



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

UPDATE ON THE GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

DDL2017 6-8 December 2017

Presented by Claudia Vincenzi on 7 December 2017
Quality Office EMA



The Aerosol Society

An agency of the European Union





Disclaimer

The views presented are those of the individual and may not be understood or quoted as being made on behalf of the European Medicines Agency (EMA) or reflecting the position of EMA or one of its committees or working parties.

Please refer to legal texts and published guidance for decision making purposes.

These PowerPoint slides are copyright of the European Medicines Agency. Reproduction is permitted provided the source is acknowledged.

Overview of the presentation

- Background information
 - Overarching inhalation guidelines
 - Demonstration of equivalence for inhalation products
- Behind the scenes:
 - Concept paper (CP) on the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products – *why?*
 - Comments overview
 - The drafting group
 - Quality topics covered in recent Scientific Advices and Business Pipeline meetings for inhalation products
 - Devices in Inhalation products
- What's next / Conclusion





Overarching Inhalation Guidelines

GUIDELINE ON THE PHARMACEUTICAL QUALITY OF INHALATION AND NASAL PRODUCTS

- “Guideline on Pharmaceutical Quality of Inhalation and Nasal Products”
EMA/CHMP/QWP/49313/2005 Corr (*OIP CMC GL*)
 - Expected quality aspects of drug products to be marketed
 - Developed in collaboration with Health Canada and adopted by Therapeutic Goods Administration
- “Guideline On The Requirements For Clinical Documentation For Orally Inhaled Products...” CPMP/EWP/4151/00 Rev. 1 (*OIP equivalence GL*)
 - Multidisciplinary guideline on:
 - Clinical documentation including establishment of **therapeutic equivalence** of two orally inhaled products (“generic products”)
 - Revised GL: equivalence only

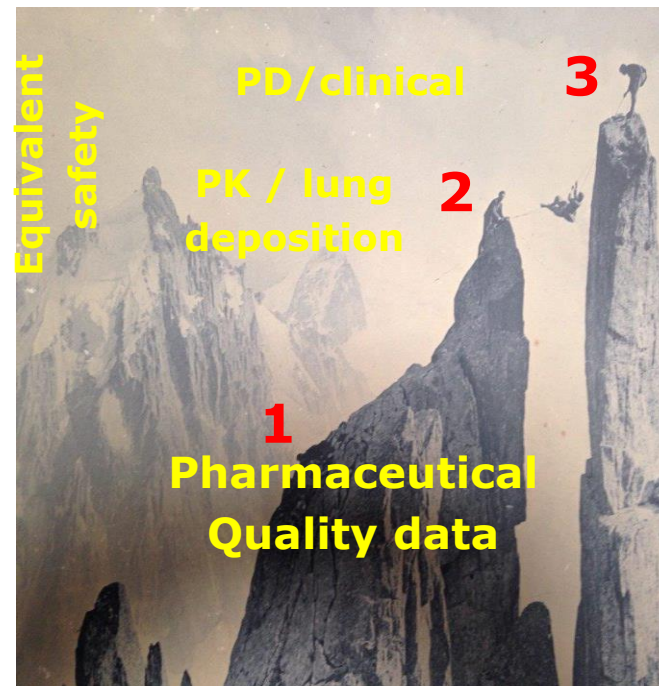
GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS

Written to complement each other

- Q&A on EMA website Quality of medicines questions and answers: Part 2 > Specific type of products > OIP

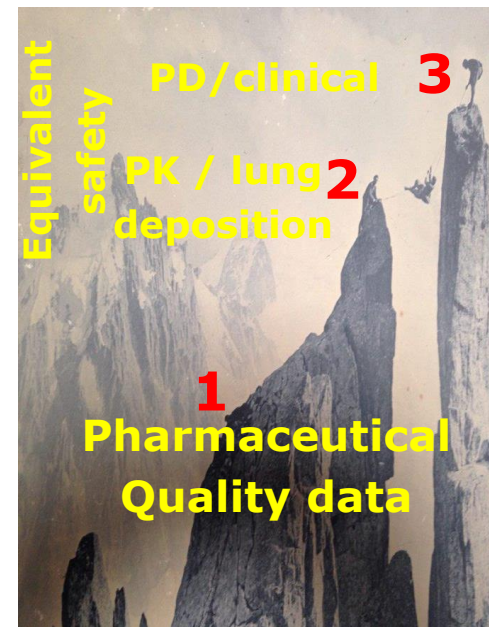
'Generic' inhalation products in EU

- Hybrid applications Article 10(3)
 - Bioequivalence cannot be demonstrated through bioavailability studies
- Abridged application: Complete quality data (Module 3), appropriate preclinical (Module 4) and clinical data (Module 5)
- Demonstration of equivalence to inhaled reference product in EU:
 - Stepwise approach
 - In-vitro only (step 1) is possible (but not easy)



Quality (in-vitro) data to support

- Demonstration of therapeutic equivalence:
 - Aerodynamic particle size distribution (APSD) comparison
 - Stage grouping justification
- In vivo studies:
 - Choice of representative batches
 - Dose proportionality (strength waiver in PK studies)
 - Airflow resistance (waiver of patients vs volunteers)



CP on the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products – *why?*

- Driven by the need to clarify aspects related to the establishment of therapeutic equivalence based on pharmaceutical data (step 1).
 - Changes to the guideline on therapeutic equivalence will have impact on the quality guideline
 - Experience gained since 2009
- Both guidelines are under parallel revision
- Opportunity to align the requirements for orally inhaled product
 - *The main focus of the revision will be on the inhalation part*



CP on the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products – *why?*

Since 2006 a lot of experience has been gained with regard to:

- New actives combinations
- New chemical entities

Additionally:

- Advances in inhalation technologies:
 - Better drug delivery characteristics
 - Addition of dose counter/indicator



Timeline CP on the Guideline on Pharmaceutical Quality of Inhalation and Nasal Products

- Released for consultation on 01/04/2017
- Deadline for comments 30/06/2017
- Draft guideline, when published, 3 months consultation period
- Same timeline as OIP equivalence GL



CP Proposal & comments received - comments are in light blue -

All CP proposals well received and supported:

1. Topics identified in the CP for Equivalence OIP GL
 - a. Requirements for dose proportionality
 - b. Flow-rate dependency
 - c. Stage grouping
 - d. Data for an inhalation spray together with a spacer/holding chamber
2. Use new abbreviated methods for determination of aerodynamic particle size distribution.
 - Welcome but contradictory recommendations from stakeholders on its suitability for QC release and level of detail to be provided.
 - Requirement of alignment with Ph. Eur. highlighted.

Most comments are supportive of additional granularity/details on requirements for these quality aspects. However, for stage grouping a comment requested to not include more specific details





CP Proposal & comments received

3. One test for intra- and inter-device variability for delivered dose uniformity in the finished product specification.
 - Welcome; need for alignment with Ph.Eur.
4. Justification of standard manufacturing process for OIP.
 - Fully supported, should be risk based and the guideline should highlight the requirements.
5. Evaluating essential requirements for CE marked and non-CE marked devices.
 - Generally, highly supported, however as *"it may be premature as supporting guidance to the essential requirements may be update in line with Medical Device Regulation"*.

CP Proposal & comments received

6. Updating of relevant parts to reflect the concepts of ICH Q8/Q9/Q10.

- Supported.
- *"The Development process for all OINDPs should start by first identifying the user's capabilities in the form of a Design Space (e.g. breathing studies/models for MDIs, pMDIs and DPIs, and hand ergonomic studies for nasal sprays) or set of Design Spaces as applicable".*

7. Include a chapter on lifecycle management.

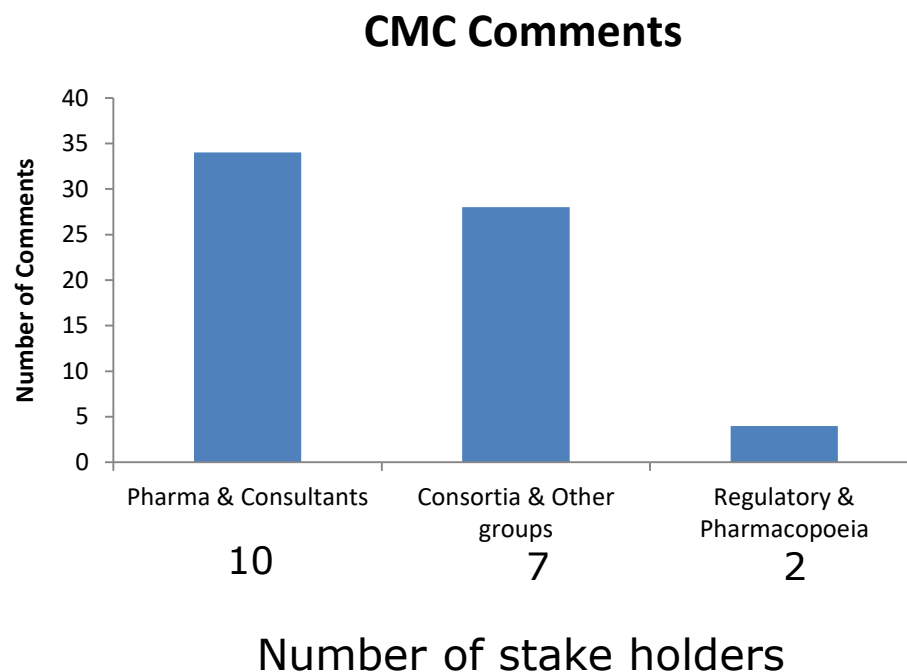
- Supported. Case studies welcome.

8. Inclusion of requirements in published Q&A, such as robustness test after dropping of an inhalation device and an acceptable range of fine particle dose (FPD) in the finished drug product specification.

- Supported. Many comments received on devices (see following slides). Several recommendations given for specification; inconsistency of assessment highlighted.

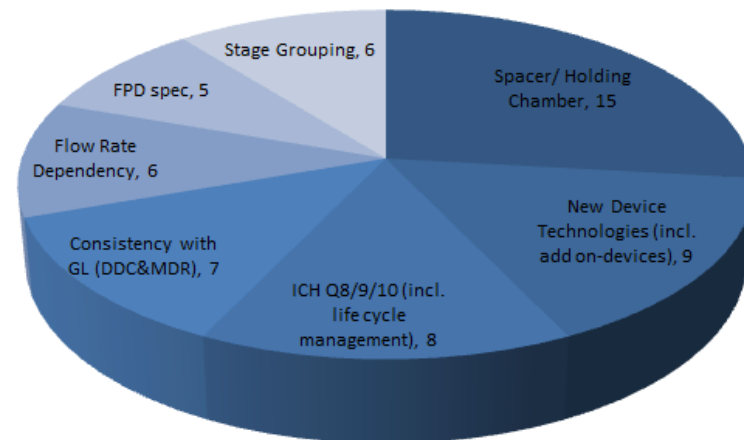
Stakeholders and number of comments

- From industry/consultants, regulatory, consortia and other groups, agencies and EDQM
- 70 comments (with several sub-bullets, effectively over 100 comments)
 - Of which 20 on topics shared with multidisciplinary GL
- Additional 36 comments, referencing quality aspects of OINDP, submitted for equivalence OIP GL and for drug device combination GL (DDC GL)



Common topics also shared with OIP Equivalence and DDC GL

Key Word	Number of Comments	OIP CMC	Equivalence OIP	DDC
Spacer/ Holding Chamber	15	6	5	4
New Device Technologies (incl. add on-devices)	9	6	1	2
ICH Q8/9/10 (incl. life cycle management)	8	8	0	0
Consistency with GL (DDC&MDR)	7	3	2	2
Flow Rate Dependency	6	3	3	0
FPD spec	5	4	1	0
Stage Grouping	6	3	3	0
Data in eCTD document	4	2	0	2



Overview of comments received CP OIP CMC

Device related topics

- Data requirements for spacer and holding chamber
- Consistency with OIP equivalence GL, DDC GL & Medical Device Regulation (MDR)
 - Greater details of requirements in OIP GL; difficulty of alignment with MDR as it will come into force in 2020
- Comments on devices, especially focus on e-connective and add-on devices
 - Need for guidance
- Align patient handling studies with current practice (i.e. human factors)



Overview of comments received

Example of **additional** comments:

- **Statistical** approach to use for quality data
- **Step 1** demonstration of equivalence:
 - *"Should be maintained as supported by literature"* (association)
 - *"Should not be maintained as supported by literature"* (innovator)
- Harmonisation with FDA **eCTD location** and **DDC requirements**
 - But not with demonstration of equivalence
- Consultation period should be **6 months**
- Collaboration with **Health Canada** (Consortium, Regulatory body)

The drafting group



Diana Riet-Nales (NL)
DDC GL DG



Anna Hillgren
(SE –chair–)



Joseph Lim
(UK)



Cornelia
Nopitsch-Mai
(DE) Inhalanda
Working Party
-Ph.Eur.-



Jan Joseph
(AT)



Claudia Vincenzi
(EMA)



Ian Dobson
(HC)



Christopher
Crane (TGA)
Observer



Meetings

TCs are planned monthly, focus either on quality or equivalence

The equivalence TCs are generally joint with the Respiratory drafting Group (responsible for the clinical GLs but also for the equivalence GLs).



On going quality discussions

Equivalence/ Quality

- Stage grouping
- Flow rate dependency
- Dose proportionality/linearity
- Equivalence acceptance limits
- Devices and spacers
 - Handling of devices and human factors
- In-vitro in-vivo correlation

Quality

- Extractables/leachables
- Devices and spacers
- Dissolution test
- Intra- and inter-device variability for delivered dose uniformity
- CQA for inhalation products
- Information in the product information



Quality topics covered in recent Scientific Advices and Business Pipeline meetings for inhalation products

- In vitro bioequivalence for lifecycle management 
- Extractable and leachables 
- Add on devices and e-connective apps
- CE – marking and new requirements as mandated by new Medical Device Regulation

Devices in Inhalation Products

- Need for:
 - Clear requirements for devices used in inhalation product (integral –regulated under the Medicinal Products Directive 2001/83/EC- and non-integral, regulated under the Medical Device Directive)
 - Requirements of new technology (e.g. add on-devices and apps) should be included
- Need for alignment with:
 - CP on DDC

"Developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product"

 - End of consultation May 2017
 - In EU no legal definition of 'drug device combination' as per FDA
 - New Medical Device Regulation: coming into force May 2020
 - E.g. New classification 'rules'



Devices in Inhalation Products: Proposed amendment to Medicinal Products Directive 2001/83/EE - Article 117

In Annex I of Directive 2001/83/EC, point 12 of Section 3.2. is replaced by the following:

‘(12) Where a product is governed by this Directive in accordance with the second subparagraph of Article 1(4) or the second subparagraph of Article 1(5) of Regulation (EU) [.../...] on medical devices, **the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements of Annex I** of that Regulation contained in the manufacturer’s EU declaration of conformity **or** the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

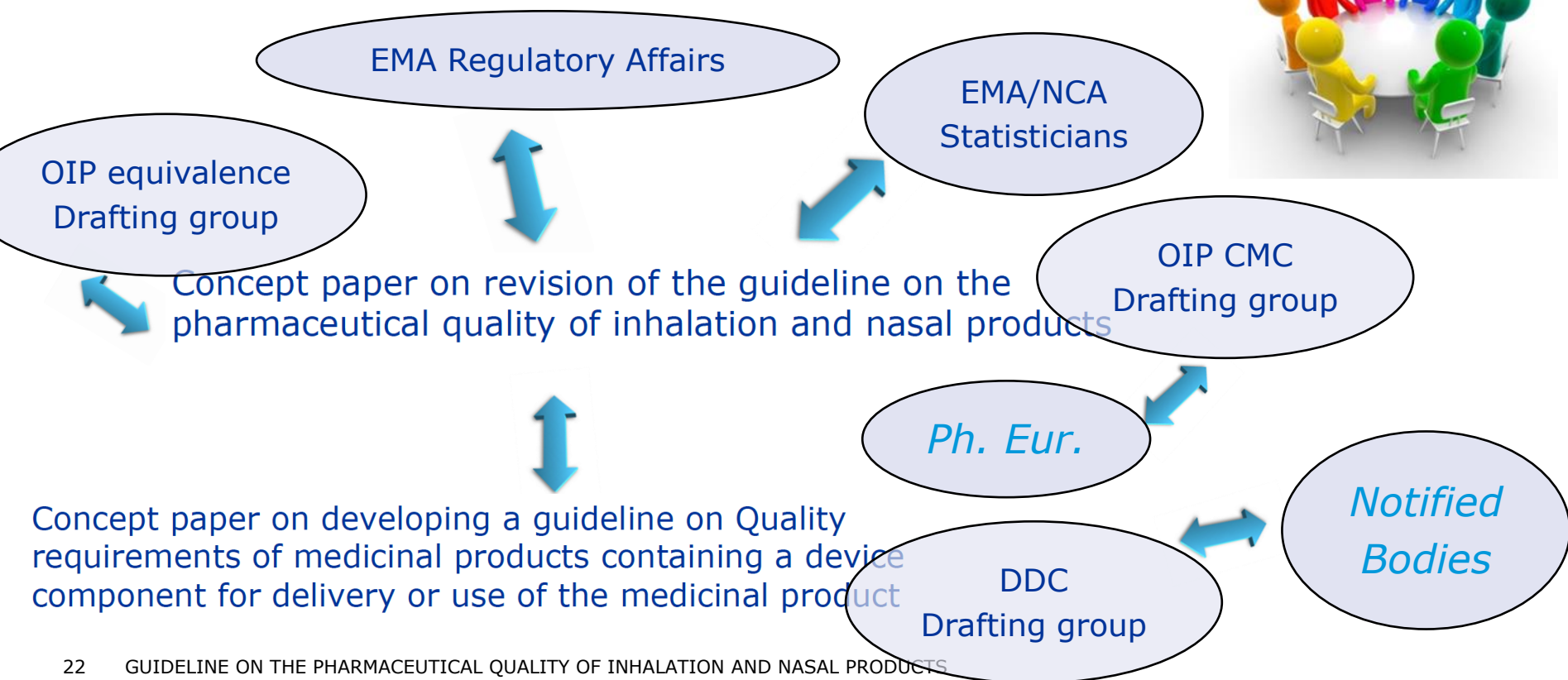
INTEGRAL AND
NOT INTEGRAL DEVICES

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) [.../...], **the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements of Annex I of that Regulation issued by a notified body** designated in accordance with that Regulation for the type of device in question, ~~unless the authority is advised by its experts for medical devices that involvement of a notified body is not required.~~

INTEGRAL
DEVICES ONLY

What exactly should be provided?

What's next? Holistic multidisciplinary approach



Conclusions

- Comments received for the CP have confirmed the need for update of the 2006 OIP CMC GL.
- The proposed topics of the update have been supported.
- All additional comments will be given due consideration.
- Alignment efforts are in place at EMA to ensure consistency with DDC GL and MDR.
- The GL is being updated in parallel with the equivalence OIP 2009 GL to reflect the current standards and to provide a transparent approach on expectations not yet described.



Acknowledgements

Armin Ritzhaupt (EMA)

Joseph Lim (MHRA)

Anna Hillgren (MPA)

Cornelia Nopitsch-Mai (BfArM)

Patrick O'Dwyer (PEARRL project PhD student)





Any questions?

Further information

Claudia Vincenzi

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

Follow us on  **@EMA_News**



Back-up slides



Medical device

Any instrument, apparatus, appliance, material, software, or other article [...], alone or in combination, intended by the manufacturer to be used in humans for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
 - diagnosis, monitoring, treatment, alleviation of or compensation for an injury/handicap
 - investigation, replacement, modification of the anatomy; control of conception
- and which does **not achieve its principal intended action** in or on the human body **by pharmacological, immunological or metabolic means**, but which **may be assisted in its function** by such means.

Medical Devices Directive 93/42/EEC as amended:

- safety and performance
- manufacturer responsible for affixing CE mark
- involvement of notified bodies depending on risk classification
- European wide market access

Medicinal product with integral device

Medical Devices Directive 93/42/EEC as amended, Article 1, (3):

"Where a device is intended to administer a medicinal product within the meaning of Article 1 of Directive 2001/83/EC (1), that device shall be governed by this Directive, without prejudice to the provisions of Directive 2001/83/EC with regard to the medicinal product.

*If, however, such a device is placed on the market in such a way that the device and the medicinal product form **a single integral product** which is intended **exclusively for use in the given combination** and which is **not reusable**, that single product shall be governed by Directive 2001/83/EC. The **relevant essential requirements of Annex I** to this Directive **shall apply as far as safety and performance-related device features are concerned.**"*

- No text contained in Directive 2001/83/EC;
- No details on what is expected and how the assessment to Annex I of MDD should be conducted



Gap in legislation



Medicinal product

Any substance or combination of substances:

- having properties for treating or preventing disease in human beings or;
 - may be used in or administered to human beings with view to restore, correct, modify physiological function
- by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Medicinal Products Directive 2001/83/EEC as amended

- quality, safety and efficacy
- authorisation required for each member state