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European Confederation of Pharmaceutical Entrepreneurs AISBL

Regulatory / PV / Medical Devices Working Group

Brussels, 05 November 2019

Welcome/ Next Events

Agenda

- **Welcome / next events**
- **EMA Focus groups in R&D in light of the EMA Regulatory Science Strategy 2025**
  - Opportunities leading to a more integrated R&D product support: Analysis of existing engagement platforms (Lucia D'Apote, Amgen)
  - Qualification of novel methodologies for medicine development: Regulatory acceptability of a specific use of digital methodology (Joao Duarte, Alexion)
- **Clinical Development**
  - Current status of the CTIS report from the latest EMA stakeholder meeting (Roberta Bernardelli, Gilead)
- **Nitrosamines**
  - Background and implications for manufacturers (Sylvie Meillerais, MSD)
- **Medical Devices – latest updates**
  - Report from the Medical Device Coordination Group (MDCG) and working groups:
  - Status of designated Notified Bodies; expected swift to DG Santé; status of the Unique Device Identification system (Jörg Plessl, Norgine)
- **Regulatory Policy**
  - Review of the EMA fee structure (OMPs / Paediatrics)
  - Drug shortage – status of discussion
- **AOB / End of meeting**

EMA Focus groups in R&D in light of the EMA Regulatory Science Strategy 2025

Opportunities leading to a more integrated R&D product support: Analysis of existing engagement platforms

(Lucia D’Apote, Amgen)

EMA Regulatory Science to 2025 - Timeline

- EMA has reviewed comments received from all stakeholders, initially blinded analysis and now unblinded and published the responses
- Briefing document possibly available before workshop.
- Draft report currently around 500 pages.
- Priorities and actions to feed in Agency's and Network programming documents

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EMA RSS workshop preparation

- Workshop agenda indicates core recommendations with stakeholders' high score. Not fully indicative of EMA's priorities (e.g. Biosimilars)
- Workshop intent: validate priorities and underlining actions; Format: more interactive compared to 2018. No presentation by Industry, expected active participation
- Stakeholders preparation and talking points:
  - Building on comments made during consultation
  - Practical suggestions for actions/initiatives
  - Out of box thinking welcomed
  - Resource issues should not limit proposals at this stage – important to map and record gaps and needs

EMA RSS Workshop Agenda: mapping against EUCOPE's comments

Session 2: ATMPs and Precision Medicine	Current level of EMA's commitment supported	Important
Session 3: Developing scientific advice/assessment pathways and exploring RWD use in benefit-risk decision-making	Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	EUCOPE's priority 3
	Diversify and integrate the provision of regulatory advice along the development continuum	EUCOPE's priority 1

EMA RSS Workshop Agenda: mapping against EUCOPE's comments

Session 3: Developing scientific advice/assessment pathways and exploring RWD use in benefit-risk decision-making	Contribute to HTA's preparedness and downstream decision making for innovative medicines	Important
	Bridge from evaluation to access through collaboration with payers	Important
	Expand benefit-risk assessment and communication	
	Promote use of high-quality real-world data (RWD) in decision making	Important

EMA RSS Workshop Agenda: mapping against EUCOPE's comments

Session 5 – Reinforcing patient relevance in evidence generation and developing research partnerships with academia	Reinforce patient relevance in evidence generation (EUCOPE's priority 2)	EUCOPE's priority 2
	Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science	Important
Session 4: Clinical trials, Digital Therapeutics and Modelling & Simulation	Foster innovation in clinical trials	Important
	Develop the regulatory framework for emerging clinical data generation	
	Optimise capabilities in modelling, simulation and extrapolation	

EMA RSS Workshop EUCOPE's talking points

Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	To avoid creating an additional complementary advice mechanism**, a more flexible and integrated R&D product support mechanism is needed, providing agile rolling advice that effectively addresses the key challenges and development milestones (e.g. PIP submissions, orphan designation, eligibility to expedited pathways, transition to patient access and HTA, etc.).** **It is highly recommended that the new system is leaner, more flexible and faster, while maintaining the open communication, interaction, and alignment between the relevant stakeholders.** **Systematic involvement of patients and other relevant stakeholders such as HTA bodies, payers, healthcare professionals and others is key to achieve access to innovative therapies**. Joint/parallel advice with Notified Bodies

Refine proposal. Move from need to solution. Address implementation.

EMA RSS workshop preparation: next steps

Circulation 1st draft talking points	5 November	Lucia-Maren
Quick round of Comments	6 November (AM)	Drafting Group
Inter-association TC	6 November	Maren- Lucia- Audrey?
Propose additional SMART solutions	7 November	Drafting Group
Refine and consolidate proposals	8 November	Lucia
TC to finalise talking points	11 November	Drafting group
Reharsal	14 November	

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Research & Development (R&D) - EMA focus group on opportunities leading to a more integrated R&D product support (Update)

EUCOPE REGULATORY / PV / MEDICAL DEVICE WORKING GROUP meeting -
5 November 2019

EMA FG integrated R&D product support

Objective and tasks

To identify ways that facilitate integrated R&D support, which is able to review developments from a project perspective (horizontally) in addition of managing individual procedures (vertically), starting from current opportunities for interactions with regulators during research and development

STEPS:

- Mapping of current interaction opportunities (including timelines of such interactions), and how they are being used in practice, based on concrete examples by companies for medicinal products, topics / project
- Principles and limitations of such interactions, including ideas for optimised management of integrated R&D support
- Developing ideas to ensure a continuum of interactions along the development life-cycle including relevant enablers and boundaries

Next Steps – ask for EUCOPE's members

Follow-up / actions

- Next meeting to address the examples from "broad scientific advice" as these were not yet discussed, and to start reflection on the propose principles for development support interactions based on the analysis so far.

Timelines

Next TC 7 October.

- Follow-up actions plus reflect on opportunities for wider outreach, respecting the initial mandate for the group.

Existing engagement platforms	Use in development programmes (time points and scope)	Strengths and limitations, based on experience	Level of familiarisation / utility from the perspective of developers and their project teams
"Broad scientific advice"	• Non-product specific advice • Useful in a very rapidly evolving condition (eg in cancer, PAH) where the discussion needs to go beyond the individual product • Was developed before the qualification procedure and many of the topics (like PROs) go there now	Strengths • Opportunity to seek to seek advice on issues related to the overall development plan • Potential opportunity to start dialogue with relevant experts on development approaches that are stretching the current regulatory paradigm • Possibility to leverage SAWP multidisciplinary expertise and representatives from other Committees and WPs Limitations • Scope and objective of the tool is not clear • Not clear whether multi-stakeholders dialogue can be included in the procedure	• Very limited experience driven by lack of clarity on the objectives and potential benefit of the procedure • Scope of this advice procedure would benefit from greater clarity and transparency. • Teams tend to be unclear on the difference between this and discussions at a business pipeline meeting
	Observations, learnings and follow-up:	• The concept of "broad scientific advice" seems not well known and the difference to business pipeline meetings seems unclear--> need to improve communication on scope of this type of advice • Reflect if the concept is still fit-for-purpose	

EMA RSS workshop preparation: next steps

Quick round of Comments on Broad SA	5 November	All
Propose principles for development support interactions based on the analysis so far	6 November	Drafting Group

Qualification of novel methodologies for medicine development: Regulatory acceptability of a specific use of digital methodology

(Joao Duarte, Alexion)

The journey so far…

- **4 TCs** so far, **one survey** on assumptions and expectations concerning qualification of digital technologies;
- **No further TCs** planned currently (last one on 11 September);
- **Lack of clear definitions** still a critical area that remains to be addressed (EUCOPE volunteered to support the drafting);
- Current draft as of 11 September 2019, comments and questions from Aparito and VSLSC.

Current structure

1. **Introduction**
2. **Definitions, scope and EMA's remit**
3. **Content of the Qualification submission documents**

3.1 Timing and planning of a qualification request

3.2 Specific expertise requirements

3.3 Critical aspects specific to the qualification of digital technologies

3.3.1 Context(s) of Use (CoU) definition

3.3.2 Digital endpoint selection

3.3.3 Demonstration of clinical utility and expected use

3.3.4 Other Aspects

Definitions, scope and EMA's remit

- **Scope clarified**

*"It is important to **clearly define early** on the components of those digital technologies that would be under EMA's remit and those who are not: as an example, if an applicant is interested in qualifying a new wearable device that is used to collect data from clinical studies, **which is expected to be later evaluated as part of an MAA**, aspects on how such data supports the benefit-risk assessment (e.g. endpoint outcomes, product information, clinical relevance of data collected, etc.) **would be seen as under EMA's remit**. However, technical aspects related to conformity of the wearable and technological parameters that **are not expected to impact benefit-risk assessment would not be under EMA's remit**, and the Agency encourages developers to consult with the **relevant stakeholders** on these issues (see chapter 4)."*

Definitions, scope and EMA's remit

- **Definitions and examples**

Digital endpoint

Digital Biomarker

Digital Clinical Outcome Assessment (COA)

Digital Measures

EMA's remit

?

Digital Therapeutics

Digital Clinical decision support (CDS)

Digital drug administration devices

NOT EMA's remit

Content of the Qualification submission documents

- **Timing**

Accommodate iterative / adaptive qualification (due to the rapid evolution of the technologies);

No need to re-qualify something due to software changes that do not affect the component dramatically (i.e. no impact to B/R and use);

Exploratory data to pivotal role.

Challenge: timelines and appetite from companies to undergo the process?

Specific expertise requirements

- **Planning and expert identification**

Pre-discussion with EMA encouraged.

Timely identification of an appropriate expert group (the “Qualification Team”) for the assessment (regulatory network).

Two main areas of expertise needed:

- Aspects for which EMA expertise is available or networking with external stakeholders is well established (EMA, WGs, HTABs, etc.)
- Aspects that will require development of further expertise or input from other relevant stakeholders (Notified Bodies)

The ambition is to create multi-expertise teams as more experience in the area is gathered. Interactions with the EMA’s Innovation Task Force (ItF) and/or national Innovation Offices is also encouraged.

Critical aspects specific to the qualification of digital technologies

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- **Clinical outcome assessment (COA)**

1. **Content validity**
   - Context of use definition
   - Variable selection to evidence that the instrument measures the concept of interest. Derive variable selection from qualitative work to select the variable of interest and select digital features based on the sensitivity to the concept of interest.
   - Patient understanding and patient burden
2. **Construct validity**
   - Correlation/concordance with other related measures (cross-sectional)
   - Discrimination of known groups (HV/ patients, different phenotypes)
3. **Reliability**
   - Test-retest reliability (variability of successive measurements of the same test carried out under the same conditions)
   - Biological/physiological and environmental variation (physiological variability of test without measurement error and under stable disease conditions; ex: data collection environment, duration of data collection period, days of the week for monitoring). Elements of data analysis: data file preparation and transfer, missing data rules,
   - Total variation (total variability of repeated measurements under stable disease conditions)
4. **Sensitivity to change**
   - Mean-to-SD ratio of decline (longitudinal change of score over time period during which disease is expected to progress relative to population variability)
   - Longitudinal correlation with clinical assessment
   - Longitudinal change predictive value (could be applicable depending on COU)

Critical aspects specific to the qualification of digital technologies

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- **Digital biomarker**

1. **Context of use and proposed biomarker category. Mostly applicable to response biomarkers.**
2. **Rationale to fulfil the unmet need:**
   - Biological/physiological rationale compared to the proposed context of use.
   - Potential added value to drug development (ex: improved clinical trial efficiency, improved subject safety)
   - Anticipated consequences if the biomarker is unsuitable for its intended use (ex: underpowered trial, inappropriate approval decision)
3. **Reliability**
   - Test-retest reliability (variability of successive measurements of the same test carried out under the same conditions)
   - Biological/physiological and environmental variation (physiological variability of test without measurement error and under stable disease conditions; ex: data collection environment, duration of data collection period, days of the week for monitoring). Elements of data analysis: data file preparation and transfer, missing data rules,
   - Total variation (total variability of repeated measurements under stable disease conditions)
4. **Sensitivity to Change and Treatment:**
   - Correlation of longitudinal change in biomarker domain score with respective change in clinical assessments of interest during the same time period
   - Correlation of longitudinal change in biomarker with a disease modifying intervention
5. **Data supporting relationship between the biomarker and clinical outcome of interest**

Critical aspects specific to the qualification of digital technologies

- **Context(s) of Use (CoU) definition**
  - Clear insight into the robustness of the method across the settings in which it is to be used, and to scientifically justify the selection of a specific technology for a specific study or given purpose.
  - "*Bring your own device*" trials" and impact on the quality of data collected.

- **Digital endpoint selection**
  - The choice of a digital method of data collection should be grounded in identifying and measuring concepts that are relevant and clinically meaningful to the target population.
  - Estimands considerations.

- **Demonstration of clinical utility and expected use**
  - Should be discussed in terms of the benefits and drawbacks of the use of digital technology.
  - Link to remit and beyond.

- **Other Aspects / conduct of the study**
  - System information
  - GCP considerations

Backup Slides

Objectives and Expected Output

- To **stimulate seeking qualification of digital technologies** by:
  - ❖ briefly summarising the circumstances where digital technologies are expected to enable some steps of the product development process (e.g. outcome measurement, study conduct)
  - ❖ describing the scope and process of a digital technology's qualification procedure, focusing in particular on:
    1. *clarification of the applicability / remit of the qualification vs other decision makers;*
    2. *identifying issues and barriers that need to be addressed to facilitate qualification of digital technologies*
  - ❖ developing points to consider for the preparation of a high-quality request for qualification dossier, including potential types of uncertainties and current and desired types of data
  - ❖ stimulating the cross-functional collaboration to ensure relevant expertise is contributing to the qualification preparations and discussions
- **Expected output:** aide memoire on opportunities, applicability and conduct related to the qualification of digital technologies for medicines development.

Focus Group

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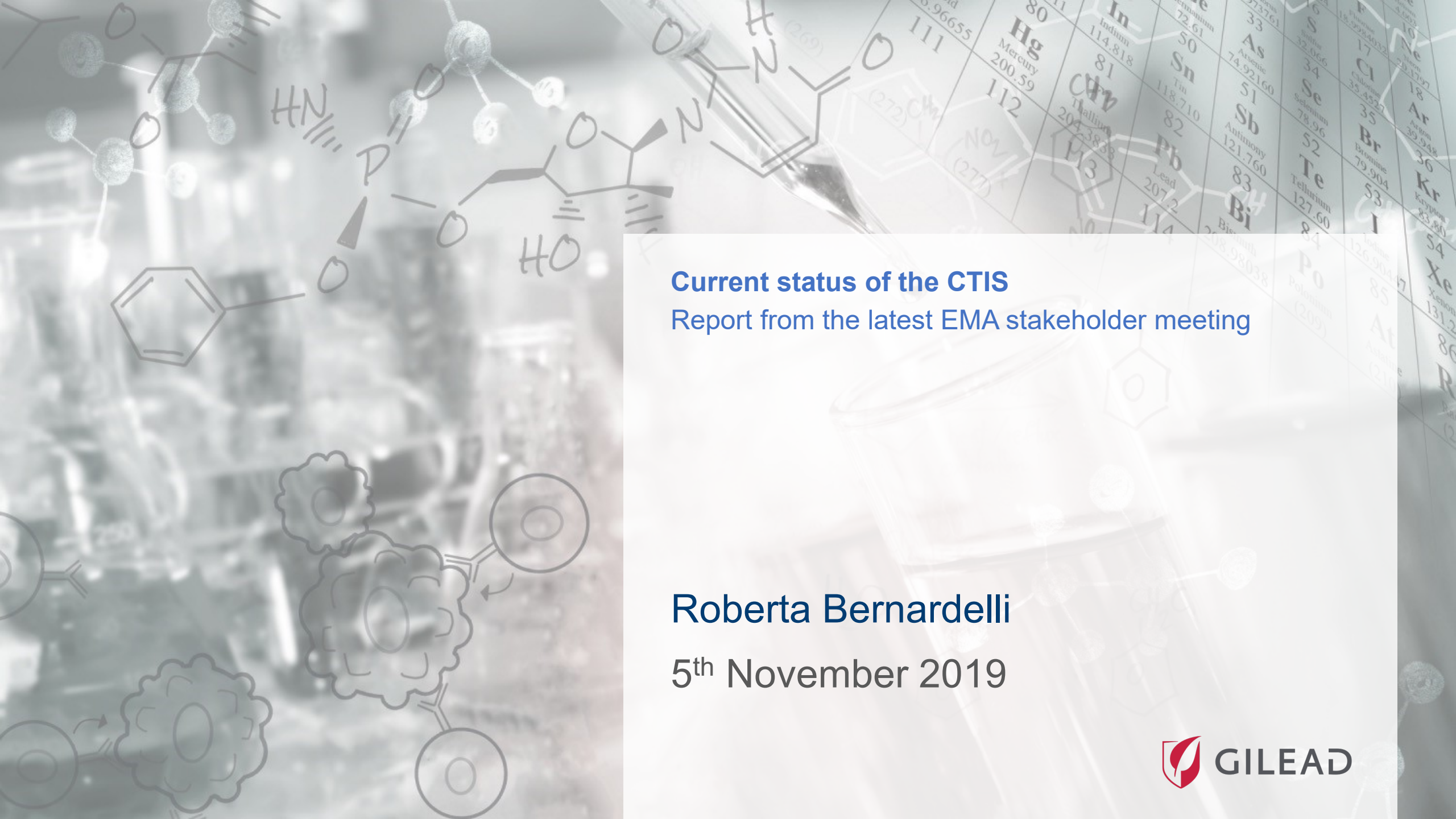
EUCOPE Active Members

- Alexion
- Aparito
- VCLSC

Clinical Development

Current status of the CTIS report from the latest EMA stakeholder meeting

(Roberta Bernardelli, Gilead)



Current status of the CTIS

Report from the latest EMA stakeholder meeting

Roberta Bernardelli

5th November 2019

GILEAD

Meeting Agenda

- **CTIS programme status update overview**
- **Revised Analysis and Design approach: clustering**
- **Sponsors Product Owners update**
- **CTIS Demo sponsor functionalities**

CTIS programme status update overview

CTIS programme status update overview

- R10 (release 10) successfully delivered, the first developed under the new delivery model with the support of the new vendor IT4U and the new PO (product owners)
- 4 validation sprint sessions focused on Application Evaluation, Access Management, Data submission and View.
- MS POs, Sponsor POs, EMA, IT supplier working together
- Common perception is that we are getting closer to the Audit
- Backlog management: distribution by cluster (not ticket by ticket but by group of similar or related tickets =10 cluster articulated in high level functionality)
- Development of R11 has just started. It will be focused on business blockers and cluster approach. Execution by mid Dec.
- At least other 2 releases are needed to have an auditable system.
- After the audit it will take 3 months for the commission approval + 6 months (therefore not before 2021, **but EMA didn't commit to any date for the system to be auditable**).

Sponsors Product Owners concerns

Sponsors Product Owners concerns

- Currently the focus is on Audit milestone versus Go Live milestone. Considering the limited time once Audit is completed to develop operationally critical functionalities, there is a need to start thinking on the planning of Tier 2 priorities already for a successful Go Live.
- Inability of overlapping Substantial Modification evaluations (and RSI updates) still poses a major operational concern for the Industry and Academia in real life implementation of the EU Clinical Trial Regulation: the commission is aware and is in the process of amending the legislation.
- **Product section structure will be populated based on EVcodes** (EU MP number = PRD code in XEVMPD - EU substance number = SUB code in XEVMPD) + additional information to cover all the details of the current EU CT form, **including the placebo. The addition of the placebo details to the XEVMPD database is considered not appropriate for the scope of the database.**
- **Part I Sponsors section will be filled in based on OMS ORG identifiers,** currently the system is open, every registered user can create or update an organisation's details. OMS maintenance is already an issue with only the MAHs included. **A different governance model is recommended to avoid IT security issues (spam) and duplicate entries.**
- **Scalability and oversight:** user management (e.g. bulk user management), lack of dashboard or alternative Business Intelligence reports, download functionality and later interconnection with Trial Master File
- **Documentation:** naming and versioning of documents
- Sponsor change: lack of functionality to change the main sponsor organization initially selected to create a new CT to a different sponsor thereafter

Sponsor Users Management Hierarchy

Organisation-centric Approach

Users are related to an organisation (sponsor) and they can be assigned one of more roles for all trials of an organisation or only selected trials.

Each user has a profile in the CTIS linked to the employer details registered in OMS.

Users cannot create a new CT if they don't have a role assigned from the sponsor administrator.

A role can be assigned to a user (by the CT admin) or it can be requested by a user to the CT admin.

The CT admin can manage only the users of the CTs he/she is administering, the Sponsor admin can manage all the users regardless the CT.

High Level Admins (Sponsor administrators): create backups, assign new roles, change/revoke roles

Medium level Admins (CT administrators)

Regular users

Viewers

- Part I (except QIMPD*)
- Part II
- QIMPD
- Notifications
- CT results

Preparer

- Part I (except QIMPD)
- Part II
- QIMPD
- Notifications

Submitter (no QIMPD viewer/preparer)

- Application
- Notifications
- CT results

*the Q-IMPD preparer role will not be restricted to have access to individual Q-IMPDs but to all Q-IMPDs submitted in a particular trial, therefore will not ensure confidentiality of proprietary information in case of several IMPs by multiple sponsors

Questions

Nitrosamines

N-NITROSAMINES IMPURITIES

EXPECTATIONS FROM MAHS?

Sylvie Meillerais

Director Global CMC Policy

EUCOPE meeting, November 5th 2019

Reminder

- 2018 - 2019: Valsartan and N-Nitrosamines impurities (NDMA) EU Article 31 referral, followed by extension to other Sartans (candesartan, irbesartan, losartan and olmesartan) (NDEA)
  - Referral outcome: 2 years to make necessary changes to manufacturing processes – see overleaf
  - The 5 relevant Eur. Ph. Monographs revised to align to the EU Decision for the transitional period of 2 years

- July 2019: EU/EMA (and Health Canada) expectations circulated for comment (**under embargo**)
  - To evaluate **ALL** chemically synthetised APIs for the potential FORMATION OF and CONTAMINATION with N-nitrosamine, even though the risk of nitrosamine presence as stated in the paper to be low
  - TAs joint response asking for proportionate, science and risk based (prioritised) position to be taken

- 13/09/2019: EMA to review medicines containing ranitidine
  https://www.ema.europa.eu/en/news/ema-provide-guidance-avoiding-nitrosamines-human-medicines
  https://www.ema.europa.eu/en/documents/referral/ranitidine-article-31-referral-annex-i_en.pdf

- 26/09/2019: Art 5(3) opinion and EMA and CMDh note to MAHs – 3 steps approach to all chemically synthetised APIs, intermediates and processes

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EU Art. 31 Sartans referral

Table 1. Temporary limits for NDMA and NDEA impurities

Active substance (max daily dose)	NDMA		NDEA	
	Maximum daily intake (ng)	Limit (ppm)	Maximum daily intake (ng)	Limit (ppm)
Candesartan (32 mg)	96.0	**3.000**	26.5	**0.820**
Irbesartan (300 mg)	96.0	**0.320**	26.5	**0.088**
Losartan (150 mg)	96.0	**0.640**	26.5	**0.177**
Olmesartan (40 mg)	96.0	**2.400**	26.5	**0.663**
Valsartan (320 mg)	96.0	**0.300**	26.5	**0.082**

Testing during and after the transition period

- While the goal is to have no quantifiable nitrosamine impurities in sartans, interim limits have been set for NDMA and NDEA in line with current international guidelines.
- Products containing either impurity above these limits or products containing both nitrosamines at whatever level will not be allowed in the EU.
- The limits are based on the maximum daily intake for each impurity derived from animal studies: 96.0 nanograms for NDMA and 26.5 nanograms for NDEA. Dividing these by the maximum daily dose for each active substance gives the limit in parts per million (see Table 1).
- The transition period, which will last for 2 years, will allow companies to make the necessary changes to their manufacturing processes and to put in place testing regimes able to detect the smallest amounts of these impurities. After the transition period, companies must exclude the presence of even lower levels of NDEA or NDMA in their products (< 0.03 parts per million).

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Requirements extended to **ALL products with chemically synthetised APIs** in **EU and Canada**

EU (EMA/CHMP Art 5(3) and CMDh), Sept. 2019 note to MAHs	Health Canada, Oct. 2019 letter to MAHs
• **Step 1: risk evaluation of all products** to be completed **within 6 months, i.e. by 26th March 2020** (based on principles of Q9, and M7). MAHs to prioritise their evaluation taking into account: products with highest daily dose, treatment duration, product criticality…	• **Step 1: Risk Assessment:** ***to be completed*** in as expeditious a manner as possible and **within 6 months of the issuance of this letter (by April 2, 2020).** MAHs to prioritise their evaluation taking into account: products with highest daily dose, treatment duration, product criticality…
• **Step 2: confirmatory testing:** in the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out. Products identified as high priority should be tested as soon as possible. Confirmatory testing of all medicinal products identified to be at risk of presence of nitrosamines and submission of required changes in the manufacturing authorisations should be concluded at the **latest within 3 years of the publication of this notification** or at an earlier time if otherwise justified. MAHs should inform the competent authorities immediately if tests confirm the presence of an nitrosamine impurity irrespective of the amount detected.	• ***Step 2: Confirmatory Testing:*** In the event that a risk of formation or presence of nitrosamines are identified, confirmatory testing should be carried out using appropriately validated and sensitive methods in accordance with the prioritisation deriving from the risk assessment conducted in Step 1, and be concluded at the **latest within 2 years of the issuance of this letter (by October 1, 2021)** or at an earlier time if otherwise justified.
• **Step 3**: implement the necessary changes to the MA, where applicable	• ***Step 3: Changes to the Marketing Authorization***

Clarification webinar Oct. 29th with EMA, EDQM and CMDh members

- Industry objectives
  - Seek extension to the 6-months deadline for step-1 (Risk Assessment)
  - Adoption of a standardised RA approach
  - Keep open dialogue and secure further discussions on the approach

- Discussion framed around questions pre-submitted by the trade groups

Q? How to deal with **products currently under filing** - *pending agreement with CHMP and CMDh (for discussion at Nov. meeting)*

  - For pre-submission products in development the risk assessment (RA) principles should be adopted.
  - For dossiers already submitted, applicants likely to get questions (the RA will need to be conducted prior to the opinion)
  - Where an opinion is imminent, a post authorisation mechanism will apply.

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Industry Questions at clarification webinar, Oct. 29th

DRAFT pending endorsement of webinar notes by Agencies

Q? Can a **standard questionnaire/RA process** be developed? i.e. find the right balance between doing it *right* and doing it *fast*, i.e. taking some time to deliver a standardised RA approach will support faster and better RA

- EMA supports an aligned industry approaches, but completion of the RA step in the 6-months timeframe is the priority (the 6-months were agreed with CHMP and CMDh, i.e. not for discussion)
- EMA has limited resources available to support the development or the review of such of guidance, i.e. EMA will not support its development nor it will endorse it

Q? Can CAs establish an overall **list of priority products** to be evaluated first by MAHs?

- No, this is the responsibility of MAHs
- EMA also noted that the risk factors in the Q&As will continue to be updated over the 6m as new knowledge emerges => creates added complexity for industry where criteria for consideration are changing!

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Industry Questions at clarification webinar, Oct. 29th

DRAFT pending endorsement of webinar notes by Agencies

Q? Risk identification for **Drug Products (DP)**

- High number of Drug Products to potentially assess, with limited analytical capacity worldwide to test a large proportion of these, even over 3 years
- EMA re-emphasized that RA should not only address APIs
- EMA will continue to update the Q&A with DP risk factors as they emerge, including in relation to packaging.
- EMA acknowledges the lack of established framework or universally understood risk factors for DP (as there are for APIs)

Q? Identifying limits vs potential presence of nitrosamines?

- Industry noted that a Step-1 RA applying ICH M7 principles to determine safe limits for potential nitrosamine impurities (i.e. using limits derived based on known toxicities and considering duration of dosing to derive an acceptable daily intake) may give a different output than a RA which considers only the potential presence of nitrosamines
- EMA: Step-2 analytical testing should be focused where there is a risk, e.g. of nitrosamines being present above the safe limit, rather than anywhere there is a potential presence of nitrosamines – in alignment with the principles of ICH M7.
- EMA confirmed that if there was “no risk”, step 2 testing is not required.

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F2F on 04/11 with HCPs and Patients organisations (with focus on experience with Sartans)

- Challenge to address the diverse audience covering HCPs and patients organisations also
- Communication session:
  - Patients getting the right balance – Agencies vs media headlines?
  - HCPs: challenging – switching product, availability?
  - Useful learning exercise from patients perspective around MAHs responsibilities, regulatory oversight…
- APIs suppliers and MAHs responsibilities?
  - Will MAHs have sufficient knowledge to carry out RA? Risk of withdrawal, shortages?... (DE assessor)
  - Roles of CEP and DMF vs MAHs responsibilities
- Next: how do we move from preventive towards predictive approach (routine testing)?

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Industry steps

- All trade groups: joint follow-up letter to clarification webinar to keep dialogue running
- EFPIA: decision tree (meeting on Nov. 7th) Microsoft Word Document
- CMDh/IP meeting (Nov. 13th): option for grouped reporting of step-1
  - *Reminder for Step-1: send the RA outcome only (risk/no risk) while the full RA is only available upon request – see Q. 5. of the EMA Q&A Q&A*
- MfEU developing a questionnaire for API suppliers also

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References

- EDQM published similar considerations for CEPs, i.e. all chemical APIs must do the risk assessments
  - Step 1 and Step 2 will be the same, within the same timelines for the MAAs
  - See: https://www.edqm.eu/en/news/announcement-all-cep-holders-synthesised-apis-regarding-presence-nitrosamines
- EMA and CMDh templates released

Step 1 - No risk identified response template (DOCX/20.21 KB)

First published: 28/10/2019

Step 1 - Risk identified response template (DOCX/21.96 KB)

First published: 28/10/2019

Step 1 - Risk identified response template (XLSX/11.27 KB)

First published: 28/10/2019

F2F on 04/11 with HCPs and Patients organisations (with focus on experience with Sartans)

- Challenge to address the diverse audience covering HCPs and patients organisations also – objective for industry was to demonstrate this is properly addressed
- Communication session:
  - Patients getting the right balance – Agencies vs media headlines?
  - HCPs: challenging – switching product, availability?
  - Useful learning exercise from patients perspective around MAHs responsibilities, regulatory oversight…
- APIs suppliers and MAHs responsibilities?
  - Will MAHs have sufficient knowledge to carry out RA? Risk of withdrawal, shortages?... (DE assessor)
  - Roles of CEP and DMF vs MAHs responsibilities
- Next: how do we move from preventive towards predictive approach? (US FDA)

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EMA and CMDh References

- EMA: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities-overview
  - CHMP opinion - Art. 5(3) outcome: https://www.ema.europa.eu/en/documents/referral/nitrosamine-impurities-outcome-article-53_en.pdf
  - Information to MAHs: https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf
  - Revised Q&A which includes new root causes, such as packaging – see overleaf
- CMDh: https://www.hma.eu/226.html#c6548

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Revised Q&A on nitrosamines to include new root causes

Q. 12. New! What are the currently identified root causes for presence of nitrosamines?

Potential sources of nitrosamine impurities currently identified are listed below:

1. Use of sodium nitrite (NaNO2), or other nitrosating agents, in the presence of secondary, tertiary amines or quaternary ammonium salts within the same or different process steps (if carry over can occur).

2. Use of sodium nitrite (NaNO2), or other nitrosating agents, in combination with reagents, solvents and catalysts, which are susceptible to degradation to secondary or tertiary amines, within the same or different process steps (if carry over can occur).

3. Use of contaminated raw materials in the API manufacturing process (e.g. solvents, reagents and catalysts).

4. Use of recovered materials (e.g. solvents, reagents and catalysts), including recovery outsourced to third parties who are not aware of the content of the materials they are processing and routine recovery processes carried out in non-dedicated equipment.

5. Use of contaminated starting materials and intermediates supplied by vendors that use processes or raw materials which may allow nitrosamine formation.

6. Cross-contaminations due to different processes run on the same line and due to operator-related errors such as inadequate phase separations.

7. Degradation processes of starting materials, intermediates and drug substances, including those induced by inherent reactivity in combination with carry-over of sodium nitrite (NaNO2), or other nitrosating agents. This could potentially occur also during finished product formulation or storage.

8. Use of certain packaging materials. Nitrosamine contamination has been observed by one MAH in a finished product stored in blister. The MAH has hypothesised that the lidding foil containing nitrocellulose printing primer may react with amines in printing ink to generate nitrosamines, which would be transferred to the product under certain packaging process conditions

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Medical Devices – latest updates

EUDAMED

May 2022

- New European database provided by MDR & IVDR
- Information on actors, UDI & devices, notified bodies & certificates, vigilance, clinical investigations and performance studies and market surveillance
- Operational May 2022 – DELAY
- Good news: more time to upload data
- Bad news: clinical investigation process delayed

Notified Bodies Designation Update

Getting there…?

- 6 NBs for MDR + 2 for IVDR
- Many others in the designation process
- Scope of both regulations is covered
- EC still optimistic (target of 20 NBs by end of year)
- Major concern for the sector
- Small companies particularly vulnerable

Corrigendum: Where art thou?

Complex procedure

- Early draft circulated:

Article 120(3):

for:

'3. By way of derogation from Article 5 of this Regulation, a device with a certificate that was issued in accordance with Directive 90/385/EEC or Directive 93/42/EEC and which is valid by virtue of paragraph 2 of this Article may only be placed on the market or put into service provided that from the date of application of this Regulation it continues …'

read:

'3. By way of derogation from Article 5 of this Regulation, a class I device that has a declaration of conformity drawn up in accordance with Directive 93/42/EEC prior to 26 May 2020 and for which the conformity assessment procedure pursuant to this Regulation requires the involvement of a notified body, and a device with a certificate that was issued in accordance with Directive 90/385/EEC or Directive 93/42/EEC and which is valid by virtue of paragraph 2 of this Article, may only be placed on the market or put into service provided that from 26 May 2020 it continues …'.

Article 120(4):

for:

'… on the market from 26 May 2020 by virtue of a certificate as referred to in paragraph 2 of this Article, may continue …'

read:

'… on the market from 26 May 2020 as referred to in paragraph 3 of this Article, may continue …'

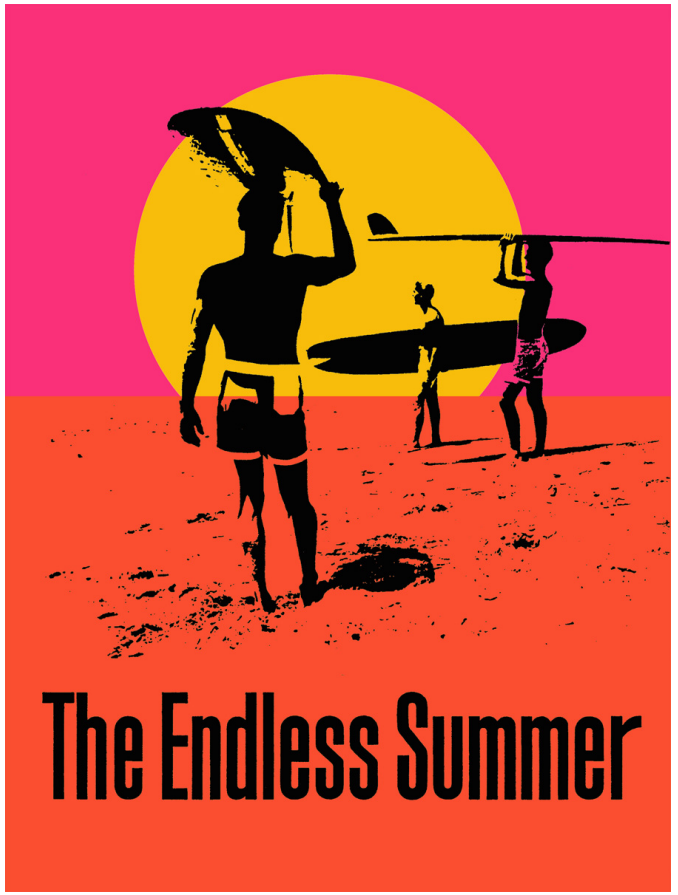
Guidances

MDCG 2019-12	Designating authority's final assessment form	October 2019
MDCG 2019-10	Application of transitional provisions concerning validity of certificates issued in accordance to the directives	October 2019
MDCG 2019-6 v2	Q&A: Requirements relating to notified bodies	October 2019
MDCG 2019-9	Summary of safety and clinical performance	August 2019
MDCG 2019-11	Qualification and classification of software	October 2019
MDCG 2019-7	Guidance on article 15 of the medical device regulation (MDR) and in vitro diagnostic device regulation (IVDR) on a 'person responsible for regulatory compliance' (PRRC)	June 2019
MDCG 2019-8	Guidance document implant card on the application of Article 18 Regulation (EU) 2017/745 on medical devices	June 2019

Consultations: Endless Summer

Closed ones

- Guidance for manufacturers of Class 1 Medical Devices (May 19)
- Clinical Evaluation of Medical Device Software (May 19)
- UDI in QMS (June 19)
- EMA guidelines on quality requirements for DDCP (August 19)
- MEDDEV 2.1/3 definitions of pharmacological, metabolic and immunological means of action and medical diagnosis (September 19)
- MDCG-NBO guidance document on sampling and explanatory note on codes (October 19)



Consultations: Endless Summer

Open ones

- IVD Classification (8 November)
- AI for Medical Devices (18 November)

Thank you

Summary and Actions

Summary and Actions

Defined during the meeting 5 Nov

- EMA Regulatory Science Strategy 2025
  - Focus group prepare talking points for EMA Workshop on 18-19 Nov (Lucia D'Apote, Andrea Braun-Scherhag, Maren v Fritschen)
- Research & Development
  - Focus group on qualification of novel methodologies for drug development: guidance to applicants: Clarification TC with EMA on next steps (Joao Duarte, Cecile Ollivier, Lucia D'Apote, Maren v Fritschen)
- Medical Devices / IVDs
  - Consolidated comments on IVD Classification and AI for Medical Devices (Jörg Plessl, Laurent Louette)
- Priorities for 2020 tbd, survey will be sent out in due time