Starting Materials For Active Substances

Workshop 1 – How to build a good CEP Application
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Redefinition of GMP-Starting Materials

- Redefinition of GMP-starting materials
  - A common question from Authorities in all procedures
  - Initiated by changes in GMP for Active Substances
  - Recent publications aim to make the situation clearer
    - Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances (EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1) New number
    - ICHQ11 (ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/biological entities))
      - Draft QA soon to be published

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Redefinition of GMP-Starting Materials

- Previously: more common with one substance manufacturer, one product manufacturer
- Nowadays complex manufacturing sections
  - Often several substance manufacturers sourcing intermediates from several third parties
    - *External sources for any steps in a manufacturing process may lead to a higher degree of risk to quality of the active substance than would be expected were the full manufacturing process to be carried out by the applicant or a single active substance manufacturer alone*
- Manufacturing route begins from starting material(s) – GMP applies from here onward
  - Start of GMP defines what can be inspected and the extent of information in the dossier

Redefinition of GMP-Starting Materials

- The current guidelines are intentionally high level to allow the wide range of chemical syntheses submitted
- Challenges for both Industry and Regulators
  - Different interpretations region to region
  - Changes in SMs lead to changes in GMP scope and QP declarations
    - May be challenging to solve during the scope of a Procedure
  - Industry often have to meet criteria not only from EU
  - Recent publications provide a clearer picture of the Authorities' guidelines

Length of Synthesis

- Increasingly common for applicants to propose very short synthetic routes
  - What constitutes "a sufficient number of steps"?
    - The synthesis and control strategy both have to be taken into account
  - Common situation: wet intermediates, one-pot reactions with poor control strategy
  - Common situation: short synthesis compensated by control strategy
    - How to ensure adequate control over the lifecycle of the drug product?
    - Critical steps close to the GMP-border?

Length of Synthesis

- Common situation:
  - Purification, salt-forming, simple removal of protection-groups counted as synthetic, chemical transformation steps
    - A sufficient number of chemical transformation steps so that generation, fate and control of impurities can be understood. Typically multiple chemical transformation steps needed
    - The term "significant structural fragment" is frequently misinterpreted
      - This does not mean that a compound with a similar structure as the SM can be accepted
    - Critical steps should normally be carried out under GMP
      - Critical steps far removed from the finished active substance may be outside of GMP-scope if properly justified

Length of Synthesis

- Examples of critical steps
  - Steps involving formation and/or purge of key impurities
  - Steps which introduce key structural features of the active substance, for example key functional groups or stereochemistry
  - Steps where careful control of stoichiometry, temperature, pH or other process variables is crucial for active substance quality;
  - Steps which employ or generate genotoxic compounds;
  - Steps which employ class I solvents and/or toxic metals;
  - Complex chemical transformations where multiple variables could impact reaction outcome (multiple reagents, catalysts, solvents, etc.)
  - The final purification step

Length of Synthesis

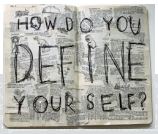
- A short synthesis may be accepted but this should be for clear scientific reasons and is expected to be the exception rather than the norm
  - Typically very small APIs
  - In such cases, steps to synthesize the GMP-starting materials should be demonstrated not to be critical and the avoidance of contamination from non-GMP steps should be integral to the control strategy
  - SMs in one-step reactions should be redefined
- Assessors often have an overview of many syntheses/applications
  - EDQM staff of great help to the Technical Advisory Board
- Borderline cases
  - Dose? Indication? Pharmaceutical form? Length of treatment? Pediatric population?

Definition of GMP-starting Materials

- Information on GMP-starting materials
  - All manufacturers must be defined (can only be changed by variation)
  - Syntheses of GMP-starting materials should be presented
    - Syntheses from all manufacturers
    - Necessary to understand the risk of impurity carry-over and to support the proposed control strategy
    - The closer to the finished API the more important
  - Specifications of GMP-starting materials are requried
    - Typically including specified, any other and total impurities
- Why?
  - Risk of carry-over
  - Risk of contamination from non/pre-GMP manufacture
  - Risk of new impurities from future changes to SM manufacturing route

Definition of GMP-starting Materials

- Starting material should be a substance of defined chemical properties and structure
  - "significant structural fragment" often misinterpreted
- Commercially available commodity chemicals normally need not be justified as starting materials
  - Commercially available = available in pre-existing non-pharmaceutical market
  - The applicant must be able to present information supporting this statement
    - At times misinterpreted to include anything listed for sale
  - Information on synthesis still necessary for justification of the starting material specification and carry-over discussion
  - Further purification may be needed



Definition of GMP-starting Materials

- A justification for the Starting Materials should be supplied
  - Starting materials can only be justified once the criticality of all steps has been discussed
  - Often, starting materials are selected and then only subsequent steps are discussed. This is not sufficient
- Complexity is not a term used in Q11
  - GMP-starting materials should not be assessed based on their complexity

JUSTIFY
JUSTIFY
JUSTIFY

Length of Synthesis and Control Strategy

- Both Length of Synthesis and Control Strategy are important
- Length of Synthesis
  - A number of chemical transformations need to separate the GMP-starting material and the final API
    - The fewer synthetic steps carried out under GMP, the higher the risk to the quality of the active substance (impurities, cleaning, cross-contamination)
  - Manufacturing steps which impact impurity profile of API should normally be included in process description

Length of Synthesis and Control Strategy

- Control Strategy
  - Enough of API manufacturing process must be disclosed so impurity fate/purge can be understood
  - The control strategy ensures the individual batch quality, but relies on GMP to ensure that the conditions do not change over time.
- Length of Synthesis and Control Strategy
  - A long synthesis (many transformation steps) with a poor control strategy - **very likely not accepted**
  - A short synthesis with an advanced control strategy - **very likely not accepted**

Third Party Information Not Accepted

- Assessors will not accept third party confidential information
  - *E.g. …the manufacturer of Starting Material X commits to inform the Authority directly concerning the synthesis of Y and any changes will be communicated…*
- The applicant's responsibility for the quality of the drug substance must be clear
  - Subsequent changes in the supply chain could neither be requested nor enforced
  - Any acceptance of GMP declarations of this nature would not translate to the lifecycle of the product

What Do the Authorities Wish To See?

- A distance from the GMP-starting materials and the finished drug substance
  - Typically several synthetic steps
- A good control strategy
  - *E.g.* starting material specifications, in-process controls and/or intermediate specifications, carry-over discussions, genotoxicity discussions, spiking studies (empirical results strongly encouraged)
- Justified GMP-starting materials
  - Clearly stated in S.2 (for ASMFs both in AP and RP)
- Information on synthetic steps preceeding the GMP-starting materials
  - Would redefinition put a critical step under GMP-control?

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