Quality and Regulatory: new frontiers in API manufacture
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Selection of API starting material: GMP and regulatory approaches

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The views expressed in this presentation
are my own views
and do not necessarily represent official policy

API Starting materials (SM): background

- More and more manufacturers of APIs propose short steps (1 or 2) synthesis
- Proposed API SM with a structure very close to the final API
- Manufacturers of the proposed API SM are often external suppliers
- Poor level of information on manufacture of API SM, level of impurities and their control from SM

Why this situation?

The Starting Materials in the application:

- Mark the beginning of the detailed description of the manufacturing process and controls = binding information
- Are the starting points for Variations and the lifecycle of the dossier
- Are the starting point for implementation of GMP

Regulatory guidance

- ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (November 2000)
- EU NfG on the Chemistry of new active substance CPMP/QWP/130/96, Rev 1 (February 2004)
- ICH Q11: Development and manufacture of drug substances (May 2012)

ICH Q7 – API Starting Materials

- For synthetic processes the production of the API starts with the introduction of the starting materials
- The approved starting materials are therefore the starting point for GMP and variations and must be representative of the overall synthetic process.

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging

ICH Q7 – API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or purchased in-house. API starting materials are normally of defined chemical properties and structure.

EU nfg chemistry of new active substance

According to the guideline, all the synthetic steps critical for the safety and the efficacy of the API should be included in the description of the process.

Description of the process in S.2.2 of the dossier shall include all the steps starting from the API starting material to the isolated intermediates and ultimately to the final API.

EU nfg chemistry of new active substance

- “Significant structural fragment”
- Name and address of suppliers should be listed
- Full characterisation, complete specifications including an impurity profile/ method validation
- Discussion on impurities present in the API SM + possibility of their carry over (or as derivatives) into the final API
- Acceptance criteria for API SM to be set based on evaluation of the fate of impurities when subject to the normal process/synthesis
- Information about its synthesis (flow-chart) to enable assessors to judge of the suitability of the proposed specifications

EU nfg chemistry of new active substance

- A one step synthesis is not acceptable unless in certain specific circumstances:
  - ✓ If API SM described in Ph. Eur. and covered by a CEP presented in S.2.3
  - ✓ If API SM is an active substance authorised in a marketing application in EU.

ICH Q11 - API Starting Materials

Principles in determining where the API process begins:

- Changes in material attributes or in operating conditions occuring near the beginning of the process have lower potential to impact the quality of final API
- Relationship between risk and number of steps from the end of the manufacturing process results from two factors:
  - The physical properties of the drug substance (final crystallisation and subsequent operations, all occuring usually at final stages)
  - Formation, fate and purge of impurities (impurities generated early in the process are more likely to be removed in purification operations than those generated late in the process, therefore consider risk of carry over into the final API)

ICH Q11 Principles (cont.)

- To assess suitability of controls (including on impurities) in place on the API and manufacturing process, description of sufficient information of the API process

  ⇒ This implies description of multiple chemical steps

- Manufacturing steps which are critical = impacting the impurity profile of the API should be included in the process description

- Each branch of a convergent synthesis begins with one or more starting materials. The GMP provisions described in ICH Q7 apply to each branch from the introduction of a starting material.

ICH Q11 - Principles (cont.)

- A SM of defined chemical property and structure (non-isolated intermediates are not appropriate SMs)

- SM incorporated as a significant structural fragment into the the structure of the drug substance

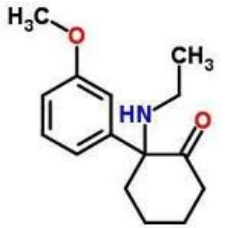
All the above principles should be applied TOGETHER in the selection of SMs rather than applying them in isolation

ICH Q11 - Control strategy to assure quality of API

- Definition of control strategy:

  A planned **set** of controls, derived from current product and process understanding, that assures process performance and product quality.

  Every API process has an associated control strategy.



ICH Q11 - Control strategy (cont.)

- A control strategy can include but is not limited to
  - Controls on material attributes (raw materials, starting materials, intermediates....)
  - Controls implicit in design of the process (order of steps or addition of reagents)
  - In-process controls (IPC tests and process parameters)
  - Controls on drug substance (e.g. release testing)

API Starting material - experience of assessors

- 1-step synthesis is not acceptable (generally)
- Inappropriate to pre-define a number of steps needed
  - Synthetic step involves cleavage and/or formation of covalent bonds, the molecular structure of the SM or intermediate is modified
  - Key stereo-centre generating steps, genotoxic impurities & class 1 metal catalysts would normally be expected to need to be covered under GMP since they would be considered critical.

API SM – experience of assessors

- Purification, salt formation, salt transformation or milling are not considered synthetic step (but contribute to the overall control strategy)
- One pot synthesis without isolated intermediate & insufficient IPCs will also often trigger redefinition request
- Commercial availability on its own is not a criterion of selection of a SM
  - API SM prepared by custom synthesis should meet the requirements of ICH Q11

Description of the SM

- SM should generally not have a structure close to that of the final substance

  « Significant fragment » does not mean « close to the final API »

  - Info on manufacture of the SM is needed to judge suitability of its specification. Binding part of the dossier
  - Names and address of manufacturers of SM are required
  - Declarations that steps before the proposed SM are carried out under GMP is not taken into consideration

Description of the SM (2)

- The impurities of the SM should be known, origin and fate of these impurities and their carry over to the final API should be described
- Application of stringent specifications for SM is part of the control strategy BUT should not be the only criteria to guarantee the quality of the API
- The specification of the SM should include suitable limits for known impurities, unspecified impurities and total impurities
- The specification should address limits for solvents, reagents, and catalysts used, as needed

Redefinition requested

- Where the API SM is not acceptable by assessors, redefinition of SM is requested.
- Request for re-definition of SM has been a top deficiency in CEP applications since end 2009.
- This has significant consequences, additional work for Industry and authorities, and is therefore to be avoided

Redefinition requested, new actors…

New actors in the supply chain: manufacturers of intermediates

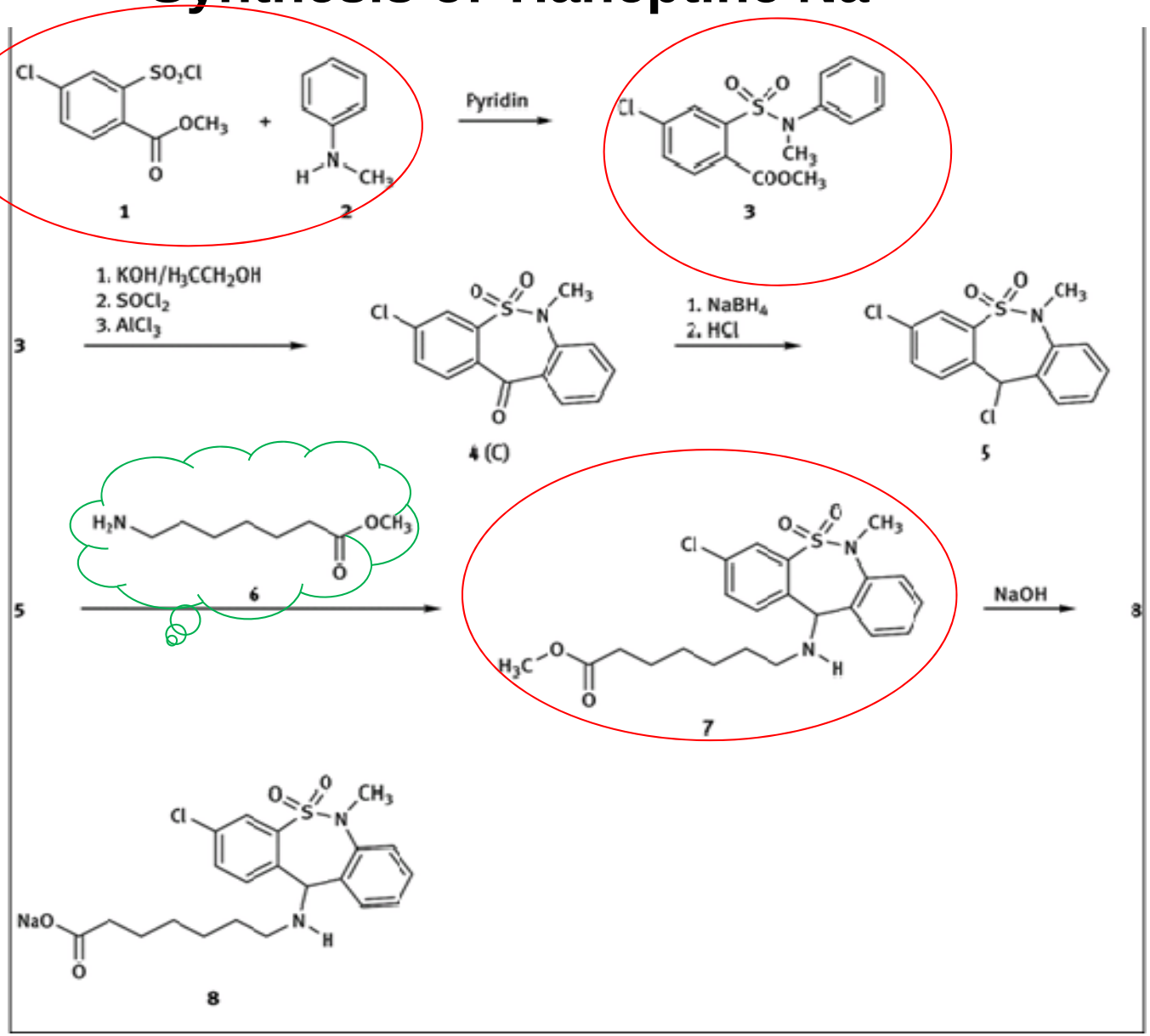
- Need to manufacture under EU GMP Part II
- Ultimate responsibility is on the QP of the manufacturing authorisation holder
- Need to share full information on manufacture and controls of their material with the API manufacturer (and marketing authorisation holder)

New actors in the supply chain

- Issues related to disclosure of proprietary information related to API SMs: is often limited to preserve API SMs producers know-how and expertise.
- "3rd party" information not accepted by EDQM nor by the licensing authorities in EU

➔ For some dossiers: the API manufacturer has to change their supplier after a request for redefinition of SM.

Synthesis of Tianeptine Na



Get it right first time!

- API starting materials is a very important topic for the quality of APIs
- Assessed based on the science and the knowledge presented in the dossier
  - Synthesis and dossier dependent, no unique rules
- Provide a good, well supported justification explaining the choice of starting material(s), based on the principles of ICH Q11, particularly with respect to formation of, purging of and control of impurities

Get it right first time!

- Applicant should display their expertise in their synthesis and this helps to increase confidence in the knowledge held by applicants of their process.
- Critical steps of the synthesis should be under GMP.
- During lifetime of the API, be aware that any changes in the manufacturing process (including change in suppliers of starting materials) may impact the impurity profile, and have to be notified to authorities.

Conclusion

Use ICH Q11. Assurance of quality of API results from choice of:

- **appropriate starting materials**
- **application of suitable control strategy**
- **and manufacture under GMP.**

‘Watch this space….’

EU will publish an explanatory note to ICH Q11 to emphasize how it should be used.

THANK YOU !