

New legislation impacting IMP QPs

Presentation from dr. Susanne Ding, QP IMP working group



Legislation impacting IMP QPs: look forward and backwards

- Definitions
- New & upcoming guidance
- Selected guidance – and the impact for the IMP QP
- Other topics – within and outside the EU

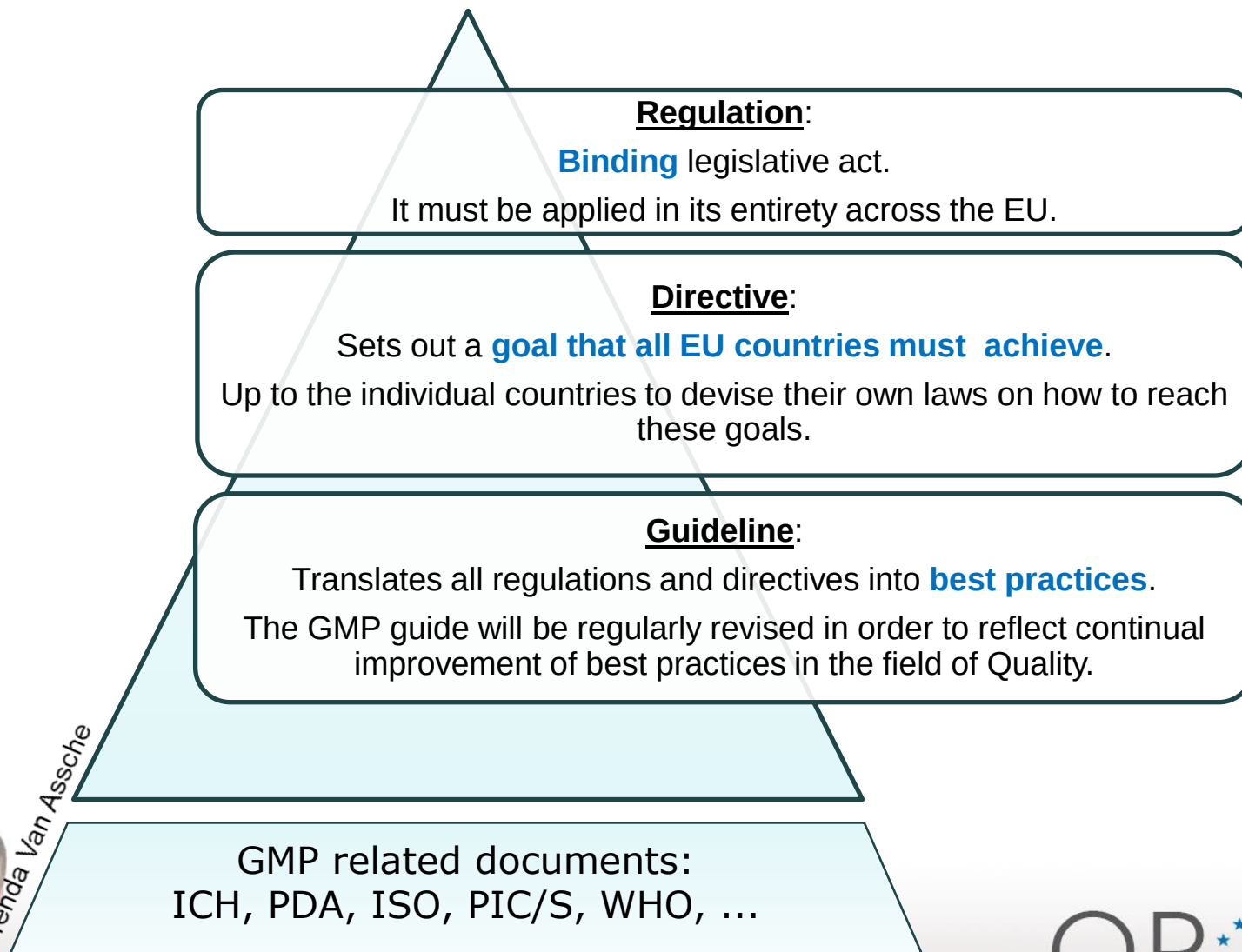


Acknowledgement

2017 Presentation from Susanne Ding,
IMP Pre-conference 2017, Budapest
Design & ideas from Brenda's slide deck
IMP Pre-conference 2016, Madrid



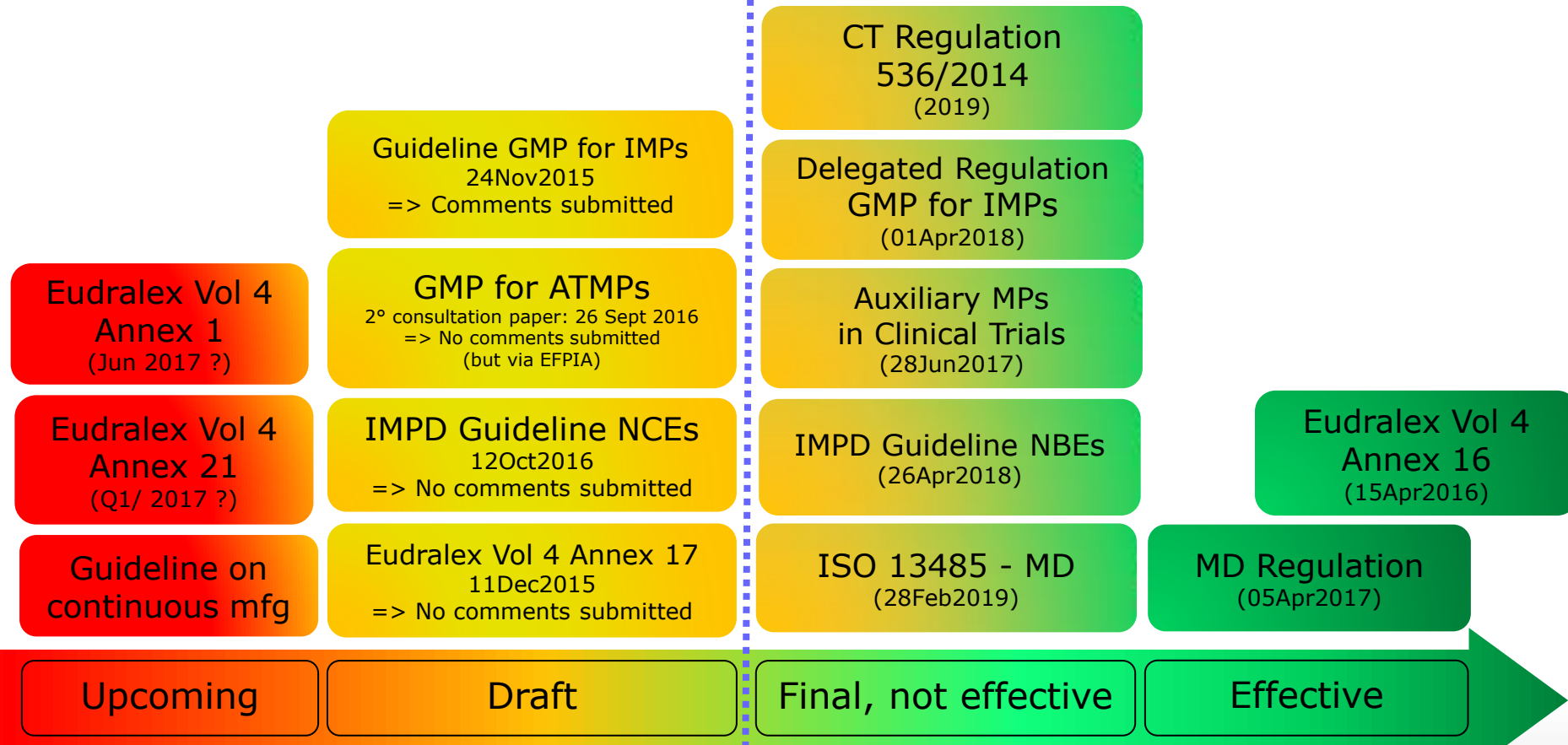
Definitions



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New and upcoming legislation

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Annex 16

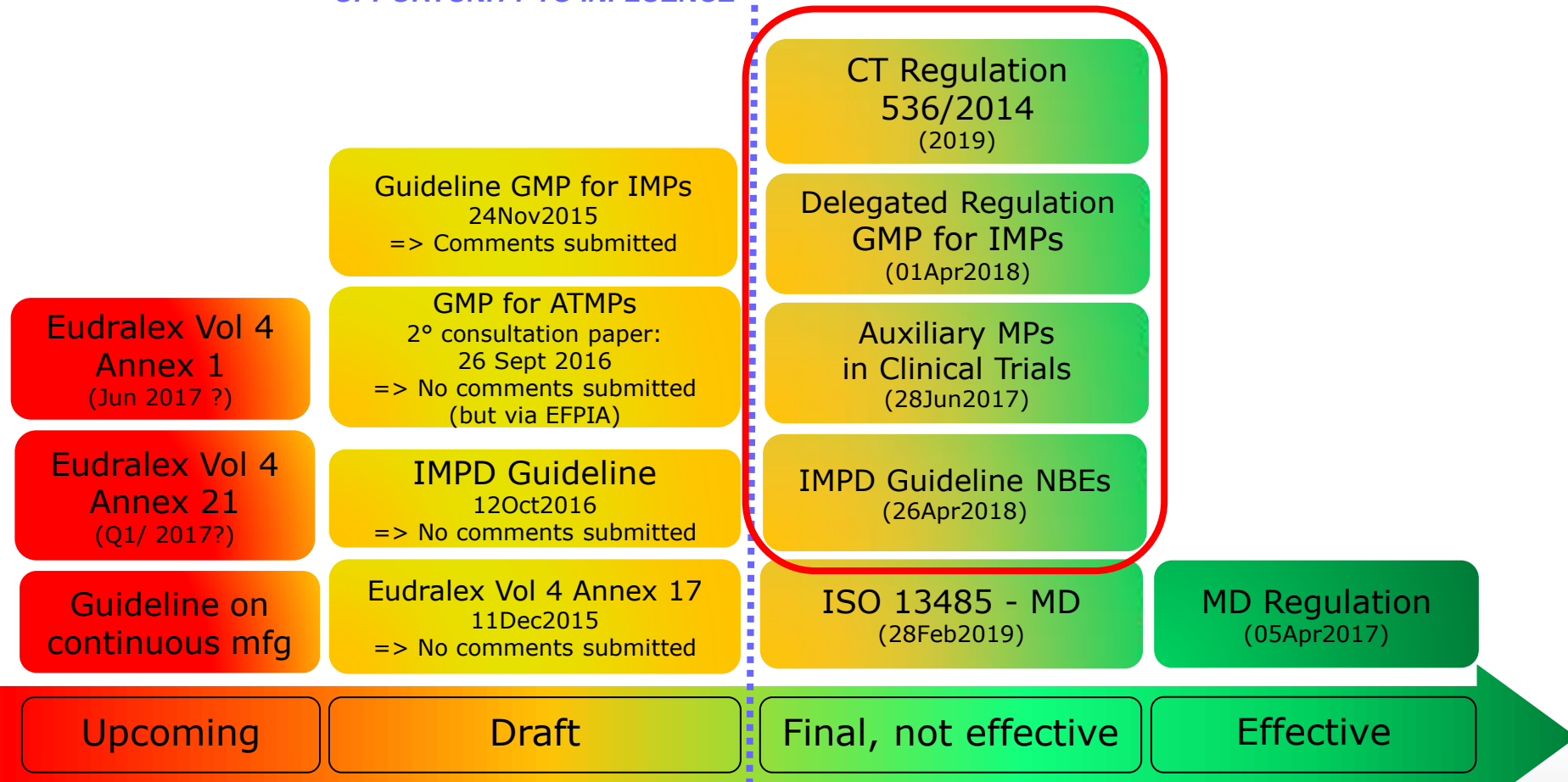
■ Annex 16 QP Certification and Batch Release – Frequently Asked Questions – part 2

Alan Moon and Trevor Watson on 14 Aug 2017
application of Annex 16 to IMPs



New and upcoming legislation

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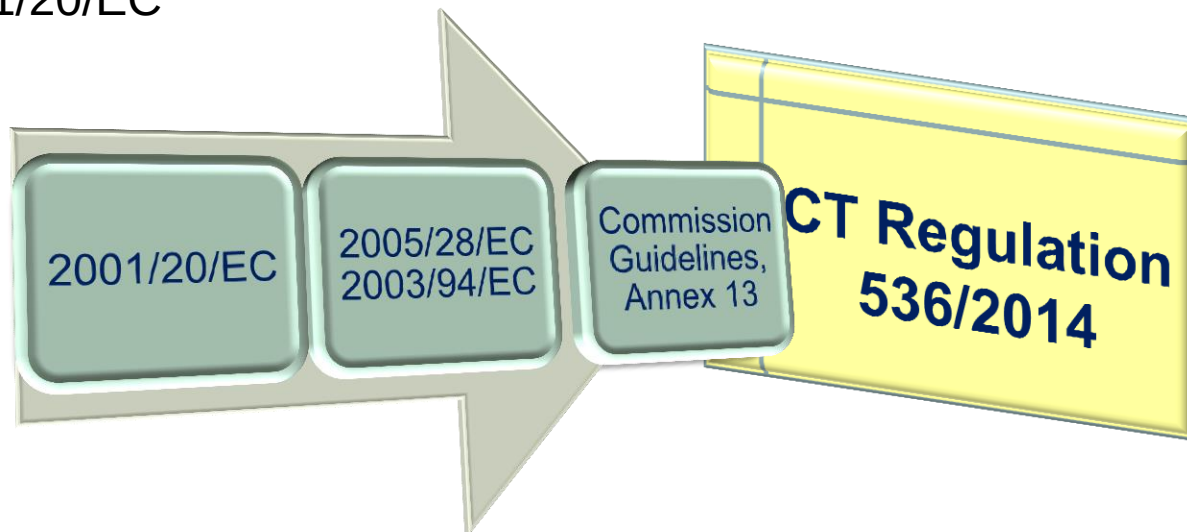


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Clinical Trial Regulation

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT
AND OF THE COUNCIL of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Dir
2001/20/EC



Entry into application
postponed to
2019

[EMA Management Board Oct 2017](#)



Delegated Regulation – GMP for IMPs

Commission Delegated Regulation
(EU) 2017 /1569 of 23 May 2017
supplementing Regulation (EU) No
536/2014 of the European Parliament and of
the Council

by specifying principles of
and guidelines for good
manufacturing practice for
investigational medicinal
products for human use
and arrangements for
inspections

published 16 Sep 2017
Entry into application 01 Apr

2019
together
with CT
Reg



laying down the
principles and
guidelines of good
manufacturing
practice in respect of
medicinal
products for human
use and
investigational
medicinal products
for human use

- 

1

Delegated Regulation – GMP for IMPs

- Chapter I - General Provisions
- Chapter II - Good Manufacturing Practice
 - Art 3 Conformity with GMP*
 - Art 4 Compliance with clinical trial authorisation*
 - Art 5 Pharmaceutical quality system*
 - Art 6 Personnel*
 - Art 7 Premises and equipment*
 - Art 8 Documentation*
 - Art 9 Production*
 - Art.10 Quality control*
 - Art 11 Retention samples used for quality control*
 - Art 12 Responsibilities of the Qualified Person*
 - Art 13 Outsourced operations*
 - Art 14 Complaints, product recall and emergency unblinding*
 - Art 15 Self-inspection by the manufacturer*
 - Art 16 Advanced therapy investigational medicinal products*



Delegated Regulation – GMP for IMPs

■ Chapter III - Inspections

- Art 17 Supervision by inspection*
- Art 18 Cooperation and coordination of inspections*
- Art 19 Recognition of inspection conclusions*
- Art 20 Empowerments of the inspectors*
- Art 21 Competence and obligations of the inspectors*
- Art 22 Quality system*
- Art 23 Impartiality of inspectors*
- Art 24 Access to premises*
- Art 25 Suspension or revocation of manufacturing authorisation*

■ Chapter IV - Final Provisions

- Art 26 Transitional provision*
- Art 27 Entry into force*



Delegated Regulation – GMP for IMPs

- Major changes compared to former IMP GMP
 - **QP register** at the disposal of the competent authority min. 5 years after completion / formal discontinuation of the last clinical trial in which the product batch was used
 - Clear delineation of responsibilities between **manufacturer / sponsor**



Delegated Regulation – GMP for IMPs

- Major changes compared to former IMP GMP
 - **IMPD compliance**
regular review of manufacturing records – scientific & technical progress + experience gained by the sponsor
 - **Pharmaceutical Quality System**
 - Documentation → **data integrity**



Delegated Regulation – GMP for IMPs

- Major changes compared to former IMP GMP

- **New Chapter III Inspections**

→ supervision, cooperation & coordination, recognition of inspections conclusions, empowerments of the inspectors, ..., access to premises, suspension or revocation of manufacturing authorisation.

→ **third country manufacturers** based on an assessment of risk, at least if the Member States have grounds for suspecting that the quality standards ... are lower ...



Auxiliary MPs in Clinical Trials

- Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

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IMPD guideline biological IMPs



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2017
EMA/CHMP/BWP/534898/2008 rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials



Document history

Revision 1
In progress

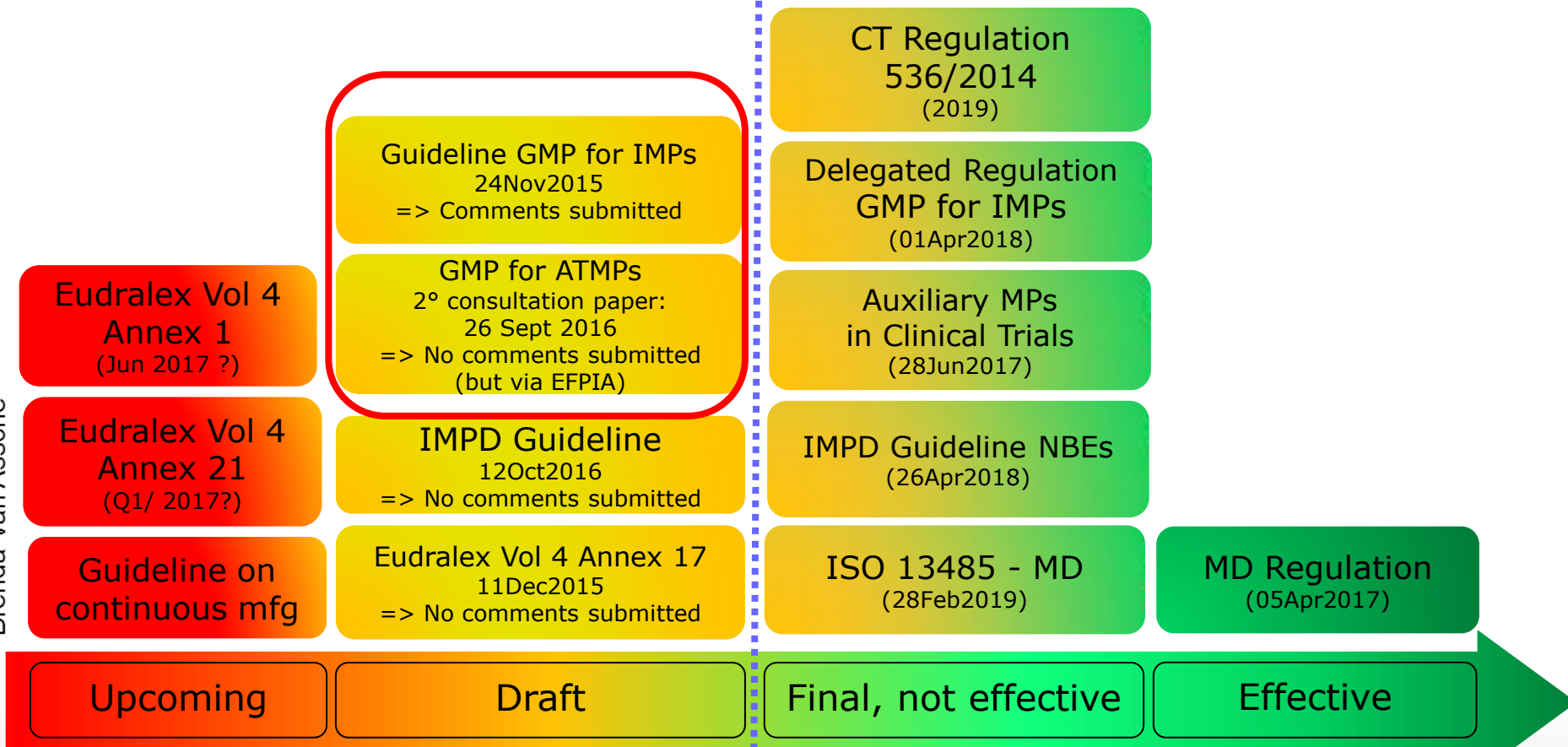


Adopted guideline

Published: 26/10/2017
Effective from: 26/04/2018

New and upcoming legislation

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Detailed Commission Guidelines on GMP for IMPs for human use

Detailed Commission
guidelines on good
manufacturing practice for
investigational medicinal
products for human use,
pursuant to the second subparagraph of
Article 63(1) of Regulation (EU) No
536/2014

Consultation document, issued 28 Aug
2015



EC Guidelines to
Good Manufacturing
Practice

Investigational
Medicinal Products



Detailed Commission Guidelines on GMP for IMPs for human use

Consultation document EC

- Comments submitted, no further activities observed
- Synopsis available (Annex 13 vs. consultation document EC)

Annex 13, EudraLex Vol 4, link 1	Detailed Commission guidelines on GMP for IMPs for human use, link 2
PRINCIPLE Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). Other guidelines published by the European Commission should be taken into account where relevant and as appropriate to the stage of development of the product.	2.1. Introduction These guidelines are based on the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014. These guidelines complement the Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products for human use referred to in the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014. These guidelines lay down appropriate tools to address specific issues concerning investigational medicinal products with regard to good manufacturing practice. Article 63(1) of Regulation (EU) No 536/2014 provides that investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ("good manufacturing practice"). Good manufacturing practice for investigational medicinal products is set out in the Delegated Act referred to in the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014 and in these guidelines. [The Delegated Act and these guidelines are developed in parallel]. Furthermore, where applicable, the manufacturers and the competent authorities should also take into account the detailed guidelines referred to in the second paragraph of Article 47 of Directive 2001/83/EC, published by the Commission in the "Guide to good manufacturing practice for medicinal products and for investigational medicinal products" (EudraLex, Volume 4). Examples of applicable parts of EudraLex, Volume 4 to investigational medicinal products, not specifically mentioned in these guidelines, are Part 1, Chapters 1, 4 and 6.
Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.	66 Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.
68 In clinical trials there may be added risk to ~~participating~~ subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or	68 In clinical trials there may be added risk to the subjects compared to patients treated with ~~subjected~~ medicinal products. The application of GMP for the manufacture of investigational medicinal products is intended to ensure that subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate ~~qual~~ or



Detailed Commission Guidelines on GMP for IMPs for human use

Consultation document EC

Upcoming guidance to be added to EudraLex upon deletion of Annex 13
(discussed at EMA GMP/GDP Inspectors Working Group Meeting, Sep 2017, source ZLG)

- *Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice (draft)*
→ EudraLex 10
- *Batch Certificate Template for IMPs (draft)*
→ EudraLex 4



GMP for ATMPs

GMP for ATMPs
2° consultation paper:
26 Sept 2016
=> No comments submitted
(but via EFPIA)

- Lecture & discussion Christina Meissner, AGES at IMP Pre-conference 2016 in Madrid
- Intensive discussion between PIC/S and Commission
- Multi-stakeholder workshop hosted by EMA, 27 May 2017
- Representation in ATIMP network via EQPA Task Force within ATMP Interest Group ECA
- Current status on ATIMPs → separate presentation

EudraLex - Volume 4

Issued 22 Nov 2017

Part IV - GMP requirements for Advanced Therapy Medicinal Products

- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products 



Qualified Persons in Europe

Others

Falsified Medicine Directive out of scope for IMPs

- It will effect handling of comparators – how to book out ?
→ *Still under evaluation*

ICH M7 (R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, July 2017

- Application of the principles of the ICH M7 guideline to calculation of compound-specific acceptable intakes (→ list included)



Cross-contamination

Q&A EMA Dec 2016



Questions and answers on implementation of risk based prevention of cross contamination in production and
'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'

(EMA/CHMP/CVMP/SWP/169430/2012)



Data integrity

Q&A EMA Aug 2016



- by GMP/GDP Inspectors Working Group
- 23 questions related to data integrity
 - paper-based & electronic systems
 - how to assess risks to data integrity
 - data lifecycle and various stages of risk management measures
 - responsibilities – outsourced activities



MRA between EU and USA

[source: MRA article - pink sheet](#)



[MRAs – EMA website](#)



EU-US REGULATORS AGREE ON MUTUAL RECOGNITION OF DRUG INSPECTIONS

Source: Shutterstock

- However, no direct impact on IMP topics
- Out of scope: blood products, human plasma, human tissue and human organs, immunological veterinary products, ATMPs
- Croatia, France, Italy, Malta, Spain, Austria, Sweden, UK (Nov 2017)



Qualified Persons in Europe

GCP Interface

- EMA Draft Guidance – [Trial Master File](#)
31 Mar 2017
- ICH E6 [Guideline for Good Clinical Practice](#), Addendum 2
09 Nov 2016

[presentation ICH E6 expert group](#)



Brexit (1)

EMA board meeting June 2017



Source: EU-Kommission,
Wikipedia, UK, Public Domain

- EMA: “UK to become a 3rd country as of 30 Mar 2019”

Preparatory work is ongoing in several work streams

- Physical relocation of the agency from London
- Re-distribution of the workload
- Provision of guidance & information to pharmaceutical companies

19 offers to host EMA



- Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralized Procedure



Brexit (2)



The screenshot shows the EMA website with the following elements:

- Logo:** A blue circle containing a white stylized 'E'.
- Text:** EUROPEAN MEDICINES AGENCY, SCIENCE MEDICINES HEALTH
- Navigation Bar:** Home, Find medicine, Human regulatory (highlighted in blue), Veterinary regulatory, Committees, News & events, Partners & n
- Search for medicines:** Search our database of medicines - including human medicines, veterinary medicines and herbal medicines. Quick search (with a magnifying glass icon). Or go to the [medicines](#) section for more options to help you find what you need.
- EMA to relocate to Amsterdam:** EU Member States decide EMA's new location in three rounds of voting. Read more...
- Image:** A photograph of a canal in Amsterdam with colorful buildings and a bridge.



Summary & take home

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Eudralex Vol 4
Annex 1
(Jun 2017 ?)

Eudralex Vol 4
Annex 21
(Q1/ 2017?)

Guideline on
continuous mfg

Guideline GMP for IMPs
24Nov2015
=> Comments submitted

IMPD Guideline
12Oct2016
=> No comments submitted

Eudralex Vol 4 Annex 17
11Dec2015
=> No comments submitted

CT Regulation
536/2014
(2019)

Delegated Regulation
GMP for IMPs
(01Apr2018)

Auxiliary MPs
in Clinical Trials
(28Jun2017)

GMP for ATMPs
EudraLex 4, Part IV
(22May 2018)

IMPD Guideline NBEs
(26Apr2018)

ISO 13485 - MD
(28Feb2019)

Eudralex Vol 4
Annex 16
(15Apr2016)

MD Regulation
(05Apr2017)

Upcoming

Draft

Final, not effective

Effective

Thank you very much

