Presentazione: Evoluzione nell'identificazione dello starting material nella produzione di un API: aspetti GMP e regolatori

Relatore: Luca Ginnari Satriani

data: 19/04/2016

Agenzia Italiana del Farmaco

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Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	x	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	x	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	x	☐	☐	☐ facoltativo
2. Consulenza per una società	x	☐	☐	☐ facoltativo
3. Consulente strategico per una società	x	☐	☐	☐ facoltativo
4. Interessi finanziari	x	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	x	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	x	☐	☐	☐ facoltativo
7. Sperimentatore	x	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	x	☐	☐	☐ facoltativo
9. Interessi Familiari	x	☐	☐	☐ facoltativo

* Luca Ginnari Satriani, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 25.03.2015 e pubblicato sulla Gazzetta Ufficiale del 15.05.2015 in accordo con la policy EMA /626261/2014 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

N.B. Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva.

Regulatory guidance/documents

- November 2000 - ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
- February 2004 - EU NfG on the Chemistry of new active substance - CPMP/QWP/130/96, Rev 1
- May 2012 - ICH Q11: Development and manufacture of drug substances
- June 2012 - Top ten deficiencies - New Applications for Certificates of Suitability (2011) - PA/PH/CEP (12) 15
- September 2014 - Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active subsances – EMA/448443/2014

API Starting Material definition

ICH Q7:

An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance.

ICH Q11:

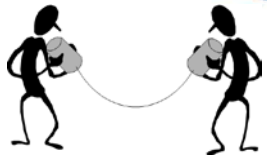
"A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials"

API Starting Material definition

From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps.

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

API Starting Material definition



Significant structural fragment: a great misunderstanding!?

ICH Q11:

"Significant structural fragment" in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials.

Reflection Paper EMA/448443/2014:

The term "Significant structural fragment" is frequently misinterpreted by applicants as meaning structural proximity to the active substance.

Justification of a late intermediate as starting material by claiming it is a significant structural fragment is not considered a valid argument as this could apply to any intermediate in the manufacturing process.

Selection of API Starting Material

Redefinition of API SM in further back in the synthesis: experience of assessors

Top ten deficiencies - PA/PH/CEP (12) 15:

"TOP 2 (3.2.S.2.2) / (3.2.S.2.3): Proposed starting material not accepted:

More and more frequently, applicants propose short synthesis, with complex products proposed as starting materials in the application. This is generally not acceptable and the complex material is considered by the assessors as an intermediate in the synthesis.

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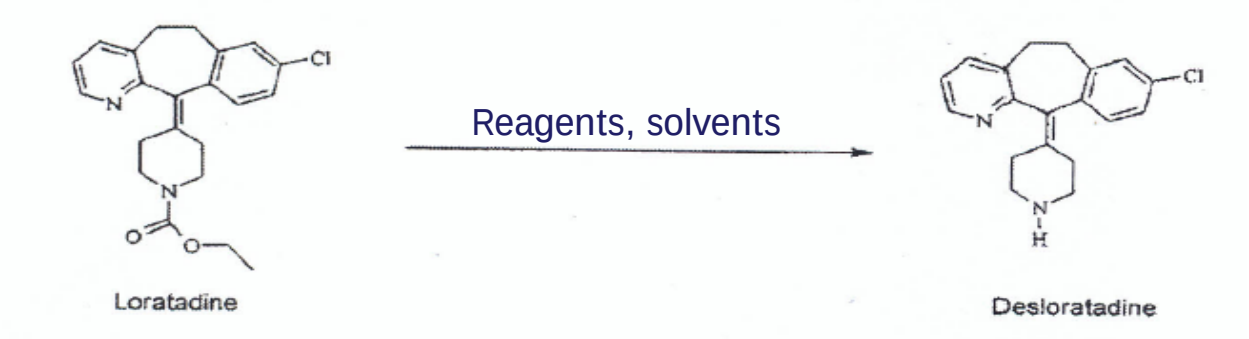
Commercial availability is an insufficient justification to accept a SM.

Selection of API Starting Material

Short synthesis



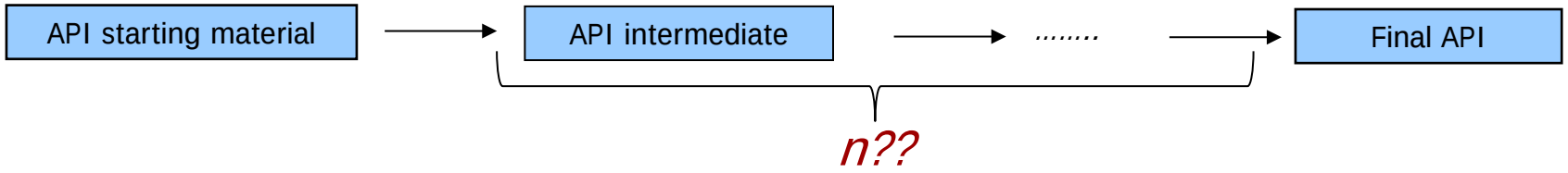
Short synthesis is not acceptable unless in certain circumstances (RP EMA/448443/2014):

1. If API SM is itself an active substance described in Ph.Eur. and covered by a valid CEP;

2. If API SM is authorised as an active substance in a valid MA in th EU (same API manufacturer, site, process, impurity profile and specification).

Selection of API Starting Material

How many steps you have to consider?

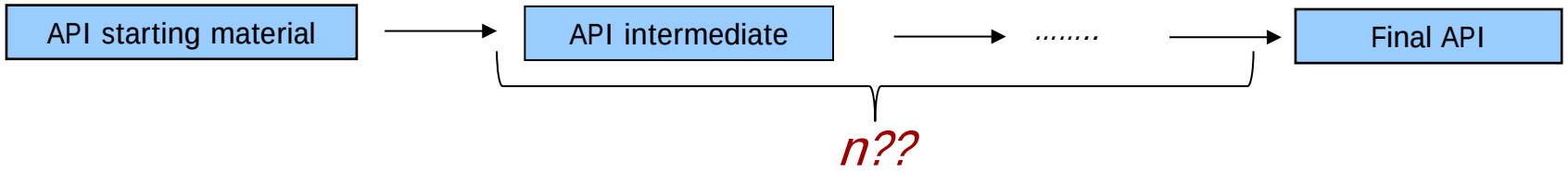


- Top ten deficiencies - PA/PH/CEP (12) 15 - TOP 2 :

"Multiple synthesis steps should separate the starting material(s) and the active substance. A synthesis step is a step in the synthesis where covalent bonds are formed or broken. A process consisting of only 1-2 steps is generally not sufficient to ensure full control of the quality of the final substance."

Selection of API Starting Material

How many steps you have to consider?



- Reflection Paper EMA/448443/2014:

"A sufficient number of chemical transformation steps, as defined in the glossary of ICH Q11, need to be included so that the generation, fate and control of impurities can be understood."

Selection of API Starting Material

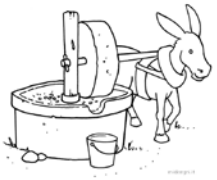
How many steps you have to consider?

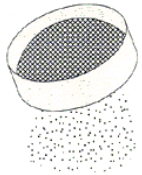
ICH Q11 (Glossary):

Chemical Transformation Step:
For Chemical Entities, a step involved in the synthesis of the chemical structure of the drug substance from precursor molecular fragments. Typically it involves C-X or C-C bond formation or breaking.

Reflection Paper EMA/448443/2014:

"Neither recrystallization nor salt formations are considered chemical transformation steps, and neither are activities unlikely to have an impact on API purity such as milling or sieving."





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Selection of API Starting Material

How many steps you have to consider?

Reflection Paper EMA/448443/2014:

A sufficient number of purification steps need to be documented so that the fate and purge of impurities can be understood.

Multiple synthetic transformations carried out in one vessel without intermediate isolations (sometimes referred to as telescoped steps or "one pot reactions") provide fewer opportunities for purification than if isolation of intermediates were carried out.

As with any complex reaction, a high number of variable parameters lead to a higher risk of producing active substance of variable quality.

Regulators will therefore expect a commensurately high level of process understanding and control.

One-pot reactions

Selection of API Starting Material

How many steps you have to consider?

- ICH Q11:

Relationship between risk and number of steps from the end of the manufacturing process results from two factors:

1. *The physical properties of the drug substance (final crystallisation and subsequent operations, all occuring usually at final stages)*
2. *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)*

Selection of API Starting Material

How many steps you have to consider?

Reflection Paper EMA/448443/2014:

EU Authorities are concerned that introduction of impurities into the active substance from non-GMP manufacture, (e.g. from poor cleaning of vessels previously used for other purposes or inadequate control of processes), which would not necessarily be picked up by routine analytical testing is a significant risk.

The fewer synthetic steps carried out under GMP, the higher the risk to the quality of the active substance.

The control strategy in place for a given manufacturing route mitigates the risk associated with the manufacturing process and assures the quality of the active substance.

Selection of API Starting Material

Critical steps

- ICH Q11:

"Manufacturing steps that impact the impurity profile of the drug substance should normally be included in the manufacturing process described in section 3.2.S.2.2 of the application."

- Reflection Paper EMA/448443/2014:

"It therefore follows that steps critical for the purity of the active substance should be performed under GMP, which forms an integral part of any control strategy."

Selection of API Starting Material

Critical steps

Reflection Paper EMA/448443/2014:

The criticality of a given step is related to its distance (in terms of synthetic steps) from the active substance, the subsequent processing and the overall control strategy being applied.

The control strategy mitigates the risk associated with a given critical step, but does not necessarily affect its criticality.

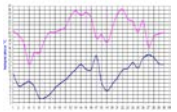
Selection of API Starting Material

Critical steps

Critical steps could be for instance:

- *Steps which introduce key structural features of the active substance, for example key functional groups or stereochemistry;*

- *Steps involving formation and/or purge of key impurities (including works-ups, phase separations and crystallisations);*
- *Steps where careful control of stoichiometry, temperature, pH or other process variables is crucial for active substance quality;*



- *Steps which employ or generate genotoxic compound;*

- *Step which employ class I solvents and/or toxic metals;*

- *Complex where multiple variables could impact reaction outcomechemical transformations (multiple reagents, catalysts, solvents, etc..);*

- *The final purification step.*

Selection of API Starting Material

The control strategy

- ✓ *Set suitable specifications of starting materials,*
- ✓ *Evaluate the API production process impact on the fate and purge of SM impurities (including synthetic and purification steps);*
- ✓ *Set suitable process parameters and IPC to assure a GMP process control of API production process;*
- ✓ *Evaluate the potential carry-over of impurities from starting material in API (or in a suitable intermediate);*
- ✓ *Set suitable specifications of intermediates/API.*

Selection of API Starting Material

Justification of SM selection

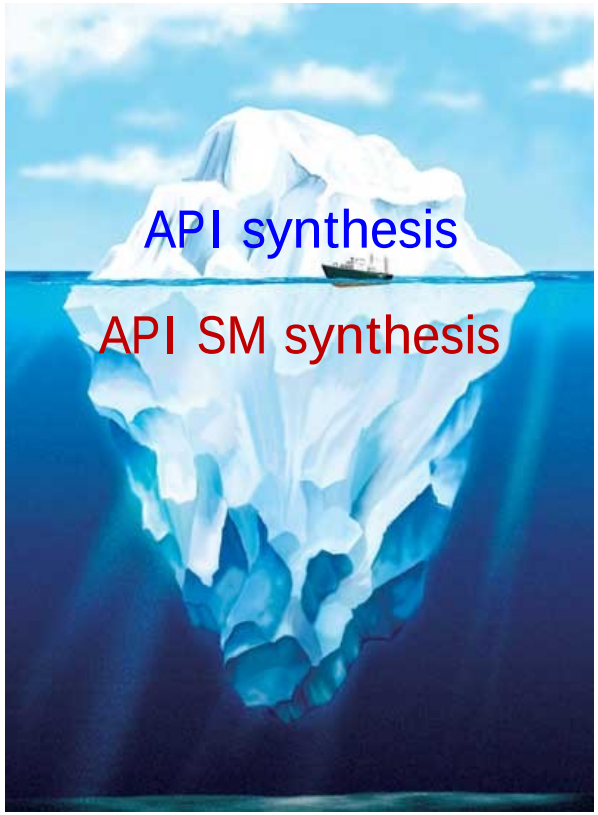
- *The suitability of a starting material needs to be justified against the principles above discussed.*

- *The dossier must contain an appropriate discussion on known and unknown impurities (including residual solvents, catalysts, metals and reagents) and the description of their formation, fate and purge.*

- *The starting material specifications should include tests and acceptance criteria for specified, unspecified and total impurities (including (potential) genotoxic) and where appropriate, limits for solvents, reagents and catalysts used during their synthesis.*

Selection of API Starting Material

API SM information



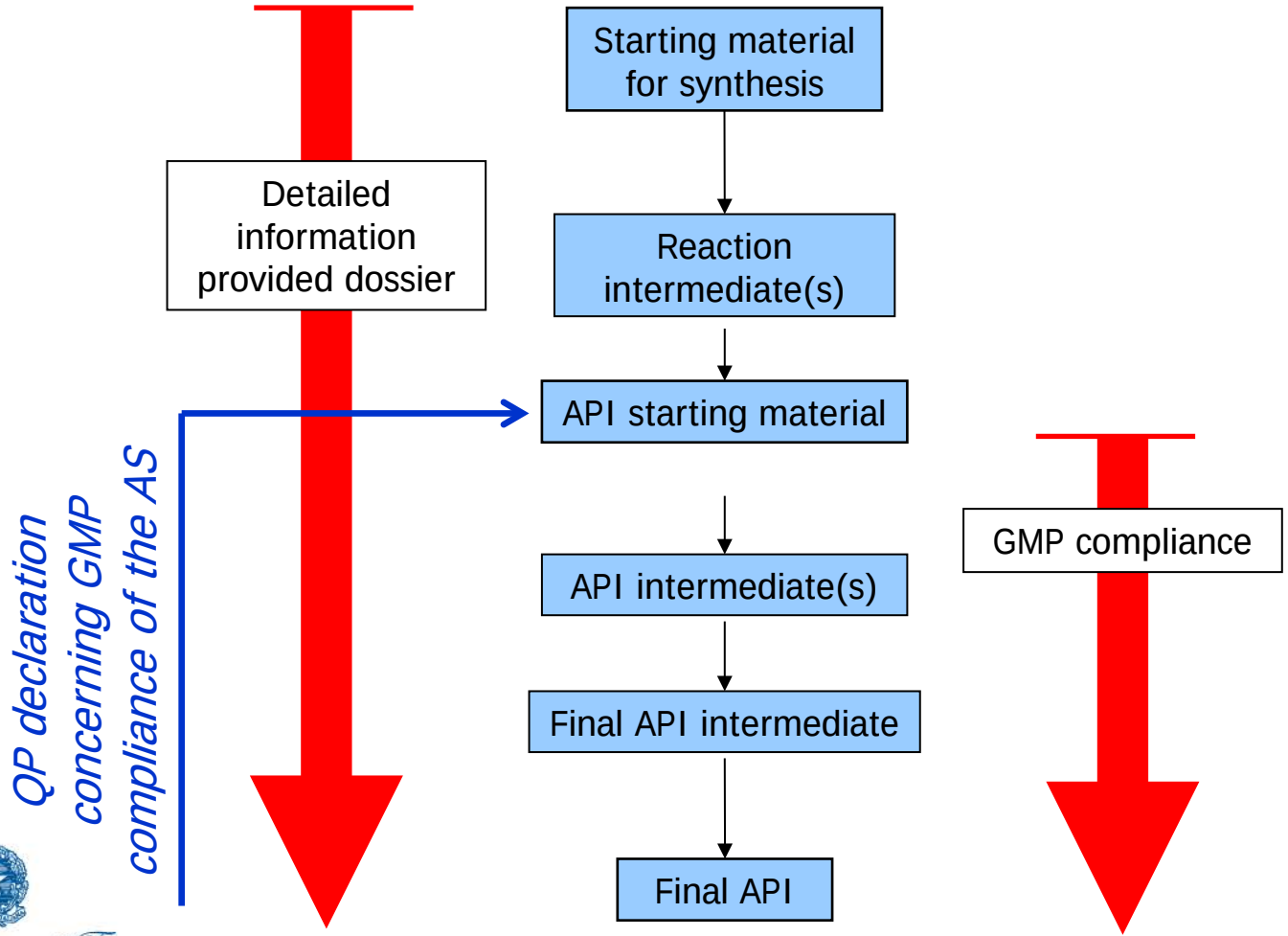
Top ten deficiencies - PA/PH/CEP (12) 15

TOP 5 (3.2.S.2.3) Incomplete specifications for the declared starting materials:

- *"The specifications of the declared starting materials are often not sufficient and fail to include suitable limits for relevant impurities/solvents/catalyst"*
- *"Information on the synthesis of the starting materials (flow diagram) should be provided to support the description of the impurity profile and the proposed specification. "*

Selection of API Starting Material

API SM information



Selection of API Starting Material

API SM information

Reflection Paper EMA/448443/2014:

- ✓ *Information on the SM manufacturers/suppliers of starting materials (including name and address);*
- ✓ *Scheme of the synthetic route used to manufacture the SM, showing all reagents, catalysts and solvents used;*
- ✓ *The specification for a starting material should address impurities and is expected to consider suitable limits for known, unknown impurities and total impurities and where appropriate, limits for solvents, reagents and catalysts used during synthesis of a starting material;*
- ✓ *A tabulated summary of the results of the analytical methods validation carried out should be provided if critical for the quality of the active substance. However, it is not necessary to provide a validation report.*

Selection of API Starting Material

Supplier approval: an integral part of the Control Strategy

- ✓ Perform an analytical evaluation on at least three batches of SM (Eu GMP part II 7.31);
- ✓ Evaluate the flow-chart of synthesis of the new API SM manufacturer and API SM specification (Eu GMP part II: 7.12);
- ✓ Perform a focused audit (on cleaning procedure, control of processes, QC, etc..) (Eu GMP part II: 7.11);
- ✓ Evaluate the need to repeat the API process validation (Eu GMP part II: 7.14)
- ✓ Evaluate the need to perform carry over study of SM impurities/solvents/metals in a suitable API intermediate or in final API (Eu GMP part II: 11.22);
- ✓ Compare the impurity profile of the API manufactured from the SM provided by the new/proposed suppliers (Eu GMP part II: 11.22)

Define a robust Quality Agreement (EU GMP part II: 16.12)

Define a suitable re-inspection frequency based on a Risk Approach (EU GMP part II: 7.14)

Conclusions

- ✓ Scientific reasoning with appropriate justification, considering the whole synthetic approach and control strategy should be used in order to justify the selection of the API starting materials;
- ✓ Control strategy alone is not a sufficient justification of a starting material. Equally, a long synthetic process will not necessarily compensate for a poor control strategy;
- ✓ The selection of the API starting material can be a complex exercise which involves many quality and GMP aspects....

Regulatory

R&D

QC

QA

Production