



# **ICH Q11 Q&A, a Supporting Document for the Selection and Justification of Starting Materials**

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# Overview

- ICH Q11 brief background
- ICH Q11 general principles and key concepts
- Clarifications and recommendations on some critical questions and answers
- Case Study
- Conclusions

# Background



- **ICH Q11 Development and Manufacture of Drug substances (chemical entities and biotechnological/biological entities)**
  - Became effective in May 2012
  - Section 5 belongs to Selection of Starting Materials and Source Materials
- **ICH Q11 Questions and Answers**
  - Became effective in August 2017
  - A supporting document for ICH Q11 (Section 5) which provides more clarification to the issues pertaining to the selection and justification of starting materials

# ICH Q11 Section 5



- **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
- 5.2.2 Qualification of Source or Starting Materials for biotechnological/biological Drug Substances (guidance is contained in ICH Q5A, Q5B and Q5D)

# What is the ICH Q11 Q&A document?



- Contains 16 Questions and Answers which are intended to provide additional clarification and to promote convergence and improve harmonization.
- Clarifies the ICH Q11 general principles (section 5.1.1) concept for the selection of starting materials and should be used in conjunction with the ICH Q11 document.
- Recommends the designation of appropriate starting materials should be based on the knowledge of the proposed commercial manufacturing process and controls.
- Contains a decision tree as a pictorial example to clarify Q & A with the support of all ICH Q11 general principles for the selection and justification of starting material.

# Scope of Q&A



- Follows that of ICH Q11 -may not be directly applicable to biotechnological/biological entities
- Applies to commercial DS manufacturing processes submitted as part of marketing authorization applications and/or Drug Master files
- Not intended to be applied retrospectively to previously reviewed manufacturing process unless significant changes are made to the manufacturing process
- 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

# Summary of General Principles (ICH Q11, 5.1.1)



- In general, changes that occur near the beginning of the process have lower potential impact to the quality of DS.
- Enough of the DS 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.
- Manufacturing steps that impact the impurity profile of the DS should normally be included in Section 3.2.S.2.2.
- Each branch of convergent synthesis begins with one or more starting materials. GMP provisions described in ICH Q7 apply to each branch with the first use of a starting material.
- A starting material (SM) should be a substance of defined chemical properties and structure.
- A SM is incorporated as a significant structural fragment into the structure of the DS –to distinguish SM from a reagent, solvent, catalyst or other raw material.
- Non-isolated intermediates are generally not considered appropriate starting materials
- **Section 5.1.1 clearly states that “All the general principles should be considered in selecting Starting Material(s), rather than strictly applying each general principle in isolation.**

# Common issues/problems with SM justifications



- Not enough steps are included in the process. Late stage intermediates are sometimes proposed as SMs
- All ICH Q11 general principles are not considered for the selection of SMs
- Information regarding upstream process, impurities of SM(s) not included
- Not understanding the difference between commercial and custom-made chemicals
- Late stage intermediate referenced in Secondary DMF is sometimes considered as SM instead of intermediate



# Difference between Commercially available & Custom Synthesized Chemicals (based on Q&A 5.6)



Custom Synthesized Chemicals			Commercially Available Chemicals
1 A chemical made in-house specifically to a DS manufacturer's requirement	2 A chemical externally made specifically to DS 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 commodity in a pre-existing, non-pharmaceutical market in addition to its proposed use as starting material

- A Drug substance manufacturer should justify each proposed starting material if it is custom synthesized chemical based on ICH Q11 general principles for the selection of starting material in Section 5.1.1.
- A Drug substance manufacturer generally does not require to justify the use of a commercially available chemicals as a starting material.

# Key Considerations: Steps that impact the impurity profile of the DS (Q&A 5.7)

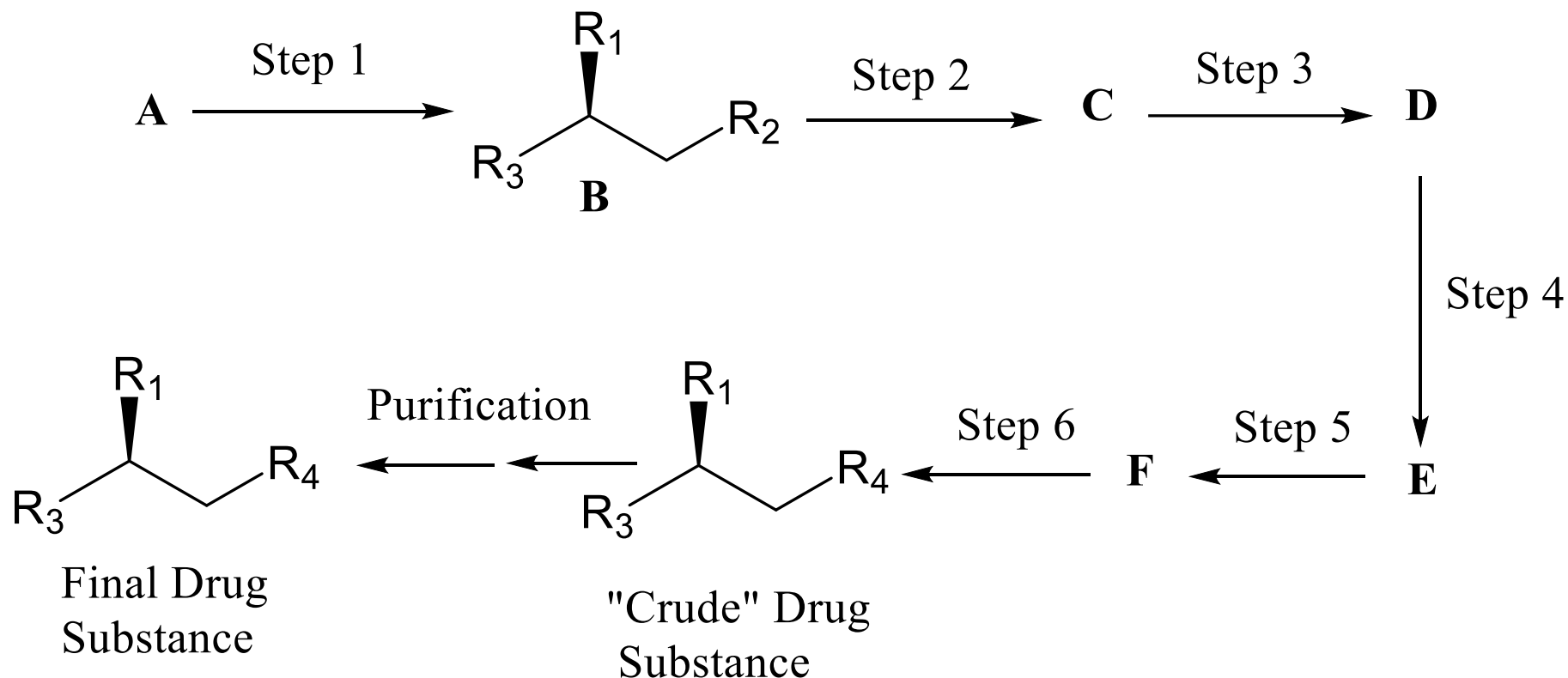


- Understanding of the process and the origin, fate and purge of impurities (non-mutagenic and mutagenic) are necessary before defining the starting material(s).
- For non-mutagenic impurities- the level above ICH Q3A identification threshold impacts the drug substance.
- For mutagenic impurities- the 30% threshold of the ICH M7 acceptable limit serves to identify the level above which a mutagenic impurity impacts the drug substance (Section 8 of ICH M7).
- When the drug substance is itself genotoxic- mutagenic impurities are not considered to impact the impurity profile of the drug substance unless they are above the ICH Q3A identification threshold (IT).

# Key Considerations: Impurities that persist across multiple steps (Q&A 5.8)

- 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, this principle does not necessarily apply when impurities originate early and “persist” across multiple steps to the drug substance.
- In the following slides (taken from ICH training material slides from ICH web site), Example 4 from ICH Q11 has been expanded to illustrate different scenarios of impurities that impact the impurity profile of the DS.

## Example 4 from ICH Q11

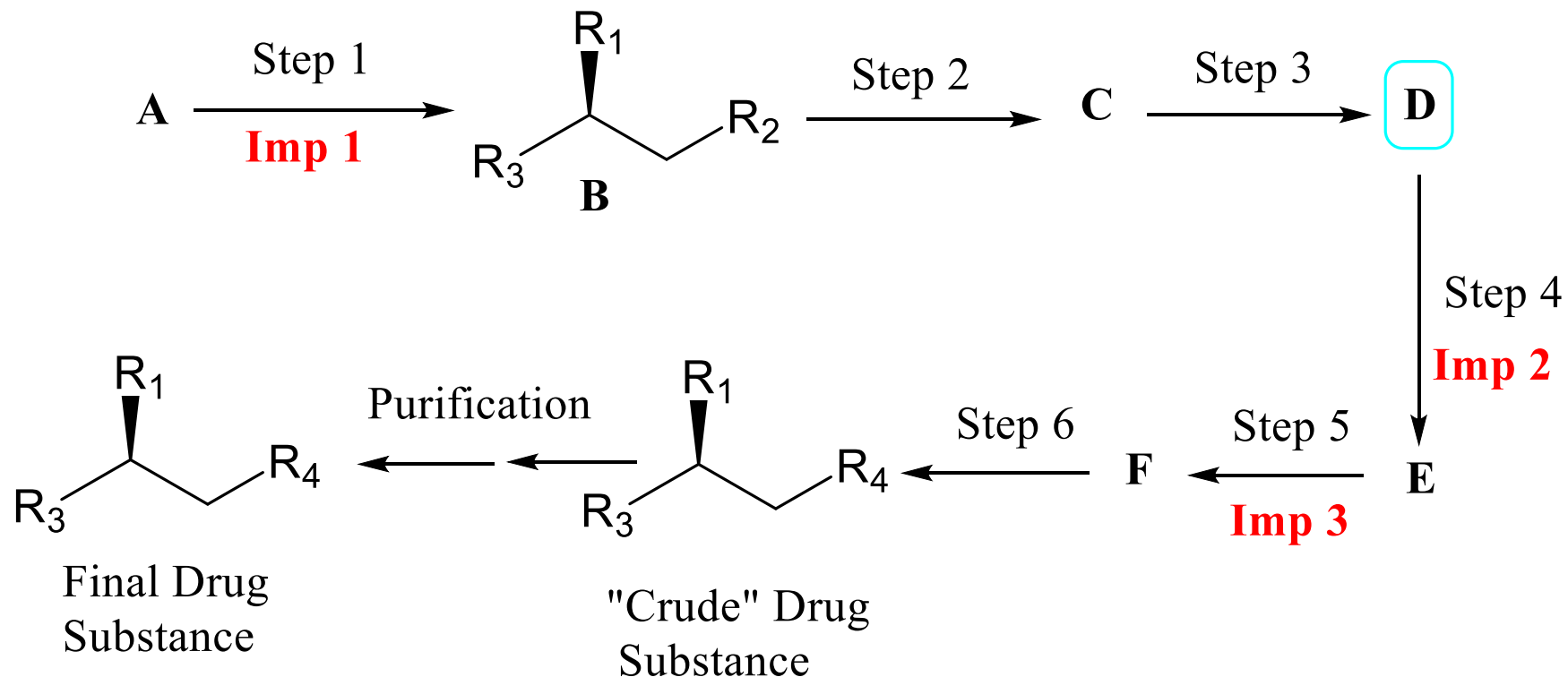


Step 1 results in the formation of the opposite enantiomer of compound B. This impurity persists in the DS (referred as Imp 1 in subsequent slides). All of the significant impurities in the DS other than enantiomer arise from steps 4, 5, and 6. (Note: although the example in ICH Q11 is a chiral impurity, this concept is not limited to chiral impurities)

# Expanded Example 4 from ICH Q11



  Proposed Starting Material



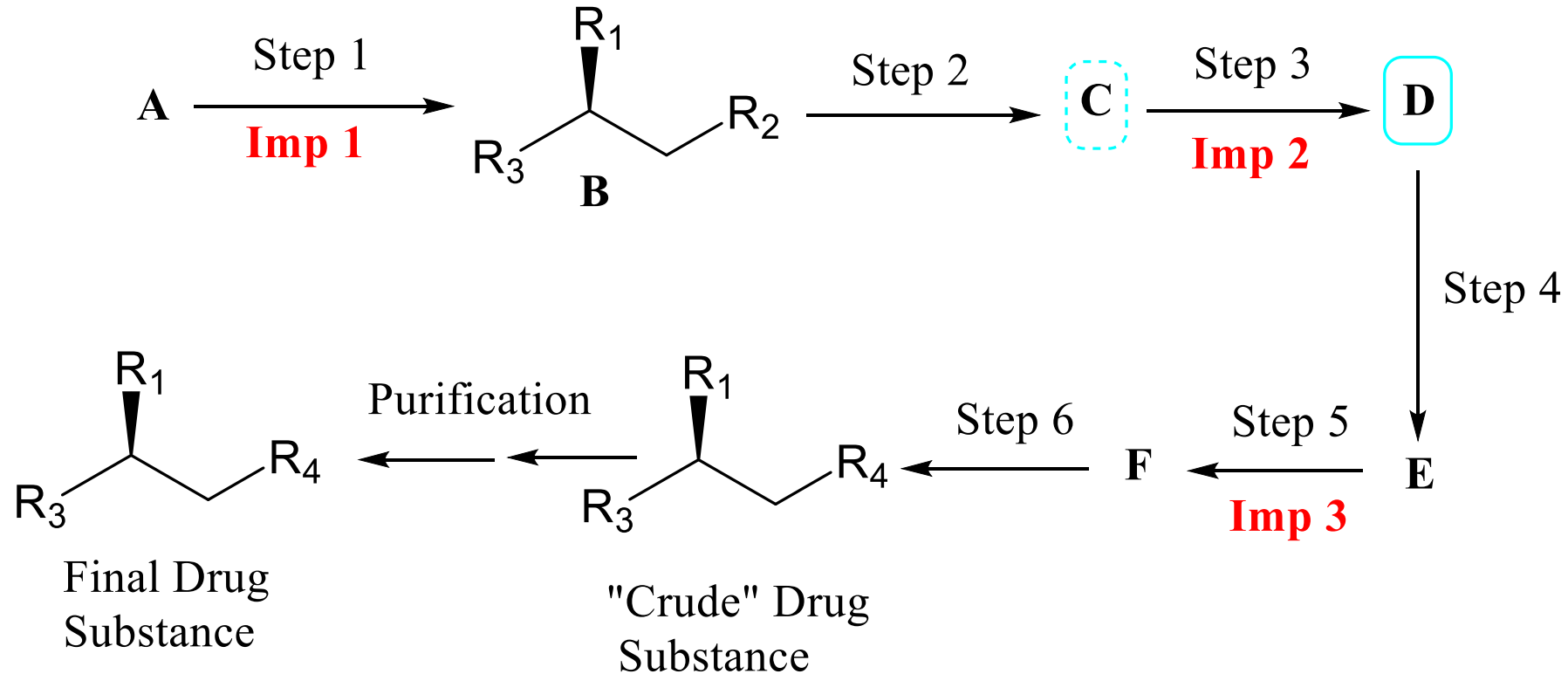
**Imps 1+2+3**

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

# Expanded Example 4 from ICH Q11



 Proposed Starting Material



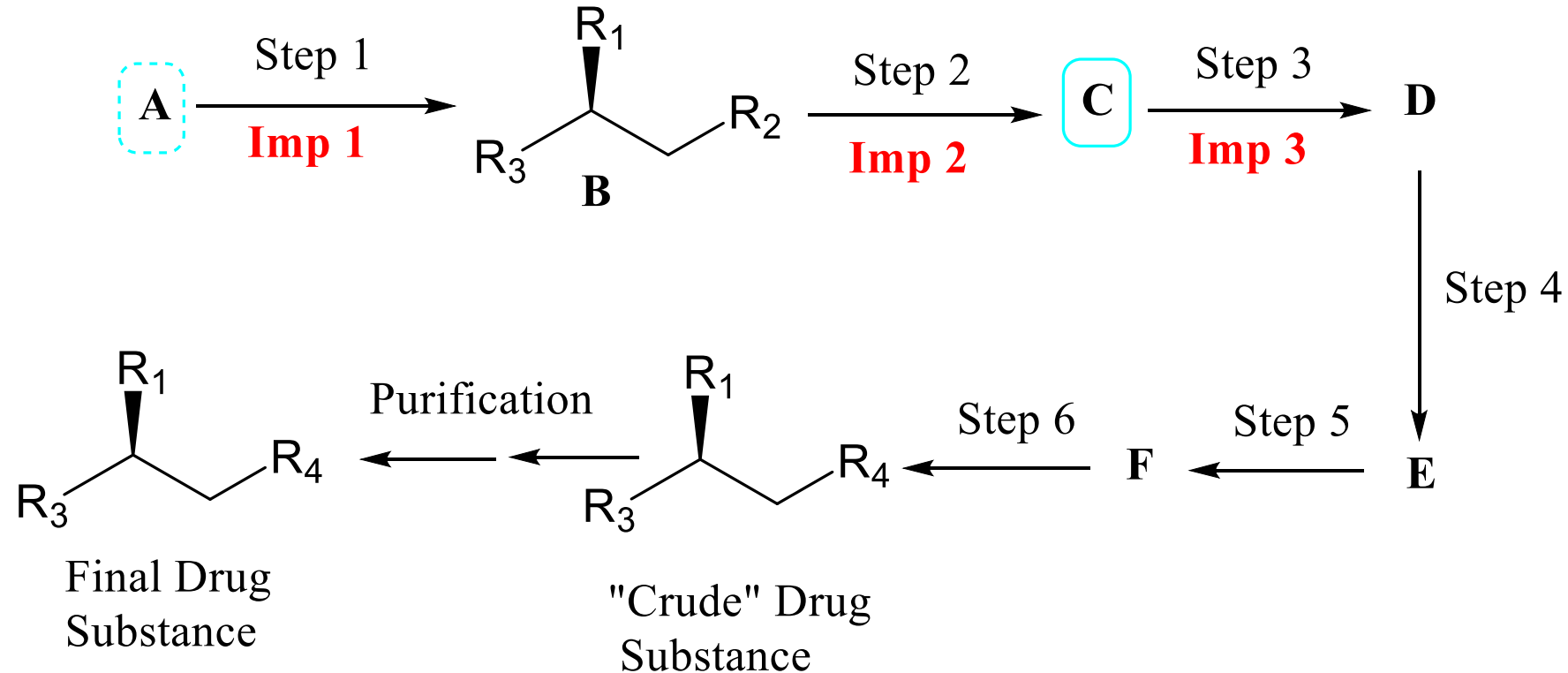
**Imps 1+2+3**

Impurities 1, 2, and 3 impact the impurity profile of DS  
Impurities 2 and 3 originate in Steps 3 and 5 respectively  
D no longer suitable as a SM-should redefine to C

# Expanded Example 4 from ICH Q11



  Proposed Starting Material



**Imps 1+2+3**

Impurities 1, 2, and 3 impact the impurity profile of the DS and originate in Steps 1, 2 and 3 respectively  
C no longer suitable as a SM-should redefine to A

# Approaches to Mutagenic impurities in selection of starting materials (Q&A 5.9)



How to apply ICH M7 principles in the selection of SM:

- Identify mutagenic materials that are likely to be formed or introduced in the manufacturing process.
- Use Hazard Assessment Elements from ICH M7 (Section 6) to determine which of the actual and potential impurities are considered to be mutagenic.
- Hazard assessment involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify them as Class 1, 2, or 5 according to Table 1 per ICH M7.
- A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay per ICH M7. Hazard assessment should be included in the application.
- Generally, the impact level of mutagenic impurities is more than 30% of TTC. Approaches described in Section 8 of ICH M7 can be used to control mutagenic impurities.



# Approaches to Mutagenic impurities (Continued)



The following approaches are recommended for the selection and justification of starting materials:

- Actual impurities- should be assessed for mutagenicity.
- Reagents and intermediates used in the synthesis from commercially available chemicals to the API- should be assessed for mutagenicity. This also includes steps upstream of the proposed starting material.
- Mutagenic Impurities in commercially available chemicals or synthetic intermediates, or formed by side reactions during the synthesis- should be assessed by using risk-based reasoning to determine which steps to include in the hazard assessment. A discussion of the risk assessment should be included.
- If the DS is itself genotoxic and/or used for advanced cancer indications- mutagenic impurities are not considered to impact the impurity profile of the DS and can be controlled per ICH Q3A.
- The ICH Q11 exception for impurities that “persist” is also applicable to mutagenic impurities.

# Key Considerations/recommendations regarding Q&A 5.11



## ICH Q11 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”*

Provided more clarification in ICH Q&A. The DS manufacturer should apply the following considerations/recommendations:

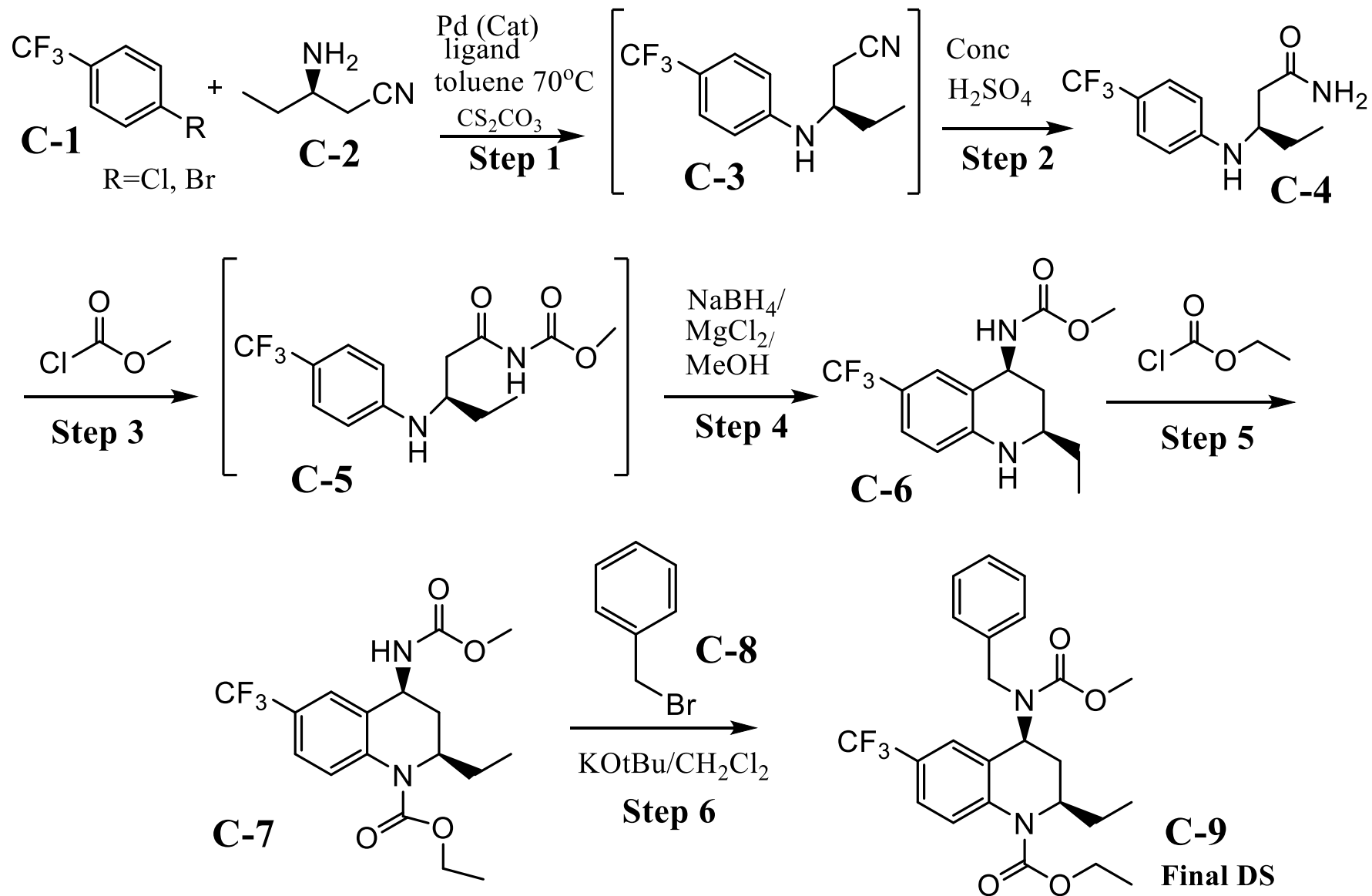
- The chemical transformation steps in the manufacturing process which impact the impurity profile of the DS -should be included in Section 3.2.S.2.2.
- The steps immediately upstream of those steps that impact the impurity profile of the drug substance -should generally be included in Section 3.2.S.2.2.
- If the evaluation results in only a small number of chemical transformation steps, then it is generally appropriate to include one or more additional steps in Section 3.2.S.2.2 to mitigate risks associated with contamination and future changes to the synthetic route or supplier of the starting material.
- Potential risks from future changes to the starting material synthesis should also be considered.

# Case Study



- Case study slides are from ICH Training Material posted in ICH web site
- Please note that this study is not intended to convey whether or not a given number of steps are enough in the DS manufacturing process

# Synthetic Route



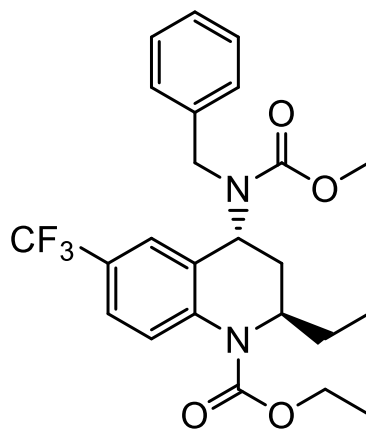
\*Methyl chloroformate (Step 3) and Ethyl chloroformate (Step 5) are reagents in this example.

# Impurities in API specification



Impurity	Specified limit in DS	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, transform to C-9-D1, a diastereomer of C-9 (DS)
Individual related substances	NMT 0.10%	All non-mutagenic impurities identified during development of the commercial process
Mutagenic Impurities		Based on maximum daily dose, TTC for API is 25 ppm
C-8	NMT 25 ppm	Unreacted proposed SM C-8 from step 6- known mutagen, specification set at TTC, provided batch data
C-6	NMT 25 ppm	Upstream intermediate controlled in earlier step at higher limit. C-6 impacts the DS and should be specified
C-3, C-4, C-5	Not applicable	The applicant chose to control them in intermediate C-7 with acceptable limits. Therefore, they do not impact the DS.

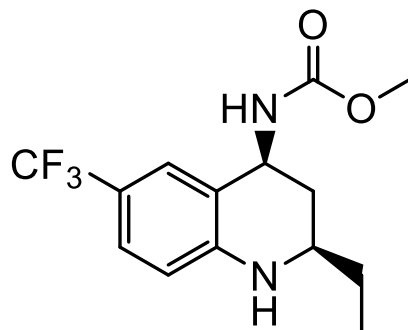
# Impurities in API: Impurities that impact the DS



**C-9-D1**

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

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



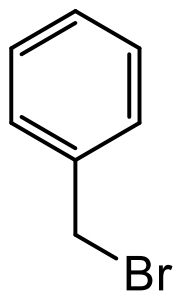
**C-6**

Intermediate in the synthetic route

Mutagenic impurity in DS specified at 25 ppm which is at TTC-considered to impact the DS impurity profile

# Commercially available chemicals-

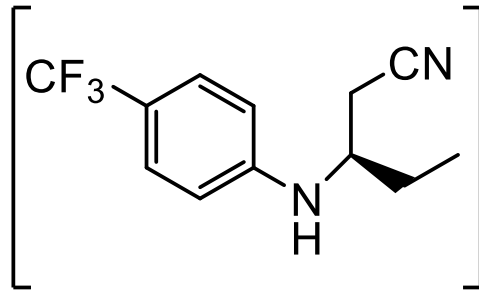
## Benzyl bromide



**C-8**

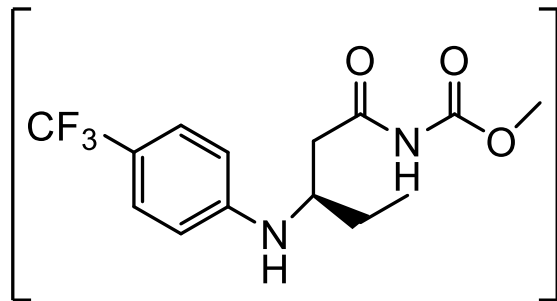
- Commercially available commodity in non-pharmaceutical markets
- Significant structural fragment (not a reagent)
- Introduced in the last step of synthesis
- Acceptable as a starting material**
- Impurities in BnBr do not impact the impurity profile of the DS
- If BnBr did contain impurities which needed to be removed prior to its use to ensure the quality of DS, then any purification operations should be described in 3.2.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 as a SM since it is commercially available.

# Non-Commercially available chemicals



**C-3**

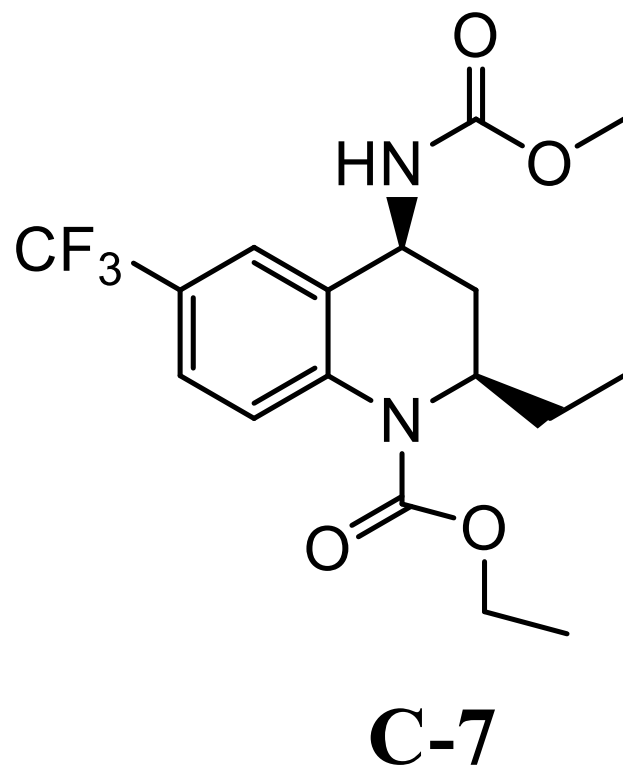
➡ **Non-isolated intermediates-not usually suitable as starting materials (see Q&A 5.4)**



**C-5**



# ICH Q11 principles of note



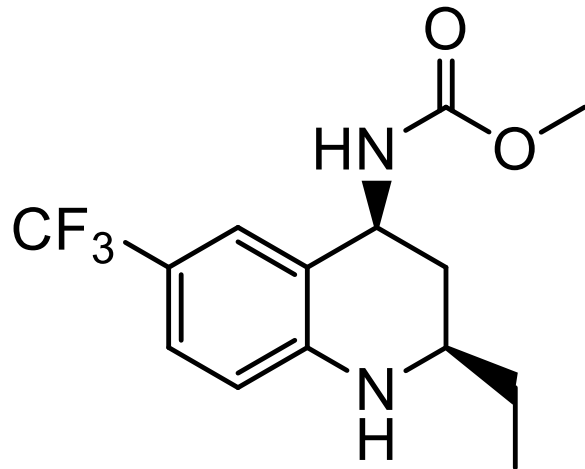
-Last chemical intermediate-multiple transformation steps would not be described if this was selected as a starting material (ICH Q11 principle)

-Steps upstream of C-7 generate impurities which impact the impurity profile of the DS

-Not enough of the manufacturing process under GMP (Q&A 5.11)

**-Not acceptable as a starting material**

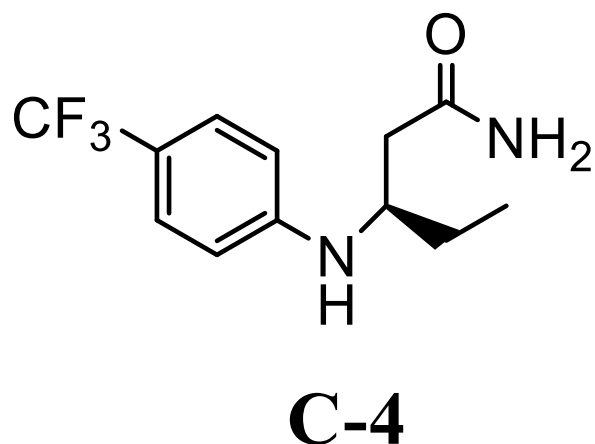
# ICH Q11 principles of note



**C-6**

- Steps upstream of C-6 generate impurities which impact the impurity profile of the DS
- 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



-Impurities that are defined to impact the impurity profile of the DS do not originate in this intermediate. The enantiomer is controlled in C-2 specification. Spiking studies show that it is purged to well below the ID threshold in the DS\*

-Steps upstream are simple. Regioisomers can be controlled in C-1 and/or C-4 specifications

-Multiple chemical transformation steps are described in 3.2.S.2.2

**-Acceptable as a starting material provided that it was justified in accordance with the other Q11 principles**

\*If the enantiomer of this material did carryover to the DS at an impactful level, it could be considered an impurity that persists across multiple steps (Q&A 5.8).

# Conclusions



- Proposed starting material(s) should be justified based on all general principles outlined in ICH Q11 (Section 5).
- Designation of starting materials should be based on process knowledge of the proposed commercial process.
- Understanding of impurities (non-mutagenic and mutagenic and “persist impurities”) generated or introduced in the upstream and downstream of the process that impact the drug substance is necessary before defining the starting materials and the steps which impact the impurity profile of the drug substance should be included in Section 3.2.S.2.2.
- Hazard assessment of mutagenic impurities even present in the starting material manufacturing process should be performed per ICH M7 and included in the application.
- If additional purification steps are performed for commercially available starting material, these steps should be included in Section 3.2.S.2.2 (Q & A 5.14).



# Thank You!

Send questions regarding this presentation to: [DMFWorkshop2021@fda.hhs.gov](mailto:DMFWorkshop2021@fda.hhs.gov) by 3/19/2021 for inclusion in the follow-on webinar April 9, 2021.

Please refer to the following poster for cross-referenced materials:

*“Mutagenic impurities from a Drug Substance Perspective: Highlight from the ICH M7 Question and Answer Draft Document” by David Green et.al.*

Please refer to the following presentations on March 4<sup>th</sup> for additional information:

*“ICH M7 (R1)-Chemistry and manufacturing control (CMC) Perspective on Impurity Hazard Assessment” by Barbara Scott*

*“Application of (Q)SAR and Expert knowledge for ICH M7 Impurity Classification” by Naomi L. Kruhlak*