2018

ICH GUIDELINE TRAINING

NIFDS

KoBIA & KRPIA

ICH Q11 Guideline and QnA

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Session: ICH Q11 Q&A

Presentation Title:

ICH Q11 Guidelines

Questions & Answers

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28 November 2018

ICH
harmonisation for better health

ICH Q11 Questions & Answers – Selection & Justification of Starting Materials.

Training Material

Q11 Implementation Working Group

22 May 2018

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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Training Material overview

- ICH Q11 brief background
- ICH Q11 General Principles and key concepts
- Case study examples to illustrate general principles and Q&As
- Conclusions

Background

- **ICH Q11 Development and Manufacture of Drug Substances (chemical entities and biotechnological/biological entities)**
  - Step 4, 1 May 2012
  - Section 5 Selection of Starting Materials and Source Materials
- **ICH Q11 Questions and Answers**
  - Step 4, 23 August 2017
  - Q&As focus on issues related to the selection and justification of starting materials (Section 5 of ICH Q11)

ICH Q11 Section 5: Selection of Starting Materials and Source Materials

- **5.1 General Principles**
  - 5.1.1 Selection of Starting Materials for Synthetic Drug Substances
  - 5.1.2 Selection of Starting Materials for Semi-Synthetic Drug Substances
  - 5.1.3 Selection of Source and Starting Materials for Biotechnological/Biological Drug Substances
- **5.2 Submission of Information for Starting Material or Source Material**
  - 5.2.1 Justification of Starting Material Selection for Synthetic Drug Substances
  - 5.2.2 Justification of Starting Material Selection for Semi-Synthetic Drug Substances
  - 5.2.3 Qualification of Source or Starting Materials for Biotechnological/Biological Drug Substances (guidance is contained in ICH Q5A, Q5B and Q5D)

ICH Q11 Questions & Answers – Selection & Justification of Starting Materials

- **Clarifying how to apply the ICH Q11 general principles – selection of appropriate starting materials based on science and knowledge of the proposed commercial manufacturing process and controls.**
- **Contents:**
  - 16 Questions and Answers intended to provide additional clarification and to promote convergence and improve harmonisation
  - Should be used in-conjunction with the ICH Q11 document
  - Also contains a decision tree to support the understanding and implementation of the ICH Q11 general principles and the clarifying Q&A
- **Note from Q&A 5.1:**
  - Applicants should consider all of the ICH Q11 principles in the selection and justification of proposed starting materials, rather than selecting just a few principles and using them to justify starting materials. If a proposed starting material does not meet all of the general principles, a rationale should be provided explaining why the starting material is considered appropriate.

What is the scope of the ICH Q11 Questions and Answers relative to the parent guideline ?

- **The scope of the Q&As follows that of ICH Q11, however it has a focus on chemical entities/synthetic drug substances, as defined in ICH Q6A (may not be directly applicable to biotechnological/biological entities)**
- **Applies to commercial drug substances - not in the clinical phase (starting materials are designated based on information gained in the development of the commercial drug substance process)**
- **The focus is for designation of starting materials for the assessment of drug substance manufacturing processes submitted as part of marketing authorisation applications and/or Master Files**
- **This guidance is not generally intended to be applied retrospectively to manufacturing processes which have previously been reviewed and form part of marketing authorisations (unless significant changes are made to the manufacturing processes and controls)**
- **A starting material accepted for one manufacturer's process may not be considered acceptable for a different manufacturer's process, if the proposal does not comply with the guidance in ICH Q11**

General Principles: ICH Q11

5.1.1 Selection of Starting Materials for Synthetic Drug Substances

The General Principles are summarized below (see Appendix 1 for full text):

1. In general, changes that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance.
2. Enough of the drug substance manufacturing process should be described in the application to understand how impurities are formed in the process and why the proposed control strategy is suitable for the drug substance manufacturing process. This will typically include a description of multiple chemical transformation steps.
3. Manufacturing steps that impact the impurity profile of the drug substance should normally be included in Section 3.2.S.2.2.
4. Each branch of a convergent synthesis begins with one or more starting materials. GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material.
5. A starting material should be a substance of defined chemical properties and structure. These should usually be isolated compounds.
6. A starting material is incorporated as a significant structural fragment into the structure of the drug substance.

Section 5.1.1 clearly states that "**All the ~~General~~ ~~P~~rinciples** above should be **considered** in selecting Starting Material(s), rather than strictly applying each general principle in isolation"

Important Information to Apply the General Principles

- **Sufficient knowledge of the manufacturing process and understanding of the origin, fate and purge of impurities is necessary before defining the starting material(s)**
- **This can include:**
  - Understanding of the origin of impurities that impact the drug substance
  - Understanding of how impurities are generated and removed during the manufacturing process
  - Evaluation of the risk of carryover of any mutagenic materials into the drug substance
  - Understanding of the impact of variability on the operating conditions required to control the quality of the drug substance.

Key Consideration: The significance of describing "enough" of the manufacturing process in S.2.2

ICH Q11 Section 5.1.1 states that

- "*enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process, how changes in the process could affect the formation, fate, and purge of impurities, and why the proposed control strategy is suitable for the drug substance manufacturing process*"

Q&A 5.11 further clarifies how to ensure enough of the manufacturing process is described, an applicant should:

- First, identify which steps impact the impurity profile of the drug substance
- Then, consider which of the steps immediately upstream should be included in S.2.2 if they need to be carefully controlled
- If these considerations lead to only a small number of chemical transformation steps, then in order to mitigate the risks associated with contamination or future changes to the synthetic route, one or more steps would generally be added in S.2.2.
- The role of the control strategy in mitigating risks from changes will also be a consideration.

Key Consideration: Steps that impact the impurity profile of the drug substance

"…manufacturing steps that impact the impurity profile of the drug substance should normally be included ….in Section 3.2.S.2.2" **(ICH Q11 principle and Q&A 5.7)**

For non-mutagenic impurities, the ICH Q3A identification threshold serves to identify the level above which the impurity impacts the drug substance (Q&A 5.7)

For mutagenic impurities, the 30% of the ICH M7 acceptable limit serves to identify the level above which the impurity impacts the drug substance (Q&A 5.7)

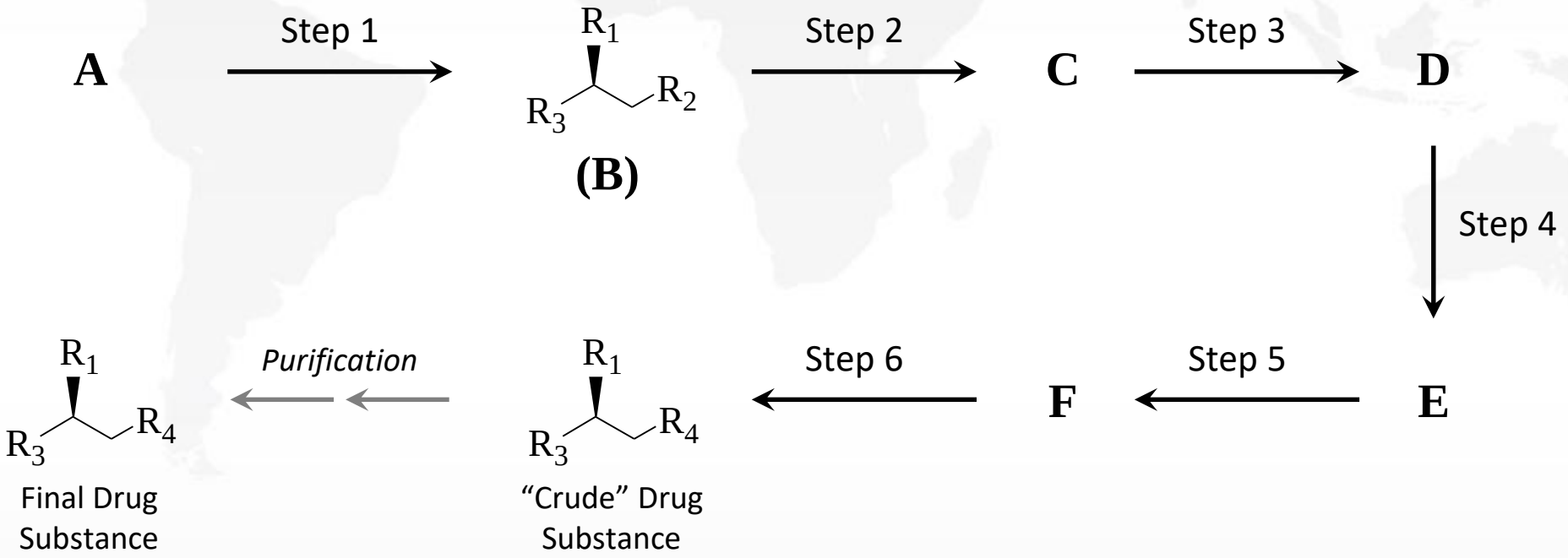
Key Consideration: Impurities that persist across multiple steps

ICH Q11 recommends that "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." However, as described in ICH Q11 Example 4, this principle does not necessarily apply when impurities originate early and "persist" across multiple steps to the drug substance. It is normally expected that the justification for an impurity that persists will be based on it being carried across one or more manufacturing steps upstream of the proposed starting material, when these steps do not otherwise impact the impurity profile of the drug substance (for "impact", see Q&A 5.7).

In the following four slides, Example 4 from ICH Q11 has been expanded to illustrate different scenarios of impurities that impact the impurity profile of the drug substance, e.g., those that are introduced early (Imp 1), relative to when other impurities that impact the impurity profile of the drug substance are introduced (Imp 2 and Imp 3).

ICH Q11 Q&A 5.8 – Persistent Impurities

- Example 4 from ICH Q11

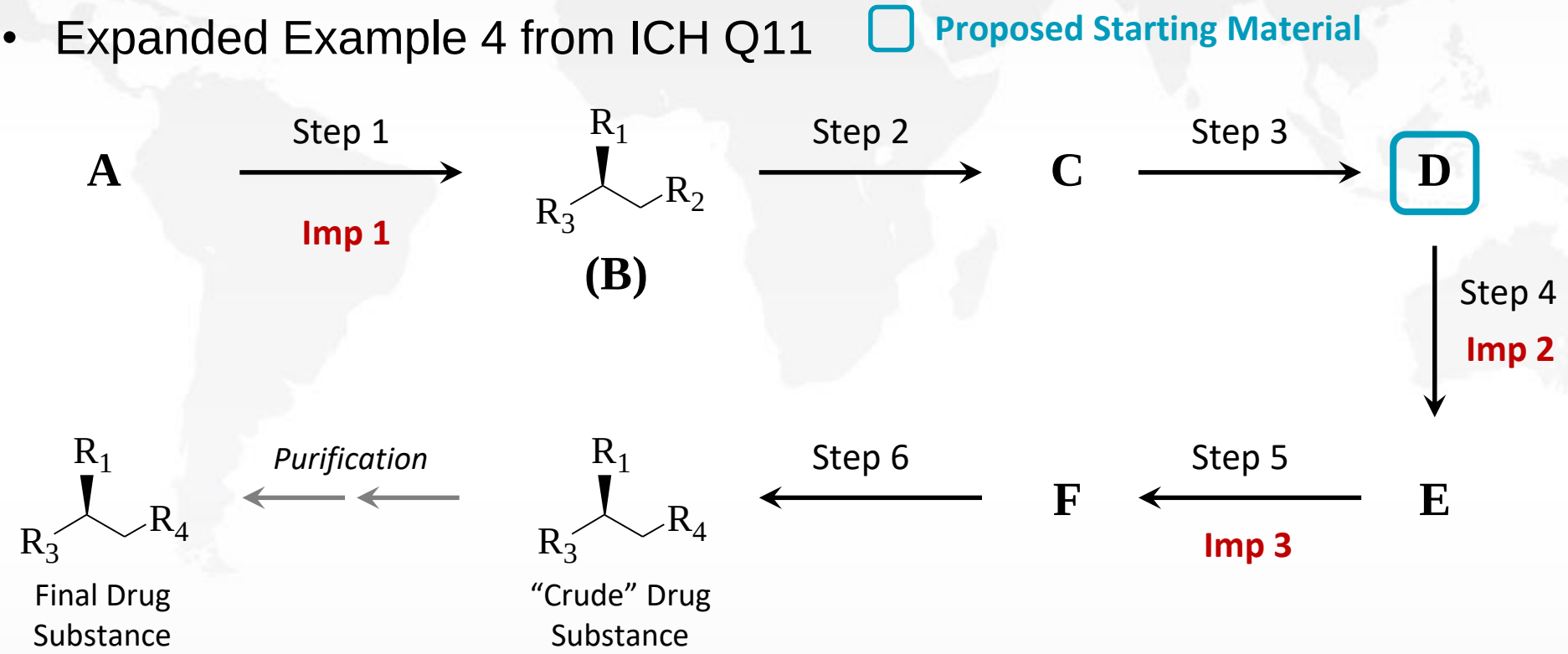


Step 1 results in the formation of the opposite enantiomer of Compound B. This impurity persists to the drug substance (this is referred to as Imp 1 in subsequent slides). All of the significant impurities in the drug substance (other than opposite enantiomer) arise from Steps 4, 5, and 6.

(Note: although the example in ICH Q11 is a chiral impurity, this concept is not limited to chiral

ICH Q11 Q&A 5.8 – Persistent Impurities

- Expanded Example 4 from ICH Q11

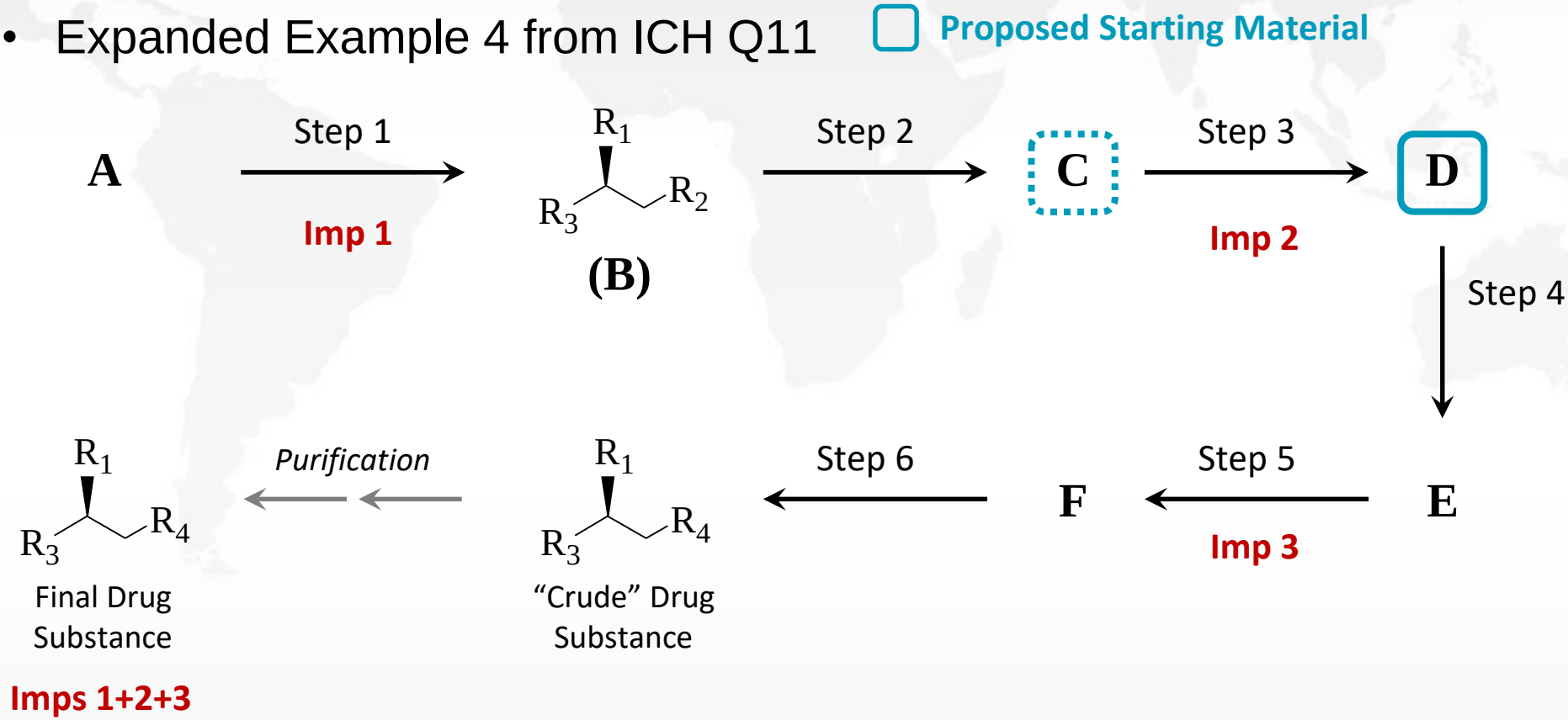


Imps 1+2+3

Impurities 1, 2, and 3 impact the impurity profile of the drug substance; no impurities originate in Steps 2 and 3 that impact the impurity profile of the drug substance. D proposed as starting material.

ICH Q11 Q&A 5.8 – Persistent Impurities

- Expanded Example 4 from ICH Q11



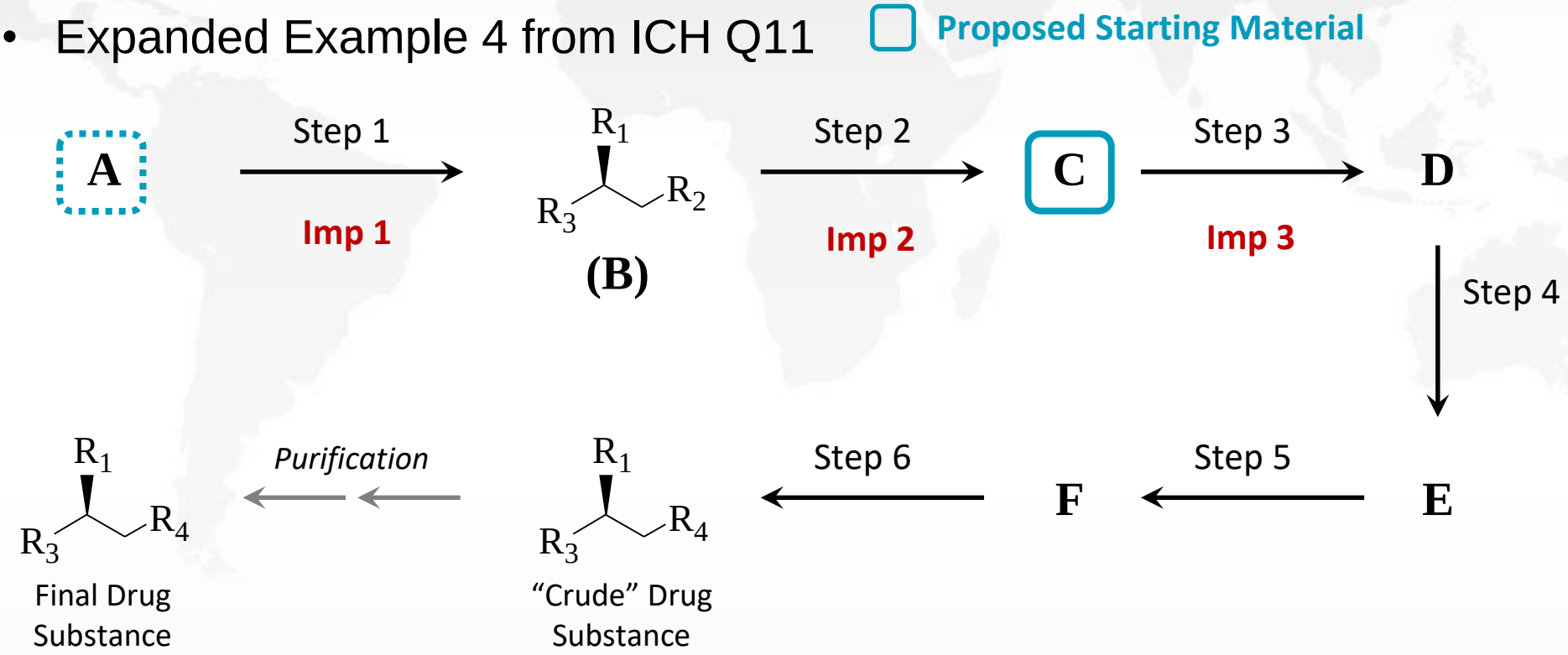
Impurities 1, 2, and 3 impact the impurity profile of the DS

Impurities 2 and 3 originate in Steps 3 and 5 (respectively)

D no longer suitable as a SM – should re-define to C

ICH Q11 Q&A 5.8 – Persistent Impurities

- Expanded Example 4 from ICH Q11



Impurities 1, 2, and 3 impact the impurity profile of the DS and originate in Steps 1 + 2 + 3 (respectively)

C no longer suitable as a SM – should re-define to A

Approaches to Mutagenic Impurities (MI) in selection of starting materials

How to apply ICH M7 principles to SM selection

- Identify mutagenic materials *likely* to be formed or introduced in the process (actual and potential)
  - Use M7 Hazard Assessment Elements to determine which are considered mutagenic

Three approaches are recommended (continued on the following slide):

1. Actual impurities – assess for mutagenicity
2. Reagents + intermediates from commercially available raw materials to API – includes steps upstream of SM
   - Assess for mutagenicity if likely to impact the impurity profile of the DS

Approaches to Mutagenic Impurities (Continued)

3. Impurities in commercially available chemicals, intermediates, etc.

- Likely present in much lower concentration; Inherently lower risk
- Could be present – use risk-based reasoning to assess impact

Steps which introduce impurities that “impact” the impurity profile of the drug substance should be included; generally impact level is >30% of TTC for mutagenic impurities

- In cases when the drug substance is itself genotoxic and for advanced cancer indications, mutagenic impurities are not considered to impact the impurity profile of the drug substance unless they are above the ICH Q3A identification threshold.
- Exception for “persistent” mutagenic impurities – can control in SM specification

Not all steps that include mutagenic impurities need to be included in S.2.2 (see Q&A 5.10)

After SM is defined, for consideration of mutagenic impurities related to changes, refer to ICH M7.

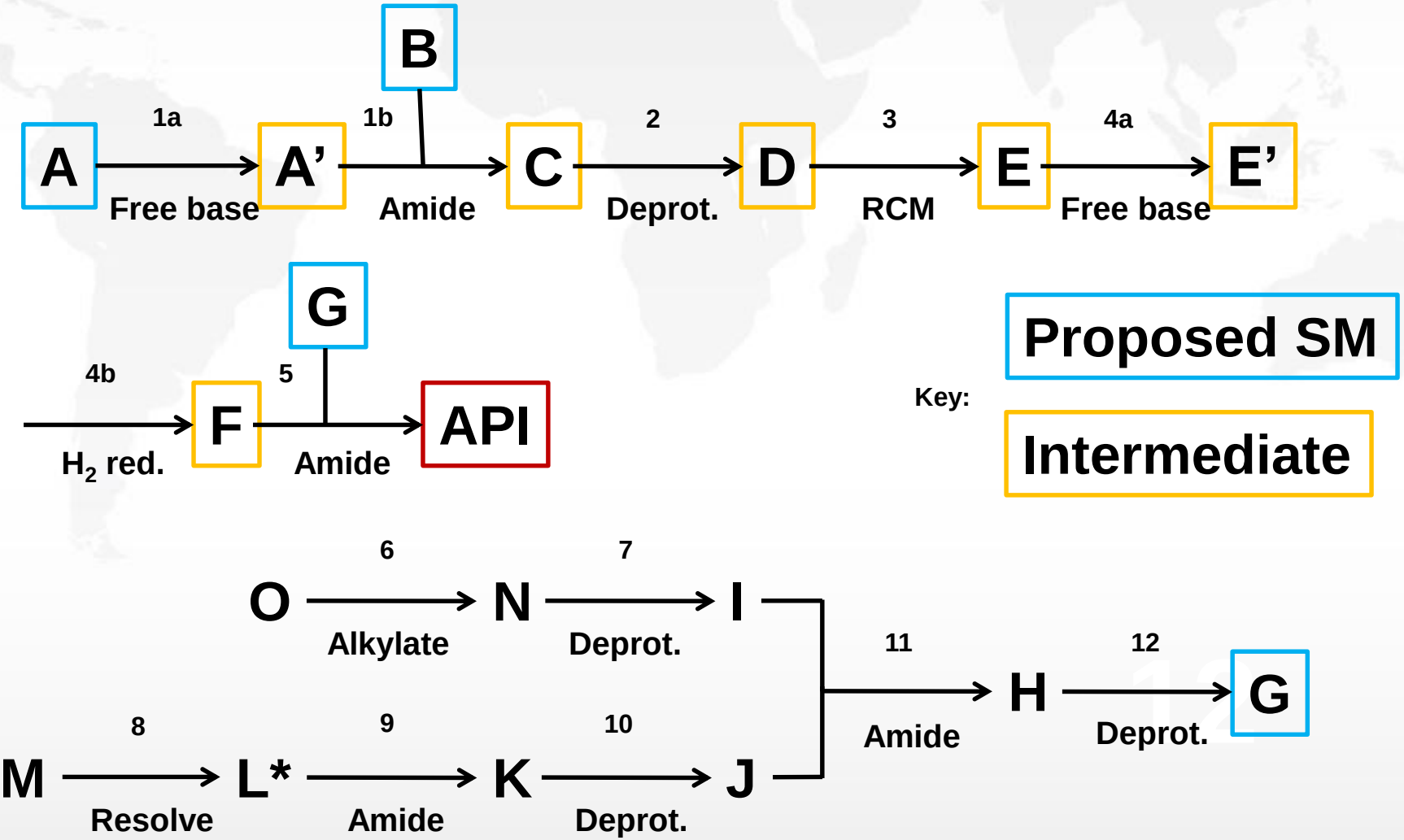
Commercially Available vs Custom Synthesised Chemicals (Based on Q&A 5.6)

	Custom synthesised chemicals		Commercially available chemicals
1 A chemical made in-house specifically to a drug substance manufacturer's requirement	2 A chemical externally made specifically to a drug substance manufacturer's requirement	3 A chemical available for purchase but where the only use is for pharmaceutical manufacture	4 A chemical that is sold as a commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as a starting material
Note from Q11 Section 5.2.1:	**An applicant should provide a justification for how each proposed starting material is appropriate in light of the general principles for the selection of starting materials in Section 5.1.1**		**An applicant generally need not justify the use of a commercially available chemical as a starting material.**

Case Studies

The following case studies are intended to exemplify the principles discussed above. It is not intended to convey whether or not a given number of steps is enough, nor is it intended to convey a particular way of presenting data (e.g. the table in slide 22 is a tool used to summarize information for this example, it is not expected that applicants create such a table in an application).

Case Study 1: Synthetic Route + Proposed SMs, using Q&As and decision tree



Note: * indicates single enantiomer; RCM indicates "ring closing metathesis"

Q11 Q&A Selection & Justification of Starting Materials

Impurities in API for Case Study 1

This table summarizes data and proposed controls on impurities in the drug substance (e.g., origin, imps. > the identification threshold for non-mutagenic impurities, potential mutagenic impurities)

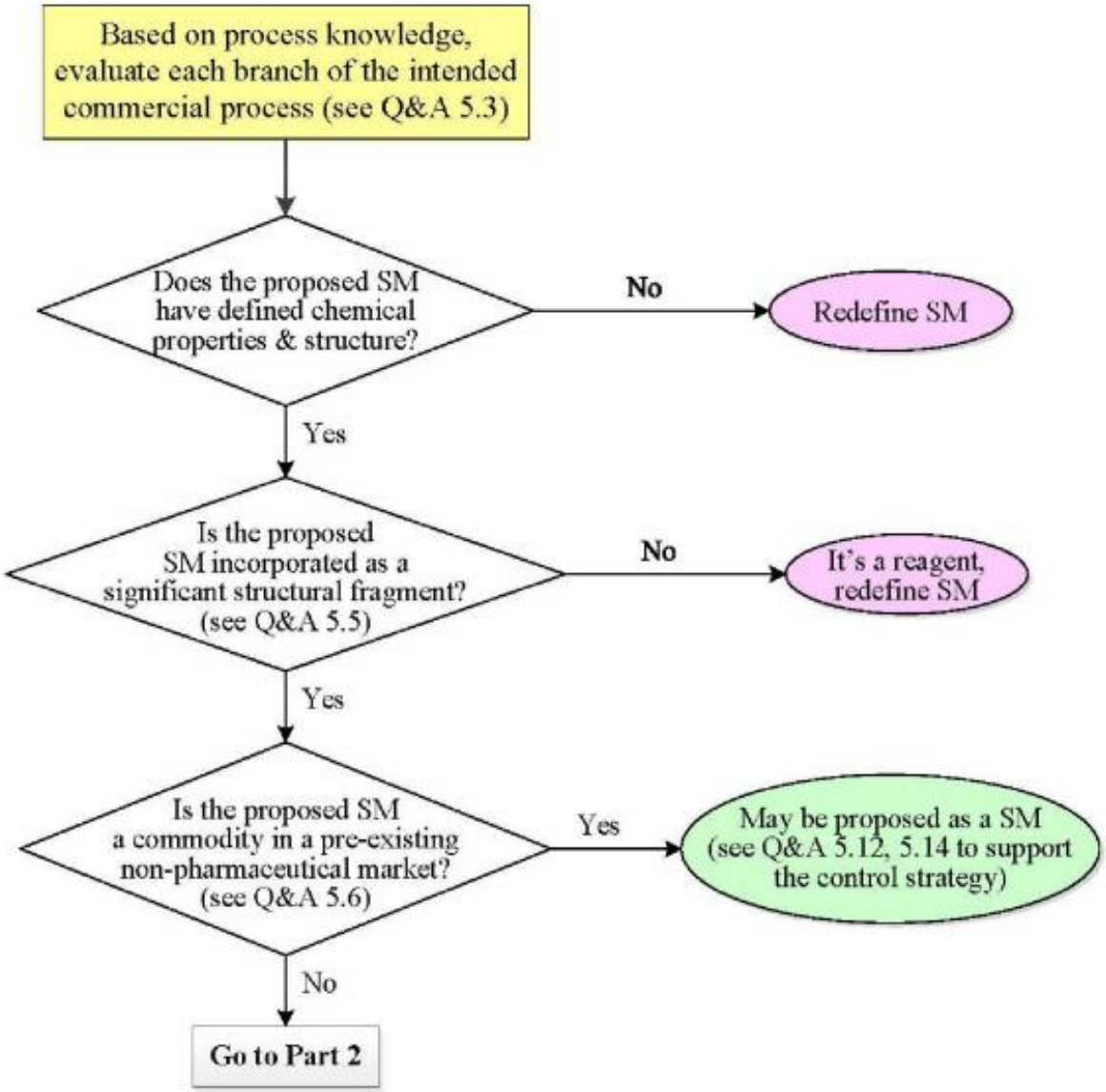
Impurity	Specified limit in API	Origin (described by applicant to support justification)
i	Not Specified	Step 6 (specified in G to Not More Than Threshold of Toxicological Concern): a mutagenic impurity; an impurity that persists
ii	0.5%	Step 4b
iii	0.3%	>4 steps upstream of SM A (specified in SM A)
iv	0.3%	Step 5
v	0.3%	>2 steps upstream of SM B (specified in SM B)
vi	0.3%	>2 steps upstream of SM B (specified in SM B)
vii	0.3%	Step 8 (specified in SM G); an enantiomeric impurity; an impurity that persists
viii	0.3%	Step 5
ix	0.2%	Step 5

Points for consideration for Imp i which is mutagenic

- **The applicant assessed reagents and intermediates for mutagenicity which were likely to impact the impurity profile of the DS and identified Impurity i as mutagenic (see Q&A 5.9)**
- **Without additional control, Impurity i was found to be present in the DS at a level > 30% of the ICH M7 acceptable limit and therefore impacted the impurity profile of the DS (see Q&A 5.7)**
- **Impurity i (originating in Step 6) is an impurity that persists because:**
  - It is not purged during subsequent steps and is present in the DS
  - Step 7 does not introduce any additional impurities that impact the impurity profile of the DS, and therefore Steps 6 and 7 do not need to be included in the S.2.2 (see Q&A 5.8 & 5.9)
- **The applicant chose to control Impurity i by specifying it in compound G with acceptance criterion of NMT the M7 acceptable limit (Option 2 per M7)**

Q11 Q&A Selection & Justification of Starting Materials

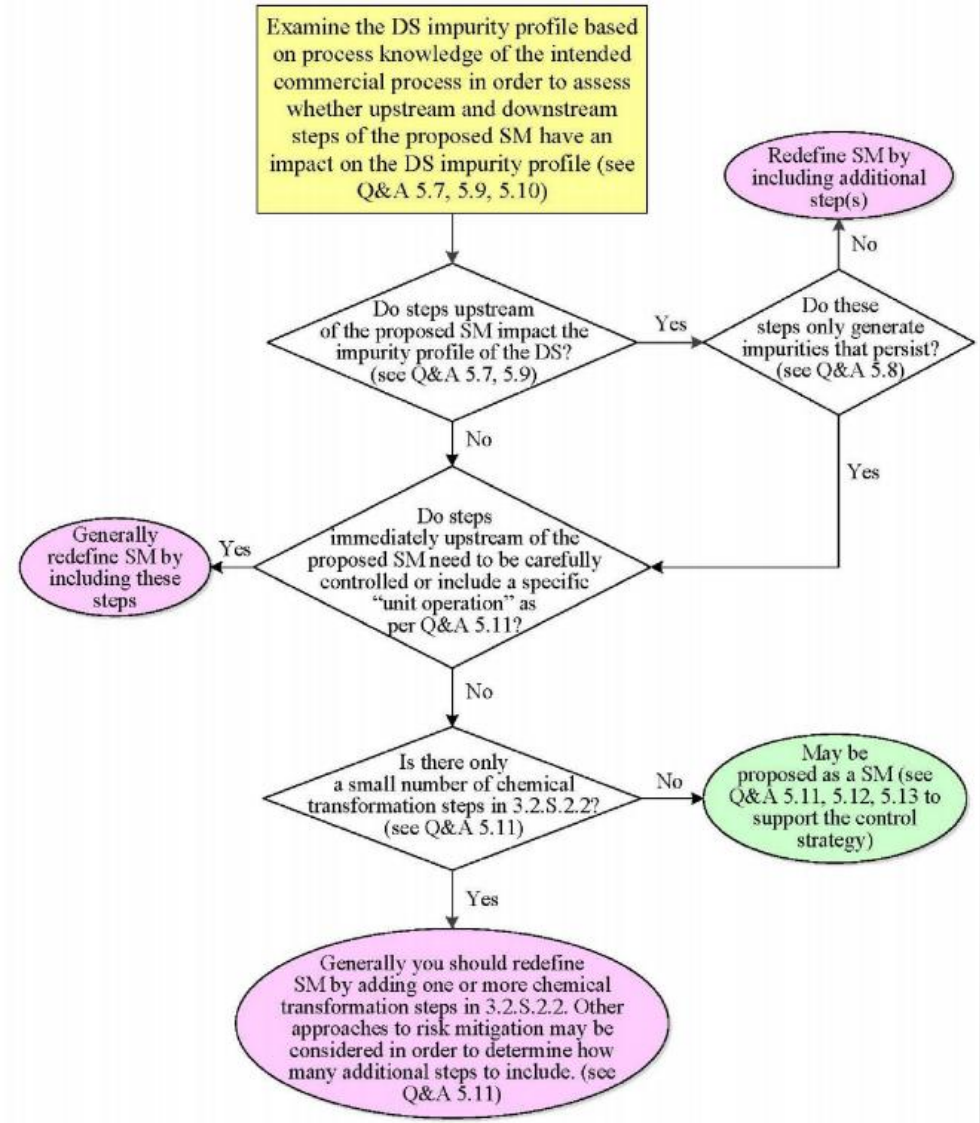
Decision Tree Part I Focuses on: the evaluation of the proposed SM from its chemical structure perspective



SM	A	B	G
Defined properties and structure?	Yes	Yes	Yes
Significant structural fragment?	Yes	Yes	Yes
Commodity in pre-existing non-pharmaceutical market?	No	No	No

Q11 Q&A Selection & Justification of Starting Materials

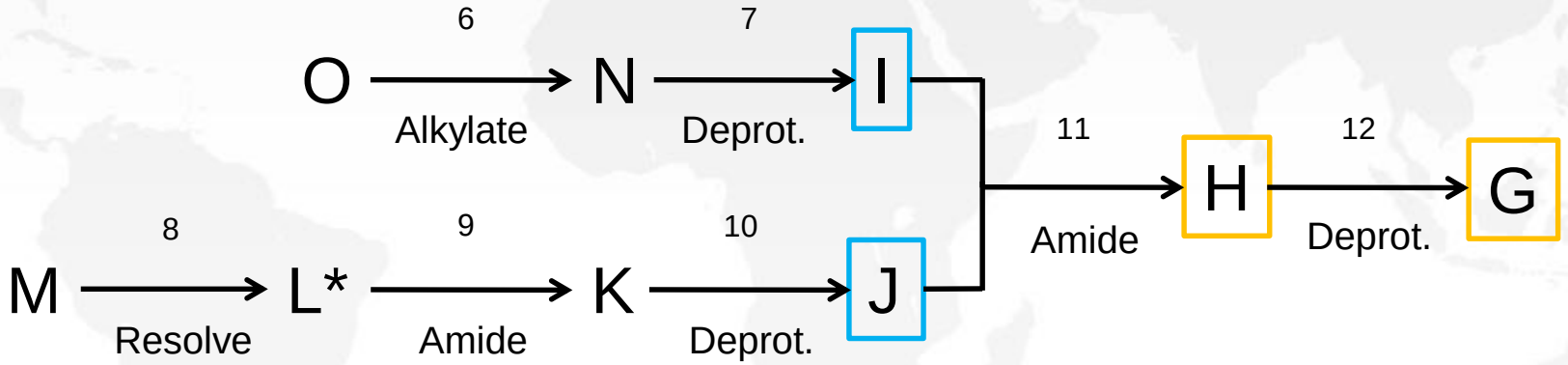
Decision Tree Part II Focuses on: impact on the DS impurity profile and if enough of the manufacturing process is conducted under GMP



SM	A	B	G
Do upstream steps impact DS impurity profile?	Yes	Yes	Yes
Do these steps only generate impurities that persist?	Yes	Yes	Yes
Do steps immediately upstream of proposed SM need careful control or include a specific unit operation?*	No	No	No
Is there only a small number of chemical steps?	No	No	Yes

*data was provided by applicant to show the details of the upstream process steps and unit operations.

Conclusion of Case Study 1: Re-definition of SM G



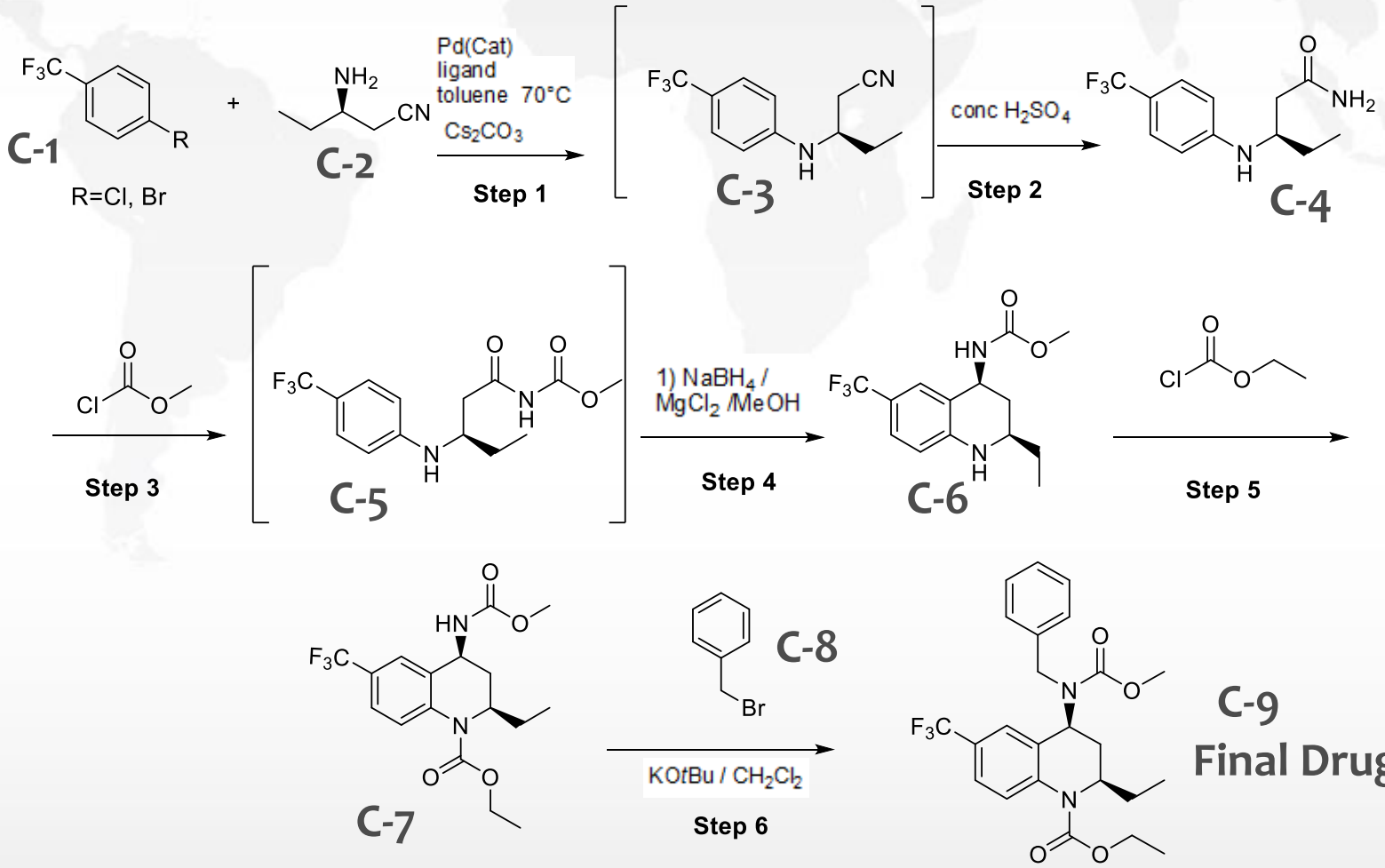
- Impurities originating in steps 6 and 8 – persist to DS
  - Steps prior to I and J do not introduce additional impurities that impact the impurity profile of the DS, No need to include Steps 6-10 in S.2.2
- After these considerations, only a small number of chemical transformation steps were originally proposed to be included in S.2.2, therefore G would not be considered an acceptable SM
- SM G now re-defined as an intermediate
- Applicant proposed I and J as starting materials and they were deemed acceptable.
- Following re-definition, enough of process is now included in process description

Case Study 2

Case study 2 is based on the Sakuramil mock dossier http://www.nihs.go.jp/drug/section3/H23SakuramillMock(Eng).pdf however the reader should note that the synthesis used for Sakuramil has been significantly modified (structures, impurities, reactions, controls) for the purpose of these training slides in order to exemplify specific aspects of the ICH Q11 Q&A. This case study is not intended to be read in conjunction with the Sakuramil mock dossier and no inferences are intended.

Q11 Q&A Selection & Justification of Starting Materials

Synthetic Route



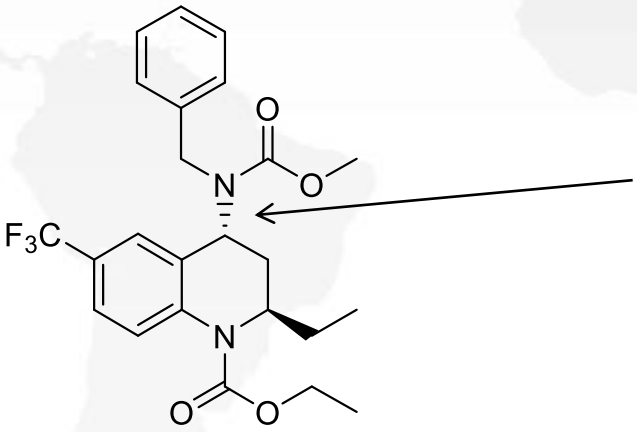
* Methyl chloroformate (Step 3) and Ethyl chloroformate (Step 5) are reagents in this example.

Q11 Q&A Selection & Justification of Starting Materials

Impurities in API: This table summarizes data on non-mutagenic impurities in the drug substance > the identification threshold, and mutagenic impurities that may be introduced in a proposed starting material or later

Impurity	Specified Limit in API	Considerations described by applicant to support justification
C-9-D1	NMT 1.0%	Impurity introduced in step 4 and is a residual impurity in intermediate C-7, transforms to C-9-D1, a diastereomer of C-9 (the drug substance)
Individual related substances	NMT 0.10%	All non-mutagenic impurities identified during development of the commercial process
Mutagenic Impurities		**Based on daily dose the M7 threshold for toxicological concern (TTC) for the API is 25 ppm**
C-8	NMT 25 ppm	Unreacted proposed starting material C-8 from step 6 – known mutagen, spec. set in line with TTC and batch data
C-6	NMT 25 ppm	Upstream intermediate controlled in an earlier step. However, C-6 impacts the API and should be specified
C-3, C-4, C-5	Not applicable	C-3, C-4, C-5 do not impact the API, (i.e. they are not specified above 30% the TTC). The applicant chose to control them in intermediate C-7.

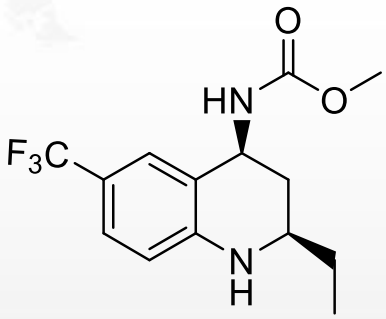
Impurities in API: Impurities that impact the drug substance



C-9-D1

Diastereomer with opposite configuration at benzylic nitrogen. Formed in step 4 cyclisation.

Specified in drug substance at 1.0%, i.e. above the identification threshold – considered to impact the drug substance impurity profile

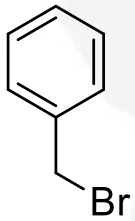


C-6

Intermediate in the synthetic route.

Mutagenic impurity in drug substance specified at 25 ppm which is at the TTC – considered to impact the drug substance impurity profile

Commercially available chemicals – benzyl bromide



C-8

- Commercially available commodity in non-pharmaceutical markets
- significant structural fragment (not a reagent)
- Introduced in the last step of the synthesis

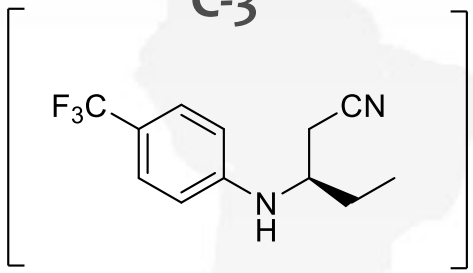
→ **Acceptable as a starting material**

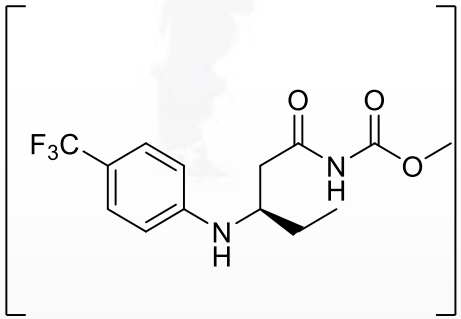
- Impurities in BnBr do not impact the impurity profile of the drug substance

- If BnBr did contain impurities which needed to be removed prior to its use to ensure the quality of the drug substance, then any purification operations should be described in S.2.2 and performed under GMP (see ICH Q11 5.2.1 / Q&A 5.14), with specifications for pre-purified incoming material and purified material. However, it would still be considered acceptable as a starting material since it is commercially available.

Non-commercially available chemicals

C-3

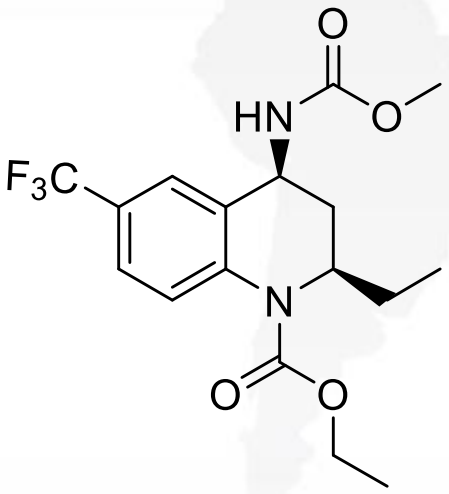




C-5

- **Non-isolated intermediates –not usually suitable as starting materials (see Q&A 5.4)**

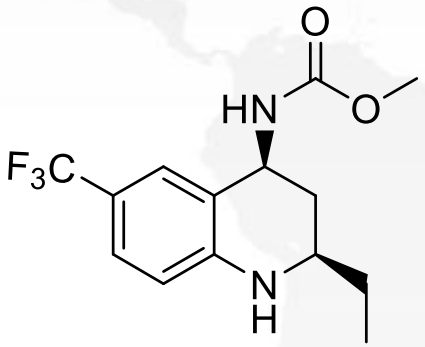
ICH Q11 principles of note



C-7

- Last chemical intermediate – multiple transformation steps would not be described if this were selected as a starting material (ICH Q11 principle)
- Steps upstream of C-7 generate impurities which impact the impurity profile of the drug substance.
- Not enough of the manufacturing process under GMP (Q&A 5.11)
- **Not acceptable as a starting material**

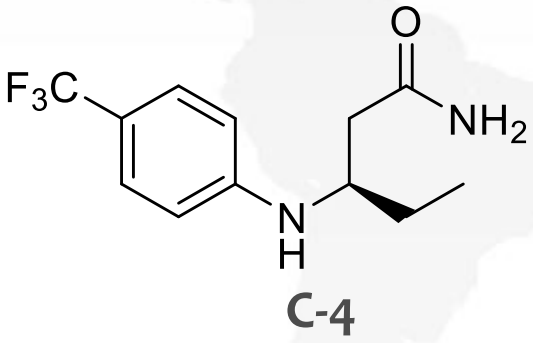
ICHQ 11 principles of note



C-6

- Steps upstream of C-6 generate impurities which impact the impurity profile of the drug substance
- Step 4 needs to be controlled in order to ensure the required stereoselectivity at the benzylic nitrogen
- Potentially not enough of the manufacturing process under GMP (Q&A 5.11)
- **Not acceptable as a starting material**

ICH Q11 principles of note



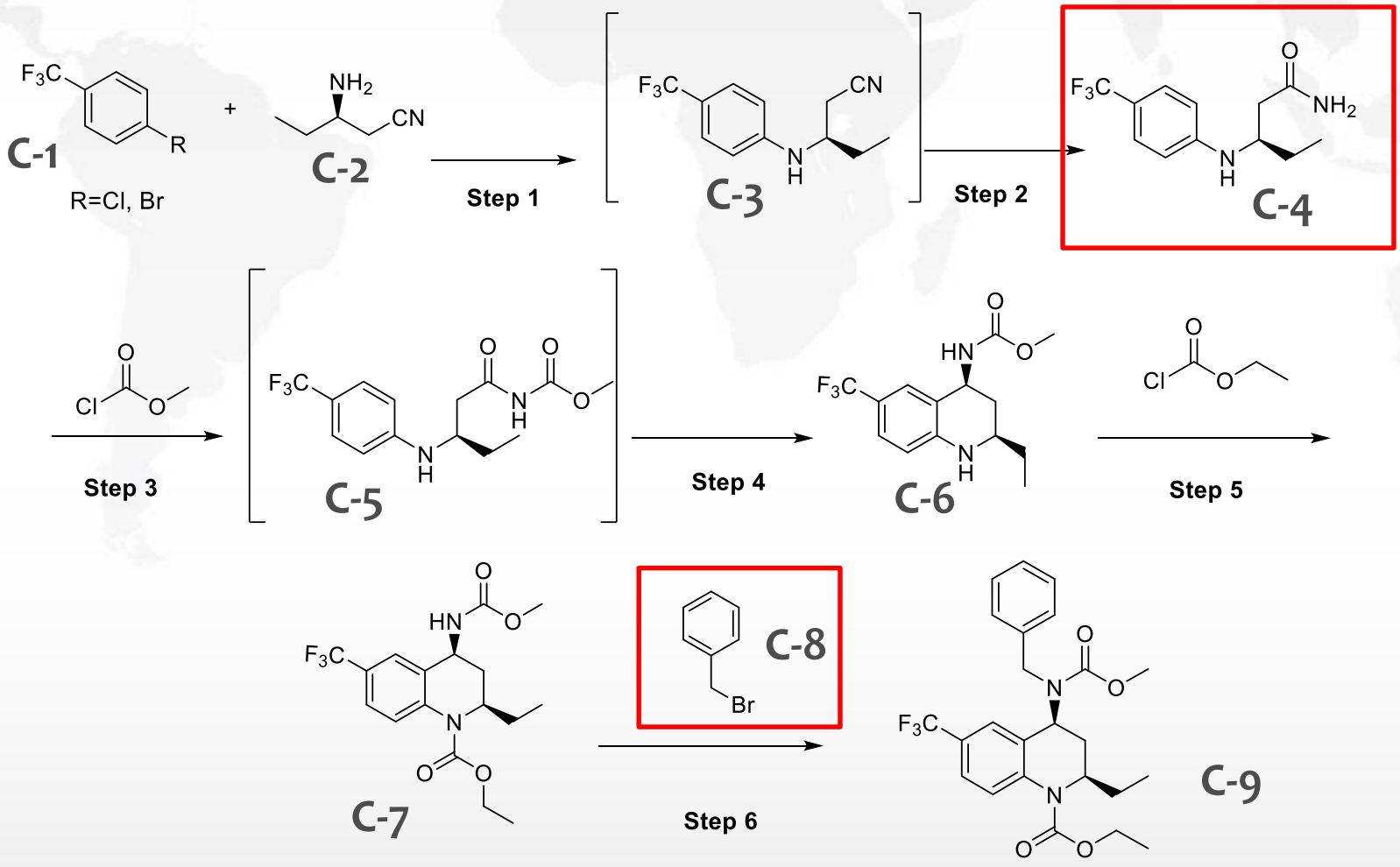
C-4

- Impurities that are defined to impact the impurity profile in the drug substance do not originate in this intermediate. The enantiomer is controlled in C-2 in accordance with the vendor specification. Spiking studies show that it is purged to well below the ID threshold in the drug substance*
- Steps upstream do not require careful control in order to assure the quality of this chemical nor do they include unit operations specifically added to ensure adequate purity (see Q&A 5.11).
- Multiple chemical transformation steps are described in S.2.2.

→ **Acceptable as a starting material**

- *If the enantiomer of this material did carry through to the drug substance at an impactful level, it could be considered an impurity that persists across multiple steps (see Q&A 5.8) so C-4 could be acceptable provided that it was justified in accordance with the other Q11 principles

Case Study 2: Conclusions – The Designated Starting Materials are Displayed in the Red Boxes



Overall Conclusions

- **ICH Q11 and supporting Q&A sections describe principles for selection and justification of drug substance starting materials**
- **Appropriate identification of drug substance starting materials should be based on science (data) and knowledge (demonstration of process understanding)**
- **All of the guidance in ICH Q11 and the supporting Q&A sections should be considered when proposing a starting material**

Appendix 1:

Full text from ICH Q11 5.1.1 General Principles Selection of Starting Materials for Synthetic Drug Substances

General Principles: ICH Q11 5.1.1 Selection of Starting Materials for Synthetic Drug Substances

- In general, changes in material attributes or operating conditions that occur near the beginning of the manufacturing process have lower potential to impact the quality of the drug substance;
  - The relationship between risk and number of steps from the end of the manufacturing process is the result of two factors, one concerning the physical properties of the drug substance and the other concerning the formation, fate, and purge of impurities. The physical properties of a drug substance are determined during the final crystallisation step and subsequent operations (e.g., milling, micronising), all of which occur at the end of the manufacturing process. Impurities introduced or created early in the manufacturing process typically have more opportunities to be removed in purification operations (e.g., washing, crystallisation of isolated intermediates) than impurities generated late in the manufacturing process, and are therefore less likely to be carried into the drug substance. However, in some cases (e.g., when peptides or oligonucleotides are synthesised on a solid support), there is a more limited relationship between risk and the number of steps from the end of the manufacturing process;

General Principles: ICH Q11 5.1.1
Selection of Starting Materials for Synthetic Drug Substances

- Regulatory authorities assess whether the controls on the drug substance and drug substance manufacturing process can be considered adequate, including whether there are appropriate controls for impurities. To conduct this assessment, enough of the drug substance manufacturing process should be described in the application for regulatory authorities to understand how impurities are formed in the process, how changes in the process could affect the formation, fate, and purge of impurities, and why the proposed control strategy is suitable for the drug substance manufacturing process. This will typically include a description of multiple chemical transformation steps;
- 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;
- Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The Good Manufacturing Practice (GMP) provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug substance;

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Selection of Starting Materials for Synthetic Drug Substances

- A starting material should be a substance of defined chemical properties and structure. Non-isolated intermediates are usually not considered appropriate starting materials;
- A starting material is incorporated as a significant structural fragment into the structure of the drug substance. “Significant structural fragment” in this context is intended to distinguish starting materials from reagents, solvents, or other raw materials. Commonly available chemicals used to create salts, esters or other simple derivatives should be considered reagents.