



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# The regulatory environment for Radiopharmaceuticals

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**The National Academies of Science, Engineering, Medicine : Opportunities and Approaches for Supplying**

**Molybdenum-99 and Associated Medical Isotopes to Global Markets, Vienna, July 18, 2017.**

An agency of the European Union





## Sustainability of supply - EMA Role

EMA and the European Commission organised a Workshop on Current Use and Future Needs of Radiopharmaceuticals Labelled with Radionuclides Produced in Reactors and Possible Alternatives (February 2010) and the organization of a series of stakeholders meetings.

- *analysed the situation.*
- *developed approach to address the problems (ad hoc procedure to change national licences was applied),*
- *developed a communication strategy (a public statement was issued on EMA website).*

EMA participates to the EU Observatory and OECD HLG, supporting the work of the EC and ESA, Member States, NEA.



## Introduction to EU Regulatory environment

EU regulatory environment for radiopharmaceuticals is complex and complicated.

Current MA status for diagnostic Radiopharmaceuticals in EU:

- The majority of radiopharmaceuticals are authorised in EU under national marketing authorisations. (purely national MA's).
- A small number are nationally authorised through MRP/DCP procedures. (MRP/DCP MA's).
- A very small number are authorised through centralised procedure. (CAP's).



## Regulatory Procedures Available to Marketing Authorisation Holders

**Change of reactor / change from HEU to LEU** – could be a Type II variation - Substantial change to the starting material and to manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.

- Utilise Work-sharing and Grouping Provisions set out in Commission Regulation (EC) No 1234/2008
  - Work Sharing avoids duplication of work: one authority examines the variation on behalf of all the others.
  - Grouping Reduces administrative burden
- Utilise ASMF Assessment Work-sharing Procedure (*new voluntary procedure started 2016*)

**MAH's should adopt a proactive regulatory strategy to conversion of HEU to LEU and seek advice.**



.... *“a favourable regulatory environment”...*

- Industry association AIPES formally registered at EMA as Industry Association Stakeholder – 2H 2014.
- CMD(h) Letter to AIPES September 2014 – confirming use of work-sharing and grouping for conversion.
- Confirmation at February 2015 meeting of ASMF WG & CMDh of eligibility of ASMF in radiopharmaceuticals to the work-sharing procedure starting in 2016.
- CMD(h) Presentation @ EU Observatory Plenary Meeting in March 2015
- CMD(h) – AIPES Interested Parties Meeting June 2015.
- CMD(h) letter to AIPES February 2016 - agreement that well defined chemical precursors for preparation of radiopharmaceuticals are eligible for the active substance master file procedure: supporting innovation in the sector.



## For INDUSTRY:

- Avoid duplication of inspections from different Authorities.
- Waive of import testing of products imported.
- Encourage greater international harmonisation.

## For AUTHORITIES:

- Encourage greater international harmonisation.
- Better use of resources.
- Focus on sites of higher risk.

- Manufacturing authorisations.
- Inspection outcomes.
- Manufacturers' certification of the conformity of each batch to its specifications (without re-control at import)

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## Marketed finished pharmaceuticals for human use:

- Medical gases
- Radiopharmaceuticals / radioactive biological products
- Herbal products (\*)
- Homeopathic products

## Marketed biological products for human use:

- Therapeutic biotechnology -derived biological products
- Allergenic products

## Intermediates.

Active pharmaceutical ingredients  
IMPs (\*\*)

## Veterinary products:

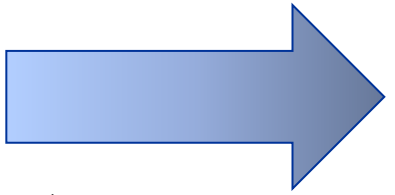
- Veterinary Pharmaceuticals
- Pre-mixes for the preparation of vet medicated feeds

## Vaccines for human use

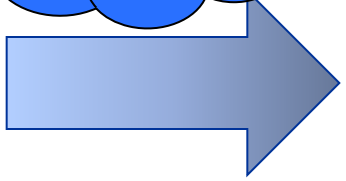
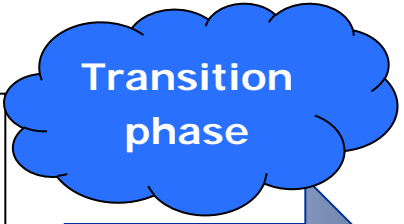
Plasma derived pharmaceuticals

15<sup>th</sup> July 2019

15<sup>th</sup> July 2022



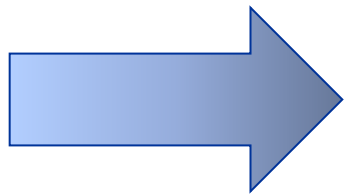
**1<sup>st</sup> July 2017:**  
EU assessment of  
FDA (human)



## Signature

**1<sup>st</sup> November 2017**  
- Entry into force  
- 8 MSs recognized

**15<sup>th</sup> July 2019**  
- All EU MS recognized  
- Batch testing  
- Decision on Vets



**15<sup>th</sup> July 2022**  
- Broaden scope (products)





## Conclusions

EMA role has been long standing and seeking solutions. Support the work of ESA, EC and Member States and OECD.

- Attending and participating in EU Observatory Meetings and OECD HLG Meetings.

EU national competent authorities want to minimise the risk of delay of approvals of variations supporting conversion from HEU to LEU:

- As majority of radiopharmaceuticals in EU are non-centrally authorised, very important for MAH's to involve and inform the national competent authorities, CMDh and EMA for CAP's about plans. Formal scientific advice may be sought.
- A work-sharing procedure is highly preferable to manage this change to warrant a higher level of evaluation and to avoid waste of time/resources among EU agencies and MAH's.
- Manufacturers and MAH's should have identified products that will be switched from HEU and working out appropriate regulatory strategies and timetables to ensure continuity of supply and prevent shortages.

Recent MRA covering GMP inspection contributes to the favourable regulatory environment<sup>9</sup> for radiopharmaceuticals.



## Acknowledgements

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- Dr. Silvy Dias Da Rocha @ EMA
- Dr. Ruben Pita @ EMA
- CMDh secretariat @ EMA



# Thank you for your attention

## Further information

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## Supporting Slides

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## Post-authorisation procedures to existing Marketing Authorisations.

### Single “reference” authority

- **CAP/ MR/DC/Purely National:** Co-ordination by EMA
- EMA Guidelines:  
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000026.jsp&mid=WC0b01ac0580023b14](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000026.jsp&mid=WC0b01ac0580023b14)
- **MR/DC/Purely National:** Reference authority chosen by CMDh (reg. 712/2012/EC amending reg. 123/2008).
- CMDh Best practice guides available : <http://www.hma.eu/96.html>



## Post-authorisation procedures to existing Marketing Authorisations.

### Variations (Commission Regulation (EC) No 1234/2008)

#### Worksharing

“..to avoid duplication of work in the evaluation of variations to the terms of several marketing authorisations, ... one authority, chosen amongst the competent authorities of the Member States and the Agency, should examine the variation on behalf of the other concerned authorities”.

#### Grouping

“Grouping of variations ..., in order to facilitate the review of the variations and reduce the administrative burden. Grouping of variations to the terms of several marketing authorisations from the same marketing authorisation holder should be allowed only insofar as all concerned marketing authorisations are affected by the exact same group of variations”



## Basic Overview of EU regulatory system - Glossary

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MRP – Mutual Recognition Procedure

MRA - Mutual Recognition Agreement

DC – Decentralised Procedure

CAP – Centrally Authorised Product

CMDh - The Co-ordination group for Mutual recognition and Decentralised procedures – human

NCA – National Competent Authority

Ph. Eur. – European Pharmacopeia

EDQM – European Directorate for Quality of Medicines



## Links to guidance

- Guideline on the ASMF procedure (CHMP/QWP/227/02/Rev3/Corr)

[http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500129994](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500129994)

- Additional guidance on documents relating to an active substance master file

[http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500133204](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500133204)

- CMD Q&As on the ASMF procedure + Q3.4 of the CMD Q&A on Variations (concerning ASMF updates)

<http://www.hma.eu/306.html>

- EMA Q&As on the ASMF procedure

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000020.jsp&mid=WC0b01ac0580022713](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000020.jsp&mid=WC0b01ac0580022713)

- The ASMF assessment worksharing procedure

<http://www.hma.eu/306.html>

- Training material on the ASMF assessment worksharing procedure

<http://www.hma.eu/306.html>

- CMD Q&As on the ASMF assessment worksharing procedure

<http://www.hma.eu/306.html>