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Comprehensive Approaches for Developing Overall Control Strategies for Impurities in Drug Substances and Drug Products

Bharathi Mamidipudi, Hiral Gutka, Prabu Nambiar
Syner-G Pharma CMC Consulting LLC

SYNER-G

Purpose

Impurities in pharmaceutical products do not offer any therapeutic benefit for the patient and sometimes they are potentially toxic. Impurity level is a critical quality attribute for a drug substance or a drug product because levels higher than the toxicologically qualified amount could affect the safety and efficacy of the product. Control of impurities in drug substance and drug product is described in ICH Q3A, Q3B and Q3C guidance documents. Generally, acceptable limits for impurities are indicated by threshold values and impurities exceeding the qualification threshold should be toxicologically qualified. Control of impurities by end-product testing used to be the typical approach. With thorough product and process knowledge gained from pharmaceutical development under QbD paradigm, an efficient and comprehensive overall impurity control strategy can be developed to achieve the desired quality of the drug substance/ product

Methods

Instead of controlling the impurities by exhaustive testing of the end-product, the QbD paradigm allows strategic and science based approaches to control impurities at various stages. Control points such as material controls (in-coming materials), process controls, intermediate quality controls and drug substance/product quality controls are various points to potentially control the impurities from different sources. Based on the knowledge of the types of impurities and their potential sources, a comprehensive control strategy is designed via material quality control and process control steps and ultimately by drug substance/product specifications.

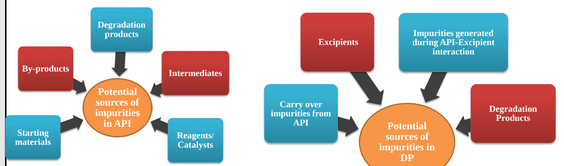
Results

An overall impurity control strategy was developed to achieve the desired quality of the drug substance/ product by utilizing the regulatory and scientific principles from ICH Q3A, Q3B, Q3C, Q6A, Q8, Q9, Q10 and Q11 guidance documents in combination with the product/process knowledge including the type of impurities in the drug substance/product and their potential source/origin including the mechanism of formation of the impurity.

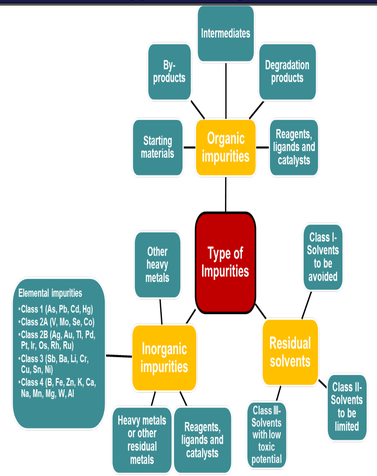
Impurities

- Any unwanted substance which either enters into the process via materials used or formed during the manufacturing of Drug Substance and/or Drug Product is called as Impurity.
- Impurities do not have any therapeutic value and may affect safety and efficacy and ultimately the quality of the product.
- Impurities can arise during the synthesis, purification, and storage of a new drug substance and/ or drug product.
- How can they be controlled?
  - By understanding the formation, fate and purge of the impurities during the manufacturing process
  - By setting up appropriate controls at places where they either enter or form during the manufacturing process of drug substance and/ or drug product

Sources of Impurities



Types of Impurities



Defining Control Strategy (CS)

- A planned set of controls, derived from current product and process understanding that ensures 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).

A over all CS should ensure that all the CQAs (impurities) are with in the appropriate range, limit or distribution to assure the desired quality target of the drug product

- A control strategy for impurities may include, but is not limited to, the following: (ICH Q8, ICH Q11)
  - Control of input material attributes (e.g., starting materials, API, reagents, intermediates, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
  - Control of In process materials;
  - Product specification(s);
  - Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation);
  - In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
  - A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models

CS for impurities in Process materials for API Synthesis

- **Starting materials:** First check point where we can control the impurities that can enter into the API synthetic route
- Can be obtained by various synthetic routes and impurity profile for each route is different from the other
- Impurity profile for starting materials can be developed based on knowledge of manufacturing process used to synthesize it
- **Materials other than Starting Materials:** These include reagents, process aids and solvents used in various steps of manufacturing of API
- It is also important to control the amount of these substances that are used in the manufacturing as they could be potentially genotoxic

Impurities in Starting Materials and Reagents can be controlled by Release Specification and Supplier Qualification Protocol.

CS for impurities formed during API Synthesis

- The impurities that are formed during the API synthesis are typically, residual starting materials, residual intermediates, by –products, degradants and residual solvents which can be toxic if present beyond qualification threshold
- Identification of impurities (CQAs) that can be formed during the manufacturing process is a critical step in manufacturing a high quality of drug substance.
- Development of robust process which can minimize or eliminate these unwanted impurities can be achieved by performing series of experiments

Identification of Unit operations that would be involved in the manufacturing of drug substance (for eg: Reduction on temperature, Crystallization, Hydrolysis)

- Impurities in API synthesis can be controlled at incoming stage, in process stage and at the end of synthetic process with appropriate specification based on acceptance limits (ICH Q3A)

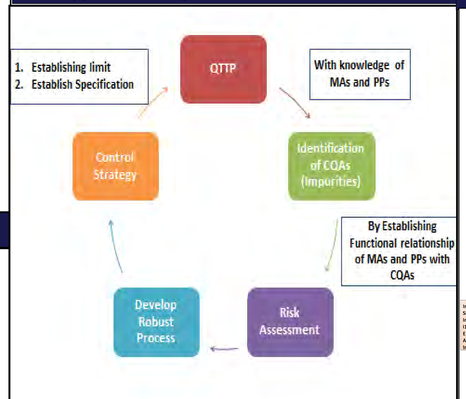
CS for impurities from Excipients

- Excipients are components of DP other than API which do not have any therapeutic value but are intentionally added to bulk up the dosage form.
- Impurities from excipients may include starting materials, solvents, reagents and intermediates.
- No formal guidance for controlling of impurities in excipients but QbD approach can help.
- For known excipients, compendial monographs can be source for impurity specifications and acceptance limits. However, additional tests may be needed on case by case basis.
- For new ones FDA & EMA require toxicological qualification to the same level as a new drug substance

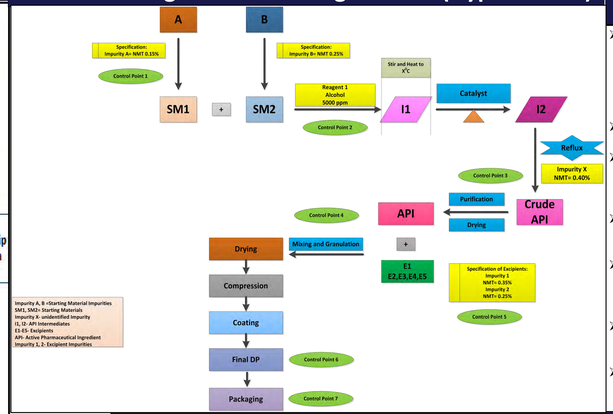
ICH limits for Impurities

- ICH Q3A: Attachment 1 gives us the thresholds based on which the limits for impurities in Drug Substance can be set up.
- ICH Q3B: Attachment 1 gives us the thresholds based on which the limits for impurities in Drug Product can be set up.
- ICH Q3C: Residual Solvents-Refer this guidance
  - For Class I Solvents, See Table 1
  - For Class II Solvents, See Table 2
  - For Class III Solvents, 5000 ppm is acceptable without further justification; might be controlled by LOD (0.5%)
- ICH Q3D: For Elemental Impurities See Table A.2.1: Permitted Daily Exposures for Elemental Impurities

QbD Approach for Impurities: Elements to be considered



Manufacturing Process of Drug Product (Hypothetical)



CS for Impurities from Container Closure System (CCS)

- Impurities in DS or DP can be formed not only during the manufacturing process but also during storage . Therefore, it is important to select appropriate CCS for the dosage form

For e.g.: Photo sensitive materials are stored in amber colored bottles to avoid degradation due to oxidation of light

- Impurities with Container closure system also include leachables and extractables of the CCS into the Drug Product. More importantly seen in solid dosage forms
- Critical CCS parameters for compatibility should be identified early on so that there are no unacceptable changes in the quality of dosage form or interactions such as loss of potency, degradation, changes in pH, absorption/adsorption, precipitation, discoloration and of course leaching.
- The CCS materials can be evaluated for these quality attributes, taking into consideration the interaction between the critical component extractable and drug product leachable
- Guidance for Industry titled – "Container Closure Systems for Packaging of Human Drugs and Biologics" provides guidance on the information of packaging materials needed on drug products. Attachment C of the guidance provides information on various extraction studies.
- USP <661> and USP <381> for the characterization of plastics and elastomers, respectively, and USP <87> and USP <88> for the biological reactivity of plastics and elastomers, respectively.
- The leachables can also come into the product from an indirect contact (e.g., imprinting on the bottle or adhesives, inks or varnish from labels) or from surrounding air.

Traditional Vs. Enhanced approaches for Pharmaceutical Development

TRADITIONAL	ENHANCED
• Developmental research conducted one variable at a time	• Multivariate experiments to understand product and process via establishment of design space and utilization of PAT Tools
• Fixed manufacturing process • Focus on optimization and reproducibility	• Adjustable within design space • Focus on control strategy and robustness
• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feed forward and feedback controls • Continual improvement post- approval efforts support
• Product Quality controlled primarily by intermediates and end product testing	• Risk based control strategy employed to ensure product quality • Quality controls shifted upstream, with possibility of real time release or reduced end product testing.
• Reactive i.e. problem solving and corrective actions	• Preventive actions with continual improvement.

Various Approaches to CS for Impurities

- **Material controls:**

  Based on the knowledge gained on synthetic route of materials, impurities can be controlled by testing them according to the specifications set for them thereby we can eliminate the impurities before entering into the process.

- **Process controls:**

  These are the controls which are put into place in order to monitor and adjust the process there by ensuring that API or its intermediates conforms to its specifications.

If the in process controls are robust enough to decrease the level of impurities in the product, the quality target is obtained even with out performing end product testing.

- **End Product Testing:**

  Impurities which are formed during late stages of the product development can be controlled by end product testing with appropriate specification

Conclusion

This poster outlines the development of an efficient overall CS for impurities by utilizing QbD principles and the knowledge of the types of impurities and their potential sources. Overall control strategy is achieved by incorporating controls in the material quality control and process control steps and ultimately by drug substance/product specifications.

A systematic control of impurities via QbD approach has following benefits

For Patients : They receive product of high quality

For Regulators: A clear control strategy from the manufacturers provide transparency and added assurance that risk of impurity has been adequately controlled

For Pharmaceutical companies: A clear control strategy is identified which ultimately facilitates successful launch of product and also various post approval supplements like scale ups, tech transfers etc.

- References: 1. ICH Q3A(R2) : Impurities in New Drug Substances (Oct, 2006)
  2. ICH Q3B (R2): Impurities in New Drug Products (June 2006)
  3. ICH Q3C(R5) : Guideline for Residual Solvents (Feb, 2012)
  4. Draft Consensus Guideline ICH Q3D: Guideline for Elemental Impurities (July, 2013)
  5. ICH Harmonized Tripartite Guideline: Pharmaceutical Development Q8R(2) (Aug, 2009)
  6. ICH Harmonized Tripartite Guideline: Quality Risk Management (Q9) (Nov, 2005)
  7. ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System (Jun, 2008)
  8. ICH Harmonized Tripartite Guideline: Development And Manufacture Of Drug Substances (May, 2012)