Table 5: Scope of Analytical Target Profiles (ATP) in Biotherapeutic Drug Development

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SCOPE:

There is considerable interest in enhancing approaches for analytical methods and their lifecycle management which are aligned with Quality by Design (QbD) approaches to drug development. These approaches identify controls to ensure that the measurement uncertainty of a reportable result is controlled to a level that ensures intended method performance. Predefined criteria can be established in the form of an Analytical Target Profile (ATP), which contains the desired performance criteria for the measurement of the attribute(s), e.g., impurities, API content, potency, etc. The ATP defines the appropriate performance criteria for the analytical result and is method-independent. This table will brainstorm on the approaches and issues through open discussion based on currently implemented strategies and future directions.

QUESTIONS FOR DISCUSSION:

1. What is an ATP, and why is it useful?
2. How can the ATP criteria (data quality attributes) be established?
3. How can an ATP be applied during the three stages of the Method lifecycle (Design, Qualification, and Performance Verification)?
4. What is the linkage between ATP and Analytical Control Strategies?
   a. How does one determine which analytical method is best suited to the phase of development and type of question being asked?
   b. How is ATP linked to Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)?
   c. ATP versions along the drug development cycle: Generic ATP vs Commercial ATP
5. What is the linkage between ATP and Specification?
   a. What is the impact of Specification changes on method capability? How does Agency’s requests for changing Specification limits impact methods that are validated?
   b. Multiple ATPs across different markets and need for globally approved specification limits and methodology

NOTES:

What is ATP?
ATP is a prospective summary of method objectives, and method controls and their pre-defined acceptance criteria (which are method independent) collectively called quality requirements, to
ensure the uncertainty of the reportable result is controlled to a level the method is performing for its intended purpose, i.e. the adequate measurement of the quality attributes (QAs) of the drug product. They can include list of acceptance criteria for method performance characteristic listed in ICH guidance, e.g., LOQ, precision, accuracy, linearity, and other method performance characteristics, as well as operation related criteria such as assay turn around time. The latter is especially true for IPC tests

What is the linkage between ATP and Analytical Control Strategies?
Product Control Strategy (i.e. raw material, process, testing controls) defines Analytical control strategies (i.e. which methods and where in the process they must be implemented) which defines ATP (method controls and pre-defined acceptance criteria). Locked Product control strategy is not available until late in the development of the product. Similar to how Product control strategies evolve along the development cycle, analytical control strategies evolve, and so does ATP.

c. How does one determine which analytical method is best suited to the phase of development and type of question being asked?
Product control strategy dictates the Analytical control strategy, which methods are suitable for which phase of the development? Analytical control strategy is driven by CQAs. CQAs are derived from QTTP that takes into consideration of a large number of factors (Safety, Efficacy, literature, existing product/process knowledge, knowledge on platform molecule, etc.)

d. How is ATP linked to Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)?
e. ATP versions along the drug development cycle: Generic ATP vs Commercial ATP

Who has used ATP?
A couple participants reported that their companies have started using ATP concept in the product development

Why is it useful?
- Perspective evaluation on how well methods need to perform to meet QTTP, and provide clear rationale to regulatory on the acceptance criteria for method performance
- From patient perspective, the method performance is related to product quality.
- Consistent format for method development and validation performance criteria
- Can be used to resist the temptation to continuously improve the method as long as the method meet the ATP.
- When ATP is accepted and approved by the HA, the MAHs can have more flexibility on change of method provided the new method meet the ATP. Linkage to clinical experience is likely expected for change of analytical method, even it meets ATP

How is ATP different from method validation acceptance criteria?
ATP is a front loaded method performance criteria while method validation acceptance criteria is often set based on existing method performance data.

How can an ATP be applied during the three stages of the Method lifecycle (Design, Qualification, and Performance Verification)?
Draft ATP (Generic ATP) during method design and evaluation, which is locked before validation and gets finalized (becomes effective) after validation (Commercial ATP).
Is ATP product specific or quality attribute specific?
ATP should be more dependent on product QTTP.

For approved products, do you go back to establish ATP?
Maybe, there are a few reasons one may want to go back to retrospectively establish ATP for approved commercial products. One hypothetical situation: there is a QC method with high OOS rate, as part of LCM activity, MAH may decide to re-assess if the method capability is adequate for its purpose, and also set ATP for the new method if needed. Other example is, CMO and CRO may not be able meet the same tight performance requirement as ran in house. An ATP is a useful tool to assess if the method performances criteria can be loosen up.

How are ATP criteria established?
The ATP is established by taking into consideration of product specification which covers safety, efficacy product knowledge, literature, process design space), process capability, and specific application needs such as speed of test for IPC tests. In the meantime, the analytical method’s capability can pose limit on the specification. For example, given the current potency method variability, the specification of potency can not be tighter than method capability of precision. This is a valid point and justifiable provided that the state of art technology has been used and available varieties of technologies have been evaluated. Product specifications are almost always discussed and negotiated with regulatory agents.

How is ATP evolved over the life cycle of product?
ATP is not locked, and goes through revision. In early stage of product development, the ATP can be broader and with less criteria, and tighter with added performance objectives in late stage or commercial stage. Whenever there is re-evaluation of specifications, the ATP should also be re-evaluated. The ATP should be phase appropriate.

Can you use ATP for method transfer?
Yes, the ATP gives the guidance on method performance requirements. Method validation acceptance criteria should be within the range of ATP.

Is ATP built into quality system?
For companies that have started to use ATP, they only use it as business process not in quality system

What is the impact of spec change on method validation status?
Some companies have establish change control process to ensure that impact assessment is performed to ensure that method capability and method validation support the updated specification. If not, new method needs to be developed, and method validation would need to be performed again.