The Israel Chapter of PDA

העמותה לקידום המדע והטכנולוגיה הפרמצבטית בישראל

Hot Topics in Quality and Regulations

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For Israel Chapter of PDA

Annual Meeting

Draft version of Annex 1

Annex 1

Manufacture of Sterile Medicinal Products

Document map

Section Number	General overview
1. Scope	Additional areas (other than sterile medicinal products) where the general principles of the annex can be applied.
2. Principle	General principles as applied to the manufacture of medicinal products.
3. Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile medicinal products.
4. Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance to the qualification of personnel.
5. Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of barrier technology.
6. Equipment	General guidance on the design and operation of equipment.
7. Utilities	Guidance with regards to the special requirements of utilities such as water, air and vacuum.
8. Production and specific technologies	Discusses the approaches to be taken with regards to aseptic and terminal sterilisation processes. Also discusses different technologies such as lyophilization and Blow Fill Seal (BFS) where specific requirements may be required. Discusses approaches to sterilization of products, equipment and packaging components.
9. Viable and non-viable environmental and process monitoring	This section differs from guidance given in section 5 in that the guidance here applies to ongoing routine monitoring with regards to the setting of alert limits and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulation.
10. Quality control (QC)	Gives guidance on some of the specific Quality Control requirements relating to sterile medicinal products.
11. Glossary	Explanation of specific terminology.

EU GMPs for IMPs
01 April 2018

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

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to 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 Directive 2001/20/EC (1), and in particular Article 63(1) thereof,

Whereas:

(1) The good manufacturing practice for investigational medicinal products for human use ensures that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified. The manufacturing of investigational medicinal products presents additional challenges comparing to the manufacturing of authorised medicinal products because there are no fixed routines, there is a variety of clinical trial designs and consequently packaging designs. Those challenges are due to the need, often, of randomisation and to disguise the identity of the investigational medicinal products for the purpose of clinical trial (blinding). The toxicity, potency and sensitising potential of investigational medicinal products for human use may not be fully understood at the time of the trial, and the need to minimise all risks of cross-contamination is therefore of even greater importance than for authorised medicinal products. Because of this complexity, the manufacturing operations should be subject to a highly effective pharmaceutical quality system.

(2) Good manufacturing practice as regards both medicinal products authorised to be placed on the market and investigational medicinal products are based on the same principles. The same manufacturing sites will often manufacture both investigational and medicinal products authorised to be placed on the market. For that reason the principles and guidelines of good manufacturing practice for investigational medicinal products for human use should be aligned as much as possible with those applicable to medicinal products for human use.

(3) In accordance with Article 61(5) of Regulation (EU) No 536/2014 certain processes do not require the authorisation referred to in Article 61(1) of that Regulation. In line with Article 63(2) of Regulation (EU) No 536/2014 good manufacturing practice for investigational medicinal products does not apply to those processes.

(4) For the manufacturer to be able to comply with good manufacturing practice for investigational medicinal products, cooperation between the manufacturer and the sponsor is necessary. Likewise, for the sponsor to comply with the requirements of Regulation (EU) No 536/2014 cooperation with the manufacturer is necessary. Where the manufacturer and the sponsor are different legal entities, the obligations of the manufacturer and sponsor vis-à-vis each other should be specified in a technical agreement between them. Such an agreement should provide for the sharing of inspection reports and exchange of information on quality issues.

(5) Investigational medicinal products imported into the Union should be manufactured by applying quality standards at least equivalent to those in the Union. For this reason, only products manufactured by a third country manufacturer that is entitled or authorised to do so in accordance with the laws of the country where the manufacturer is located, should be allowed to be imported into the Union.

(6) All manufacturers should operate an effective quality assurance system of their manufacturing or import operations. Such a system in order to be effective requires the implementation of a pharmaceutical quality

(1) OJ L 158, 27.5.2014, p. 1.

EU Concept Paper on MAH responsibilities

concept paper on MAH responsibilities (2).pdf

FDA Supply Chain Dec 2016

supply chain security notification.pdf

ICH Q12 draft
Lifecycle Management

INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Draft version

Endorsed on 16 November 2017

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Proposed New USP General Chapter: The Analytical Procedure Lifecycle *⟨1220⟩*

- These concepts are described here for the purpose of offering an alternative approach to the classical analytical validation and subsequent verification and transfer
- Viewing these activities as a continuum and closely interrelated rather than as discrete actions

Proposed New USP General Chapter: The Analytical Procedure Lifecycle *⟨1220⟩*

- Natural follow on from FDA Process Validation Guidance of January 2011
  which used similar language regarding process validation / process performance qualification

Proposed New USP General Chapter: The Analytical Procedure Lifecycle *⟨1220⟩*

Advantages of this approach:

- Improved understanding of procedure
  - Control sources of variability linked to the intended use of method as described in the Analytical Target Profile (ATP)
- Procedures that are more robust, resulting in fewer failures during use and during qualification in a new laboratory
- Reduction of overall resources required for a new or revised procedure. The levels of effort, formality, and documentation should be commensurate with the level of risk
- Identification of adverse trends, allowing proactive measures and facilitation of continued improvements and change control through continued monitoring

THE LIFECYCLE APPROACH

Analytical Method Premise: *⟨1220⟩*

- Reportable values generated using qualified analytical procedures provide the basis for key decisions regarding compliance of a test article with regulatory, compendial, and manufacturing limits
- These values may be applied against decision rules that provide a prescription for the acceptance or rejection of a drug product or drug substance
- This is based on the analytical measurement, the uncertainty of the measurement, and the acceptance criteria, taking into account the acceptable level of risk of making a wrong decision

THE LIFECYCLE APPROACH

⟨1220⟩

- In order to provide a holistic approach to controlling an analytical procedure throughout its lifecycle, use a three-stage concept aligned with current process validation terminology:
- Stage 1: Procedure Design and Development
- Stage 2: Procedure Performance Qualification
- Stage 3: Continued Procedure Performance Verification

THE LIFECYCLE APPROACH

TMU *(1220)*

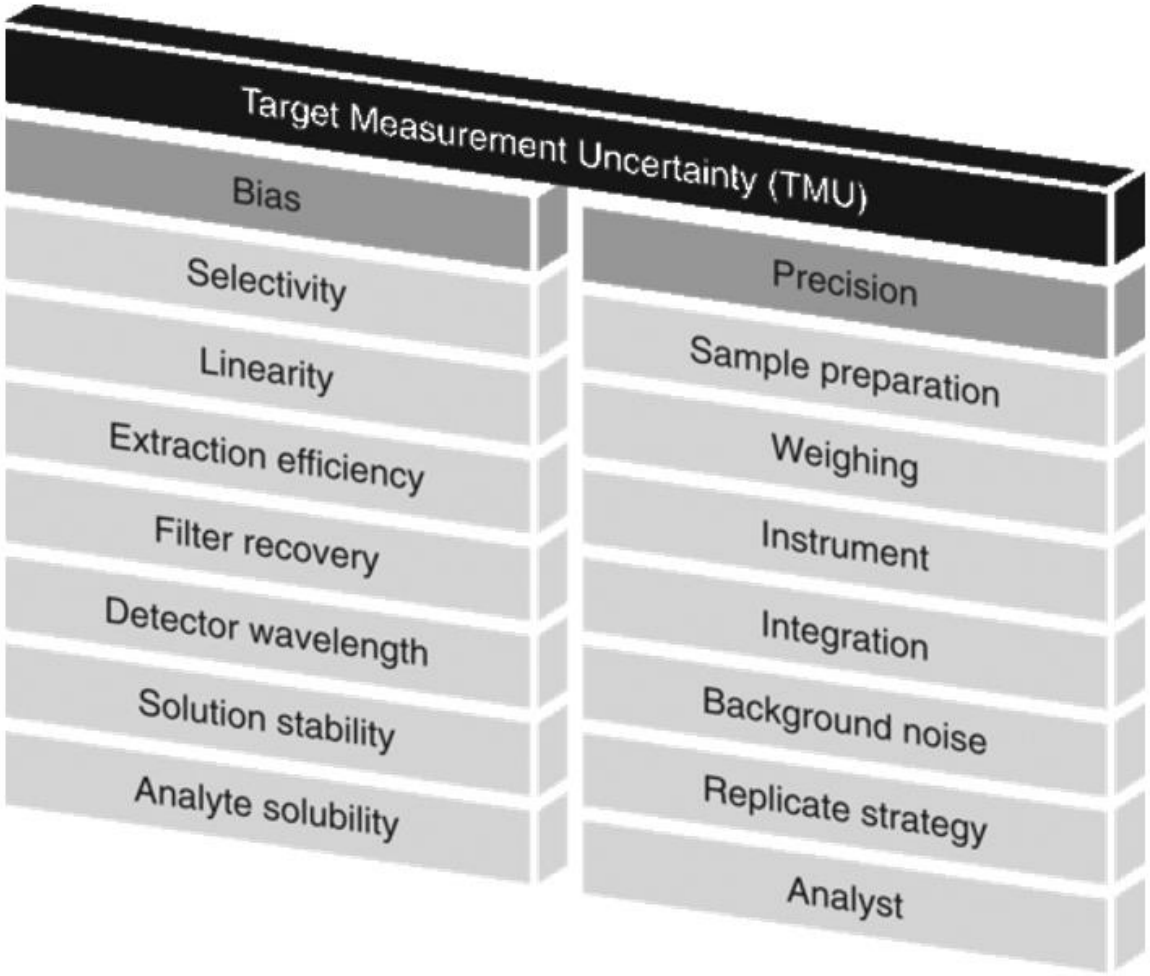

Figure 2. Consolidation of attributes contributing to TMU through accuracy (bias) and precision.

THE LIFECYCLE APPROACH

TMU *⟨1220⟩*

- TMU is the maximum uncertainty that can be associated with a reportable result while still remaining fit for its intended purpose
- TMU is a consolidation of the uncertainty from all sources
- IF the variability of an analytical method is ±5% and the specification is 95 – 105% - every result could be OOS

STAGE 1: PROCEDURE DESIGN AND DEVELOPMENT
Knowledge Gathering

When the need for a procedure is identified, relevant information should be gathered prior to conducting laboratory studies. Such information may include known chemical structures, solubility, reactivity, and stability of the molecules of interest. A literature search may also be useful to understand how the procedure has been applied or modified by others. The intended purpose and fitness for routine use must always be considered. Any relevant information identified during the knowledge-gathering stage—such as the range over which the procedure will be used, criteria for run time, equipment type, and other information—is also considered during the design and development stage. However, this information is not captured in the ATP.

Once the knowledge-gathering phase is complete, the information is used to select an appropriate technology and procedure likely to meet the requirements defined in the ATP.

THANK YOU FOR LISTENING!