e.g. via EUDAMED, and other websites).
    - Enable patients to identify themselves as persons requiring special care in relevant situations e.g. security checks.
    - Enabling e.g. emergency clinical staff or first responder to be informed about special care/needs for relevant patients in case of emergency situations.

Notified Bodies Designation Update

Getting there…?

- 10 NBs for MDR + 2 for IVDR
- Many others in the designation process
- Scope of both regulations is covered
- EC still optimistic (although target of 20 NBs spectacularly failed)
- Major concern for the sector
- Small companies particularly vulnerable
- EUCOPE Letter to DG SANTE in February 20

EMA Meeting on DDC products – 31 March

Support implementation of Art 117 of the MDR affecting drug-device combinations (DDC)

The objective of the workshop is to facilitate an interactive expert discussion on practical examples using specific case studies and exchange of views between EU Regulators, EC, Notified Bodies and Industry representatives, both from pharmaceutical and medical device sectors.

Case studies which could be used during the workshop taking into account the following:

- Initial MAA and variation
- Different device technologies and supply chain considerations – e.g. in-house manufacture vs external supply of device constituents (e.g. platform technologies, contractual obligations).
- Changes in medicinal product composition that could potentially affect device performance requiring new Notified Body opinion; variations for changes in device potentially requiring new Notified Body opinion.
- Clinical trial requirements vs marketing authorisation (e.g. interdependencies between process development activities and the respective medical device development; stability studies for medicinal product / device).
- Applicability and use of standards (Ph. Eur., ICH/EU guidance, GMP, ISO)
- Illustration of overlap of General Safety Performance Requirements with Drug Device Combination dossier requirements.

EMA Meeting on DDC products – case 1

Case study proposal: Co-packaged diluent – device or container closure?

Problem Statement: The EMA Q&A on Implementation of the MDR includes pre-filled syringes as an example of an integral product. Many diluents are presented in a syringe format and Article 117 could be considered to apply.

Background/Discussion:

Many lyophilized products are **co-packaged with a diluent for reconstitution**. These diluents may be presented in a syringe format for ease of reconstitution. The diluent syringe is presented with a cap rather than a needle and the syringe is discarded after reconstitution. In this case, the syringe is considered a **container closure and not an administration device**. The syringe is not intended for a medical purpose and the requirements of the Medical Devices Regulations (EU) 2017/746 (MDR) do not apply.

Incorrect application of Article 117 would result in:

- The diluent medicinal product being considered an integral drug device combination
- A medicinal product co-packaged with the diluent being considered a non-integral drug device combination

Medicinal product manufacturers often source diluent components from a third-party supplier and, in turn, the third-party supplier may provide the same component to multiple other end users. Although according to Art 4(3) of the MDR, consistent approach of classification is targeted, there is potential for the different parties in the component supply chain to apply a divergent classification to the same component depending on the particular use of the component. To prevent any confusion, it is recommended to revise the Q&A to specifically indicate Article 117 does not apply to diluents presented in syringe format for reconstitution only.

EMA Meeting on DDC products – case 2

Case study proposal: Improve efficiency by avoiding duplicate assessment

Problem statement: According to the EMA draft guideline on the quality requirements for DDCs, the **usability/human factor study report** has to be included in the MAA dossier. For the medical device part, the same document could be required for the technical document and subject to notified body review depending on product risk classification.

Background/Discussion:

Two overarching principles should be envisioned for DDC products under the new regulation:

1. Each file should be presented only once in the application (cross reference may be useful).

2. Clear allocation of responsibilities should be determined between EMA and NB.

Usability studies or human factor studies for medical devices are divided into two categories: formative and summative studies. Formative studies are done during development of the medical device to inform about the design, and the summative study is the final validation of the concept. The usability/human factor reports for singe Medical Devices are usually compiled in the technical document. If applicable, depending on the risk classification of the product, a summary of the technical file is subject to notified body review.

For DDCs regulated under Directive 2001/83 as amended by Article 117 of the MDR, the documentation for usability should be part of the MAA. This should also include the usability risk analysis (usability FMEA) to justify that the user risk is acceptable.

Consequently, the dossier for a notified body opinion should only contain the technical design elements without the documentation for usability.

In conclusion, reviewing of usability and human factor reports should solely be under the CHMP/NCAs remit for MDR Article 117 DDC products. This approach would avoid confusion and clarify responsibilities while at the same foster an efficient operational model to the benefit of all stakeholders.

EMA Meeting on DDC products – case 3

Case study proposal: Implementation of SME specific provisions for DDC product development

Problem statement: SME's have very limited resources to capture the new requirements of the MDR with regards to DDC products. This is acknowledged by the Recommendation 2003/361/EC and several political statements. Although substantial administrative, regulatory and financial support is provided for the Medicinal Product component (e.g. direct assistance, help to navigate the complex system, assistance with translations, **SME** briefing meetings, etc.) **comparable support for the Medical Device part is missing.**

Background: For DDC products, the MDR will have to be taken into consideration by the EMA.

Recital (2) of the MDR states "*This Regulation aims to ensure the smooth functioning of the internal market as regards medical devices, taking as a base a high level of protection of health for patients and users, and taking into account the* ***small- and medium-sized enterprises*** *that are active in this sector."* This approach is in alignment with Recommendation 2003/361/EC.

Some concrete provisions are expressed in the MDR, e.g.

- Person responsible for Regulatory Compliance for Small and Micro sized entities not needed within companies, but permanently at disposal Art 15(2)
- Fee reduction for expert panel, expert laboratory and clinical evaluation consultation procedure (Art 106(14))
- NB shall take into account interest of SMEs as defined in Recommendation 2003/361/EC in relation to fees (Annex VII (1.2.8.))

Discussion: Several innovative medicinal products developed by SMEs have been substantially supported by the EMA's SME provisions, incl. incentives and special services provided by the EMA SME office. Many of PRIME granted innovative products (predominantly DDC) have been developed by SMEs. Can we assume that this service will be extended by the EMA to cover specific aspects to DDC products?

AOB

Next meeting dates

- 19 May TC
- 10 September f2f, EUCOPE offices, Brussels
- 8 December TC

- Additional meetings of dedicated focus groups

Thank you