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

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Summary of presentation:

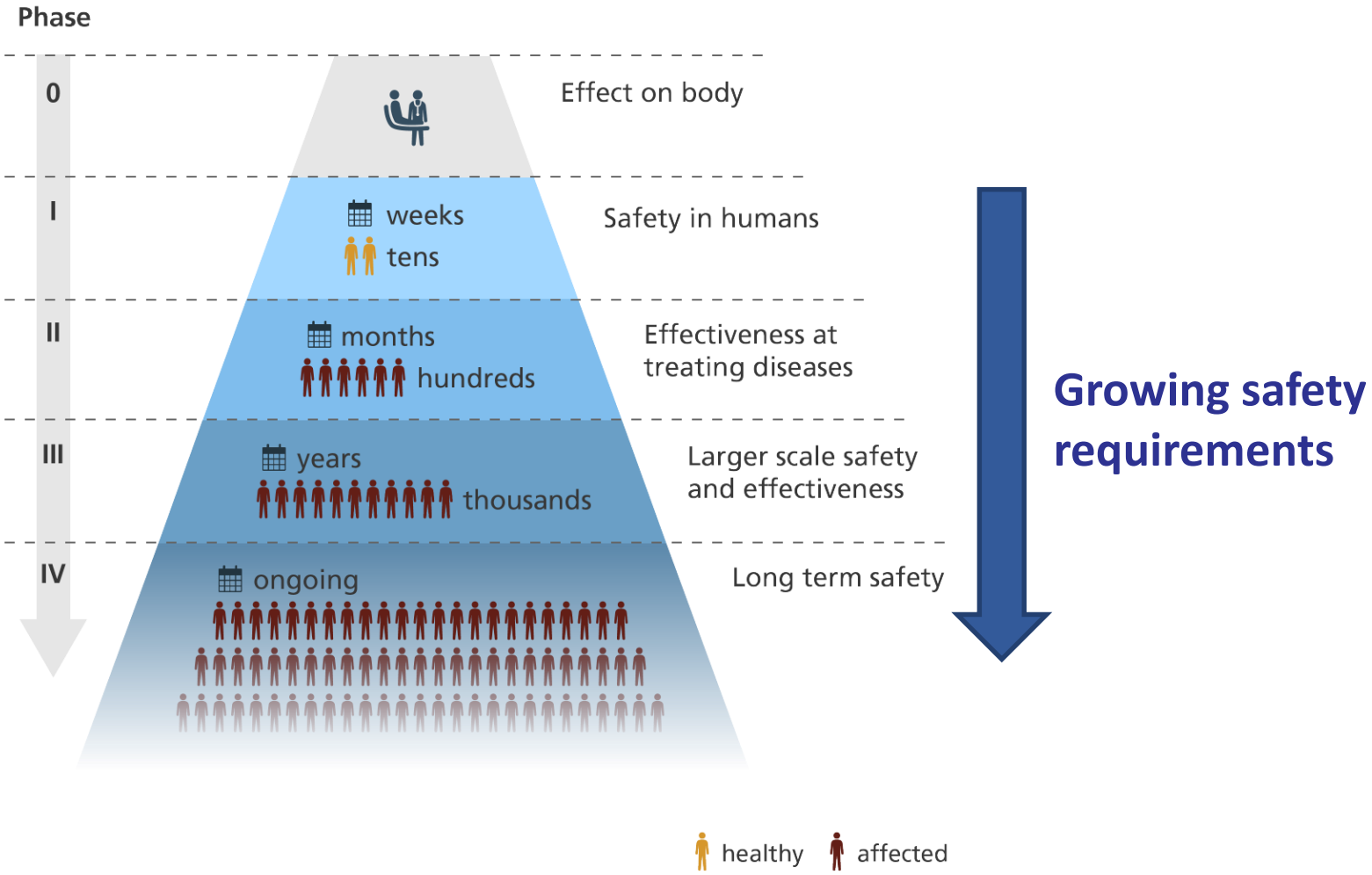
Introduction – clinical trials phases

Changes in the guideline – step by step

Harmonization in practice

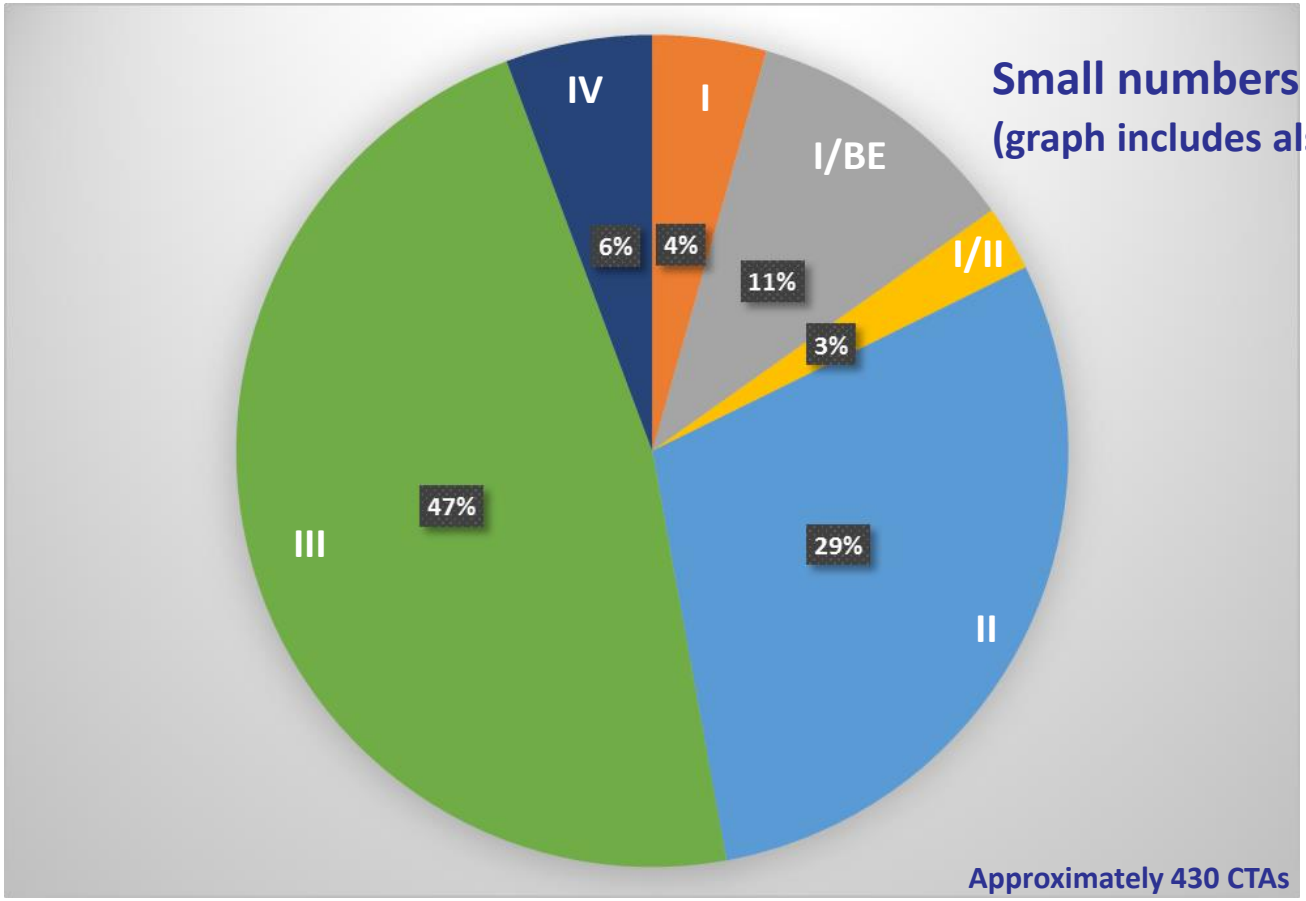
Description of clinical trials phases

- Phase I
  - first in human
  - pharmacokinetic/pharmacodynamic
  - tolerability
  - safety
  - **very low numbers of healthy volunteers**
- Phase II
  - first in patients
  - efficacy / dose
  - **small group of specific patients**
- Phase III
  - multicentric, international
  - confirmation of efficacy and safety
  - **hundreds or thousands of patients**
- Phase IV
  - post-authorisation
  - adverse effects
  - long-term use
  - drug interactions
  - **thousands of patients**



Situation in the Czech Republic

5/16 - 4/17



Small numbers of phase I and II trials
(graph includes also chemical products)

Approximately 430 CTAs

Available guidance (for different requirements)

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

  - updated

- Guideline on virus safety evaluation of biotechnological investigational medicinal products

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

For all clinical development phases, it is the responsibility of the applicant (sponsor) to ensure protection of the clinical trial subjects by using of Investigational Medicinal Product (IMP) which quality is adequate with respect to the specific phase of development and its quality attributes that may impair patients' safety are appropriately addressed.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

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

Draft Agreed by Biologics Working Party	May 2016
Adoption by Committee for Medicinal Products for Human Use for release for consultation	23 June 2016
Start of public consultation	1 July 2016
End of consultation (deadline for comments)	31 December 2016
Agreed by Biologics Working Party	14 June 2017
Adopted by Committee for Medicinal Products for Human Use	14 September 2017
Date for coming into effect	6 months after publication

Note: The revision of this Guideline was prepared by the CHMP Biologics Working Party with a mandate from the European Commission, to facilitate the implementation of Regulation (EU) No. 536/2014

Keywords	***Biological product, investigational medicinal product (IMP), clinical trial, quality***

The **Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials** has been revised

Clinical Trial Regulation EU No. 536/2014 will replace the existing EU Clinical Trial Directive (EC) No 2001/20/EC and national legislation that was put in place to implement the Directive.

The way clinical trials are conducted in the European Union (EU) will undergo a major change when the Clinical Trial Regulation comes into application in 2019. The Regulation harmonizes the assessment and supervision processes for clinical trials throughout the EU, …….

What kind of changes have been introduced and why?

Changes and implications

- Wording changed to clarify the requirements
- Wording added, removed or changed to reflect the experience with IMPDs during the last years.
- Wording changed to improve the language
- Some chapters aligned with the guideline for chemical IMPs

Scope

- GL applies to proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates).
- GL also applies to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances. The requirements depend on the type of the product (authorised / not authorised / modified / non-modified medicinal product).
- ATMPs are excluded from this guideline.

No IMPD required

- If the active substance used is already authorised in a finished product within the EU/EEA, in one of the ICH regions ~~or one of the Mutual Recognition Agreement (MRA) partner~~ countries, reference can be made to the valid marketing authorisation. A statement should be provided that the active substance has the same quality as in the approved product.
- The name of the finished product, the marketing authorisation number or its equivalent, the marketing authorisation holder and the country that granted the marketing authorisation should be given. (Reference is made to Table 1 of Regulation 536/2014)

S.2.2. Description of manufacturing process and process controls

- A flow chart of all successive steps including relevant process parameters and in-process-testing should be given. The control strategy should focus on **safety relevant IPC** and acceptance criteria for critical steps (e.g. ranges for process parameters of steps involved in virus removal) should be established for manufacture of Ph I/II material. These in-process controls (IPCs; Process parameters and in process testing as defined in ICH Q11) should be provided with action limits or preliminary acceptance criteria. For other IPCs, monitoring it might be appropriate and acceptance criteria or action limits do not need to be provided. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Reprocessing

- Any reprocessing during manufacture of the active substance (e.g. filter integrity test failure) should be described and justified. Reprocessing could be considered in exceptional circumstances. For biological products, these situations are usually restricted to certain re-filtration and re-concentration steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

Cell bank system, characterisation and testing

- Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB if used should be characterised and results of tests performed should be provided. Clonality of the cell banks should be addressed for mammalian cell lines. The generation and characterisation of the cell banks should be performed in accordance with principles of ICH Q5D.
- As for any process change, the introduction of a WCB may potentially impact the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development).

S.2.6 Manufacturing proces development – Process improvement

- Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the development phase and early phases of clinical trials. ~~These improvements and optimisations are considered as normal development work, and should be appropriately described in the submitted dossier.~~ Changes to the manufacturing process and controls should be summarized ~~and the rationale for changes should be presented~~. This description should allow a clear identification of the process versions used to produce each batch used in non-clinical and clinical studies, in order to establish an appropriate link between pre-change and post-change batches. Comparative flow charts and/or list of process changes may be used to present the process evolution. ~~Process modifications may require adaptation of in-process and release tests, and thus these tests and corresponding acceptance criteria should be reconsidered when changes are introduced.~~
- If process changes are made to steps involved in viral clearance, justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable.

Characterisation

In vitro bioassay

- Usually, prior to initiation of phase I studies, the biological activity should be determined using an ~~relevant~~ appropriate, reliable and qualified method.

S.4.1 Specification

- Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a limit of 'record' or 'report results' will not be acceptable for these quality attributes. A test for biological activity should be included unless otherwise justified. …
- Product characteristics that are not completely defined at a certain stage of development (e.g. glycosylation, charge heterogeneity) or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits.

S.4.3. Validation of analytical procedure

Information phase I/II

For phase I and II clinical trials, the suitability of the analytical methods used should be confirmed. ……

should be presented in a tabulated form. If validation studies have been undertaken for early phase trials, a tabulated summary of the results of analytical method validation studies could be provided for further assurance.

Information for phase III clinical trials

Validation of the analytical methods used for release and stability testing should be provided. A tabulated summary of the results of the validation carried out should be submitted (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). By the end of phase III full method validation must be completed, including confirmation of robustness. It is not necessary to provide a full validation report.

S.4.4. Batch analyses

- For early phase clinical trials where only a limited number of batches of active substance have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For active substances with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified. ….
- A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the Investigation Medicinal Product Dossier (IMPD) might be used.

S.5. Reference standards or materials

- If available, an international or Ph. Eur. standard should be used as primary reference material. Each in-house working standard should be qualified against this primary reference material. However, it should be noted that the use of an international or Ph. Eur. standard might be limited to certain defined test methods, e.g. biological activity. If an international or Ph. Eur. standard is not available, an in-house standard should be established during development as primary reference material. The stability of the reference material should be monitored. This can be handled within the Quality System of the company

S.7. Stability

Stability data / results

- Stability data should be presented for at least one batch made by a process representative of that used to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant development batches or batches manufactured using previous manufacturing processes should be provided, if available. Such batch data may be used in the assignment of shelf life for the active substance provided an appropriate justification of the representative quality for the clinical trial material is given.

S.7. Stability

Shelf-life determination

- The requested storage period should be based on long term, real time and real temperature stability studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material.

- The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es). However, extension of the shelf life beyond the intended duration of the long term stability studies is not acceptable.

P.3.4. Control of critical steps and intermediates

- For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable, ~~depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, it is necessary to use a pre-filtration through a bacteria-retaining filter to obtain a sufficiently low bioburden. Due to limited availability of the formulated medicinal product, a pre-/filtration volume of less than 100 ml may be tested if justified.~~
- Test volumes of less than 100 ml may be used if justified.

P.5.4.Batch analysis - same as S.4.4

- For early phase clinical trials where only a limited number of batches of active substance have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For active substances with a longer production history, it could be acceptable to provide results for only a number of representative batches, if appropriately justified. ….
- A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the Investigation Medicinal Product Dossier (IMPD) might be used.

P.7. Container closure system

- If a medical device is to be used for administration it should be stated whether the device is CE marked for its intended purpose. In the absence of a CE mark for the intended purpose, a statement of compliance with the relevant essential requirements of medical devices with regards to safety and performance related device features is required. An integral device component of a drug-device combination product, as defined in the MDD, is exempt from CE-marking.

- For products intended for parenteral use where there is potential for interaction between product and container closure system, more details may be needed (e.g. extractable /leachable studies for phase III studies).

New sections

- 3. Information on the quality of authorised, non-modified biological test and comparator products in clinical trials
- 4. Information on the quality of modified authorised biological comparator products in clinical trials
- 5. Information on the chemical and pharmaceutical quality concerning placebo products in clinical trials

- Reference to the GL for chemicals (5.)

6. Changes to the investigational medicinal product and auxiliary medicinal product with a need to request a substantial modification to the IMPD

- In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions. The following is a non-exhaustive list of modifications that are typically 'substantial' and need to be notified to the competent authorities.
- changes in the manufacturer(s) of the active substance or the medicinal product
- ….

- any extension of the shelf-life outside the agreed stability protocol or without prior commitment (see section S.7 and P.8)
- However, shelf-life extension based on the agreed protocol is typically not considered as substantial modification if:
- each additional extension of the shelf-life is not more than double, and is not more than twelve months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol.
- the extension is covered and in compliance with the approved stability protocol
- no significant trends or out-of-specification results (OoS) have been detected in ongoing stability studies at the designated storage temperature
- the applicant commits to inform Competent Authorities of unexpected stability issues in the ongoing study (including trends and OoS) and to propose corrective action as appropriate

Industry comments

5 topics selected of particular interest/ concern industry that focus on:

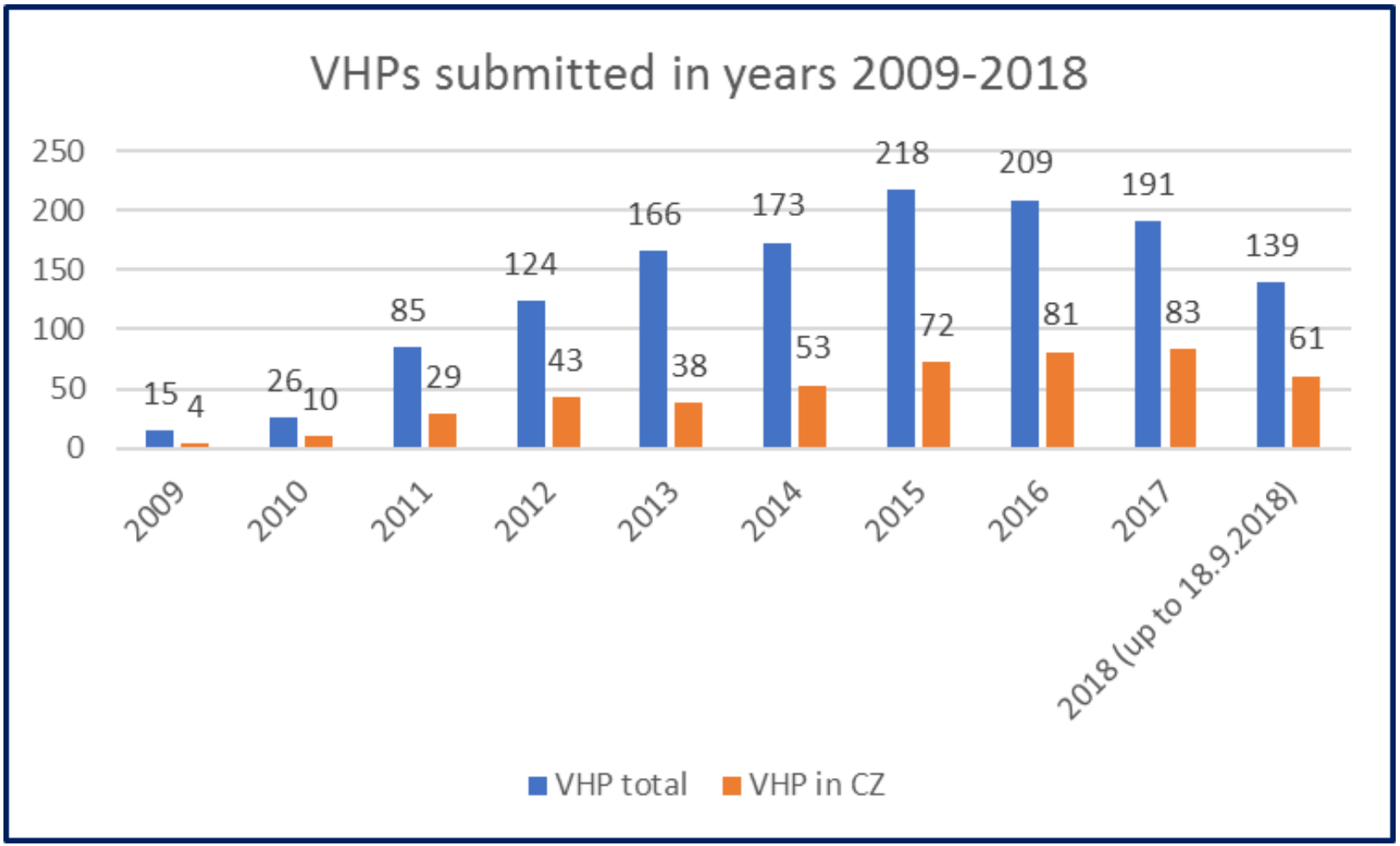
- Validation of Analytical Methods
- Drug Substance and Drug Product Manufacturing Controls
- Clonality
- Specifications
- Batch Analyses
- Use of prior knowledge / risk-based approach

Harmonization of quality requirements in practice

- Clinical trial assessors trainings / workshops
- Suitable assessment approach
  - nice-to-know and trendy questions
  - questions that are too much and should not be asked
- Prior knowledge

Harmonization in practice – VHP

- Since 2009
- Last guidance – Version 4, June 2016 (HMA website)
- The VHP comprises three phases:
  - **Phase 1**: Request for VHP and validation of the application (5 days, Sponsor has 3 days to response)
  - **Phase 2**: Assessment step: review of a CTA by the NCAs of the participating MS (Assessment Step I: D1 – D32; Sponsor has 10 days to response, Assessment Step II: D42 – D60)
  - **Phase 3**: National step, with formal CTAs to all concerned NCAs (within 20 days submission + 10 days for NCA approval)



Harmonization in practice…sometimes is difficult…

Děkuji za pozornost
Thank You for Your Attention

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