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2 EMA/INS/GMP/705479/2012
3 GMP/GDP IWG

4 **Concept paper on revision of Annex 17 of the GMP guide**
5 **Draft**

Adoption by GMP/GDP Inspectors Working Group for release for consultation	October 2012
Start of public consultation	27 November 2012
End of consultation (deadline for comments)	28 February 2013

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7 The proposed guideline will replace the current version of Annex 17 on Parametric release.

8 **Comments should be provided using this [template](#). The completed comments form should be sent to ADM-GMDP@ema.europa.eu**

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Keywords	Annex 17, parametric release
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11 **1. Introduction**

12 This concept paper addresses the need to update Annex 17 (Parametric release) of the GMP Guide. At
13 the time the original guideline was adopted (January 2002), the main foreseen application area was
14 sterility testing, with particular focus on the release of terminally sterilised medicinal products. Since
15 then, there have been significant changes in GMP consequent to the adoption of the ICH Q8, Q9 Q10
16 and Q11 guidelines. Furthermore the Quality Working Party has recently published a Guideline on Real
17 Time Release Testing

18 The current Annex 17 is therefore being reviewed in order to implement the concepts highlighted in the
19 aforementioned ICH guidelines and to extend the underlying concepts to areas other than sterility
20 testing.



2. Problem statement

Since Annex 17 was published in 2002, introduction of the relevant ICH concepts and consequential regulatory changes and technological advancements are not reflected in the current GMP guideline. Therefore an update to this annex is required to reflect this changed environment.

Discussion (on the problem statement)

The current GMP guideline on parametric release was developed before the elaboration of the ICH tripartite guidelines as well as the new ICH Q11 guideline on development and manufacture of drug substances. The Q8 Pharmaceutical Development guideline provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process, Q9 offers a systematic approach to Quality Risk Management, and Q10 describes a modern quality system in order to establish and maintain a state of control, the realisation of product quality and to facilitate continual improvement over the entire life cycle. It is widely recognised that quality cannot be tested into a product, but it should be built in through design with an understanding of both the product and the process used to make it.

The revised guideline will clarify to what extent Q8, Q9 Q10 and Q11 should be followed in order to implement Real Time Release testing (RTRT). Moreover, it will detail how to set a system of release that provides assurance that the product or active substance is of the intended quality, based on the information collected during the manufacturing process, through product knowledge and process understanding and control.

The current guideline is only focused on the application of Parametric Release for the routine release of terminally sterilised products waiving the carrying out of a sterility test, on the basis of successful demonstration that predetermined and validated sterilising conditions have been achieved. This approach is based on the assumption that a sterility test only provides the opportunity to detect a major failure of the sterility assurance system, which would be more reliably detected by other means. Although the current guideline already states that the control of certain specific parameters may be used as an alternative to routine end-product testing of medicinal products, hence allowing the application of parametric release to any stage of manufacturing and to any type of products, detailed information is only provided for its application to terminally sterilised medicinal products. The main aim of the new guideline will be to facilitate the application of the concept to other processes, including the manufacture of biologics, active substances and intermediates.

Recently, a new Guideline on Real Time Release Testing was published by the CHMP/CVMP Quality Working Party establishing the requirements for applications that propose RTRT for active ingredients, intermediates and finished products. This should be taken into account in the revision of the current GMP guideline, in order to achieve a harmonized approach to Real Time Release Testing.

3. Recommendation

The GMP/GDP Inspectors Working Group recommends that the current version of Annex 17 on Parametric Release is revised to reflect changes in regulatory and manufacturing environments. The new guideline should clarify how manufacturers can take advantage of new possibilities deriving from the application of an enhanced process understanding by using innovative tools as described in the ICH Q8, Q9 Q10 and Q11 guidelines. The revision of Annex 17 should also take into account related changes in other GMP chapters and Annexes as well as in other regulatory documents.

1 **4. Proposed timetable**

2	Preparation of draft concept paper	- September 2012
3	Approval of draft concept paper	- October 2012
4	Released for consultation	- November 2012
5	Deadline for comments	- February 2013
6	Discussion in IWG	- June 2013
7	Discussion with other WPs	- June 2013 – September 2013
8	Proposed date for release of draft guideline	- December 2013
9	Deadline for comments	- March 2014
10	Re-discussion in GMDP IWG	- May - September 2014
11	Expected date for adoption by Committee	- October 2014

12 **5. Resource requirements for preparation**

13 A drafting group will be established by GMP/GDP Inspectors Working group with a rapporteur from
14 Italy and supporting experts from other EU Member Regulatory Authorities (Ireland and UK) and from
15 non-EU PIC/S participating Authorities (Australia and USA).

16 The development of the guideline will be carried out in close co-operation with the Quality Working
17 Party, the EU PAT Team and the Biologics Working party.

18 The guideline will be discussed at GMP/GDP Inspectors Working Group as necessary and at other
19 involved Working Parties and Groups.

20 Further discussions are expected with interested parties.

21 **6. Impact assessment (anticipated)**

22 No adverse impact on Industry with respect to either resources or costs is foreseen.

23 The guidance will clarify requirements for regulators and industry with respect to parametric release
24 taking into account the concepts detailed in ICH Q8, Q9, Q10 and Q11. Revision of the guideline will
25 facilitate implementation of Real Time Release Testing by ensuring compatibility and consistency
26 between scientific and GMP guidelines.

27 Interested parties

28 EMA (GMP/GDP Working Group, Quality Working Party, EU PAT Team Group, Biologics Working party),
29 PIC/S, Member State National Competent Authorities.

30 Pharmaceutical Industry.

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1 **References to literature, guidelines, etc.**

2 1) ICH Q8 (R2) Pharmaceutical development

3 2) ICH Q9 Quality Risk Management

4 3) ICH Q10 Pharmaceutical Quality System

5 4) ICH Q11 development and manufacture of drug substance

6 5) QWP Guideline on Real Time Release testing, 2012

7 6) PIC/S Recommendation on Guidance on Parametric release PI 005-3, 2007

8 7) FDA guidance to industry: Submission of Documentation in Applications for Parametric Release of
9 Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes - February
10 2010

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