EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL
Medicinal Products – Quality, Safety and Efficacy

Consultation document: EU Guidelines for GMP:
Annex 17: Real Time Release Testing
Ref. Ares(2015)3808922 – 15/9/2015

1. General Comments:

AstraZeneca finds the document generally well written and we feel it contains the relevant aspects of RTRT on a well-balanced level of detail. However, we have some general and specific comments to raise which are described in this response document.

As the guideline does not advise on the methods that should be employed for importation testing away from the original manufacturing site that is using RTRT or very importantly, the analytical methods for stability testing for an RTRT product it is suggested that these areas be addressed in the document.

It is also suggested that this guidance document addresses how established products could be moved to RTR methods to replace traditional end product testing and how industry could minimise the regulatory burden of such a change.

The scope of this guidance is batch RTRT. Since the release principles discussed here are also highly relevant for continuous manufacturing, it is suggested that this too is mentioned in the guidance. An important aspect for continuous processes is to define the batch concept in an unequivocal way.

As there is no guidance in Annex 17 on how the application of RTRT affects how the product specification is described it is suggested to include a requirement to describe the CQA as a specification item and say that 'the test will not be performed routinely at the time of release, but would pass if tested', or that the specification item become the real-time release test.

Based on some of our experience in AZ, when we have tried to register RTRT, we have been asked by the EMA to 'should submit and justify the protocol for running in-period to be carried out at site and at testing on importation' (the running in-period is effectively a period of simultaneous in-process and end-product testing prior to full implementation of real-time-release). There is no mention of any general expectations for running-in periods or testing on importation for products with RTRT in Annex 17, and we would have expected something given that the expectations in this area may influence whether or not a company applies for RTRT.

Currently it is unclear from the guidance whether or not flexibility can be proposed to apply RTRT or end-product testing within the Marketing Authorisation, and then choose through formal change control within the quality system what to implement on a routine basis. This is not to say that end-product testing would be implemented if

RTRT is failing (this is clearly not acceptable); more that it could be a strategic decision to move to RTRT based on, for example, product volumes.

In order to make real-time release testing work properly over the whole product life cycle, it is essential that advanced RTR methods, such as spectroscopy techniques, can be maintained and updated in a seamless way, without frequent submissions of variations to Authorities. Therefore, we suggest that quality by design principles be applied to RTR methodology by introducing the concept of *enhanced analytical procedures.*[1] The pharmaceutical quality system of each company must give guidance for and set requirements on the development, validation and maintenance of advanced RTR methods in line with external guidelines, but solely for major method changes or issues, should the submission of a variation be required (see also relevant text in sections 3.5, 3.6 or 3.8 and specific comment to lines 103-107).

2. Specific Comments on Text:

Section	Page or line number	Comment and rationale; proposed changes (if any)
3	Page 2	ICHQ6a describes 'periodic or skip testing' as the performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. Please clarify if 'periodic or skip testing' would fall under the umbrella of the RTRT requirements outlined (as it is effectively RTRT, for those batches that are not tested within the scheme).
3.2	Page 2	Please clarify who determines if the in-process attributes are relevant and whether this could provide some concerns when actually filing the first documents. Please clarify whether authorities could indicate that the attributes that have been chosen are not relevant.
3.3	Page 2	The guidance describes that a RTRT master plan should be prepared which is appropriately integrated and controlled through the pharmaceutical quality system. A number of the elements described in the guidance that should be included will already be part of the site pharmaceutical quality system.

[1] Åsberg D, M Nilsson, S Olsson, J Samuelsson, A Karlsson, S Klick, J Ennis, T Fornstedt, 2015: A method enhancement concept – Continuous improvement of regulatory approved analytical methods, *submitted.*
Presented at *HPLC 2014*, May 11-15, New Orleans, Louisiana, USA and at *Analytical Days*, The Swedish Chemical Society, Stockholm, June 9-11, 2014.

		Please clarify if it would be acceptable to implement a 'Site RTRT master plan' to cover the range of products that apply an RTRT approach, or whether there is an expectation that each individual product requires a 'RTRT master plan.
3.8	Page 3/4	The text on line 95 referring to a "reactor" suggests this is specific to Drug Substance processes. It is suggested that "reactor" be replaced with "manufacturing process" as this makes it less specific and more consistent with terminology used earlier in the document.
3.10	Page 4	When new knowledge is gained throughout the product life cycle, which may be used to improve the product/process, this may require an update of the details of the RTRT scheme. It is essential that such maintenance can be made within the pharmaceutical quality system, without requirements of submitting variations (see also general comment).
4.0	Page 4	This section focuses exclusively on sterilised products and whilst the comments in the subsections appear appropriate, the principles of parametric release can also apply to other products. Please clarify the scope of parametric release beyond sterilised products in section 4 and please provide some consistency with the Glossary (lines 242 to 248)
4.8	Page 5	This section is applicable to all sterile products and not specific to drug products manufactured under the umbrella of parametric release. Suggest removing.
4.10	Page 5	Propose changing "A product segregation plan" to "A **robust** product segregation plan". The process of segregation should also be challenged and subject to constant review. It is also proposed to incorporate Visual aids to demonstrate sterilisation has taken place.
4.11	Page 5	Please clarify if alternative sterilisation cycles other than those described in the monographs are acceptable for parametric release, or clarify if only overkill cycles are acceptable.