Module 6

Control of Elemental Impurities

ICH Q3D Elemental Impurities

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This presentation includes the authors' views on Elemental Impurities theory and practice.
The presentation does not represent official guidance or policy of authorities or industry.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Overview

- Purpose
- Control Strategy – Definition and Key Principles
- Control of Elemental Impurities
- Periodic Testing
- Life-cycle approach to Control Strategy
- Regulatory Submission
- Considerations for Biotech Products

Purpose

- To provide guiding principles for establishing a control strategy for elemental impurities in a drug product across the life-cycle
- In conjunction with the Product Risk Assessment and Converting between PDEs and Concentration Limits training modules, and the Case Studies, provides an integrated approach on the quality considerations for controlling elemental impurities, using a science and risk based approach

Control Strategy - Definition

- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality.
- The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Control Strategy - Key Principles

- The control strategy is designed to ensure that a product of required quality will be produced consistently in alignment with the Quality Target Product Profile (ICHQ8(R2))
- Reviewers will evaluate and approve the control strategy; and investigators (inspectors) will verify the implementation of the control strategy at the manufacturing site
- The control strategy needs to be maintained across the product life-cycle

Control of Elemental Impurities 1

- Control of elemental impurities is an important component of the overall control strategy for a drug product that assures that elemental impurities do not exceed the PDEs
- It is not expected to tighten the limits based on process capability, provided that the elemental impurities in drug products do not exceed the PDEs
- Lower levels of elemental impurities may be warranted when levels below toxicity thresholds have been shown to have a negative impact on quality attributes of the drug product
  - For example, element catalyzed degradation of drug substances

Control of Elemental Impurities 2

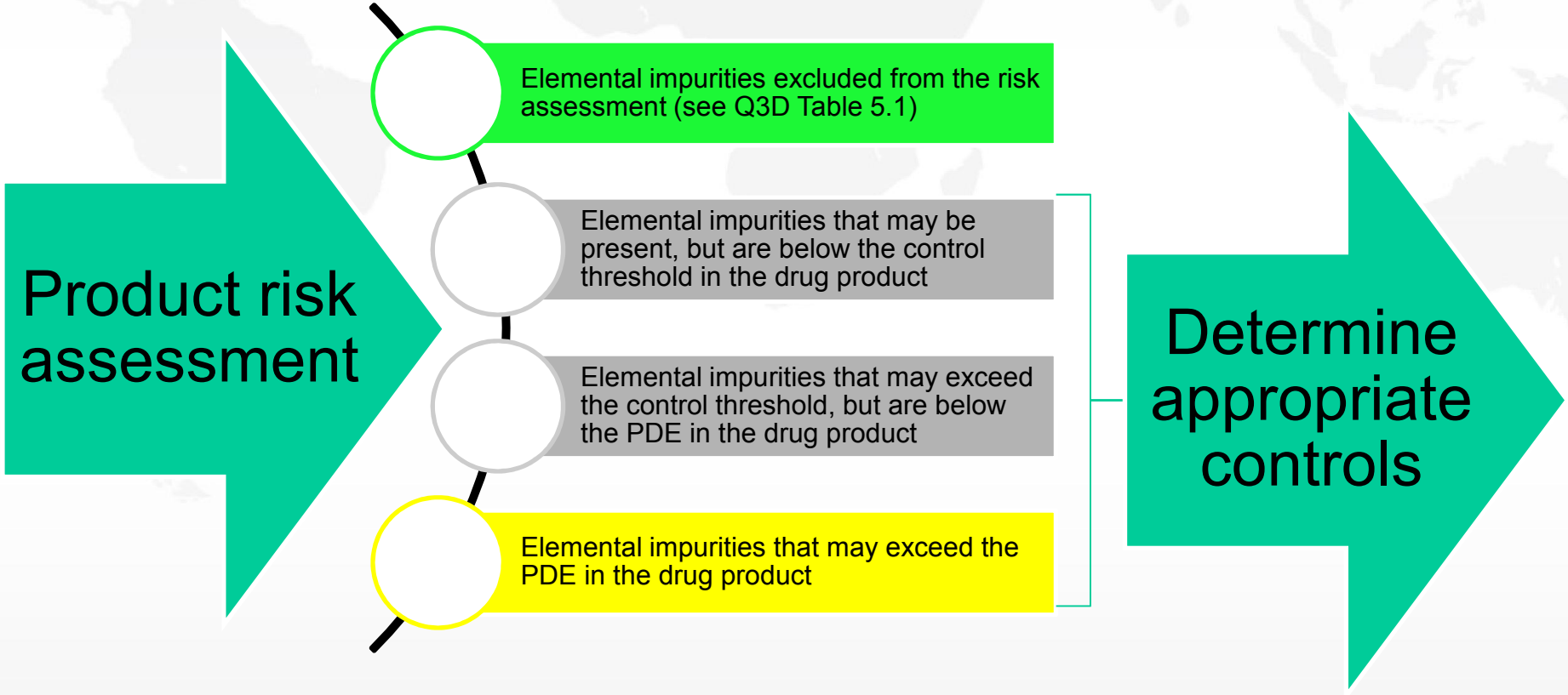
- Q3D does not apply to drug products used during clinical research stages of development
  - However, as the commercial process is developed, the principles contained in the guideline may be used to develop the controls for elemental impurities

- The principles in this guideline can be applied to evaluate the controls for elemental impurities in existing products

Control of Elemental Impurities 3

- If the risk assessment fails to demonstrate than an EI level is consistently below the control threshold, then controls need to be established to ensure the EI level does not exceed the PDE
- **Routine testing of elemental impurities (including Class 1 elements i.e. Cd, Pb, As and Hg) is not expected, unless the risk assessment indicates this is needed**
- Application of the principles outlined in Q3D provides a platform for developing a risk-based control strategy to limit elemental impurities in the drug product

From Risk Assessment to Controls on Elemental Impurities



From Risk Assessment to Controls on Elemental Impurities

- The output of the risk assessment classifies elemental impurities to be considered in the control strategy into one of the following categories:
  - Elemental impurities that may be present, but are below the control threshold in the drug product
  - Elemental impurities that may exceed the control threshold, but are below the PDE in the drug product
  - Elemental impurities that may exceed the PDE in the drug product

Below the Control Threshold

- The control threshold is defined as 30% of the PDE.
- When the levels of the EI are consistently below the control threshold no additional controls are deemed necessary provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities
- If changes are introduced to the manufacturing process or components of the drug product across the life-cycle, the risk assessment should be reviewed and existing controls may need to be re-evaluated.

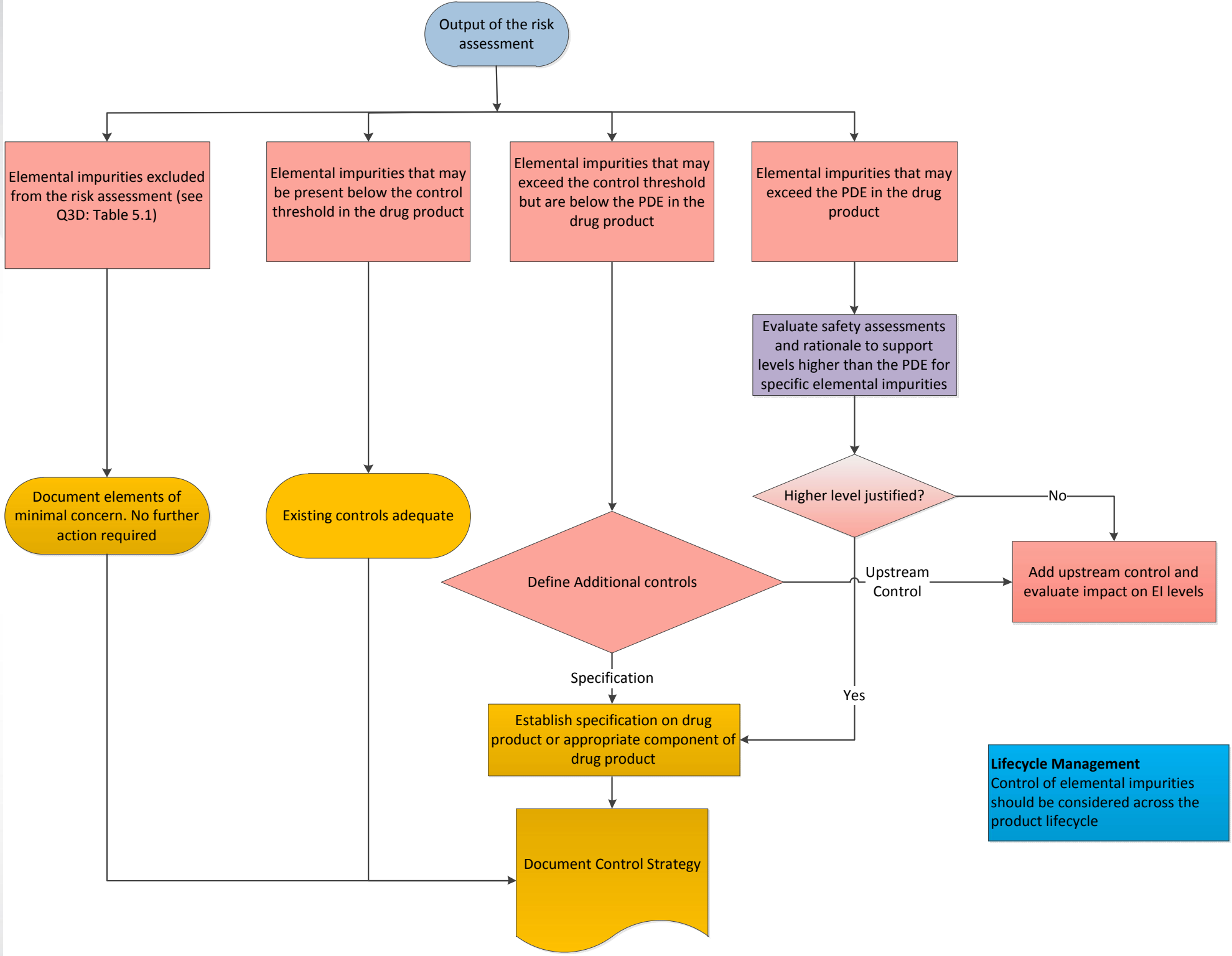
May exceed the control threshold but below PDE

- When the level of an elemental impurity may exceed the control threshold, additional measures may need to be implemented to ensure that the level does not exceed the PDE.
- These additional measures include, but are not limited to:
  - Reduction of elemental impurities to levels that do not exceed the control threshold through purification steps or implementing in-process or upstream controls
  - Selection of components of improved quality, if appropriate
  - Establishment of specification limits for the drug substance, excipient or drug product, if appropriate
  - Selection of appropriate container closure system

Exceeding the PDE

- When the level of an elemental impurity exceeds the PDE additional measures should be considered to bring the levels below the PDE
- When additional measures are either not technically feasible or have been unsuccessful, levels of elemental impurities higher than the established PDE may be justified in certain circumstances, for example:
  - Intermittent dosing
  - Short term dosing (i.e. 30 days or less)
  - Specific indications (e.g. Life threatening, unmet medical needs, rare diseases)

  (Refer to training module 2 for further details on safety considerations)
- Recommend early dialogue with Regulatory Authorities to discuss appropriate control strategy in this situation


Output of the risk assessment
Elemental impurities excluded from the risk assessment (see Q3D: Table 5.1)
Elemental impurities that may be present below the control threshold in the drug product
Elemental impurities that may exceed the control threshold but are below the PDE in the drug product
Elemental impurities that may exceed the PDE in the drug product
Evaluate safety assessments and rationale to support levels higher than the PDE for specific elemental impurities
Higher level justified?
No
Yes
Document elements of minimal concern. No further action required
Existing controls adequate
Define Additional controls
Upstream Control
Add upstream control and evaluate impact on EI levels
Specification
Establish specification on drug product or appropriate component of drug product
Document Control Strategy
Lifecycle Management
Control of elemental impurities should be considered across the product lifecycle

Periodic Testing

- Periodic testing may be applied to elemental impurities according to the principles described in ICH Q6A.
  - Application of periodic testing to drug products and components of drug products will depend on regional regulations.
- Where the risk assessment indicates that routine testing is considered unnecessary but some additional assurance is needed post approval, periodic testing of the drug product or one or more individual components may be proposed by the applicant and implemented upon acceptance by the regional regulatory authority.

Application of Periodic Testing to Drug Substance – an example

- An applicant has the developed a new tablet form medicine:
  - The active substance is manufactured by a route where the last step is a catalytic hydrogenation with platinum on carbon as catalyst. After filtration to remove the catalyst, the substance is isolated by crystallisation.
  - In the risk assessment the applicant concludes that the filtration and the crystallisation are likely to reduce the levels of Pt. This is also confirmed on three production scale batches where Pt where found in 24%, 19% and 22% of an amount corresponding to a PDE calculated by Option 2b.
  - For these three batches the levels of Pt is below 30% of the PDE. However, impurities introduced late in the synthesis constitutes a higher risk of being carried through (ICH Q11) and the control threshold could be exceeded.
  - A specification for the drug substance was set that ensures compliance of the drug product with the PDE. The applicant proposed to apply Periodic Testing (ICH Q6A) after confirmation on 10 batches.

Regulatory Submission

- The information on the control of elemental impurities that should be provided in a regulatory submission includes a summary of the risk assessment, appropriate data as necessary, and a description of the controls established to limit elemental impurities (if needed).

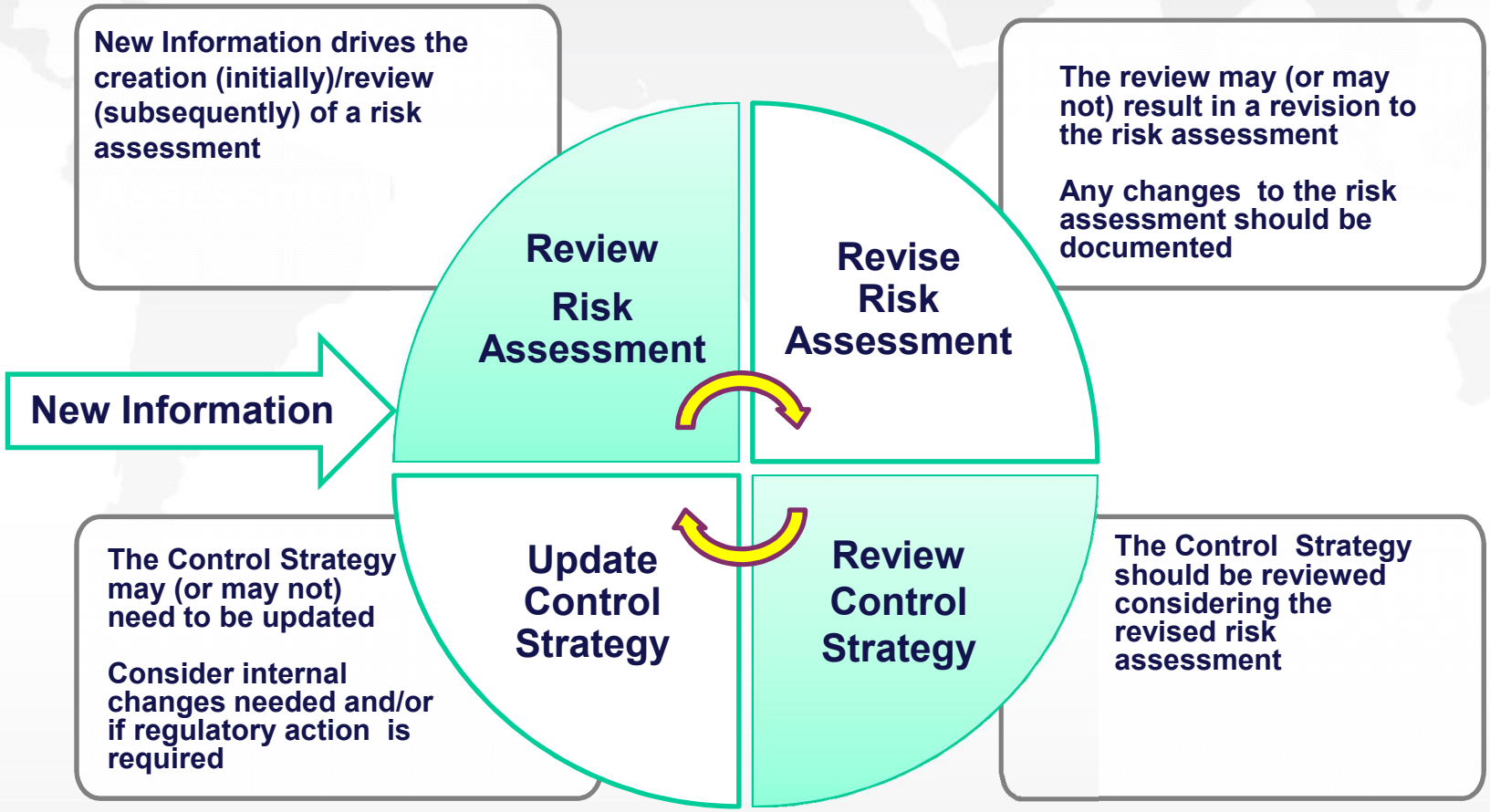
Life-cycle approach to Control Strategy 1

- Product and/or process changes across the product lifecycle have the potential to impact (positively or negatively) the elemental impurity content of the drug product.
- Changes could include, but are not limited to:
  - Changes in synthetic routes, excipient suppliers, materials, processes, equipment, container closure systems or facilities
- The impact of such changes on the original risk assessment should be evaluated, and implications for the control strategy should be considered
- The regulatory implications of modifications to the risk assessment and control strategy should be considered, and appropriate variations submitted according to specific regional requirements
- Consideration should be given for periodic review of the control strategy, as part of ongoing continual improvement

Life-cycle Approach to Control Strategy 2

- Elemental impurity data for some components may be limited during drug development, which may direct the applicant to a particular control strategy.
  - For example, the applicant may choose to carry out end product testing as the initial strategy.
  - As additional experience and knowledge is gained with time, an applicant may determine that a change in the calculation option, risk assessment and/or control strategy may be warranted
    - See next slide for pictorial representations

Life-cycle approach to Control Strategy 3



Special Considerations for Biotechnologically-Derived Products

- It is recognized that the risks associated with the presence of elemental impurities at levels of safety concerns for biotechnology-derived products are low
- This is generally due to the absence of use of elemental impurities as catalysts or reagents and to the typical purification schemes used in the manufacture of biotechnology-derived products
- In general, a specific control strategy for elemental impurities up to the biotech drug substance is not needed. However, potential elemental impurity sources (e.g., excipients, environmental sources, container/closure) in drug product should be considered.

Links to other training modules

- This module has been developed to be considered in conjunction with the following Q3D quality and safety training modules :
  - Module 0 - Overview
  - Module 2 - Justification for Elemental Impurity Levels Higher than an Established PDE
  - Module 5 - Product Risk Assessment : General Approaches
  - Module 7- Converting between PDEs and Concentration Limits
  - Module 8 - Case Studies
  - Module 9 - FAQs