21 March 2017
EMA/71927/2017

Overview of comments received by EMA on 'ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities) – questions and answers' (EMA/CHMP/ICH/809509/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Gilead Sciences International Limited
2	German Pharmaceutical Industry Association (BPI e.V.)
3	Teva Pharmaceuticals Ltd
4	EFPIA
5	APIC

Please note that comments will be sent to the **ICH Q11 IWG** for consideration in the context of Step 3 of the ICH process.

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1. General comments – overview

Stakeholder no.	General comment (if any)
3	This Q&A is very important and will assist us to justify the chosen starting material, for example by referring to the definition of "manufacturing steps that **impact** the impurity profile of the drug substance".
4	Overall comments on the Q&As - EFPIA are supportive of these Q&As. They add considerable clarity to the Q11 information on the selection and justification of starting materials. We have a number of comments that apply across several Q&As and provide these here. First, we recommend alignment of the terms used in the document with wider ICH terminology - e.g. consider use of the term 'risk management' rather than the term 'risk mitigation'; use of the term 'risk assessment' rather than 'hazard assessment'; avoid use of the word 'recommended' (replacing with 'consideration'). Secondly, we question whether the order of the presentation of the Q&As is optimal. Thirdly, we recommend referring to the 'number of steps' topic in Q&A 5.6 rather than through the Q&As. In addition we request that the EU Reflection Paper on this topic is either withdrawn or shortened / revised to avoid contradiction with the agreed text of the Q11 Q&As. It would be helpful if the Preface were to state that the intention of the Q/A is to support the same starting material being acceptable in all regions. The text of the Q&As does a good job at adding further clarity to the understanding of the justification needed in support of appropriate selection of a starting material as presented in a registration (or PAC) submission. This expected justification of a SM, as framed in the Q&As, utilises the full understanding of DS quality that is generated across development. Thus, logically, the optimal selection of a starting material for future commercial supply will be best done at the end of development, when this full understanding is in place. The reasoning for this use of all development knowledge is understood, but in actual practice the selection of the starting material (and associated suppliers) will need to be conducted and developed earlier in the development process. This can be at a point in time when the understanding of each factor in the Q&As (e.g. in Q&A 5.6) may still be less than perfect.

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	This could mean that, in practice, an applicant may have selected a SM and supplier in good faith, in development, only to discover, close to the submission of the registration application, that a particular factor (e.g. a late-emerging impurity) might provide an argument against the SM proposed and suggest that an earlier SM may be 'more appropriate'. It may be that at this later point in development starting material supplies for launch stocks of drug substance have been made. This would leave the immediate supply of the product at risk unless a way is found to allow for supply of the initial Drug Substance (e.g. perhaps by a modification of the proposed SM to be a post-approval commitment OR by accepting that the impurity can be, in such circumstances, risk managed analytically rather than by addition of the step generating it.) We wish to highlight this issue of development being a process, and Starting Material selection being a matter that is selected earlier in development than the full and final understanding of all matters included in the Q&As is available. We believe such situations might have to be managed in future. *May need case-by-case consideration.*
5	This expected justification of a SM, as framed in the Q&As, utilises the full understanding of the setting of DS quality that is generated across development. Thus, logically and in reality, the optimal selection of a starting material for future commercial supply will be best done at the end of development, when this full understanding is in place. The reasoning for this use of all development knowledge is understood, but in actual practice the selection of the starting material (and associated suppliers) needs to be conducted and developed earlier in the development process. This can be at a point in time when the understanding of each factor in the Q&As (e.g. in Q&A 6) may still be less than perfect. This could mean that, in practice, an applicant may have selected a SM and supplier in good faith, in development, only to discover, close to the submission of the registration application, that a particular factor (e.g. a late-emerging impurity) might provide an argument against the SM proposed and suggest that an earlier SM may be 'more appropriate'. It may be that at this later point SM supplies for launch stocks of drug substance have been made. This would leave the immediate supply of the product at risk unless a way is found to allow for supply of the initial DS (e.g. perhaps by a modification of the proposed SM to be a post-approval commitment OR the accepting that the impurity can be, in such circumstances, risk managed analytically rather than by addition of the step generating it.) **Proposed change:**

Stakeholder no.	General comment (if any)
	We wish to highlight this issue of development being a process, and SM selection being a matter that is selected earlier in development than the full and final understanding of all matters included in the Q&As is available. We believe such situations might have to be managed in future.
5	We welcome the clarifications provided in this Q/A document and in general the answers to most questions are acceptable and clear. As Industry Association we do not necessary agree on the additional steps in a registration dossier for GMP reasons. According to our vision Starting Materials should be defined based on scientific understanding and should already include risk management strategies so that no additional steps should for other reasons e.g. GMP have to be added. We believe that GMP-aspects should be assessed and enforced by field inspections rather than by additional information (not required for a scientific review) in a filing and making that information also subject to (sometimes cumbersome) variation procedures. The text of the Q&As does a good job at adding further clarity to the understanding of the justification needed in support of appropriate selection of a starting material as presented in a registration (or PAC) submission.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
Preface	3	**Comments:** "*Generally, it is anticipated that API starting materials that have already been accepted by regulatory authorities (eg for use in authorized medicinal products) would not need to be re-justified against the ICH Q11 general principles or the recommendations in this Q&A document, unless significant changes are made to the manufacturing process and controls.*" We welcome this message and would like to have the Authorities to have the responsibility to consider if the ASMF has been reviewed before or not (which we believe is not always done right now).
Preface lines 14 - 17	5	**Comments:** Can 'significant changes' be better (more specific) clarified? **Proposed change:** Can additional clarification (e.g. only major changes to the manufacturing process) or more examples be given?
26 (5.1)	1	**Comments**: The differentiation between a starting material and reagents, catalysts and solvents is clear as these components are not incorporated to the drug substance structure. What is less clear is the differentiation between a starting material and "other raw materials." The current text mentions that raw materials do not contribute a "significant structural fragment" to the molecular structure of the drug substance. How is "a significant structural fragment" determined? Is this based on the relative size of the fragment compared to the drug substance structure, the presence of significant functional groups on the fragment, a specific role in forming the drug substance scaffold, or other considerations? Widely varying interpretations of this text are possible which could lead to inconsistent application of this principle between regulatory agencies.
5.1	2	**Comments:** The term Starting material is not properly defined

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		And only later the differentiation is made. **Proposed change:** A clear differentiation between commercially available vs. other material sources should be given (examples would be helpful). A decision tree (maybe with given examples) would be most helpful for clarifying the new distinction between different sources of starting materials (e.g. commercial or other).
5.1	3	**Comments:** The answer looks clear with the exception of the statement 'A proposed starting material may be several steps from commercially available materials, provided it is not a small number of chemical transformation steps from the drug substance, and provided the justification acceptably addresses the ICH Q11 general principles.' This statement on number of steps seems to belong more to other questions and is creating confusion on the question about 'significant structural fragment' **Proposed change:** Leave this sentence out of the document.
5.1	4	**Comments:** The text states "A proposed starting material may be several steps from commercially-available materials, provided it is not a small number of chemical transformation steps from the drug substance, and provided the justification acceptably addresses the ICH Q11 general principles'. We believe this sentence could remove the words "provided it is not a small number of chemical transformation steps from the drug substance' and remain appropriate. This would be simpler for the reader. **Proposed change:** Remove the words "provided it is not a small number of chemical transformation steps from the drug substance'.
5.1	4	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Typo **Proposed change:** TYPO - remove 'of' from 'sole basis for of starting material selection'.
5.1	4	**Comments:** Several companies have commented that it is unfortunate that the term 'complex' when referring to starting materials has not been used explicitly in the Q&As, given that this concept has been a stated reason for the rejection of starting material proposals in the past. We consider and believe that the IWG intend complex materials to be potential starting materials when the other selection principles are suitably met. **Proposed change:** Consider whether it would be possible to use the word 'complex' explicitly in the text.
5.1	5	**Comments:** The answer looks clear with the exception of the statement '*A proposed starting material may be several steps from commercially available materials, provided it is not a small number of chemical transformation steps from the drug substance, and provided the justification acceptably addresses the ICH Q11 general principles.'* This statement on number of steps seems to belong more to other questions and is creating confusion on the question about 'significant structural fragment'. **Proposed change:** Leave this sentence out of the document.
26 (5.2)	1	**Comments**: In section 4.4 of ICH S9, guidance is provided that "exceeding the established limits for impurities identified in these ICH guidelines [ICH Q3A and Q3B] could be appropriate for anticancer pharmaceuticals." As such, exceeding the ICH Q3A identification threshold may not be a meaningful level for a drug substance intended to treat advanced cancer and therefore in the scope of ICH S9. In these cases a different threshold for determining whether impurities impact the purity profile of the drug substance may be appropriate and should be justified in the application.

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26 (5.2)	1	**Comments**: The scope of ICH S9 applies to "pharmaceuticals that are intended to treat cancer in patients with serious and life threatening malignancies" and does not differentiate these drugs depending on whether they are themselves genotoxic or not. The phrase "when the drug substance is itself genotoxic" is not reflective of ICH S9 and should be deleted. **Proposed change**: "In line with ICH M7 and ICH S9, there are situations (e.g., ~~when the drug substance is itself genotoxic~~, and other circumstances as described in these guidelines) when the selection of the starting material for a drug substance does not need to specifically consider the mutagenic impurity profile at the levels described above."
5.2	4	**Comments:** The sentence on 30% TTC serving an analogous function should be expanded to classify. **Proposed change:** Change to 'When determining whether a mutagenic impurity impacts the impurity profile of the drug substance, the 30% threshold serves to identify the level above which a mutagenic impurity is considered to have an impact on the impurity profile of the drug substance. "
26 (5.3)	1	**Comments**: In the fourth paragraph, the word "steps" implies that multiple steps are required to meet this condition which may not be appropriate for all synthetic routes. It is proposed to modify to "in combination with the understanding that the step or steps immediately prior to D do not impact the purity profile of the drug substance." **Proposed change**: "In the case of Example 4, application of the ICH Q11 principles includes control of the enantiomer in the specification of the proposed starting material D, in combination with the understanding that the **steps or** steps immediately prior to D do not impact the impurity profile of the drug substance."

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5.3	4	**Comments:** Overall, the wording of Q&A 5.3 is not considered clear and would benefit from simplification (e.g. the phrase "without this exception" is not considered clear. Also, remove repeated references to 'steps which impact'. **Proposed change:** Please rephrase "without this exception" for clarity. Also, remove repeated references to 'steps which impact'.
5.3	4	**Comments:** Add commas to clarify the text. **Proposed change:** Change to "However, as described in Example 4, this principle does not necessarily apply when impurities originate early in the process and 'persist' across multiple steps, provided that the steps prior to the proposed starting material, over which the impurities persist, do not themselves impact the drug substance impurity profile.
5.3	4	**Comments:** It would be beneficial to include more than one example of 'persistent impurities'. **Proposed change:** Include additional examples of 'persistent impurities'. (e.g. regioisomers of aromatics / heteroaromatics)
26 (5.4)	1	**Comments**: The second bullet point is not aligned with ICH M7. Reagents, solvents and chemicals used in the synthesis are considered to be potential impurities and assessment for mutagenicity is only required if these potential impurities are likely to be present in the drug substance. As described in section 5.1 of ICH M7 the risk of carryover for identified impurities should be evaluated and "a risk-based justification provided for the point in the synthesis after which these types of impurities should be evaluated for mutagenic potential." **Proposed change**: "Reagents, solvents, and chemicals used in the synthesis from commercially available chemicals to the drug substance

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		should be assessed for mutagenicity **if they are likely to be present in the drug substance**. Note that this **may** ~~will likely~~ include assessment of the mutagenicity of some reagents, solvents, and chemicals that are used in the steps before the starting material that is eventually proposed."
5.4	3	**Comments:** Page 8 "… the applicant should use risk-based reasoning…" In our opinion examples for reasoning should be given. One can propose tools like purge factor calculations that are based on Andrew Teasdale's' approach* which assesses the fate of an impurity based on factors linked to the impurity's physicochemical properties and the process conditions employed in the route of manufacture to the API. In addition, reasoning can be based on the likelihood of the impurity to remain, namely, second level impurities like impurities of impurities. * Teasdale A., Elder D., Chang S-J, Wang S, Thompson R, Benz N, Sanchez Flores I, (2013). Risk assessment of genotoxic impurities in new chemical entities: strategies to demonstrate control. Org Process Res Dev 17:221-230.
5.4	4	**Comments:** It is important that this Q&A remains focused on the selection and justification of the starting material and does not become a clarification of the ICH M7 text. Guidance should only be included if it helps in the selection and / or justification of the starting materials. **Proposed change:** Bullets 3 and 4 are considered contradictory to some degree. Recommend keeping fourth bullet (to best align with ICH M7).
5.4	4	**Comments:** In particular, the text should be aligned with the text of ICH M7 - "the risk of carryover into drug substance should be assessed … for starting materials that are introduced late in the synthesis of the drug substance (and where the synthetic route of the starting material is known) the FINAL STEPS of the starting material synthesis should be evaluated for potential mutagenic impurities." The current text seems to expect QSAR assessment of all pre-starting material steps when the probability of the presence of residues from steps prior to the starting material is low. After all,

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		the starting material is selected on the basis of carryover, so earlier steps are not likely to contribute and should not need assessment of potential impurities. **Proposed change (if any):** As above
5.4	4	**Comments:** Avoid wording 'recommended'. **Proposed change:** Consider replacing 'recommended' with 'should be considered'.
5.4	4	**Comments:** The concept of 'hazard assessment' is understood but we note that ICH Q9 talks about 'risk assessment'. In Q9 the level of effort reflects the level of risk, not the hazard. **Proposed change:** Consider replacing 'hazard assessment' with 'risk assessment'.
4	5	**Comments:** The current text seems to require a full QSAR assessment of all pre-SM steps starting from commercially available chemicals. The probability of the presence of residual reagent in the drug substance from steps prior to the starting materials is extremely low (after all the SM is selected on the basis of carryover from manufacturing steps so earlier steps are unlikely to contribute). The number of steps between commercially available chemicals and the drug substance can be high (>10 in many occasions). The risk arising from reagents present in steps well away from the drug substance is minimal. Assessing for the presence of known mutagens in steps prior to the starting materials is proposed to be provide enough diligence to ensure patient safety. **Proposed change:** Reagents, solvents and chemicals used in the synthesis of the proposed starting materials from commercially available

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		chemicals should be assessed for known mutagenicity. Mutagenicity of reagents, solvents and chemicals used between the starting materials and the drug substance should be assessed.
26 (5.6)	1	**Comments**: The use of the phrase "a small number of chemical transformation steps" is ambiguous and could be invoked during the review of a starting material proposal to demand additional steps without assignable cause for concern. Also, since "small" is a vague term, the meaning of this could vary over time resulting in escalating regulatory requirements. As ICH Q11 already includes the recommendation for the inclusion of "multiple chemical transformation steps" in Section 3.2.S.2.2, it would be consistent with the existing guidance to edit this section to refer to one chemical transformation step instead of a "small number". Maintaining the phrase "include one or more additional transformation steps" in the text allows for regulatory discretion in the remedy of a one-step manufacturing route proposal. **Proposed change**: "After these considerations, if the evaluation would result in **one** ~~only a small number of~~ chemical transformation step~~s~~, then it is generally appropriate to include one or more additional chemical transformation steps in Section 3.2.S.2.2."
5.6	3	**Comments:** We would like to propose to define with examples the term 'unit operation'. For example: crystallization, distillation, extraction & phase separation.
5.6	3	**Comments:** This section starts very well, making it clear that a scientific evaluation is required to evaluate how many steps should be in the detailed description of the process (i.e. based on those steps that impact on the impurity profile/physical properties of the drug substance). However, it then says: *"After these considerations, if the evaluation would result in only a small number of chemical transformation steps, then it is generally appropriate to include one or more additional chemical transformation steps in Section 3.2.S.2.2. This is to ensure that enough steps are conducted under GMP and to mitigate risks associated with contamination and future changes to the synthetic route or supplier of the starting material. The following paragraphs provide further clarification on this risk mitigation and should be considered together."*

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		In our opinion, this directly contradicts all the rest of the guidance and basically comes back to the need to include multiple steps, seemingly regardless of whether it can be scientifically justified to have a small number steps with suitable control measures. **Proposed change:** Please reword or reconsider this.
5.6	3	**Comments:** We would like to define 'Chemical transformation step' as chemical step regardless the isolation of the step product (as mentioned in Q. 5.8). A chemical step product doesn’t have to be an isolated chemical, namely doesn't have to be crystalline solid material, but also can be intermediate that is immediately used in the next step. For example, there can be a multi-step reaction sequence where intermediate is being distilled out or filtered and tested in-process before they continue to the next step; this kind of intermediate will not be considered isolated per se, but this step is chemical step since covalent bonds are broken or made and product is obtained.
5.6	4	**Comments:** We understand that adding multiple purification steps to the manufacture of a proposed starting material (to remove impurities that might otherwise be present in the SM, tho which may or may not carryover to the active substance) is not considered good practice in the justification of the selected starting material. However, it has been / is quite normal to consider purification of a starting material (as the starting material is often crystalline and purifiable). We would consider it would be appropriate to purify the starting material and not include earlier steps that generate the removed impurities (especially when these impurities would not carryover to drug substance.) **Proposed change:** Suggest the text makes it clearer that a starting material can be purified and that the earlier steps need not be included only driven by the purification of the proposed starting material.
5.6	4	**Comments:**

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		Companies remain disappointed that it is considered necessary to add steps to manage against contamination risk when this risk could also be managed against by employment of quality agreements with starting material suppliers. We understand that ahead of ICH Q12 it is considered that there is no way to recognise this alternative approach. We believe and hope however that in the future, e.g. after the finalisation of ICH Q12, such alternative quality management approaches will be given more credibility and that this can become part of the future state for the management of starting material and active substance quality in a holistic manner. **Proposed change:** It would be useful to include some text to allow for this possibility in the future and not close off this potential quality risk management approach too early.
5.6	4	**Comments:** The first sub-bullet in the Q&A 5.6 text states 'include a unit operation' that removes an impurity. 'Unit operation' is an unfortunately broad term - such a 'unit operation' could be a normal part of a designed process that removes an impurity without it being a formal repurification operation. **Proposed change:** Suggest this term 'unit operation' is reworded as 'a specifically-conducted re-purification operation'
5.6	4	**Comments:** We do not agree that there is an increased likelihood of changes just because a proposed starting material is many steps downstream of a commercially available chemical. We do not think this contextual sentence is necessary to support the rest of the Q&A text. **Proposed change:** We recommend the removal of this sentence.
5.6	4	**Comments:** It is good that the draft has included text to acknowledge the value of analytical methodologies in the control of risk in managing SM quality (e.g. through change).

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		It would be useful and reasonable to allow this alternate approach (alternate to adding more steps) to be utilised at an early-as-possible stage in the management of SM quality. In particular, at present the employment of analytical approaches to managing risk is allowed when managing change, and it would be scientifically-reasonable, and valuable, if an applicant had the option to provide analytical justification instead of adding steps e.g. when considering risk management of immediately prior steps needing to be operated under narrow ranges. This would be suitable IF and WHEN the impurity that is threatened to form is included in the analytical risk management and specification and capability of the established analytical methodology. It may also be possible to cover the risk to quality coming by analytical approaches instead of adding step when an operation is included to remove a particular impurity. **Proposed change:** Allow for the use of alternative analytical approaches at any well-justified point after establishing the steps that generate significant impurities.
5.6	4	**Comments:** Is 'risk mitigation' an ICH term? **Proposed change:** Consider replacing 'risk mitigation' with risk management.
5.6	4	**Comments:** The company comments received by EFPIA suggested that the intended logic laid out in the text of 5.6 may be open to misunderstanding and interpretation, even with the 'first' / 'then' structure utilised. **Proposed change:** Continue to clarify the logic of the text.
5.6	5	**Comments:** The focus is clearly on the chemical transformation steps impacting the impurity profile. Also purification steps impact

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		the impurity profile (by definition). These purification steps should also count as a real step when it comes to adding additional steps for GMP reasons, as these steps, when in the filing, occur also under GMP. **Proposed change:** Clarify that for the number of steps, not only chemical transformation steps, but all steps under GMP (e.g. purification) should be taken into account.
5.6	5	**Comments:** The number of chemical transformation steps is not clearly defined. Therefore it can be understood differently amongst applicants and between applicants and assessors. **Proposed change:** Can more clarification/guidance be provided on 'small number of chemical transformation steps'.
5.6 Lines 31 - 34	5	**Comments:** The phrasing of this sentence is rather confusing. **Proposed change:** We think it is more clear by eliminating the 'strikethrough' text: '*Potential risks from future changes to the starting material synthesis should also be considered (see Q&A 5.14).* ~~*In particular when the proposed stating material is many steps downstream from commercially available chemicals, there is an increased likelihood of changes to its route of synthesis.*~~
5.6	5	**Comments:** The interpretation of statement '*unit operation that has been added to the manufacturing process to control specific impurities that would otherwise impact the impurity profile of the DS'* could vary a lot and would benefit from having examples to show what is intended to be in scope. **Proposed change:** Add examples of "unit operation that has been added to the manufacturing process to control specific impurities that

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		would otherwise impact the impurity profile of the DS
5.7	4	**Comments:** Is this Q&A needed given the wording of the preface? **Proposed change:** Remove this Q/A
26 (5.8)	1	**Comments**: In the final sentence of the first paragraph, the word "purge" should be replaced with "control". Purge generally has the meaning of complete removal. Appropriate control over impurities is necessary and not complete purge. **Proposed change**: "The drug substance synthetic process should include appropriate unit operations that **control** ~~purge~~ impurities."
5.8	4	**Comments:** How should an applicant apply the 'number of steps' expectation provided in Q&A 5.6 when multiple chemical transformations are run without isolation of intermediates? **Proposed change:** Consider if clarification needed.
5.8	4	**Comments:** The final sentence of paragraph 1 of this text seems to suggest that impurities must be fully removed by processing. This is not the intent of the text and is not considered necessary. **Proposed change:** Add the word 'adequately' to the end of this sentence. (This final sentence may be duplicative of the prior sentence and could perhaps be removed.)

Line no.	Stakeholder no.	Comment and rationale; proposed changes
26 (5.10)	1	**Comments**: In the final sentence of the last paragraph, the word "purge" should be replaced with "control". Purge generally has the meaning of complete removal. Appropriate control over impurities is necessary and not complete purge. **Proposed changes**: "The justification of the specification should include evaluation of the risks and the ability of the subsequent steps to **control** ~~purge~~ impurities."
5.10	4	**Comments:** The statement that a starting material should include tests for elemental impurities and potential mutagenic impurities is considered inconsistent with Q3D and M7, where it is made clear that specification and testing should be based on the outcome of a risk assessment. **Proposed change:** Add 'where applicable'.
5.10	4	**Comments:** The text as written may suggest that a specification for a starting material is expected to contain a test for purity AND a test for assay. We believe that the intent is not to require both these tests. **Proposed change:** Consider rewording as "should include tests for identity and purity (e.g. assay or controls on impurities) and could include acceptance criteria for specified, …."
Q 5.10 Lines 4 -7	5	**Comments:** It is good that the draft has included text to acknowledge the value of analytical methodologies in the control of risk in managing SM quality (e.g. through change). It would be useful and reasonable to allow this alternate approach (alternate to adding more steps) to be utilised at an early-as-possible stage in the management of SM quality.

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		In particular, at present the employment of analytical approaches to managing risk is allowed when managing change, and it would be scientifically-reasonable, and valuable, if an applicant had the option to provide analytical justification instead of adding steps e.g. when considering risk management of immediately prior steps needing to be operated under narrow ranges. This would be suitable IF and WHEN the impurity that is threatened to form is included in the analytical risk management and specification and capability of the established analytical methodology. It may also be possible to cover the risk to quality coming by analytical approaches instead of adding step when an operation is included to remove a particular impurity. **Proposed change:** Optimise utility and flexibility of approaches to the risk management of quality
5.11	4	**Comments:** To remain aligned with other Q&A texts , we recommend that this text also includes that the information on the manufacture of the starting material be provided (1) when this information is available and (2) should not be needed when the material enters the manufacturing process at a very early step. **Proposed change:** Reword as "Information on how the proposed starting material is made (e.g. a flow chart of the starting material manufacturing process, showing all reagents, catalysts and solvents used) should be provided, when known to the applicant, to help justify the controls applied to the starting material. Information about the actual and potential impurities in the proposed starting material should be included. The information on starting material manufacture is less relevant if the proposed starting material is many steps from the drug substance. "
5.12	2	**Comments**: The distinction should be better clarified by a decision tree. The requirement of "non-pharmaceutical market" cannot always be checked entirely. **Proposed change:** Include a decision tree for starting materials.

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5.12	4	**Comments:** The exemplification with only 'protected natural amino acids' is not considered helpful. Further examples should be included to avoid giving an impression that only this type of material will be acceptable. **Proposed change:** Consider providing additional examples.
5.12 Lines 1-8	5	**Comments:** Can it be clarified how applicants are expected to justify 'commercial availability' of a chemical.
5.12 last paragraph	5	**Comments:** This last paragraph is creating confusion, after a clear explanation on the differences between 'commercial available' and 'custom synthesised' chemical **Proposed change:** Please clarify more what is meant exactly by providing more examples or a scientific description of '*simple enough in structure'.*
5.13	4	**Comments:** The text states "well documented synthetic routes that are publically available can provide important information that should be considered when evaluating potential impurities." This is understood but is a 'how' aspect rather than a 'what' and ideally ICH guidance will focus on 'what' needs to be done. In addition, the publically available routes may suggest more approaches than are in practice utilised and thus suggest a wider specification be established than is necessary. **Proposed change:** For these reasons we recommend and request omitting this sentence beginning "However, well-documented…"
5.13 Line 1 - 2	5	**Comments:** How does an applicant have to justify a chemical is a commercially available chemical?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
5.13 lines 10 - 12	5	**Comments:** Intellectual property restrictions are also applicable for externally made 'custom synthesised' chemicals as Starting Material (or Intermediates). **Proposed change:** Can it be clarified what the Health Authority expectations are in these cases and can guidance be given how to deal with these issues e.g. direct communication between supplier and Health Authorities…
5.13	5	**Comments:** It may be very dangerous to check public available information when the information on the synthesis of a starting material is not disclosed to the API manufacturer. In that case you have to make certain assumptions that may lead to incorrect conclusions.
5.14	3	**Comments:** The numbering in the answer is probably a typo. 6. No. Post-approval changes to steps prior to starting materials are not explicitly covered in ICH Q11. However, ICH Q11 does describe fundamental science and risk-based concepts that should be used to evaluate the impact of post-approval changes to the process after the starting material (ICH Q11 Section 9 – Lifecycle Management), and these same concepts should be applied to evaluate the impact of changes prior to the starting material. 7. For example, changes prior to the starting material should be evaluated for their impact on the starting material (e.g., on current and potential new impurities, including potentially mutagenic and elemental impurities) and when appropriate on the drug substance. The evaluation could be based on risk assessment and scientific understanding of the proposed change and its proximity to the starting material. The evaluation should include an assessment of the control strategy (e.g., adequacy of the specification for the starting material, including analytical procedures' abilities to detect.
5.14	4	**Comments:** A reference to ICH Q12 on lifecycle management / management of post-approval change would be useful.

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		Proposed change: Consider if a reference to ICH Q12 can be added.
Q 5.14	5	**Comments:** Please delete '6' line 1 and '7' line 7.
5.15	4	**Comments:** The current text "should address residual risks to the drug substance quality associated with future changes" suggests a need to mitigate risks for changes to starting material syntheses before these changes are planned or executed. It should not be necessary to build potential future changes into the specification established for a starting material. **Proposed change:** Remove word 'future'.
5.16	4	**Comments:** CRITICAL - The final sentence states that "when a chemical , including one that is also a drug substance, is proposed to be a starting material, all ICH Q11 principles still need to be considered". This needs to be reconsidered. Such a material should be a suitable starting material provided it is made under GMP and controlled as per its existing quality. Concerns about risk from contamination etc. are less, as such a material will be manufactured to the API specification under GMP (and can be specified as such). **Proposed change:** Change to 'A proposed starting material that is already an approved active substance should be acceptable as a starting material provided it is manufactured under GMP to a suitable specification".
5.16	4	**Comments:** It may also be relevant to consider if an excipient material that meets monograph quality can be considered as a suitable starting material.