Whitepaper

Is your Active Pharmaceutical Ingredient quality control strategy up to standard?

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STAR DUB
Experts in Regulatory Affairs

White paper

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The last couple of years we see a trend of health authorities (HAs) across the globe increasingly raising questions on the control strategy of active pharmaceutical ingredients (APIs) when reviewing Drug Master files (DMFs, including CEP DMFs) or drug substance sections (3.2.S).

Based on ICH Q11 [1] and related guidance, HAs are expecting more information on how API manufacturers control and maintain the quality of their APIs, from development throughout the lifecycle. The GDUFA guideline from the FDA (Guidance for Industry: "Completeness assessments for Type II API DMFs under GDUFA")[2] is referring to ICH Q11 [1]. EMA also published a guideline (EMA/454576/2016 [3]) and a reflection paper (EMA/CHMP/CVMP/ QWP/826771/2016 - Corr. 1; [4] marked as "no longer valid", but to date not replaced with a more recent version) with additional clarification.

> *"A control strategy is a planned set of controls, derived from current and process understanding, that assures, process performance and product quality" (ICH Q10* [5]*; ICH Q11* [1]*)*

> *"Specifications of starting materials, intermediates and the active substance, reaction parameters (stoichiometry, temperature, pH, reaction times, etc.), in-process controls, release testing, and working under GMP all form an integral part of the control strategy" (EMA/CHMP/CVMP/QWP/826771/2016 - Corr. 1, Reflection paper on the Requirements for Selection and Justification of Starting Materials for the Manufacture of Chemical Active Substances* [4]*)*

In this whitepaper we will explain what is understood with a control strategy for APIs. API manufacturers are expected to demonstrate full knowledge and full control of all aspects that are related to the API:

- The choice of the Regulatory Starting Material (or Registered Starting Material; RSM),
- Knowing the potential impurities in the RSM (by knowing how the RSM is synthesized),
- Knowing the quality of all materials used in manufacturing,
- Understanding the potential impurities formed during processing,
- Knowing the critical unit operations that need to be controlled (either by maintaining/monitoring process parameters and/or by conducting in process tests)
- Identify the potential impurities that may be formed during the process steps.
- Knowing which impurities are actually formed and understanding how and in which step(s) these are removed,
- Identifying the quality attributes and which need to be tested or confirmed with justifiable acceptance criteria.

At the end of this white paper a useful checklist is provided.

Choice of Regulatory Starting Material

The term (regulatory) starting material has been adopted to indicate the point where regulatory change control and current good manufacturing practices (CGMPs) are introduced into the process steps of a drug substance (chemical syntheses, purifications, physical processing). When authoring a DMF, the choice of the regulatory starting material (RSM) is important: The RSM should be a significant structural fragment of the final API. If multiple structural fragments are introduced at different stages of the route of synthesis, multiple RSMs may need to be identified/defined and described.

To demonstrate knowledge of the (potential) impurities present in the RSM (including the “fate and purge” of these impurities) details on how the regulatory starting material (RSM) is synthesized should be provided to HAs. DMF holders are expected to submit a basic flow diagram towards the RSM with the used chemistry (no in-depth process details). Although details on the synthesis of the RSM are described in the DMF, GMP obligations do not apply to pre-RSM processes (ICH Q7 [6]).

Route of Synthesis

Where in the past information on the route of synthesis (starting material → intermediates → API) was sufficient to meet the requirements of HAs, ICH Q11 [1] clearly outlines the current expectations:

- The HAs are expecting companies to file detailed information how the structure of the API is formed and in at least 2 synthesis steps (crystallizations, salt formations and physical processing steps not included). The intermediates should be isolated before going into the next synthetic step.
- The chemistry used in the process steps should be discussed in depth and should comply with the ICH quality guidance (e.g. ICH Q3C on residual solvents [7], ICH Q3D on elemental impurities [8]).

- The manufacturer has to demonstrate a high level of understanding of the processes towards the final API by, describing the potential API impurities, how they are formed and how this could be prevented or minimized, and how the subsequent manufacturing process steps have impact on these impurities, e.g. will these be converted in the next steps into other impurities or will these be removed in further processing steps (carry-over; fate and purge).

Critical quality attributes, critical process parameters and controls

Critical quality attributes (CQAs) are physical, chemical, biological, or microbiological properties or characteristics of the API that should be within an appropriate limit, range, or distribution to ensure the desired product quality. Impurities are important CQAs. Examples of API impurities are related substances, residual solvents, residual chemicals and elemental impurities.

When API manufacturers understand which process parameters affect the defined CQAs and how the CQAs are affected, monitoring and controlling of the so-called critical process parameters (CPPs) leads to successfully achieving the desired product quality. The European Medicines Agency (EMA) describes it as follows:

> *"A critical step is defined as one where the process conditions, test requirements or other relevant parameters must be controlled within predetermined limits to ensure that the drug substance meets its specification." - [EMA guideline EMA/454576/2016* [3]*]*

Two examples of critical process parameters and their relation to CQA's:

1.) Reaction temperature (range). Reaction temperature may be crucial to prevent or reduce formation of impurities (temperature too high) or to assure a complete conversion of the intended chemical reaction (temperature too low).
2.) Presence of oxygen. When the intermediates or API are sensitive to oxidation, presence of oxygen must be prevented by conducting the process steps under an inert atmosphere (e.g. nitrogen, argon).

In order to establish a constant and reproducible quality of the API for every batch, the CPPs should be monitored and/or controlled adequately.

Overall, all CQAs should be identified to manage all known risks related to the manufacturing processes and to assure individual batch quality. The set of CQAs may be partially addressed by analytics and setting specifications and may be partially risk based with an appropriate risk assessment.

Is your Active Pharmaceutical Ingredient quality control strategy up to standard? Potential requests from HAs

A DMF is expected to describe a well-defined starting material, route of synthesis with sufficient number of chemical steps (>1) and an adequate set of defined CQAs and CPPs. Suboptimal choices and descriptions may result in HAs requesting redefinition of the RSM or more information on the control strategy. This poses a risk for delayed approval and/or increased costs.

> *"It does not follow that a short route of synthesis can be accepted if a good control strategy is in place, nor that a poor control strategy can be compensated by a longer synthetic route carried out under GMP." - (EMA/CHMP/CVMP/QWP/826771/2016 - Corr. 1, Reflection paper on the Requirements for Selection and Justification of Starting Materials for the Manufacture of Chemical Active Substances* [4]*)*

For example, when the RSM needs to be redefined and the number of registered steps is extended, the current RSM supplier(s) will become intermediate suppliers. Intermediates suppliers need to become GMP compliant which may affect the cost price. In addition, API manufacturers need to seek agreement with new RSM and intermediates suppliers on using their intellectual property. In case new information is provided and reviewed by the HAs, additional questions may need to be resolved before the updated DMF is accepted.

It is our opinion that describing an adequate control strategy will reduce the risk of agency questions and/or requests to update the DMF in accordance with ICH Q11 [1]. Pro-actively updating current DMFs will save time and resources and should be regarded as a sound investment in continued market access.

When you need help with the description and set up of a control strategy, which is acceptable for HAs, don't hesitate to contact the regulatory experts of Starodub B.V.

Checklist for your Quality Control Strategy for APIs

- Name and address of RSM manufacturer
- Known manufacturing route to RSM; Flow chart (process steps, reagents, solvents) from RSM manufacturer
- Details on the RSM
    - Well defined structure, significant structural part of the API.
    - Identity testing (HPLC, TLC, melting point); sometimes adding IR, MS or NMR data for confirmation of structure
- Quality control of RSM
    - Specification
    - In-house testing of RSM (e.g. assays and related substances)

- Control of related substances in RSM
    - Which related substances can be expected based on flow diagram (assessment)?
    - Control via fate and purge in route RSM to API, either by risk assessment or by determining purge factors of the different (purification) steps.
    - Control via API specification with defined acceptance criteria in case RSM impurities may carry over to the final API.
- Adequate number of chemical conversion steps from RSM to API (> 1)
- Control of residual solvents, reagents, catalyst(s) and auxiliary materials used in route RSM to API; Fate and purge, via risk assessment or analytically determined.
- Control of (potential) genotoxic impurities used in route RSM to API; Report with assessment on genotoxic potential of reagents and catalysts used in route to RSM and in route to API
- Control of ICH Q3C Class I solvents (such as benzene, chloroform) [7]
    - Used in route towards RSM and/or API.
    - Introduced directly or indirectly via e.g. acetone, hexane, methanol, toluene, dichloromethane.
- Control of related substances specified for API
    - CQAs
    - Compliance compendia
    - Compliance ICH (ICH Q3A-D [9] [10] [7] [8])
- Control of solvents, reagents, auxiliary materials and catalyst(s) in API
    - Specification (always: when used from final intermediate onwards)
    - Fate and purge (risk assessment)
    - Batch analysis results
- Control of elemental impurities; Report with assessment/evaluation in accordance with ICH Q3D [8].
- Polymorphism; If polymorphism is observed, report with a summary of available information.
- Particle Size Distribution; When relevant, demonstrate consistency in Particle Size Distribution

References

[1] ICH Q11, “Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities).”

[2] FDA, “Guidance for Industry: Completeness assessments for Type II API DMFs under GDUFA.”

[3] EMA, “Guideline on the chemistry of active substances,” *EMA/454576/2016*, 2016.

[4] EMA, “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*, 2017.

[5] ICH Q10, "Pharmaceutical Quality System."

[6] ICH Q7, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients."

[7] ICH Q3C, "Impurities: Guideline for Residual Solvents."

[8] ICH Q3D, "Guideline for Elemental Impurities."

[9] ICH Q3A, "Impurities in New Drug Substances."

[10] ICH Q3B, "Impurities in New Drug Products."

About Starodub

Reliable, Efficient and Knowledgeable

Starodub BV was founded in May 2014. The company started with one employee, the founder Valentyna Starodub. By today, our team has grown to round 20 employees and has a valuable network of specialized experts. We partner with (bio)pharmaceutical and medical device companies worldwide to ensure that regulatory requirements are met and business goals, such as quick market access and compliance, are achieved. Please check the Our services page to learn how we can support you with meeting your business goals.

Our lean and powerful team strives to be of added value to our clients. All employees are highly educated and obtained degrees in pharmacy, chemistry, biology or related. Our short reporting lines are key to finding the most efficient road to your success. One of our experts will be your primary contact and the team's collective knowledge and resources are available to give reliable advice and execute projects in the most efficient way. Together, we connect the dots and look beyond the scope of projects to make sure all aspects of importance are addressed.

At Starodub BV consistency and assurance of quality are considered as being highly important. A quality management system has been implemented and we strive to comply with GxP and ISO 9001/13485 constantly. In addition, we have an external board of control, acting as the sparring partner to set the optimal course for our company.

We strive to be a true partner to Our clients, who rate our services as ≥4.5 on a scale of 1 (poor) to 5 (excellent). This motivates us to maintain the highest professional standards and to implement continuous improvement.

About the Author

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Nicon Moers is a former Senior RA Manager of Starodub BV (2014-2019). He is an expert on all quality aspects of active pharmaceutical ingredients and small molecule products. In case you would like to ask a question on this white paper, please contact Valentyna Starodub at info@starodub.nl.