10 November 2016
EMA/454577/2016
Committee for Medicinal Products for Human Use (CHMP)

Submission of comments on 'Draft guideline on the chemistry of active substances' – EMA/CHMP/QWP/96664/2015

Comments from:

Stakeholder Number	Name of organisation or individual
1	AESGP (Association of the European Self-Medication Industry)
2	APIC (Active Pharmaceutical Ingredients Committee)
3	ASCHIMFARMA (l'Associazione Nazionale dei produttori di principi attivi e intermedi per l'industria farmaceutica)
4	BMS (Bristol-Myers Squibb)
5	EFPIA (European Federation of Pharmaceutical Industries and Associations)
6	EGA (European Generic and biosimilar medicines Association)
7	SciencePharma
8	Gilead Sciences International Ltd.
9	IFAH-Europe (International Federation for Animal Health Europe)
10	Takeda

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
1	The guideline does not adequately address existing APIs with an unchanged manufacturing process and a well-established control strategy, which have been marketed for a long time. Minor changes should not require a full update of the dossier to fulfil the requirements of this guideline. A general update of the documentation should only be required for a major change. (Variation II).	Existing active substances have been defined in the revised guideline.
1	The guideline should solely describe requirements for the submissions. GMP aspects should be deleted and are subject to inspections.	Requirements solely related to GMP aspects have been deleted.
2	The concept paper for this guideline (EMA/CHMP/QWP/752676/2013) stated: “The revised guideline will not introduce new requirements on medicinal products already authorised and on the market.” It is understood that the discussed guideline will not introduce any new requirements for existing APIs. However, in several sections of this draft existing requirements for NCEs are stated without distinguishing to requirements for existing APIs. By this approach this draft does not follow the intention of the concept paper.	It is not the intention to introduce new requirements and the guideline should not be applied retrospectively, but it is intended that this guideline will act as a stimulus to establish best practice.
4	The guideline should allow for inclusions to accommodate new technology development such as continuous API manufacturing.	New technology development is not excluded from this guideline.
5	EFPIA welcomes the effort made to combine the	The comment is noted.

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	expectations for active substances (whether new or existing) in one guideline and offers the following recommendations. Detailed comments on the text are also provided that may be helpful to the drafting team.	
5	**Scope - Investigational Medicinal Products (IMPs):** Efpia recommends that Investigational medicinal products (IMPs) are clearly excluded.	Agreed. The following wording has been added: 'The guideline does not apply to contents of submissions during the clinical research stages of drug development. Nevertheless, the development principles presented in this guideline are important to consider during the investigational stages.'
5	**Scope - Active substances derived from semi-synthetic, fermentation processes etc.:** Efpia recommends that the guideline clarifies the applicability to small molecule active substances derived from fermentation processes, or from semi-synthetic processes (e.g. a combination of fermentation to generate intermediates) Semisynthetic active substances are no longer specifically addressed, although they were in the scope of the previous guideline version) Efpia also recommends that the guideline clarifies the applicability to active substances that are peptides/oligonucleotides.	No. A positive and negative statement leaves room for gaps – therefore, only a list of what is excluded is given.
5	**Scope - Active substances manufactured by continuous processing:** Efpia notes that parts of the guideline might not be applicable to products manufactured using continuous manufacturing, where drug substance (DS) per se would not be isolated. Efpia recommends that the guideline should allow for appropriate exclusions to accommodate these manufacturing technologies.	See response above.
5	**GMP aspects should not be included:** Efpia recommends that the guideline should solely describe requirements for regulatory submissions. GMP aspects should be deleted and are subject to inspections (for example line 249 on validation, or line 421 on	See response above.

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	reference standards).	
5	**Applicability to existing active substances:** Efpia recommends that consideration is given to clarifying throughout the Guideline which requirements are applicable for new or existing active substances (for example the section on selecting the starting materials).	See response above.
5	**Active Substance Master Files:** Efpia recommends that the expectations for information to be provided in applicants/restricted part when using the ASMF procedure are clarified.	Not agreed. The requirements on the information to be provided in applicants/restricted part when using the ASMF procedure are described in the Guideline on Active Substance Master File Procedure. Duplication is not intended.
5	**Implementation - Effective date:** Efpia recommends that the effective date of the guideline is 2 years after the publication of the final guideline to enable a smooth implementation of the new requirements.	This will be determined at the time of adoption.
5	**Implementation - Changes to existing active substances:** Efpia believes that minor changes to existing active substances which have been marketed for a long time, with an unchanged manufacturing process and a well-established control strategy should not require a full update of the dossier to fulfil the requirements of this guideline, as this may inhibit the introduction of such changes. Efpia recommends that major changes (e.g. Type II Variation) only should necessitate a general update of the documentation in line with the new requirements.	It is not the intention to introduce new requirements and the guideline should not be applied retrospectively, but it is intended that this guideline will act as a stimulus to establish best practice.
5	**Implementation - Summary of changes:** Efpia recommends that final publication of the guideline includes a summary of the important changes e.g. the issue and/or the gaps in the current guidelines and revision in the new guideline provide that closes the gaps. This will assist industry to focus on the implementation of these changes.	After adoption by the CHMP a short summary will be published in the CHMP meeting minutes available publicly.

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5	**Incorporation of concepts from emerging ICH Guidelines**: Efpia recommends that the final publication incorporates the latest developments in the ICH Q11Q&As, and that the order of data presented on properties versus elucidation of other characteristics is aligned with the ICH guidance on the eCTD format. Efpia also recommends that consideration is given to further revisions that may be necessary to incorporate concepts from ICH Q12, for example, and that regionally-specific requirements or differences are avoided as far as possible.	It is not possible to include concepts from these guidelines as these guidelines are not yet finalised.
6	The EGA welcomes the 'Guideline on the chemistry of active substances' and would like to make the following 3 general comments :	See below.
6	1. In order to efficiently reconcile the need for transparency in the API supply chain and resilience in the supply chain, the EGA would like to highlight that there should not be more additions of API GMP or supply chain elements into the regulatory dossier. The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s), where applicable. All other involved sites (e.g. starting materials site, brokering site, testing site, stability site) should be omitted from the regulatory dossier, while appropriately managed through manufacturers' quality systems (including audit and audit programmes) and subject to regulators' supervision as part of GMP inspections of both API and Finished Product (FP).	Not agreed. Information on the manufacturers as described in the draft guideline is an essential part of the dossier.

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6	2. The EGA would like to stress the importance of harmonised submission and acceptance of the ASMF throughout Europe. Still some of the EU countries are not accepting the ASMF submissions through CESP and some of EU Countries are accepting ASMFs only for the Centralized Procedure. It would be helpful if all the EU Countries accepts the ASMF submission through CESP with regards to reducing time, consumption of paper, courier charges, tracking and archival of documents aspects. We would also like EU Agencies to assign the ASMF Numbers for the ASMFs submitted in a consequent and harmonised way.	The harmonisation of ASMF submissions is of high priority for the EMA and the Heads of Medicines Agency. The Active Substance Master File Working Group has been established. The comment is noted, however, not relevant for this guideline.
6	3. The EGA asks EMA to look into the possibility to define a procedure to review the ASMFs independently, similar to the process adopted by the EDQM and WHO Agencies.	The harmonisation of ASMF submissions is of high priority for the EMA and the Heads of Medicines Agency. The Active Substance Master File Working Group has been established. The comment is noted, however, not relevant for this guideline.
7	It is mentioned (lines 59-62) that the guideline is planned to be applicable for both existing and new chemical entities. Moreover it is stated that “the differences in requirements for new or existing active substances are clarified in the relevant paragraphs of the guideline where applicable”. While it is generally acknowledged that in some areas less extensive data may be required for existing substances than for new ones, the approach presented in the guideline is not entirely clear and therefore more details are recommended to be provided.	Existing active substances have been defined and specific stakeholder comments have been addressed in the relevant sections of the revised guideline.

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	For example, in respect to the section on manufacturing process development it is written than in case of existing active substances “all provided data might be obtained on production scale batches manufactured according to the presented manufacturing description” (lines 258-259), while it seems that this approach could be applicable also for new active substances. In respect to elucidation of structure it is stated that “section 3.2.S.3.1 describes the information which is expected for a new chemical entity” while for existing active substances “not all items might be necessary to prove the identity of the material” (lines 264-265). This paragraph is recommended to be reworded to better reflect stricter requirements on structure elucidation of new active substances in comparison with existing ones. Provisions of the “Recommendation on the assessment of the quality of medicinal products containing existing / known active substances” (EMA/CHMP/CVMP/QWP/450653/2006) are recommended to be considered and – if applicable – included in the guideline.	
9	IFAH-Europe welcomes the opportunity to comment on this draft Guideline. According to the information provided during the QWP Interested Parties meeting last May 2015, it is the understanding of IFAH- Europe that a specific Veterinary guideline will be published for consultation at a later time point. However IFAH-Europe is happy to provide	The comment is noted.

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	comments already at this stage.	
9	This GL should not be used by NCAs as a reference for the review of veterinary submissions in particular for "existing veterinary active substances (APIs)". For existing APIs, many of the requested development data might not be available. In addition, many synthesis routes established for years might not be in line with the requirements laid down for starting material definition as described in the guideline draft and the referenced reflection paper. If all current requirements will be applied (retrospectively) to existing APIs now, this will not only cause a high workload to generate data in order to comply with the guideline but can also lead to non-acceptance of several APIs due to the established short synthesis routes. As a consequence, the related finished products might disappear from the market because no alternative API route or supplier can be established with reasonable costs and efforts. To that respect and regarding the applicability of new guidelines to existing products, IFAH-Europe would like to refer to the "Guideline for guidelines" - PROCEDURE FOR EUROPEAN UNION GUIDELINES AND RELATED DOCUMENTS WITHIN THE PHARMACEUTICAL LEGISLATIVE FRAMEWORK – Reference EMEA/P/24143/2004. Under Implementation chapter, last §, this guideline states: "Guidelines are normally prepared for application prospectively. However, there may be exceptional situations in relation to risks to public and/or animal health where a guideline would need to be applied to medicinal products already authorised and on the market. In such circumstances, this would be announced at the consultation stage of the concept paper and draft guideline and will include an explanation as to the rationale. A clear statement to this effect will	Existing active substances have been defined and specific stakeholder comments have been addressed in the relevant sections of the revised guideline.

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	also be included in the final published guideline. In these instances, competent authorities will generally prepare a timetable for the application of the guideline to products on their market". This guideline should include a general comment that these requirements should not be applied retrospectively in a systematic way.	
10	It is recommended to combine this guideline with the 'Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier, CHMP/QWP/297/97'. This would be more user friendly and cover all requirements for the drug substance part in one guideline.	Not agreed. The 'Guideline on the Summary of Requirements for the Active substance in the Quality Part of the Dossier' is a procedural guideline whereas the current guideline is a technical guideline.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
2, 52 and 59	7	Proposed change: 'Guideline ~~Note for guidance~~ on chemistry of new active substances'.	Agreed
52 - 54	1	Existing APIs should be addressed: Please change the text: This guideline replaces the 'Note for guidance on chemistry of new active substances' (CPMP/QWP/130/96, Rev 1) and 'Chemistry of active substances' (3AQ5a). It has been revised to cover new and existing active substances in one guideline. For existing APIs produced and tested according to well-established procedures this guideline only applies in case of major changes (Variation II).	Not agreed.
52 - 54	5	How the guideline will be applied to approved APIs should be addressed: Please consider change the text; for example, add: ….. for existing APIs, produced and tested according to well-established procedures, this guideline only applies in the case of major changes (Type II Variations).	Not agreed.
62	10	It is recommended to refer also to active substances described in the European Pharmacopoeia. These are also in scope of the guideline.	"Existing active substance" has been further defined.
62-63	3	Comment: *it would be better to also include a list of substances for which guideline is actually applicable (i.e. semi-*	No. A positive and negative statement leaves room for gaps. Leave as is.

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		synthetic products, fermentation products…)	
65	5	ICH Q11 applies to both traditional and enhanced submissions, and defines some minimum expectations. Also, much ICH detail on what to include for a Design Space is provided in other ICH guidelines (e.g. ICH Q8, 9, 10 points to consider etc). Overall, it is not clear how the Agency distinguishes between "traditional" and "enhanced" approaches. How can applicants understand where a "traditional" development approach can be reviewed as such (and not based on "enhanced" principles) ? Suggest review wording to clarify; For example, consider: "Manufacturing process development should always include, at a minimum, the following elements: • Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug product quality can be studied and controlled; • Defining an appropriate manufacturing process; • Defining a control strategy to ensure process performance and drug substance quality. When an "enhanced" approach is used, the additional information provided in sections 3.2.S.2.2 to 3.2.S.2.6., should be prepared and organised according to ICH Q11 a**nd**	Reference to relevant ICH guidelines (Q8-11) added.

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		other relevant guidelines."	
76-79	5	**Comment**: it would be useful to clarify the role of the Annexes, where not familiar with the EU framework. **Proposed change**: add at the end of line 79: …, and which set out the requirements for presenting the particulars and documents accompanying an application to a MA.	Not agreed, leave as is.
82	5	Comment: The term 'identity' in this context could be omitted. Proposed change: 'This section deals with the ~~identity,~~ nomenclature and chemical structure …' etc.	Proposal acknowledged. The substance needs to be named (=identified). Therefore "identity" will be kept. This should not be confused with "characterised" (section 3.2.S.3.1). The comment is not related to a change introduced in the draft document. No change.
87	5	**Proposed change** (if any): "The following information on the … should be provided, if applicable, to an existing or new active substance: …"	Proposal acknowledged. The term "if relevant" implies that not all information is applicable to new active substances. No change.
91	5	**Comment:** Company or laboratory code is provided in the same line as National Approved Names. It does not fall under this category, and thus should be moved to a separate line. **Proposed change**: • National approved Names: … • Company or laboratory code	Proposal accepted.

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97 - 102	5	**Comments** - This section should be more specific to address the representation of salts, solvates, hydrates and cocrystalline compounds that are the final form of the drug substance. As currently written, this paragraph appears to address only the active moiety of the drug substance, not the final form, and would benefit from clarification in that regard. - Edits: to reword the first two sentences (lines 97 to 100) as follows: "The chemical structure of the active substance should be provided and the depiction of the chemical structure should accurately represent the relative and absolute stereochemistry of the molecule. In addition, the molecular formula and the relative molecular mass should be provided.	Proposal acknowledged. The proposed wording is similar to the original text. In practice it has not been observed that the current wording is misleading. No change.
98	5	please insert "Mr" after the first time mentioning "relative molecular mass", then use "Mr" in the following text, or replace Mr with its expansion throughout	Proposal accepted.
104-107	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): *A list of physicochemical and other relevant properties of the active substance should be provided, unless this information (i.e. existing apis) is already available from scientific literature, in particular physico-chemical properties that affect pharmacological efficacy and*	Proposal acknowledged. If the information is available from scientific literature the applicant can provide the information from the same. No change.

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		toxicological safety such as solubilities, pKa, polymorphism, isomerism, logP, permeability, hygroscopicity, etc…	
104-107	8	Comment: The studies to measure and interpretation of the permeability of the active substance are better described in the non-clinical sections of the application. Proposed change (if any): A list of physicochemical and other relevant properties of the active substance should be provided, in particular physico-chemical properties that affect pharmacological efficacy and toxicological safety such as solubilities, pKa, polymorphism, isomerism, logP, ~~permeability~~, hygroscopicity, etc	Permeability may be important for development of the finished product, no change.
107	5	**Comment**: Permeability is a pharmacological phenomenon, and not an inherent chemical property of the active substance. It should not be included in the list. **Proposed change**: "… logP, ~~permeability~~, hygroscopicity…"	No change - see above.
109-112	6	Comment: The EGA would like to comment that there should not be more additions of API GMP or supply chain elements into the regulatory dossier. The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s), where applicable. All other involved sites (e.g. testing site, stability site, brokering site, starting materials site) should be omitted from the regulatory dossier.	There is no intention to increase the requirements on applicants from the changes to this guideline. However, the proposals from EGA are not in line with current practice and guidance, e.g. ICH Q11. Not accepted.

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		Proposed change (if any): The name, address, and responsibility of the final API manufacturer(s), including contractors, and the final intermediate manufacturer(s) where applicable should be provided.	
110	5	Suggest to change "contractors" to contract manufacturers"	No change. This changes the meaning and is not correct.
111	5	Suggest to change "introduction of" to "should be provided for the productions steps after"	Accepted.
110-112	5	**Comment**: the current wording "*manufacturing and testing after introduction of the starting material(s)*" may be interpreted as if vendors of starting materials do not need to be provided, which is contradictory to the EMA Reflection Paper (EMA/448443/2014). The 2 documents should be consistent and the wording amended accordingly. **Proposed change**: "The name, address and responsibility of each manufacturer, ~~including contractors … should be provided~~ that contributes to the manufacture of any starting material(s), intermediates(s) and the active substance, must be provided. This includes both manufacturing sites of the applicant as well as any third parties which manufacture starting material(s), intermediate(s) or active substances on behalf of the applicant."	No change. The information on starting materials sites of manufacture should be included in 4.2.3.

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111	5	Is update of approved CMC/DMF documentation needed to fulfill this requirement? Should we include also testing sites? Please clarify.	No change. No need to update already approved information, aimed at new submissions and changes to this information. Testing sites required.
114	5	Comment: this is inferring that only detail in S.2.S.2.2 is considered a “commitment”. Is this correct? Consider whether other modules represent a commitment (e.g. S2.3, S2.4?)	No change. Narrow interpretation of the phrase and all the information is a commitment.
116	5	Comment: The term “optional process” has some redundancy with “alternative process” and “reprocessing”. The requirements defined for “alternative processes” and for “reprocessing” do apply to some extent also to “optional processes”. Proposed change (if any):116: change to “Optional and alternative processes and controls….” Provide clarification on “optional processes” versus “alternative process” and “re-processing” in section Definitions (460)	Acknowledged, clarified. Optional processes, alternative processes and reprocessing with associated controls that may be completed by the intermediate or active substance manufacturer, should also be described. Example removed.
116-117	4	Comment: **Optional processes and controls that may be completed by the active substance manufacturer, for instance size reduction** Proposed change (if any):	See above.

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		The term “optional process and controls” need clarification as it may be subject to interpretation such as reprocessing or alternate process with different process parameters, reagents, & solvents. The term “size reduction” is open to interpretation. For clarity, need to state as particle size reduction or batch size reduction.	
116-117	5	The term ‘size reduction is not clear and open to interpretation. The FDA’s SUPAC – IR/MR guidance ‘manufacturing equipment addendum’ (January 1999, draft April 2013) uses the wording “particle size reduction / separation. For consistency, we suggest to use the wording ‘particle size reduction / separation’ taken from the FDA SUPAC-IR/MR.	See above.
116-118	1	The regular process description covers also size reduction. Thus, the example for the description of an optional process is not feasible. Please exchange the example: Optional processes and controls that may be completed by the active substance manufacturer, for instance introduction of a second crop or the use of an alternative catalysator with different process parameters, should also be described.	See above.
118-120, 130-132	5	Proposed change: In the process description the term ‘critical’ should be used to classify process parameters (process parameter criticality is linked to the parameter’s effect on any critical quality attribute: ICH Quality IWG Points to Consider Guide for ICH Q8/Q9/Q10 Guidelines) and in-process controls.	No change. This level of detail not appropriate.

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		In the sequential procedural narrative of the manufacturing process, critical process parameters and in-process controls could for example be **bolded** and <u>underlined</u> to emphasize them against the non-critical ones. We suggest to adapt the current wording in the guideline accordingly.	
121-125	4	Comment: **A flow diagram of the synthetic process(es) should be provided** Need clarification: is synthetic scheme and flow diagram the same and used synonymously? Yields, weights, operating conditions and unit operations should be part of process description and should not be part of the flow diagram/or synthetic scheme. Proposed change: unit operations to operational conditions Need clarification - does weight refer to molecular weight or in-put weight?	Clarification is provided by rewording: Graphical representations of the synthetic process(es) comprising a reaction scheme that include molecular formulae, chemical structures of starting materials, intermediates (it should be clear if isolated or non-isolated), reagents and active substance reflecting stereochemistry, catalysts and solvents, as applicable. A block flow diagram that identifies operating conditions, unit operations, weights, yield ranges etc. can be provided optionally.
121-125	5	Comment: For clarification: Are the terms 'flow diagram' and 'synthetic scheme' used synonymously? Weights, yield ranges, operating conditions, unit operations should not be part of the flow diagram and synthetic scheme. These should be elements of the process description. Proposed change:	See above. New wording proposed.

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		'A flow diagram of the synthetic process(es) should be provided that includes molecular formula~~, weights, yield ranges,~~ chemical structures of starting materials, intermediates, reagents and active substance reflecting stereochemistry, and identifies ~~operating conditions, unit operations,~~ catalysts and solvents'.	
121-125	6	Comment: The EGA would like to comment that for the flow diagram, the following aspects are not required: 1. Weights and Yield ranges 2. Chemical structures for reagents, catalysts and solvents 3. Operating conditions and unit operations. Since the above details (Weights, Yield ranges, Chemical structures, Operating conditions and Unit operations) are covered under the sequential procedural narrative, these are not required to be mentioned in the flow diagram. Proposed change (if any): Deletion of recurring details from flow diagram text.	See above. New wording proposed and taken into account.
122-125	7	Comment: It is unclear what exactly is meant as "unit operations". Moreover, "formula" should be replaced with "formulae".	See above. 'Unit operations' is clear but formulae can be incorporated.
122-125	8	Comment: The numerous details required for inclusion in the flow diagram result in a cluttered figure with reduced value in the application. Items likely to require significant discussion for clarity such as anticipated yield ranges, operating	See above. Taken into account.

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		conditions and unit operations would be better included in the narrative process description. Proposed change (if any): A flow diagram of the synthetic process(es) should be provided that includes molecular formula, weights, ~~yield ranges,~~ chemical structures of starting materials, intermediates, reagents**, catalysts, solvents** and active substance reflecting stereochemistry~~, and identifies operating conditions, unit operations, catalysts and solvents.~~	
128	5	Here and elsewhere – perhaps 'raw materials' belongs as is, and 'starting materials and intermediates, solvents, catalysts and processing aids' belong in parentheses after? Otherwise not sure what raw materials are. List should be consistent through guidance. e.g. line 128, 153, etc.	Accepted. Suggested rewording: This narrative should include the quantities (or ranges) of materials (intermediates, starting materials, solvents, reagents, catalysts, process aids etc.) used in a current representative production scale batch.
128	6	Comment: The EGA would like to highlight that the guideline refers both to "raw materials" and "starting materials". It would need to be clarified in the definitions section if both terms are considered to be different.	See wording above.
129	5	Criteria for distinguishing between pilot, commercial and production batches should be provided	Pilot and production scale alone are now used, no mention of commercial scale any more. The scales are mentioned in other documents.

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			See also lines 256, 258, 393, 396, 412.
129	5	Suggest to change "scale commercial" to commercial scale"	See above, accepted.
129	5	"…solvents, catalysts and reagents used in manufacture of a representative scale commercial batch." Is this referring to a representative-scale?	See above.
129-132	5	Comment: The applicant should avoid unnecessary detail in the description of the process. Not all process controls or equipment operating conditions should be presented in the Regulatory commitment to manufacture. The justification for the selection of critical controls should be presented in S.2.6. As has been previously stated by EMA (EMEA/INS/GMP/227075/2008): "*From the side of the marketing authorisation holders and clinical trial sponsors, better communication between regulatory affairs departments and manufacturing operations with respect to the level of detail provided in marketing authorisation applications or clinical trial applications should be put in place to minimise future occurrence of deviations that are caused by unnecessary detail. It should be noted that details that fall within the scope of GMP are inappropriate for inclusion in submissions."* We fully support the concept of avoiding unnecessary detail in the marketing authorisation and suggest that only those	Not accepted. Sufficient details are needed and this is what is requested.

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		controls and conditions deemed critical are appropriate for post-approval Regulatory oversight. Proposed change: The narrative should describe each step in the manufacturing process, and identify those steps, process controls, and ranges for equipment operating conditions (e.g.: temperature, pressure, pH, time, flow-rate, etc.) that are determined critical. The basis for selection of critical controls should be presented in S.2.6.	
131	5	Equipment operating conditions may not be the relevant parameter; e.g. the jacket temperature of the vessel may be fixed at equipment level, but the relevant process parameter the temperature of the mixture is relevant. Relevant process parameters should be specified. **Suggestion:** replace 'equipment operating conditions' by ' ranges for process parameters'	Proposal accepted. See below.
130	5	Also consider some reference to CPPs in addition to critical steps L130, L133, L229.	Proposal accepted. Suggested rewording: The narrative should describe each step in the manufacturing process, and identify critical steps, critical process parameters, process controls employed, and ranges for process parameters (e.g.: temperature, pressure, pH, time, flow-rate, etc.).

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134	5	Comment: It seems unusual to include a section on Manufacture, range and yield in Section S2.4	Proposal acknowledged, sub-section deleted. Content has been maintained in modified form.
134	5	Generally a ±10-fold variation in the quantities is considered to be acceptable in the field of purely synthetic API technology.	Not accepted.
134-137	5	Comment: There is no indication here of justification for the scale or yields claimed. Does scale have to be demonstrated, or can it be projected? Equally, will only demonstrated yields be considered to be justified to be claimed here? There can be significant variance on yields particularly in processes where “heels” are laid down in filters for example – but won’t necessarily be demonstrated at point of file. (these points are particularly prevalent for NCE files) Proposed change (if any): The description of the process should indicate the scale of manufacture and the range for which the considered process may be used if the applicant has not demonstrated sufficient knowledge of process capability to omit this requirement	No change. See above where clarified.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
136-137	5	Yield should only apply to intermediates if they are isolated. **Suggestion:** Add qualification …"for isolated intermediates only"…	No change. Each stage refers to isolated intermediates and active substance.
137	5	Suggest to change: "It may be helpful to indicate the yield or yield range produced at each stage." to "The yield or yield range produced at each stage should be provided as applicable.	See above.
138	3	Comment: *is "reworking" procedure considered under the definition "Alternate processes"? If so, it is suggested report it explicitly.* Proposed change (if any): *alternative processes/reworking*	Proposed clarification and additional sub-section added. Some rework (i.e. for failures) are allowed under ICH Q7. This document does not cover this option.
138 -142	4	**Alternative processes should be explained and described with the same level of detail as the primary process.** Definition of Alternative processes is unclear; need clarification - what is considered an alternate process (example: different reaction conditions to the same chemical transformation or different chemical transformation, etc.)? Does an alternate process need to be included as part of the approved process or does this difference need to be performed during validation or is development data on pilot scale sufficient as evidence to provide it has no impact on the final	See above. No need for further clarification. Alternative processes performed routinely should be described in the dossier.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		drug substance quality?	
138-142	5	Comment: Does the header “Alternative processes” cover “re-working”? If so, why is the tech term “re-working” not used? Since the term “re-working” is usually employed in the scientific literature and by many health agencies, it would make sense to include a brief explanation of reworking in this guidance and what it does imply. Proposed change (if any): Differentiate between “alternative processes” and alternative steps (re-working). It should be clarified whether alternatives in synthetic route or only alternatives in manufacturing steps/process are allowed. The question is based on the fact that the part of the requirement referring to different impurity profile is omitted. For alternative processes can we prove the equivalency on the isolated intermediate?	See above. Covered in previous changes/explanations.
142	5	“…quality of the material (i.e.: active substance or isolated intermediate) obtained remains unchanged.” Suggested change: “…quality of the material (i.e.: active substance or isolated intermediate) obtained remains ~~unchanged~~ equivalent.” “Remain unchanged” may need some clarification. Is it acceptable if the supportive data can prove that the quality variation is not related to the alternative process?	The changing of the profile should result in another CEP or ASMF, it is not appropriate to consider this as an alternative process. This has been clarified with additional wording. In an MAA there maybe (and often are) several different profiles of active substance in same submission.

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142	8	Comment: Alternate processes should provide the intermediate or active substance that is suitable for use in the downstream manufacturing process and support the overall quality of the product. Requiring that the material quality from an alternate process “remains unchanged” without any connection to the acceptable quality of the material is restrictive without increasing patient safety or product quality. Proposed change (if any): Reinstate the former language “If differences in impurity profiles are encountered they should be analysed with validated methods and shown to be toxicologically acceptable.”	The former text has been reinstated for new active substances (not CEPs or ASMFs).
143	4	**The cases where reprocessing is carried out should be identified and justified.** Based on ICH Q7, Reprocessing is allowed for batches which don’t conform to established specifications. If reprocessing used for majority of batches, such reprocessing should be included as part of the standard manufacturing process (please add reference to ICH Q7 14.2) It is more logical to include justification for reprocessing in 3.2.S.2.6 section instead 3.2.S.2.5 It is beneficial to add a brief explanation of re-work and differentiate alternate processes and alternate steps (re-working) (alternatives in synthetic route). It is understood that manufacturing steps undergoing re-work should be identified, provided the criteria for deciding when	Added “routine” in order to clarify.

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		rework can be performed and also provided same level of details as primary process.	
143	5	Comment: Reprocessing (i.e. per ICH Q7, repeating already established processing) is currently allowed to be conducted under GMP (for batches that do not conform to specifications) without specific mention in the application. There should be no need to identify 'the cases where reprocessing' are to be used. The word 'reworking' is understood to be an event where a product is subject to alternative conditions. Such conditions may require to be described and rationalized in the application in S.2.2. Proposed change (if any): Please correct this section of the text to be consistent with ICH Q7 and current harmonised regulatory expectations. Please also consider additional clarification regarding reworking.	See above.
143 - 146	1	Paragraph should be brought in line with ICH Q7 which defines and allows reprocessing in general. In case that a majority of batches needs reprocessing it shall be described in the standard manufacturing process: In cases where reprocessing is carried out the rules of ICH Q7 apply. If such reprocessing is used for a majority of batches, such reprocessing should be included in the sequential procedural narrative of the manufacturing process. Any data to support and justify should be either referenced or presented in 3.2.S.2.5. The reprocessing method should be	See above.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		clearly described and the criteria for deciding when re-processing can be performed provided.	
143 - 151	2	For existing APIs it is currently not required to describe any such details for reprocessing procedures. Manufacturing processes for these substances are established for a long production period. The manufacturers are familiar with these processes. Reprocessing is performed and documented within established GMP procedures. An additional approval via regulatory variation procedures needs not to be applied. Proposed change (if any): We suggest to keep current requirements for existing APIs.	Proposal not accepted. Data to support routine re-processing should be provided as clarified above.
144-145	3	Comment: *It is suggested to amend the text, as per the below.* Proposed change (if any): *Any data to support this justification should be either referenced or presented in 3.2.S.2.5 if/when the same are available.*	Proposal not accepted. Data to support routine re-processing should be provided as clarified above.
145	5	Is it correct to put the justification for reprocessing in S2.5. Additionally, S2.5 doesn't mention that this information belongs in this section. Proposed change: The cases where reprocessing is carried out should be identified and justified. Any data to support this justification should be either referenced or presented in 3.2.S.2.**6**.	Proposal not accepted. Data to support routine re-processing should be provided as clarified above.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
145-146	3	Comment: *we believe that the criteria used for deciding the need of reprocessing procedures are covered by the GMP system requirements in place in the API Manufacture so we would propose deleting of this requirement.* *We would propose the inclusion of data to support reprocessing procedure in alignment to the ICH Q7 and relevant Questions&Answers document Question 14.2.* Proposed change (if any): *The reprocessing method should be clearly described. if data are available to support reprocessing procedure(s) with the aim of re-assign a full retest date to drug substances which have reached/are reaching the established retest period, the same should be described.*	Proposal not accepted. Data to support routine re-processing should be provided as clarified above.
145-146	6	Comment: The guideline requires to establish "criteria for deciding when re-processing can be performed". The EGA would like to ask EMA to further clarify whether this request in the guideline is different from the current expectation in ICH Q7.	Proposal not accepted. Data to support routine re-processing should be provided as clarified above.
147	3	Comment: *"Reworking" procedure(s) seems missing from the definition.* *It is suggested to include it, as subparagraph, unless not already considered under the definition "Alternative Processes".* *See also cross link to line 138*	Proposal accepted. A new paragraph has been added.

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147	5	It would not normally be expected to have to describe the recovery of solvents and reagents or other materials in the submission. Is it an expectation that such recovery processes for solvents, reagents would be described in 3.2.S.2.2 ? This section doesn't also address what information what information should be provided Proposed change (if any): Delete solvents: "Recovery (…) of reactants, intermediates or the active substance	Clarification proposed. "Where these materials are re-introduced into the process. Suitable specifications for the intended use should be provided."
147 - 151	2	The rational regarding recovery processes is acceptable. However, it is not clearly understood how this section is related to the scope of the guidance. Is it meant as a statement of current thinking of EMA? Or is it intended to describe any dossier requirement. Proposed change: Please clarify the intention of this section.	See above.
147-151	4	Recovery: Does this section mean that the information need to be provided as part of the filed manufacturing process description or not as long as the requirements stated are available at the mfg site.	See above.
152 ff	1	4.2.3 Control of Materials 3.2.S.2.3 We think it would be helpful to reduce the requirements on starting materials only to the requirements made in the ICH Q11, because this guideline comprehensively addresses the	Acknowledged but make no change. This guideline doesn't add requirements for starting materials in comparison to ICH Q11.

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		requirements for starting materials. Additional requirements can cause confusion and possibly redundancies.	At this stage, it appears difficult to ignore the EU reflection paper but it may be possible to evolve it in the light of future Q&A on Q11.
152 - 155	2	This requirement is repeating the information requested for the flow chart. In general we suggest to give any information only once in the whole dossier. This will avoid inconsistency within the dossier especially during life-cycle management. Proposed change: Please decide where this information should be given once in the dossier.	No change in light of the re-drafted paragraph on the schematic representation.
153	6	Comment: The EGA would like to highlight that the guideline refers both to "raw materials" and “starting materials”. It would need to be clarified in the definitions section if both terms are considered to be different.	Proposal accepted, both here and above. No reference to raw materials (of which S. Mats. are a subset).
155	1	The requirement to include information on the identification of materials should be required for new APIs only. In a well-established process no benefit is taken from this new requirement: For new APIs adequate specifications including information on the identification of these materials should be provided.	Proposal acknowledged but not accepted. All the materials used in manufacture of new or existing APIs should be identified by suitable methods.
155	5	The requirement to include information on the identification of materials should be required for new APIs only. In a well-established process no benefit is taken from this new	See above.

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		requirement:	
155	5	For new APIs, please provide more understanding of the basis for “adequate” specifications, what “information” is expected for identification, and how this may apply for the different raw materials i.e. starting materials compared to processing aids.	Acknowledged. Suggested rewording: “Adequate specifications for these materials should be provided and should include an identification test. The specifications should address the characteristics of the material and its suitability for the intended use.”
155 – 156	2	As already addressed in line 150 materials used for manufacturing should meet specifications that are suitable for their intended used. The focus is clearly addressing the description of the intended manufacturing process. This is obviously only the case when the intended materials are applied. It is out of any scope of a regulatory dossier to consider any cases that are not covered by the established processes. On the other hand identity testing is indeed performed during manufacturing to assure that the intended material is applied. However, identity testing gives no information about a suitable specification of a raw material for the manufacturing process regarding the desired purity of the active substance. Testing identity of raw materials is a must for applying GMP to the manufacturing. But it is considered to be obsolete for describing the suitable chemical purity of any raw material. Proposed change: Adequate specifications of these materials should be provided.	No change. See above, ID test needed.

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155-156	3	Comment: *taking into consideration that some process aids (i.e. filtering aids, pre-filled in filtering cartridges…) are accepted on the basis of the relevant Suppliers' COA and no analysis/specification are in place by the API Manufacturer it is suggested to amend the text, as per the below.* Proposed change (if any): *Adequate specifications including information on the identification of these materials should be provided, where applicable.*	Acknowledged but make no change. Specification should be in place. The specifications of the supplier can be presented in the dossier however this will not prevent an identification testing performed by API manufacturer.
156 – 157	2	It is not clearly understood what is meant by "Information demonstrating that materials meet standards appropriate for their intended use should be provided." Proposed change: Please clarify the meaning of this requirement.	Re-drafted, see above.
156-157	5	Comment: It was surprising to see that detailed information on methods and validation of methods related to input materials is expected in the application. Providing methods and validation for input materials and intermediates (line 244) seems to represent an escalation in expectations and has not previously been expected for existing active substances. There is no dedicated section in S2.3 to submit validation data. Also, the need for maintenance of the data is not described. As with the first general comment, some ICH Q12 concept about "non-regulatory binding" information could be described	Removed from this section. Validation of analytical methods is discussed in the intermediates sections instead.

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		to avoid unnecessary regulatory dossier maintenance. Also, it is unclear what the criteria are for assessing the criticality of a material. **Suggestion:** Proposed change (if any): Reconsider if such information is needed in the application and align to current expectations. Alternatively, rephrase, clarifying scope of this expectation, for example: "*…. If the quality of a specific input material is critical for the quality of the active substance, e.g. if certain tests are performed on input material level in lieu of the final active substance, and non-compendial test methods are used to control that material, suitable validation data for control tests carried out should be submitted."*	
157 - 159	2	It is not clearly understood the meaning of "critical for the quality of the active substance" in this specific context. Proposed change: Please clarify the meaning of "critical for the quality of the active substance" regarding raw material specifications.	See above.
157 - 159	2	Raw materials applied to chemical manufacturing processes are usually not intended to be applied in manufacturing of drug products. For this reason in most cases non-compendial analytical methods are applied by API manufacturers for	See above.

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		testing on the intended quality of raw materials. However, these analytical methods are considered to be suitable for testing of materials of technical grade intended to be used in chemical manufacturing. Proposed change: Please do not require compendial analytical methods for testing of raw materials for chemical synthesis. Validation data should not be required for these methods.	
157-159	6	Comment: The guideline states that "If the quality of a specific input material is critical for the quality of the active substance, and non-compendial test methods are used to control that material, suitable validation data for control tests carried out should be submitted." The EGA would like clarification in the guideline with regards to the use of standard methods like AOAS, or other recognised international standards. The EGA would like that the guideline clearly states that validation requirement should be specified only for critical test parameters of the material. Other tests should be left to the organisation to decide based on Risk.	See above.
161-162	5	Minor clarification of scope of 'biological' **Suggestion:** rephrase to …"biological (animal and human) origin"…	Proposal accepted.

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163	5	The guideline would benefit from a clear differentiation between starting material, reagents, solvents - definitions should be added. Definition between old (existing) and new DS related to starting material - if the old substance is fully under control with regards to impurities and long time on the market - please define the criteria if re-designation of starting material is needed in line with current guidelines.	Definitions of starting materials, reagents, etc are given in ICH guidelines (Q7, Q11 etc) Comment on need to re-define starting materials for existing APIs to be covered in the general comments.
163	5	Although we largely agree with the information outlined relating to the need to discussing steps to manufacture the proposed SM, this data is not traditionally required to go in this section. This data, flow charts, and impurity knowledge, etc. of SM can also be provided in section S.2.6. ICHQ11 did not determine where this information should go and left flexibility. [ICHQ11 example 4 on SM…"The above table is based on the route of synthesis presented in Example 1. The Control for enantiomeric impurity is based on Decision Tree 5 from ICH Guideline Q6A, which allows for control of chiral quality to be established by applying limits to appropriate starting materials or intermediates when justified from development studies. In order for this approach to be acceptable data would need to be provided in 3.2.S.2.6 to demonstrate the stability of the stereocentre under the proposed manufacturing conditions.]	The route of synthesis of starting materials and their specifications are part of their justification and should be provided in this section. Some data (e.g. impurity purge studies) could be provided in S.2.6 if so desired. No change to current text.

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		Proposed change (if any): State that the location for the data, synthetic schemes, etc. for the justification of starting materials can be included in this section or in S.2.6. Also suggest referencing ICH Q11 (and the upcoming ICHQ11 Q&A).	
163 - 166	2	Scope of ICH Q11 is NCEs. However, this paragraph does not distinguish between NCEs and existing APIs. Proposed change: Please add that requirements of section “Active Substance (AS) Starting Material(s)” do not apply to existing APIs.	Proposal not accepted. As stated in the first paragraph of this section, it applies to all active substances.
165 - 166	1	Since the reflection paper is not a guideline it should not be referenced.	No change. This is the most up to date document clarifying EU position and will be referenced for the moment.
165 - 166	5	Since the reflection paper is not a guideline it should not be referenced. Instead reference the new ICHQ11 Q&A.	As above, no change.
168	5	Comment: The term isolated has been removed in the draft document; this implies that EMA request additional information on non-isolated intermediates. This new requirement might be applicable to critical non-isolated intermediates. Proposed change (if any): “proceeding from the starting material(s) to the isolated and	Proposal acknowledged but no change. The process description should include non-isolated intermediates.

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		critical non-isolated intermediate, and ultimately to the active substance."	
170 - 171	1	Comment: It should be considered that some starting materials – commodities – are not available as product manufactured under GMP. In such cases a short description of the synthesis with a quality specification of the starting material should be acceptable.	No change. Misunderstanding – GMP starts from the starting materials and there is no legal requirement for them to be manufactured under GMP.
170-171	3	Comment: *it is recommended that key point of the suitability of a proposed starting material is determinated by the control strategy (in term of impurities, carry over of the same etc...) instead of the based on the numbers of chemical steps/transformation. Hence it is suggested to amend the text, as per the below.* Proposed change (if any): *Typically, multiple chemical transformation steps should separate the starting material from the final active substance or an appropriate control strategy it is expected to be reported to justify shorter chemical transformation steps between the starting materials and the final active substance*	Proposal not accepted as not in line with ICH Q11 or EU reflection paper.
170-171	5	Comment: Commercially available substances, or relatively simple chemical structures entering the last step(s) of the synthesis should be able to be designated as starting materials based on risk assessments and appropriate control	Proposal not accepted. Requirements for commercially available substances are described in ICH Q11 whether or not used in the final step.

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		strategies. Proposed change: Add sentence in line 171: 'Starting materials entering the last step(s) of the synthesis are normally acceptable in case of simple chemical structures or well-known commercial materials, based on risk assessments and appropriate control strategies.'	
173	1	The justification of a starting material should not be written by the marketing authorisation applicant in case of CEP or ASMF applications. Proposal is to delete marketing authorisation: *The ~~marketing authorisation~~ applicant should propose and justify which substance should be considered as the AS starting material (SM), e.g. incorporated as a significant structural fragment into the structure of the active substance.*	Proposal not accepted. The MAA is legally responsible.
173	5	The justification of a starting material should not be written by the marketing authorisation applicant in case of CEP or ASMF applications. Proposal is to delete marketing authorisation: *The ~~marketing authorisation~~ applicant should propose and justify which substance should be considered as the AS starting material (SM), e.g. incorporated as a significant structural fragment into the structure of the active substance.*	See above.
173	6	Comment: The Marketing Authorization Applicant is usually the MA holder but not always the ASMF holder. This sentence requires clarification – as the proposal and justification for the starting	See above.

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		material decision is performed by the ASMF holder. Proposed change (if any): It should be corrected as "The ASMF Holder should propose and justify which substance should be considered as the AS starting material (SM)….", as the starting material for Active Substance is proposed and justified by ASMF Holder and not by marketing authorisation applicant. However, the ASMF Holder will share the defined Starting material with Marketing Authorisation Applicant while sharing the Applicant's part of ASMF.	
175-176	3	Comment: *a not isolated compounds (i.e. solutions of compounds) may be also considered suitable as Starting Materials, is appropriately caracterized. Hence it is suggested to amend the text, as per the below.* Proposed change (if any): *not fully characterized compounds are not considered appropriate to be selected as starting materials.*	Proposal not accepted as it is not in line with ICH Q11 wording.
175-176	8	Comment: The absolute statement that "Non-isolated compounds are not considered appropriate to be selected as starting materials" added to the section on active substance starting materials could be interpreted very broadly and the meaning of "non-isolated compounds" should be clarified. In certain circumstances liquid compounds, compounds in solution, or mixtures of compounds might be the most appropriate starting material for a synthesis and the use of these materials as starting materials should not be absolutely	See above.

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		prohibited.	
176	6	Comment: The regulatory dossier API information should be limited to the final API manufacturer(s) and the final intermediate manufacturer(s), where applicable (see also comment section 109-112). Proposed change (if any): Delete the following: ~~The name and address of the starting material manufacturers should be provided.~~	Not in line with ICH Q11. In EU, the name of the SM manufacturer should be provided in the dossier.
176 - 177	9	**Comment:** Also where it is requested for "The name and address of the starting material (SM) manufacturers should be provided". We would argue that the name and address of the SM manufacturers should not be included as that makes it a commitment. This should be controlled via GMP/Audit processes. **Proposed change:** Please delete this sentence: "~~The name and address of the starting material (SM) manufacturers should be provided~~"	Not acceptable – see above.
176-179	3	Comment: *The availability of this information should be considered as supportive information to justify the developed process but not mandatorily to be reported in the Drug Master File (Ref. ICH Q7 Questions&Answers document Question 1.1).*	Proposal not accepted. The EU reflection paper indicates clearly that information indicating the synthetic process prior to introduction of the SM API should be available in the dossier and not upon request.

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		it is suggested to amend the text, as per the below. Proposed change (if any): *The name and address of the starting material manufacturers should be provided. Information, in the form of a flow chart, indicating the synthetic process prior to the introduction of the starting material (including reagents, solvents and catalysts), are expected to be available upon regulatory authorities' request to evaluate the suitability of the proposed starting material and its specifications.*	
180	6	Comment: Please clarify the criteria to propose active substance starting material.	Please see ICH Q11 and EU reflection paper which are referenced.
182-186	3	Comment: *it is suggested to amend the text, as per the below. This is still in line with control strategy approach described on previous lines.* Proposed change (if any): *if applicable, to support the starting material choice and relevant control strategy when the proposed starting material is itself an active substance covered by a monograph of the European Pharmacopoeia (Ph. Eur.), and when the active substance manufacturer has demonstrated the suitability of the Ph. Eur. monograph as evident by a valid Certificate of Suitability to the Guideline on the chemistry of active substances EMA/96664/2015 Page 7/16 monographs of the European Pharmacopoeia (CEP) for the proposed starting material, this would be accepted.*	This section has been moved to the intermediates section and wording amended to prevent any confusion.

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182-188	6	Please clarify whether a starting material that is not itself an active substance can be manufactured under GMPs but it does not require GMP certification from regulatory bodies.	This section has been moved to the intermediates section and wording amended to prevent any confusion.
182 - 190	1	Sometimes not the API itself but a precursor is used as starting material in another synthesis (e.g. “crude” grade of the API covered by a CEP). This should also be acceptable and addressed in the guideline.	This section has been moved to the intermediates section and wording amended to prevent any confusion.
186-190	6	Comment: Elaboration is required on the use of API as starting material in another API where no CEP is available. Following options are proposed: 1. Inclusion of Letter of Access to the ASMF of the API which is used as starting material in another ASMF. 2. Inclusion of the below details in the ASMF of API which is to be submitted: a) Portion which is to be referred in the Starting material ASMF. b) Procedure number w.r.t. which procedure the starting material ASMF was submitted in the EU countries. c) List of countries involved in the starting materials ASMF referred procedure. d) Intimation of changes made in the starting material ASMF	This section has been moved to the intermediates section and wording amended to prevent any confusion.

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		to the referred ASMF. Proposed change (if any): Consideration on inclusion of elaborated notes for giving clarity on referencing the ASMF of API which is used as starting material in another ASMF in similar lines to use of CEP from EDQM.	
186-196	3	Comment: *it should be firstly noted that this is not information commonly available to API Manufaturers.* *Furthermore the most relevant criteria to identify the information related to the Starting material (also in the cases that they are already Active Substances themselves) should be also covered by the applied control strategy.* *For this reason, we propose the deletion of these lines.*	This section has been moved to the intermediates section and wording amended to prevent any confusion.
186 - 196	9	**Comment:** For API - starting materials used also as APIs in registered products (with certificate of suitability - CEP or ASMF), please find two areas of major concern: - <u>QP declaration</u>: In this paragraph it is proposed that when such API - starting materials with CEP or ASMF are considered intermediates, a QP declaration is requested. It is not clear who should sign such a QP declaration, whether the API manufacturer or the finished product (FP) manufacturer (in case API and FP manufacturers are different and independent companies)? Some companies, as FP manufacturer, perform company	This section has been moved to the intermediates section and wording amended to prevent any confusion. No need for SM to be manufactured under GMP. Misunderstanding about the QP declaration.

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		audits for supplier qualification at the API manufacturer. On the other hand, these companies do not typically perform audits at API-starting material manufacturers. Consequently confirmation of the GMP status of an API-starting material manufacturer (with CEP or ASMF) can, to our understanding, only be provided by the API manufacturer. Such a QP declaration might be part of/appended to the letter of access of the ASMF (in case of an ASMF) or added to the QP declaration for the FP. - Documentation in the registration file: In case the API-starting material documentation is a CEP, the CEP is part of the API documentation (either ASMF or full documentation). However, in case the API-starting material documentation is an ASMF, it is not clear if this documentation shall be provided in the FP application dossier. It should be clearly stated if "*evidence that the marketing authorisation is still valid and that the starting material is manufactured under GMP to the same quality standard as the active substance in the already-authorised product, (manufacturer, site, process, impurity profile and specifications), should be provided in the dossier*" substitutes the need of submitting an ASMF for the API-starting material. Theoretically, in case an ASMF is requested for the API-starting material, two ASMFs	

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		(one for the API-starting material/intermediate and one for the API) with open and closed parts would have to be submitted in the FP application dossier. However, an API-starting material manufacturer with ASMF documentation typically has contracts and agreements with the API manufacturer (who directly purchases the material), but not with any the FP manufacturer (who purchases the API). In consequence, it may not always be possible that ASMF documentation of API-starting materials will be disclosed to FP manufacturers in their application dossiers. There should be the possibility that such documentation can be sent directly to the competent authorities; otherwise additional contracts between FP manufacturers and API-starting material manufacturers may become necessary before any information (ASMF) is disclosed. **Proposed change:** Please amend the text to include the comments provided above.	
187-190	6	Comment: It should be clarified how the evidence that the marketing authorisation is still valid, and that the starting material is manufactured under GMP to the same quality standard, are to be provided in the dossier (eg through a statement, or in	This section has been moved to the intermediates section and wording amended to prevent any confusion.

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		another way).	
187-195	5	Please clarify if only reference to CEP or ASMF is sufficient in this case. If the drug substance with reference to CEP or ASMF is used as a starting material can the DMF include only one step that is not covalent bond transformations step (salt formation).	This section has been moved to the intermediates section and wording amended to prevent any confusion.
189	6	Comment : It should be clarified in the guideline (1) whether active substances which are starting materials for the current APIs, could be sourced from a non-COS certified supplier and (2) whether the quality standards for such APIs could be diluted from the EP monograph requirements, based on actual process requirements.	(1) CEP is not mandatory but the information on the manufacture is still required somehow. (2) If there is a monograph it should comply. This is an option; full details of non Ph. Eur. grade manufacture can be provided without reference to ASMF.
191-196	6	Comment: It is the EGA opinion that the registration of these starting materials manufacturing sites in the marketing authorisation application will lead to an increase of administrative burden on authorities and MAHs in terms of post approval variations (e.g. site address change) without any positive impact on the safety and quality of the product. Additionally, we propose to be consistent which manufacturing sites should be in the regulatory dossier (final API manufacturer(s) and the final intermediate manufacturer(s), where applicable) and refer to our comment for section 109-112). Treating these designated starting materials as intermediates may also cause confusion over terminology and inconsistency over dossier requirements	This section has been moved to the intermediates section and wording amended to prevent any confusion.

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		and no exceptions should be made for these starting materials. Proposed change (if any): Delete the following: ~~In both above cases, although defined as starting materials in the dossier, these compounds are actually considered to be synthetic intermediates since their acceptance is contingent on being manufactured under GMP in line with another dossier (CEP, ASMF or standalone dossier). For the purposes of GMP and traceability, the sites of manufacture for these starting materials should be registered as intermediate manufacturing sites in the marketing authorisation application and be the subject of a QP declaration[22].~~	
194-196	5	The wording could be taken to mean that a complete QP declaration listing all sites is needed in the dossier, when it is really meaning that clear evidence that the marketing authorisation is still valid and that the starting material is manufactured under GMP to the same quality standard as the active substance in the already-authorised product, (manufacturer, site, process, impurity profile and specifications). This could be accomplished without a QP declaration. It would also be useful to clarify if S21 of the new AS (AS1) needs to contain the manufacturers of the established AS (AS2) starting from the starting materials of AS2?	Not accepted. A QP declaration is anyhow needed for manufacturing of the active substance whether or not the SM API is covered by a CEP, ASMF, etc. This section has been moved to the intermediates section and wording amended to prevent any confusion.

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		Suggest harmonization of wording to be consistent to the "Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances" from Sept 2014.	
195	5	please specify: ...registered as intermediate manufacturing sites in chapter 3.2.S.2.1 Manufacturer(s) of the marketing authorisation application	This section has been moved to the intermediates section and wording amended to prevent any confusion.
196	5	Comment: The approach to define the site/supplier of manufacture of an active substance (used as a starting material) as an intermediate is unclear particularly with respect to any impact on the level of variation required to change the supplier/site. Please clarify the expectations.	This section has been moved to the intermediates section and wording amended to prevent any confusion.
197	3	Comment: *it is suggested to detail / define what it would be required to address a suitable "full characterization".* *See also cross link to line 175 and 247*	Reworded as per Q.11 and deleted "fully characterised"
197	5	Comment: What is "fully" characterized? What is "complete" specification ? Proposed Change: Remove "fully" and "complete".	Reworded as per Q.11 and deleted "fully characterised".
197 - 201	1	It is well acknowledged that impurity tracking from the starting material down to the API is state of the art for new APIs. Nevertheless, this should not be the only approach for	Proposal acknowledged but not accepted. The same requirements apply to new and existing APIs.

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		existing APIs. Please change the text: With regard to impurity tracking alternative approaches should be possible for existing APIs. For instance, it should be acceptable to track impurities starting from the API by going backwards in synthesis or to demonstrate peak purity of the API. Please add after line 203 …. processing conditions. For existing APIs alternative approaches may be appropriate (e.g. demonstrate peak purity, track impurities backwards in synthesis).	
197 - 201	5	It is well acknowledged that impurity tracking from the starting material down to the API is state of the art for new APIs. Nevertheless, this should not be the only approach for existing APIs. Please change the text: With regard to impurity tracking alternative approaches should be possible for existing APIs. For instance, it should be acceptable to track impurities starting from the API by going backwards in synthesis or to demonstrate peak purity of the API. Please add after line 203 …. processing conditions. For existing APIs alternative	No change. See above.

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		approaches may be appropriate (e.g. demonstrate peak purity, track impurities backwards in synthesis).	
198	5	Comment: The new wording 'any kind of impurity' is very welcome, as it reflects how comprehensive the discussion on impurities should be. Proposed change (if any): n/a	Comment acknowledged.
198	5	**Comment**: For suitability of starting materials, it is mentioned to include an "impurity profile." Does this refer to batch analyses data for proposed starting materials? If so, please provide the necessary clarification in this section.	Reworded to clarify: Complete specifications should be provided, including limits for impurities."
203	6	Comment: Clarification should be provided on the extent of identification of potential impurities which can pass on to the starting material from originating plant species. Use of chromatographic fingerprinting tool to verify potential carryover of impurities to SMs should be commented upon.	Covered in paragraph 207-216 (original line numbers).
206-216	8	Comment: A narrow definition for a "material of plant" origin should be provided. Many materials used as raw materials or solvents in chemical processing ultimately arise from plant-based materials. The chemical reaction and purification steps used to refine these plant feedstocks into synthetically useful materials would remove the concerns raised in the draft note related to potential environmental contaminants. If these requirements were applied broadly to any chemical originating from a plant source, the sourcing restrictions and documentation requirements would be a significant burden to	Re-drafted: "Information on the source, processing, characterisation and control of starting materials of plant origin…." Reference added.

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		industry without any benefit to patient safety. The related Q&A posted on the EMA website is more specifically targeted at starting materials of herbal origin used to manufacture semi-synthetic active substances such as herbal drugs, and herbal extracts. The more general wording used in the draft note could be interpreted to apply to a much wider range of materials. Proposed change (if any): Narrowly define “material of plant origin” to include only the use of unrefined plant matter in the manufacturing process described in 3.2.S.2.2.	
207	5	Comment: The text on expectations related to (all) materials of plant origin may be too stringent. For example a reagent or solvent (2-methylTHF being one example) may be of plant origin – would such a reagent or solvent require all this information? In addition, ICH Q11 noted that semisynthetic starting materials could be accepted if these met the selection principles of Q11. Does this text contradict the allowance under ICH Q11? Proposed change (if any): Please reconsider this text related to materials of plant origin. Should line 207 read “Information on the source, processing, characterisation and control of all drub substances (or ‘of all	Same as above agreed. Does not contradict Q11.

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		drug substances or intermediates / starting materials') of plant origin…."	
218	5	Need for consistency with line 156. **Suggestion:** rephrase to …" Specifications for all materials (e.g. raw materials, catalysts, solvents, reagents, processing aids) used"…	Accepted and amended both.
218-219	3	Comment*: see comment to line 155-156. it is suggested to amend the text, as per the below.* Proposed change (if any): *Specifications for all materials (solvents, reagents, processing aids) used in synthesis should be submitted, if/where relevant.*	See above.
220	5	Comment: Please clarify whether this refers to the final step in the SM synthesis or API synthesis; Please also clarify if there are any specific expectations for control of API counterion quality which is not already covered by the text ' *materials used in the final stages of the synthesis may require greater control than those used in earlier stages'*	Amended to clarify.
221-222	7	Comment: In respect to water reference is made to documents listed under "Reference" as 4 and 7-10. Only reference no 8, i.e. "Note for guidance on quality of water for pharmaceutical use", seems to be relevant.	The references refer to the whole section 4.2.4.
221-222	9	**Comment:** For the API producer it is not always clear into which kind of drug product the API will go. In addition, this	Proposal acknowledged however not accepted. Lines 221-222 are in line with the EU nfg.

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		API may be used in several different drug products. By consequence it might be difficult to know which water quality should be used at the API manufacturing step. This request may be of relevance only for substances claimed to be endotoxins free. **Proposed change:** Please amend this sentence to clarify this point.	'quality of water for pharmaceutical use' which is referenced.
223	5	Comment: Can this be clarified? The guidance for critical steps states that "Tests and acceptance criteria (with justification based on experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process should be provided." Can it be clarified that this is all that is required in this Section, as it is sometimes unclear how much information is required in Control of Critical Steps? Proposed Change This section should describe the tests and acceptance criteria (with justification based on experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process. Would this section include details of PAT controls? Proposed Change Consider including the wording from ICHQ11:	Proposal acknowledged but no change. The alternative wording to point 1 is in principle the same as in the draft guideline. Point 2: It is not intended to reproduce parts of other guidelines in this guideline.

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		"The manufacturing process development program should identify which material attributes (e.g., of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be controlled."	
224	5	Several technologies are transferred for new manufacturing plants where limited knowledge about definition of critical steps are available (mostly in cases of generics). In these cases justification of critical Steps can be based only on transfer studies (with limited justification).	No change. The sentence existed in Rev 1 version and the manufacturer should have the knowledge about the process.
227-228	5	The fact that a process step has to be run within predetermined limits does not correlate with its criticality. Most process steps have to be run within predetermined ranges to achieve conversion, yield and cycle times, which impact factors in addition or in place of, criticality. If experiments could establish that a wide range is acceptable without impact on the AS quality then the step is not critical, as the wide range can be easily achieved during AS manufacture. It is critical if a process step has to be kept within a narrow range so that the targeted AS quality can be achieved. **Suggestion:** rephrase to …" parameters must be controlled within narrow predetermined limits to ensure that the AS meets its	No change. Narrow ranges are not the only aspect of criticality. A critical step is one which impacts the quality of the active substance.

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		specification"…	
233	5	"major chemical" is not meaningful. What is the intent here? key intermediate or control of critical structural attributes of an intermediate such as stereochemistry, olefin geometry, or polymorphism	Typographical error – should have read "major chemical transformation"
233-234	5	this should be one bullet point (only plain text, no semi colon, no colon): "Steps which introduce an essential molecular structural element or result in a major chemical transformation"	Agreed.
233-234	5	Comment: formatting error "Transformation" belongs to line 233, following lines are sub-bullets to line 233?	See above.
233-234	6	Comment: It is not clear whether the sentence contains a typographical error and should read: "Steps which introduce an essential molecular structural element or result in a major chemical transformation"	See above.
233-234	8	Comment: The heading "Transformation:" appears to be broken from the sentence before. Proposed change (if any): Steps which introduce an essential molecular structural element or result in a major chemical **transformation;**	See above.

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233-234	9	**Comment:** Typo: There seems to be a formatting issue as the word “transformation” should not be a title, but part of the previous sentence in line 233.	See above.
239-240	5	“Steps which have an impact on solid-state properties and homogeneity of the active substance are always considered as critical, particularly, if the active substance is used within a solid dosage form…” Recommended change: “…homogeneity ~~**of the active substance are always**~~ **and possibly solid-state properties of the active DS could be** considered critical…” Some solid state properties might not be critical. Recommend revising.	Re-drafted in line with comment, added “Proper justification should be provided when these properties do not impact performance of the finished product.”
239-242	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): *Steps which have an impact on solid-state properties and homogeneity of the active substance could be considered as critical, particularly, if the active substance is used within a solid dosage form, since they may adversely affect dissolution of the active substance from the dosage form and thereby affect bioavailability.*	See above.
240	5	Remove ‘always’ since it would not be critical for a solution or IV drug product.	See above.
243	5	It is unclear what "characterisation" of isolated intermediates refers to. Please replace "characterisation" with specification.	Text has been amended to address the comment.

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		The reference to the ICH Q6 guideline is misleading and should be removed since this guideline refers to drug substances but not to intermediates.	
244	5	Comment: Providing methods and validation information for intermediates represents an escalation in expectations, and has not previously been required for established active substances. And non-process-specific tests (e.g. specific rotation, RoI etc) do not need such information to be provided. Proposed change (if any): Please reconsider this expectation.	Replaced with “If non-compendial methods are used to control the intermediate, they should be suitably validated. Validation data is not expected unless the test in question is essential for the control strategy of the active substance (e.g. removal of a mutagenic impurity).
244	5	Comment: This document does not clearly describe the importance of the control strategy, per ICH Q11. In reality….Information provided in 3.2.S.2.2 Description of Manufacturing Process and Process Controls, 3.2.S.2.3 Control of Materials, 3.2.S.2.4 Control of Critical Steps and Intermediates, and 3.2.S.4.1 Specifications, includes a detailed description of the individual elements of the overall control strategy. A summary of how these individual elements work together to assure drug substance quality is the example in ICHQ11. Proposed Change: It may be helpful if this were explained in the text, with a reference to ICHQ11 and suggest options as to where to put a control strategy summary. [The control strategy summary is the guide of where to find everything and	Proposal acknowledged. It is highlighted in chapter 2 (Scope) that “when an “enhanced” approach is used or a design space claimed, the information provided in sections 3.2.S.2.2 to 3.2.S.2.6., should be prepared and organised according to ICH Q11”.

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		how this all works together and can be extremely important/ valuable for enhanced submissions.]	
244 - 245	1	The stipulation to provide information on control of intermediates should be referred to critical steps: Information on the quality and control of intermediates isolated during the process should be provided for critical steps.	No change. Proposal acknowledged. Information about the control of all intermediates is expected. The level of control can be adapted to the criticality of the steps.
245	5	Comment: "which are those" is a copy paste error from former guideline. Proposed change (if any): Delete "which are those"	Redundant following rewording.
245 - 246	2	Comments: Requirements for validation of analytical methods used in API manufacturing are expected to be described in other guidances such as ICH Q7. The scope of the discussed draft guidance is understood to be restricted to the information that needs to be provided to marketing authorisation dossiers. Statements like this one often lead to misleading requests of dossier assessors that ask for providing validation reports. In addition usually intermediates would not have a monograph. Thus for many of their analyses compendial methods do not exist. In consequence applicants might often be requested for validation information. This will lead to	Amended as follows: Replaced with "if non-compendial methods are used to control the material, they should be suitably validated.". Information on compendial methods is not expected. This pertains to methods of the specific monograph used to control the crude substance or general methods used for identification or limit tests.

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		increased effort for applicant and authority. Proposed change (if any): Please erase this sentence. “”	
246 - 247	1	Information on the characterisation of these intermediates should be provided for new APIs.	See above.
246 - 247	2	Information on the characterisation of intermediates is currently not required for existing APIs. Proposed change: Please clarify that this is no additional requirement for existing APIs.	See above.
246-247	5	There is a clear increase of requirement from HA by asking for intermediate method validation. The sentence here is not clear if it has to be submitted or not. For sake of clarity, HA should clarify their position and explain when they expect the applicant to submit it proactively or not. **Suggestion:** It is suggested that consistency to the CTD requirements be maintained.	See above.
247	3	Comment: *it is suggested to detail / define what it would be required to address a suitable "full characterization".* *See also cross link to line 175 and 197.*	See above. Agreed.

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247	5	Can the phrase 'information on the characterisation of these intermediates' be clarified. What is expected to be included?	See above. Agreed.
247	8	Comment: Clarification should be provided on the meaning of the term "characterization". The scope of the information required should be appropriate for a synthetic intermediate.	See above. Agreed.
248	5	Does not address expectation that reprocessing data are included here (per line 145). However, suggest that S.2.6 is a better location.	This has been clarified earlier in the document (original line 145).
248-252	1	4.2.5. Process Validation and/ or Evaluation 3.2.S.2.5 If the process validation is not a regulatory requirement, but only a GMP requirement, there is no need to include a commitment in the 3.2.S module. GMP aspects do not need to be included in the regulatory dossier. The compliance with GMP requirements is ensured by authority inspections and thus outside of the scope of a regulatory dossier.	Agreed and amended accordingly.
248-252	5	Suggested edits to the text: "However, process validation data and/or evaluation studies for non-standard processes, such as aseptic processing and sterilization should be provided in 3.2.S.2.5 upon submission of the application."	See above.
248-252	6	Comment: The ASMF holder can propose to include the statement for the batch size within 10 folds (scale up/scale down) for each stage. However, the detailed description of manufacturing process will be included for a defined batch size	It is obvious that the EU variation guideline about batch size will apply to the description of the manufacturing process. Therefore, inclusion of such consideration is not deemed

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		under section 3.2.S.2.2. This will be supported with the following commitments from the ASMF holder. -Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment. -The process with proposed batch size will be validated and process validation report will be in place. -Quality of the API produced with the batch size (which is within 10 folds of submitted batch size) will be comparable with that of the batch size included in the submitted ASMF. -Necessary details w.r.t. the proposed batch size shall be submitted to respective EU Regulatory Agencies in the next update of the ASMF. Proposed change (if any): Consideration to have batch size within 10 fold in the initial ASMF submission.	necessary.
249	5	Process steps that have critical parameters/ steps/ attributes require validation…not “the active substance manufacturing process” (suggesting all steps regardless of criticality) . Steps that do not have critical elements do not require validation (see ICHQ7). This section suggests all steps have to be validated when the section starting on line 224 clearly states that some steps can be critical and other might not. ICHQ7 12.51 Critical process parameters should be	No change. Referenced Q7 and Q11 at the end of this sentence.

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		controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation. Note: ICHQ7 Q&A: ***4 Is a retrospective approach to validation still acceptable?*** Prospective validation is normally expected for processes introduced since the publication of ICH Q7. The concept of retrospective validation remains acceptable as an exception for existing, well established products prior to the implementation of ICH Q7 [ICH Q7, 12.44]. *"If regulatory discussions redefine a step as critical, which had previously been considered non-critical, a protocol describing retrospective analysis of data together withthe commitment for concurrent or prospective validation may be an option."* Regardless of the type of validation, the quality system should confirm the ongoing robustness of the process (e.g., product quality review).	
249 - 251	2	A commitment to do process validation is currently not required for manufacturing of existing APIs. This is reasonable since these manufacturing processes are already requested to be performed under GMP acc. to ICH Q7. Proposed change: Please clarify that this commitment is not required for existing	Removed need for a commitment and changed text accordingly.

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		APIs.	
249-251	5	A commitment to conduct process validation appears to be a GMP-type statement and it could be left out as this is already addressed in ICH Q7. **Suggestion:** rephrase to …:Even if no process validation data is provided in the application, the critical steps of the active substance manufacturing process must be validated before commercial distribution."…	See above.
249-251	7	Comment: The following change is recommended (in compliance with GMP part II, section 12.42. Proposed change: Even if no process validation data is provided in the application, the active substance manufacturing process must be validated before commercial distribution of the final drug product manufactured from the API in question and a commitment to do so should be provided.	See above.
253	1	Correction of the name of the paragraph ("manufacturing process development" instead of "manufacturing process description").	Agreed. Title 4.2.6. to be changed to Manufacturing Process Development.
253	4	Similar to ICH 3.2.S.2.6 section "Manufacturing Process Description" need to change title to "Manufacturing Process Development."	See above.

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253	5	Comment: The heading should read 'Manufacturing Process **Development**' 3.2.S.2.6	See above.
253	7	Proposed change: "Manufacturing Process ~~Description~~ Development 3.2.S.2.6"	See above.
253-261	5	**Comment**: in accordance with ICH Q11, this section could include the justification of starting materials, risk assessments, CQA definition, assessment of active substance CQAs on drug product CQAs, control strategy elements, and type of development (traditional versus enhanced) and how the development is linked to the applicant's regulatory flexibility in the process described in S.2.2.	Comment acknowledged but this is covered in Q11 so no need to repeat. No change.
254	4	**"Copies of relevant chromatograms should be provided".** The sample chromatograms are included in the analytical/validation of procedures. Need clarification why this statement is included in the guideline.	(Original) Line 354 is addressed here. Since this sentence taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here.
254-261	5	Comment: Please clarify whether the current wording applies to both, a 'traditional' as well as an 'enhanced' development programme.	Description of significant changes applies to both traditional as well as enhanced development approach. No change needed as no distinction is necessary.
256	6	Comment: Please clarify the meaning of "significant changes".	Significant changes can be those changes to the process impacting quality attributes (eg. impurity profile), changes related to the sites

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			and scales up. No change.
258-260	5	Please clarify what " Existing active substances" means.	See amendment in section 2.
264-265	5	Please clarify what the expected level of information for the existing substances is. Will it be less if the substance is covered by a PhEur monograph?	For the existing substances covered by a Ph. Eur. monograph, references to the respective monograph are acceptable. Identity can be verified by a specific test in comparison to an official standard, e.g. comparison of IR. Physico-chemical characteristics should be detailed sufficiently. No change.
266	5	**Comment**: we understand "official standard" as referring to a compendial API source, if this can be confirmed.	For example a CRS of the Ph. Eur. No change.
268	5	Comment: The sentence "The results described in this section should be reflected in the control tests on the active substance to check batch-to-batch uniformity" is very general. Proposed change (if any): Please replace sentence by: "If certain properties are considered critical to the performance of the active substance, these should be reflected in the control tests on the active substance"	Accepted as follows: "The results described in this section should be reflected in the control tests on the active substance to check batch-to-batch uniformity." will be replaced by "Relevant results described in this section should be reflected in the control tests on the active substance to check batch-to-batch uniformity."
268-269	5	Not all the tests performed for characterization of a material are needed for routine testing	As above.

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		Suggestion: rephrase to …"Relevant results described in this section should be reflected in the control tests on the active substance to check batch-to-batch "…uniformity or reproducibility	
280-283	5	Rewording is needed for clarity. **Suggestion:** rephrase to …" If the data included in this section originates from a synthetic process other than the one covered by the application (i.e. different routes), evidence may be required to confirm the structural identity of the materials covered by the application. Confirmation of the structural identity is particularly important where toxicological studies have been carried out on material from a synthetic process other than the one covered in the application"	Since these lines taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) have not been changed, no new requirement has been established here. No change.
283	5	Potential to misunderstand what is meant by 'origin' referred to here and preferable to explain what is meant with respect to different synthetic routes.	Material from different origin refers to the API prepared by another route of synthesis however since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.

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286	5	Comment: The text suggests that all the identified evidence 'will be expected' but we note that not all evidence will always be necessary to characterize structure (e.g. there may often be no need for evidence of structure of intermediates, nor for characteristic chemical reactions. Proposed change (if any): Please amend line 286 to read "The information may include, as necessary, such evidence as – "	Line 286 remains quite open to include the relevant information as per characteristics of a given API and since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
286	5	Comment: Section 4.3 states a number of points to proof the structure. We agree that it's important to provide sufficient data to demonstrate the structure; however it's important to underline that the following point is NOT a check list, but rather suggestions on what can be included. In reality, single x-ray should be enough to prove the structure, whereby all other points could be omitted, theoretically. Proposed change (if any): Clarify accordingly.	Line 286 remains quite open to include the relevant information as per characteristics of a given API and since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
286	7	Comment: The list of methods should be presented as examples of methods commonly used rather than as methods that should "normally" be used for structure elucidation. It is noted that methods applied for structure elucidation largely depend on structural characteristics of particular active substances. Proposed change: ~~The information will normally include such evidence as~~ Examples of analytical methods used to confirm the chemical structure are:	Line 286 remains quite open to include the relevant information as per characteristics of a given API and since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.

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286-299	6	Comment: Not all the listed information is relevant to all active substances. Proposed change (if any): The information will include relevant evidence such as:	Line 286 remains quite open to include the relevant information as per characteristics of a given API and since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
291,298	9	**Comment:** It is felt that the information in lines 291 and 298 might be duplicated	Line 291 comprises the complete mass spectra including fragmentation reactions and analysis of these fragments whereas line 298 relates to the relative molecular mass. No change.
292	6	Comment: See above, this sentence should be removed Proposed change (if any):	Not clear what this comment refers to.
292-293	5	Comment: Line 292 and 293 belongs to the section of key intermediates, not to elucidation of structure. Proposed change (if any): Transfer accordingly.	Actually, the route of synthesis can be one indication of evidence of structure and since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.

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293	3	Comment: *it is considered not required to mandatorily report the characterization of the key intermediates of synthesis hence we propose deletion of line 293.*	It is not required to mandatorily report the characterisation of the key intermediates of synthesis but in some cases it is necessary to have evidence of structure of key intermediates to substantiate the structural elucidation of the drug substance. Changed “intermediates or synthesis” to “intermediates.”
293	6	Comment: Requires clarification – as it looks as a duplication of 288-289-290-291	Lines 288-289-290-291 refer to the drug substance whereas line 293 refers to the structure of key intermediates. In some cases it is necessary to have evidence of structure of key intermediates to substantiate the structural elucidation of the drug substance. No change.
294	5	Comment: Line 294 is only important if the other information cannot be obtained. Proposed change (if any): Explain further or omit.	In some cases it is necessary to have information according to line 294 to substantiate the elucidation of structure of the drug substance. No change.
295	5	Reference to S.2.3 adds no value **Suggestion:** Delete reference	Accepted. “(refer to S.2.3.)” has been deleted.

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298	5	Seems redundant to MS data referenced above **Suggestion:** Delete line	Line 291 comprises the complete mass spectrum including fragmentation reactions and analysis of these fragments whereas line 298 relates to the relative molecular mass. No change.
298	5	Comment: Line 298 is not clear and should be explained further or omitted. Proposed change (if any): Explain further or omit.	See above.
298	6	Comment: Requires clarification – as it looks as a duplication of 291	See above.
299-300	5	Appears to be an impurity topic **Suggestion:** Move to Item S3.2	These lines relate to the Investigation of Chiral Active Substances 3CC29a. Evidence of the correct isomer is a topic of elucidation of structure. No change.
301-343	5	**Comment**: The physico-chemical characteristics of the active substance, and the methods used to investigate them, are not true determinants of the structure of the active substance. These components are general properties of the compound, and should instead be located in 3.2.S.1.3. For example, it is not possible to elucidate the structure of any compound with a DSC curve, solubility values, pKa or pH measurements or partition coefficients.	The CTD is the basis of the structure of this guideline. CTD states for section 3.2.S.3.1: Elucidation of Structure and other Characteristics. Consequently, elucidation of structure is one part of this section and characteristics of the drug substance is the other part which is displayed in this guideline, too. No change.

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305-308	1	There is a concern that in-vivo studies are required to demonstrate the characteristics of different modifications. In order to add no additional in-vivo-studies we suggest to modify the paragraph: ….. Information on the proposed commercial solid state form should be provided ~~and related to the in vivo performance of the finished product.~~	Proposed commercial solid state form should be stated and proved unless otherwise justified. This form should be suitable for the in vivo performance of the finished product. This should be clarified in CTD section 3.2.P.2.1.1. Additional in vivo studies are not necessarily required. "Information on the proposed commercial solid state form should be provided and related to the in vivo performance of the finished product." will be replaced by "Information on the proposed commercial solid state form should be provided in CTD section 3.2.S.3.1. This information should be related to the in vivo performance of the finished product in CTD section 3.2.P.2.1.1."
307-308	3	Comment: *please note information on in vivo performance of the drug product(s) is not commonly available to API Manufacturers. Hence it is suggested to amend the text, as per the below.* Proposed change (if any): *Information on the proposed commercial solid state form should be provided, if/where relevant.*	Partly accepted as follows as above.
307-308	5	Use ICH term of "drug substance" not API. Propose typographical change for clarity of following sentence. Proposed change: ...of said ~~API~~ <u>drug substance</u>. Information	The proposed typographical change for clarity seems not necessary.

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		on the ~~proposed commercial~~ solid state form <u>of the proposed commercial drug substance</u> should be provided....	Partly accepted as follows concerning API: "API" in line 307 will be replaced by the EU term "active substance".
307-308	5	Clarify that "related to the in-vivo performance" is talking about an assessment of the impact on in-vivo performance (e.g through consideration of the dosage form, BCS class, in-vtro data on dissolution….) rather than stipulating bioequivalence clinical studies. Would the appropriate references to BE guidelines and variations help?	Clarification is provided that "related to the in-vivo performance" is talking about an assessment of the impact on in-vivo performance (e.g through consideration of the dosage form, BCS class, in-vtro data on dissolution….) rather than stipulating bioequivalence clinical studies. Furthermore, changes to lines 307-308 have been made for clarification, see above.
307-308	6	Comment: Information related to the in vivo performance of the finished product should not be handled in the drug substance part of the dossier. An ASMF/CEP may be intended for more than 1 type of finished product. Discussions of drug substance properties related to the finished product in vivo performance is generally discussed by the drug product manufacturer in 3.2.P eg 3.2.P.2. Proposed change (if any): Information on the proposed commercial solid state form	Partly accepted as above.

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		should be provided.	
307-308	8	Comment: ICH M4Q states that section 3.2.P.2.1.1 should describe “key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.” Since it is already established that the impact of the solid state form on the performance of the drug product should be discussed in section 3.2.P.2.1.1 it is not necessary to include the same discussion in section 3.2.S.3.1. Proposed change (if any): Removal of text: *‘Information on the proposed commercial solid state form should be provided and related to the in vivo performance of the finished product.’*	Partly accepted as above.
311	5	Comment: The term "chemistry" can be a very vague term eg it can be used to describe reactivity - others the biological activity	This comment is not quite clear. Nevertheless, following change has been made by taking the original text of Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1): “Polymorphism is the property of a chemical substance to exist in the solid state in different crystalline forms having the same chemical composition.” will be replaced by “Polymorphism is the property of a solid state chemical substance to exist in different

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			crystalline forms."
323	5	Proposed editorial change: "Solid state NMR spectroscopy"	Accepted. "Solid state NMR" has been replaced by "Solid state NMR spectroscopy".
324	9	**Comment:** It is not clear why it is stated here "polymorphic forms and solvates" while before at line 309, polymorphs were only mentioned. Solvates are a different form and have not been covered above. Please clarify.	Polymorphic forms and solvates can be summarised under the main heading "Polymorphism" (line 309). This has been taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1). No change.
324-326	5	**Comment**: Section 3.2.S.3.1 is not the appropriate CTD section to discuss mechanisms of control that may be used to manufacture and test the active substance. That topic should be covered in 3.2.S.2.2, 3.2.S.2.3 and 3.2.S.2.6.	According to CTD, "potential for forming polymorphs" should be discussed in section 3.2.S.3.1. Analytical procedures to control the drug substance should be included in CTD section 3.2.S.4.2 and validation in 3.2.S.4.3 when a routine testing is set. No change.
325-326	5	Clarification that only relevant forms need be assessed **Suggestion:** rephrase to …" Similarly, if of relevance for the present active substance amorphous forms should be characterised and detection and control methods"…	Justification for not assessing is needed at any rate. Partly accepted as follows: "Similarly, amorphous forms should be characterised and detection and control methods described[4]." will be replaced by "Similarly, amorphous forms should be

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			characterised and detection and control methods described if not otherwise justified[4]."
325-326	8	Comment: The amorphous form is not relevant to many drug substances or manufacturing processes. Proposed change (if any): ~~Similarly,~~ **When relevant,** amorphous forms should be characterised and detection and control methods described.	Partly accepted as above.
327	5	Much of lines 327 – 243 are also listed in S.1.3	Since these lines taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) have not been changed, no new requirement has been established here. No change.
327-334	5	Comment: On the solubility and physical characteristics described, we would suggest that these are moved back to their original position, i.e. section 2.1, as they are important descriptors for both the chemical and pharmaceutical section of the file, why they should be very easy to find. Proposed change (if any): Transfer accordingly.	Since these lines taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) have not been changed, no new requirement has been established here. No change.
328	5	Comment: The guidance suggests solubility values be provided 'in water at various temperatures'. This is unclear and could lead to an unnecessary escalation of expectations. Please clarify what is important to the selection of these temperatures and make this text more specific.	'in water at various temperatures' has been taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1). This instruction seems to be clear enough. No change.

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		Proposed change (if any): Please clarify what is important to the selection of these temperatures and make this text more specific.	
328	5	This should be part of the FDF dossier and should be excluded from ASMF requirements.	This line has been taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1). No change.
328	10	We suggest to include the text (in red) … Numeric solubility values (e.g. mg/ml) and, if applicable, statements of solubility acc. to the General Notices in Ph. Eur. (e.g. very soluble) for the active substance in water at various temperatures and in aqueous buffer at physiologically relevant pHs should be provided	This line has been taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1). This instruction seems to be clear enough. No change.
328-331	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): *Numeric solubility values (e.g. mg/ml) for the active substance in water at various temperatures and in aqueous buffer at physiologically relevant pHs should be provided, if/where relevant, as well as the corresponding pH values for the equilibrium solubility test solutions. Data for solubility in other solvents may also be provided, if/where relevant. The test procedures used for solubilities should be described.*	The restriction “if/where relevant” seems not be adequate because information on solubility in water is very important. No change.
332	5	Physical characteristics: These parameters are also mentioned in S.1.3 “general properties”. It should be kept in mind that	Physical characteristics had been included already in the Guideline on Chemistry of New

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		S.1.3. may be disclosed to public access due to the EU transparency rules. **Suggestion:** Consider limiting information to that which is non-proprietary as per S.1.3	Active Substances (CPMP/QWP/130/96, Rev 1). No change.
333-334	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): *Physical properties should be stated here and, if significant, information on particle size (complete particle size profile), solvation, melting point, hygroscopicity, boiling point should be added, if/where relevant.*	The restriction “if significant” is already included in the text. An additional limitation like “if/where relevant” seems not necessary. No change.
333-334	5	Comment: The statement regarding particle size is confusing. ICH M4Q Questions and Answers states to include in Section S.3.1 “Studies performed to identify the particle size distribution of the drug substance”. (Whereas Sections 3.2.P.2.1.1 and 3.2.P.2.2.1 would discuss the influence of particle size on, for instance, dissolution performance.) Proposed change (if any): Physical properties should be stated here and, if significant, information on particle size distribution solvation, melting point, hygroscopicity, boiling point should be added.	Complete particle size profile amended to particle size distribution.
334	6	Comment : Please clarify whether the requested data is also required for existing drug substances?	Yes, data is required and even some can be taken from literature. No change.

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337-338	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): *The pKa values of the active substance and the pH in solutions of defined concentration should be stated, if/where relevant. In the case of a salt, the corresponding values of the base or acid should be stated.*	Since these lines taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) have not been changed, no new requirement has been established here. No change.
340-343	3	Comment: *it is suggested to amend the text, as per the below.* Proposed change (if any): Information is to be provided concerning the following: • Physico-chemical characteristics (oil/water partition coefficient, octanol/water partition coefficient, log P, etc.); and • Physical properties of significance may be stated, if/where relevant.	"Physicochemical characteristics" replaced with "partition properties."
341	5	Partition coefficients should be evaluated also in other part of the Marketing Authorisation Application (like in Environmental Assessment part of the MAA), therefore mentioning them in the ASMF could cause copy/paste problems	Since this line taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
342	6	Comment : Please clarify whether the requested data is also required for existing drug substances?	Yes, data is required and even some can be taken from literature. No change.

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345	5	Comment: The carry-over of impurities is the main justification for the starting material selection. Proposed change (if any): Carry-over/spiking experimentscan also be described in S.2.3 or S2.6 together with the justification for the starting materials.	Normally, carry-over/spiking experiments should be described in CTD section 3.2.S.3.2 but can also be included in 3.2.S.2.6 or 3.2.S.2.3 if justified. No change.
345	5	There should be a clear distinction of requirements for old and new drug substances – an old substance is well established with a defined impurity profile. What is required if only a USP monograph is available?	Information on impurities and their carry-over should also be provided for existing substances. Here, several routes of synthesis may exist for one substance from different sources and this should be considered when stipulating information on impurities. A USP monograph cannot replace this consideration. No change.
345 - 348:	9	**Comment:** The sentences: *"Information on impurities and their carry-over should be provided. This includes related substances, residual solvents, elemental impurities and those derived from reagents. The related substances considered as potential impurities arising from the synthesis should be discussed and described briefly together with an indication of their origin. The genotoxic potential of impurities and potential presence of elemental impurities should be addressed"* should not appear in a Veterinary guideline because elemental impurities as well as genotoxic impurities are not relevant to	Not agreed. Genotoxic impurities as well as elemental impurities/heavy metals are also relevant in veterinary medicines.

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		Animal Health. In addition it is IFAH-Europe understanding that studies on elemental impurities for Human products are depending on a previous evaluation of the finished product components and not necessarily have to be tested in each API. Therefore it would be more appropriate even for the human guideline to refer to the appropriate ICH guidelines. **Proposed change:** *Please amend the lines 345-348 to read "**Information on impurities and their carry-over should be provided. This includes related substances, residual solvents, ~~elemental impurities~~ and those derived from reagents. The related substances considered as potential impurities arising from the synthesis should be discussed and described briefly together with an indication of their origin. The genotoxic potential of impurities and potential presence of elemental impurities should be addressed in compliance with ICH M7 and ICH Q3d guidelines.**"*	
345 – 350	1	This paragraph does not consider that many existing APIs are subject to a Ph. Eur. monograph. In this case reference to the transparency list should be acceptable to address potential impurities.	Suitable information on impurities should also be provided for existing substances. Here, several routes of synthesis may exist for one substance from different sources and this should be considered when stipulating information on impurities. Reference to the transparency list of a Ph. Eur. monograph does not encompass necessarily all relevant impurities, e.g., residual solvents, elemental impurities, genotoxic impurities, related

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			substances of a new route of synthesis. No change.
345 – 350	5	This paragraph does not consider that many existing APIs are subject to a Ph. Eur. monograph. In this case reference to the transparency list should be acceptable to address potential impurities.	Suitable information on impurities should also be provided for existing substances. Here, several routes of synthesis may exist for one substance from different sources and this should be considered when stipulating information on impurities. Reference to the transparency list of a Ph. Eur. monograph does not encompass necessarily all relevant impurities, e.g., residual solvents, elemental impurities, genotoxic impurities, related substances of a new route of synthesis. No change.
346-347	7	Comment: Definition of related substances (“potential impurities arising from the synthesis”) is not considered to be precise enough. Therefore it is recommended to be corrected or removed.	“The related substances considered as potential impurities arising from the synthesis should be discussed and described briefly together with an indication of their origin.” will be replaced by “The related substances considered as potential impurities arising from the synthesis and degradation products should be discussed and described briefly together with an indication of their origin.”
348	2	Discussion on genotoxic potential of impurities is a new general requirement for existing APIs.	Also for existing substances, several routes of synthesis exist for one substance and this should be considered when stipulating

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		Proposed change: Please clarify that this is generally not required for existing APIs.	information on impurities. Consequently, the genotoxic potential of impurities is a matter of concern here, too and also suitable information of these impurities should be submitted. No change.
348	3	Comment: *with reference to ICH M7 guidleine we propose to clearly define the scope of application of this requirement. It is suggested to amend the text, as per the below.* Proposed change (if any): *The genotoxic potential of impurities should be addressed for new drug substances. it is also to be addressed to existing drug substances only where:* • *changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;* • *changes in the manufacturing process result in new degradants or increased acceptance criteria for existing degradants.*	The stated procedure for existing substance is adequate. Nevertheless, genotoxic impurities should be addressed suitably in section 3.2.S3..2 also for existing substances. At least clarification should be provided in this section that the complete manufacturing process of the drug substance including all solvents and reagents is not new. Otherwise, genotoxic impurities should be addressed acceptably. “Genotoxic” replaced with “mutagenic” as per ICH M7 and ref 15 deleted.
348	5	Missing a reference to ICH M7. Proposed Change: Suggest add reference to ICH M7 to sentence “The genotoxic potential of impurities should be addressed.[21]”	Accepted and “genotoxic” replaced with “mutagenic.”
349	5	Comment: The text suggests that it is necessary to state whether impurities have been synthesized for test purposes. It is unclear why this statement is needed. If an impurity have been tested it should be made clear how this was done and	Following change has been implemented for clarification:

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		whether the impurity was isolated by e.g. chromatography or independent synthesis. Proposed change (if any): Please remove /amend this expectation.	"In each case, it should be stated whether actual samples of impurities have been synthesized for test purposes." will be replaced by "In each case, it should be stated whether actual sample of impurities have been synthesized or isolated for test purposes."
349	5	In several cases a related impurity is separated from the bulk API (eg. with chromatography, extraction, etc.) and elucidation of structure is evaluated on the separated impurity. In these cases impurities are not synthetized.	The above change has been implemented for clarification.
350	5	Comment: Characterisation data for identified impurities should be provided – this term should be clarified to described what it means e.g. is it a summary of the data or simply to confirm that the material has been characterised by spectroscopic means	Clarification will be provided as follows: "Characterisation data for identified impurities should be provided." will be replaced by "Structural analysis data for identified impurities should be provided unless identity is proved by other means."
350	5	Comment: The term „identified impurities" is too general because during development a high number of impurities might have been identified which, however, are not relevant any more for the commercial drug substance Proposed change (if any): Please replace "identified impurities" by "specified impurities	Identified impurities should be addressed suitably even if not all identified impurities are specified in the drug substance specification as such. For clarification of data expected, the following change will be made:

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		in the drug substance" Please further clarify what type of data is expected and in which format (tabular summary for each specified impurity?).	"Characterisation data for identified impurities should be provided." will be replaced by "Structural analysis data for identified impurities should be provided unless identity is proved by other means."
350	5	Please clarify what characterization data are needed if the drug substance is covered by a PhEur monograph.	If the drug substance is covered by a Ph. Eur. monograph, structural analysis data for identified impurities not included in the transparency list of the monograph is expected. Changed as above.
350	5	Comment: We are unsure if characterization data on identified impurities has routinely been expected in an MAA / CEP.Is this an expectation for all specified impurities or also for all identified impurities , at drug substance and all intermediates / ingoing materials ? Where is such information to be provided in the CTD structure ? We also note that impurities above the qualification threshold need only to be qualified NOT characterized. Proposed change (if any): Please reconsider and clarify this expectation. We believe line 350 "Characterisation…" could be removed.	Chemical structure of the identified impurities should be proved by presenting structural analysis data irrespective whether identified impurities are included in the drug substance specification or not. Clarification provided as above.
350	8	Comment: "Characterisation data for identified impurities" could be interpreted in varying ways. Proposed change (if any): ~~Characterization data~~ **Analytical data establishing the structure of** identified impurities	Accepted as above.

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		should be provided.	
351	5	Comment: The text states that 'possible routes of degradation should be discussed'. Should this not be 'actual routes of degradation should be discussed' ? Proposed change (if any): Please amend this text to read "Actual routes of degradation should be discussed."	Since this sentence taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
354	5	Comment: It is requested that "Copies of relevant chromatograms should be provided." This should not be defined as requirement but rather as supportive information because other more relevant information like LOD, LOQ and general specificity of the analytical methods will have to be provided anyway. Furthermore, a discussion of the nature and levels of impurities is necessary which more important than exemplary chromatograms. Proposed change (if any): The sentence should be changed to "Copies of relevant chromatograms ~~should~~ could be provided for illustration purposes" or include this requirement as an example into the last sentence above (line 350), allow reference to selectivity chromatograms that are provided in S.4.2 or S.4.3. Alternatively, this sentence should be omitted.	Since this sentence taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) has not been changed, no new requirement has been established here. No change.
356-358	5	The following 2 sentences are open to interpretation on what is intended or applicable to this section. "In each case, it should be stated whether actual samples of impurities have	For clarification of data expected, the above change has been made.

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		been synthesised for test purposes. Characterisation data for identified impurities should be provided." Is this for impurities identified by discussion in this section, or is this for listed identified impurities in the drug substance specification, or confirmation where a structure has been assigned to a known impurity that is discussed? It's preferable that identified impurities and their characterisation is provided as part of analysis against drug substance specification and hence provided as part of Reference Materials in section S.5 and not detailed here in section S.3.2.	
358	5	This section should mention genotoxic impurities an include the reference to ICHM7 (ref 21)	Accepted. M7 reference added.
358	5	Qualification of impurities may not be addressed by section S.4.5 alone as referred to here. Suggest combine with previous sentence since impurity limits will be based on qualified levels from batches used in safety and toxicological studies. **Proposed change:** Justification of the selected impurity limits should be based on the qualification of impurities from the levels in batches used in safety and toxicological studies (e.g in S.4.5 and S.4.4).	Qualification of impurities in general is referred suitably to CTD section 3.2.S.4.5. No change.
361-367	5	**Comment**: Residual solvents are missing from this list of potential specifications and from the 'additional tests' (lines 368-370).	Impurities are included in the list of minimum tests to be performed. This term encompasses not only related substances but also residual

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		Proposed change: add to the list • Residual solvents	solvents, elemental impurities etc. No change.
364	5	Comment: The Guideline is now also applicable for CEP and ASMF substances (refer to scope). Whereas ICH Q6A says that the description is to be considered generally applicable for the specification of new substances, Ph. Eur. states under 1. General Notices – 1.4 Monographs: “CHARACTERS The statements under the heading Characters are not to be interpreted in a strict sense and are not requirements”. Since the appearance is a parameter listed under characters it is not a strict requirement for existing (Ph. Eur.) substances. This inconsistency should be addressed Proposed change (if any): Description (of note: acceptance criterion for appearance should be defined if relevant)	Appropriate acceptance criteria for description should be provided for CEP and ASMF substances too, even if the statements under the heading “characters (Ph. Eur. monograph)” are not to be interpreted in a strict sense and are not requirements. No change.
368-369	5	Please provide clarity in which specific cases these additional tests are required.	Substances with multiple polymorphic forms should be tested accordingly as well as substances with poor solubility (particle size). No change.

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368-370	5	**Comment**: Water content should be listed also.	Some additional tests are listed here only for example. Of course, this list is not complete. Water content should be considered where relevant. No change.
370	5	Ref 21 should also be included (now only have CHMP guidance on genotoxins).	Accepted. Ref 21 has been included in line 370.
372	5	Details on the analytical procedure should be limited to what is appropriate. Applicants can supply subsequent more detailed procedures later on if an agency wants to repeat in their laboratory.	It is required to describe in detail the steps necessary to perform each analytical test in the dossier unless Ph. Eur. methods are referred to. No change.
372	5	Testing of several APIs can be done only with specialist analytical techniques(eg. testing of prostaglandins). Detailing such knowledge in the dossier could damage the readability of section S.4.2. As common solution, in case of a need advice can be given to the Official Medicines Control Laboratory from the ASMF Holder.	No change as above.
375 - 382	2	For existing APIs the suitability of analytical in-house procedures are shown by validation reports in section 3.2.S.4.3. Proposed change: Please clarify that discussion of critical aspects of significance concerning analytical development is generally not required	Only unusual aspects concerning the tests dealing with the specification of the active substance should be addressed in this section. This is stated clearly in the text and no further clarification is needed. In terms of analytical development of in-house procedures, there is no difference between new and existing active

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		for existing APIs.	substances. No change.
376	5	Comment: This line is not clear – what is expected to be provided related to critical aspects of analytical development ? Proposed change (if any); Please clarify expectations or omit this text.	Criticality and significance are related to the compound in question and are part of the development work of the applicant. No change.
378-379	8	Comment: The new requirement that "Orthogonal analytical methods should be developed in the case that a lack in specificity and/or selectivity is observed for a purity method" is overly broad. Orthogonal analytical methods should be investigated where the lack of specificity and/or selectivity results in an insufficient quality control strategy for the affected impurities. Proposed change (if any): Orthogonal analytical methods should be ~~developed~~ **investigated** in ~~the case that~~ **cases where** a lack in specificity and/or selectivity ~~is observed for a purity method~~ **leads to an insufficient control strategy for the affected impurity.**	Accepted as follows: "Orthogonal analytical methods should be developed in the case that a lack in specificity and/or selectivity is observed for a purity method." will be changed to: "Orthogonal analytical methods, which are methods using different principles and providing different selectivities, should be developed in cases where a lack in specificity and/or selectivity leads to an insufficient control strategy for the affected impurities."
379	5	**Comment:** Please clarify what does "orthogonal methods" mean; suggest change to "methods with alternative selectivity". It may be helpful if examples can be provided. (e.g., a key diastereoisomer known to be potential impurities from the process, that co-elutes in the purity and impurity method requires a separate method where they can be separated).	Clarified as above.

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379	10	We suggest to explain “orthogonal analytical methods” (in red … Orthogonal analytical methods (methods that use fundamentally different principles) should be developed in the case …	Accepted as above.
379-380	4	**Orthogonal analytical methods should be developed in the case that a lack in specificity and/or selectivity is observed for a purity method.** **Comment:** Please clarify what “orthogonal methods” means; suggest change to “methods with alternative selectivity”. It will be helpful if examples can be provided. (e.g., a key diastereomer (known to be potential impurities from the process) that co-elutes in the purity and impurity method requires a separate method where they can be separated).	Accepted as above.
383	5	**Comment**: For any analytical procedures that may be performed on an intermediate, as a surrogate for an active substance method and specification, should a validation section on such an “upstream” method be included here or in 3.2.S.2.4? Please specify	A validation section for analytical procedures performed on an intermediate should be included in section 3.2.S.2.4. No change.
383-386	6	Comment: Please consider that analytical method validations are not required for the analytical methods adopted from Ph.Eur Monographs for analysing the APIs (published in the Ph.Eur).	Accepted and re-drafted as follows: “Analytical validation data, including experimental results for the analytical procedures used for the control of the active substance, should be provided.” will be substituted by “Analytical validation data, including experimental results for the

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			analytical procedures used for the control of the active substance, should be provided unless methods of the respective drug substance monograph in Ph. Eur. are referred to and the tests of the monograph have been demonstrated suitable to control the substance."
384	5	**Question:** In some cases (e.g. due to the hygroscopic nature of the AS), a different salt form of AS may be selected as the reference standard. Methods used to qualify the reference standard could be different than the methods used to qualify the AS. In a situation like this, is it required to provide the validation data for the methods only used for the reference standard?	Complete validation data is expected. No change.
387	5	development of controls throughout the development should be included here	No objection.
387-409	5	**Comment**: Should it be described to include historical analytical methods used during development in the batch analyses section?	It is agreed that section S.4.4 is the appropriate place to present such data.
389	5	Please clarify if this requirement applies for new APIs in originator's products. Please clarify the level of information for existing APIs. For example, it should be appropriate to provide actual production data and not batch data from clinical and pre-clinical development. Definitions of pilot, commercial, production batches, etc. are	Usually, data illustrating the actual results obtained from routine quality control of the active substance will be sufficient for existing APIs. Batches of which batch results are awaited should be representative (not-less-than 10%

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		needed.	of maximum commercial batch size at the time of the approval) of the active substance. Consequently, expected batch size is clarified suitably in the guideline. “Commercial scale” has been removed from the guideline.
389 – 390	1	This paragraph does not adequately address existing APIs. For existing APIs it should be appropriate to provide actual production data and not batch data from clinical and pre-clinical development.	Usually, data illustrating the actual results obtained from routine quality control of the active substance will be sufficient for existing APIs. No change.
391-396	5	Comment: The definition of “representative” in this context is inconsistent with ICHQ1A(R2) which does not provide specific scale requirements for “pilot” scale. ICH states for primary stability drug substance batches: “The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.” Pilot scale batch is defined as: “ A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch” Proposed change (if any): Recent consecutive batches (at least 3) which are	Results of batches manufactured according to the proposed process at not-less-than 10% of maximum production scale at the time of the approval should be provided. Consequently, expected batch size is clarified suitably in the guideline. The text is the same as in the GL CPMP/QWP/130/96 rev. 1 of December 17th 2003 (GL on the Chemistry of new active substances). No change.

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		representative of the active substance which will be supplied for the purpose covered by the marketing authorisation to show that the proposed methods will give routine production material which falls within the specification limits cited.	
392	5	Comment: The need to present three lots at 10% maximum commercial scale seems to be an escalation of expectations. We understood the expectation was for 'representative' material. And we note, further, that this may not be achievable for either continuous processing or in the case of accelerated / adaptive development. Proposed change (if any): Please reconsider this expectation for number and scale of lots that must be available.	Since this line taken from the 'Guideline on Chemistry of New Active Substances' (CPMP/QWP/130/96, Rev 1), it has not been changed and no new requirement has been established here. No change.
392	5	Generally a ±10-fold variation in the quantities is considered to be acceptable in the field of purely synthetic API technology.	The definition in the guideline "representative (not-less-than 10% of maximum commercial batch size at the time of the approval)" is adequate for purely synthetic API. No change.
392 and 400	5	Comment: There is some ambiguity in the language. Proposed change (if any): Change to read: 'Recent consecutive batches (at least 3 <u>from each manufacturing site</u>) which ….'	Agreed as follows: "Recent consecutive batches (at least 3)" will be replaced by "Recent consecutive batches (at least 3 from each manufacturing site)".

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395-396	5	Information on approved batch sizes is maintained in S22. The need for additional batch data on an ongoing basis post approval is unclear. Practically speaking, how should such a request be carried out? What is the procedural framework for providing this information? A variation related to S4? Or a follow-up measure? **Suggestion:** Text to be deleted: "Information on production size batches should be provided, if necessary on an on-going basis, after approval."	Accepted. Although the sentence "Information on production size batches should be provided, if necessary on an on-going basis, after approval." is taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) and has not been changed. However, this sentence will be deleted because information requested is considered not necessary.
400	6	Comment: We propose to specify 'all manufacturing sites' Proposed change (if any): Place of API manufacture (data from all final API manufacturing sites must be provided);	Agreed as follows: "Recent consecutive batches (at least 3)" will be replaced by "Recent consecutive batches (at least 3 from each manufacturing site)".
402	1	"use of batches": please clarify	"Use of batches" is taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) and has not been changed. Refers to e.g. clinical batches, stability batches, validation batches etc. No change.
404-406	5	Comment: The draft uses the undefined term 'relatively wide'. Everybody may understand that in a different way.	Agree to delete the phrase.

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		Proposed change (if any): Delete to say: 'Results which merely state that the material "complies" with the test are insufficient.'	
410-412	5	Comment: There seems to be some inconsistency with line 392 where results of batches are defined sufficient when the batch size is not less than 10 % of the maximum product batch size, and the requirement here ('if applicable') to provide results from 'production scale batches'. Proposed change (if any): Change to read: 'The specification should be based on results from preclinical, clinical and production scale (not less than 10 % of maximum commercial batch size) batches….'	No inconsistency can be seen to line 392 since "where applicable" is stated. If production scale batches are available, these should be the basis among others for justification of specification. No change.
411 - 413	1	This paragraph does not adequately address existing APIs. For existing marketed APIs it should be appropriate to provide actual production data and not batch data from clinical and pre-clinical development.	This paragraph is appropriate for new APIs. Therefore, lines 414 – 420 have been included. No change.
411-413	3	Comment: *it is suggested to amend the text, as per the below to better specify the scope of application.* Proposed change (if any): *The specification should be based on results from preclinical, clinical and production scale batches (depending from the development stage of the drug substance) and taking into account the qualification of impurities.*	The addressed text is taken from the Guideline on Chemistry of New Active Substances (CPMP/QWP/130/96, Rev 1) and has not been changed. This GL doesn't apply to investigational medicinal products.

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411-413	5	Maintain consistency to ICH Q11 **Suggestion:** rephrase to …" Justification for the control strategy and the active substance specification should be provided. The specification should be based on results from preclinical, clinical and, where applicable, production scale batches and taking into account the qualification of impurities, and providing a complete picture with tests performed on starting material or intermediate level, or as an in-process control in lieu of the final drug substance?"…	Accepted as follows: …" Justification for the control strategy and the active substance specification should be provided. The specification should be based on results from preclinical, clinical and, where applicable, production scale batches and taking into account the qualification of impurities and the overall control strategy.
411 - 413	5	This paragraph does not adequately address existing APIs. For existing marketed APIs it should be appropriate to provide actual production data and not batch data from clinical and pre-clinical development.	This paragraph is appropriate for new APIs. Therefore, lines 414 – 420 have been included. No change.
414 - 415	9	**Comment:** Impurity analysis for starting material (SM) and existing APIs appear to be included. For existing registered products this does not follow VICH GL10 which is applicable for impurities in new APIs only. **Proposed change:** Please modify this paragraph in order to clarify that only new APIs are concerned.	Not agreed. See Ph. Eur. general monograph on substances for pharmaceutical use.
415	5	**Comment**: the general monograph referred to here is '2014' not '2034'.	The general monograph of the European Pharmacopoeia *Substances for Pharmaceutical Use* has the number 2034 according to Ph.

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			Eur.
420	5	Ref 21 should also be included (now only have CHMP guidance on genotoxins).	Ref 21 included in line 420.
421	5	Comment: This section contains new expectations in terms of application content (e.g. for criteria for establishing reference substances, aliquotation, storage and handling and the strategy for expiry dating of reference standards. These seem to us to be general GMP matters that need not be specific assessment matters for a specific application. Proposed change (if any): Please reconsider the expectations in this section.	Agreed. To avoid overlapping with GMP requirements the text has been revised (see below).
415	5	**Comment**: the general monograph referred to here is '2014' not '2034'.	Mostly agreed – see below. Plus according to other comments (see below): The expiration date is deleted also. The brackets "(primary and secondary)" are deleted also. "The source of future secondary…" will change to "The procedure to establish future secondary." New text: ***Reference Standards or Materials 3.2.S.5*** Information on the reference standards or reference materials used for testing of the

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			active substance should be provided: specifications, full analytical and physico-chemical characterisations, impurities profile, etc. CRS are qualified as primary reference standards and do not need to be further qualified. The criteria for establishing the reference substances for routine analysis should be given with full analytical profiles. The procedure to establish future secondary reference standards or materials should be stated. Agreed new text *Reference CHMP Guidelines: see references 4 and 10.*
422-427	3	Comment: *we believe that procedure of aliquotation, storage. handling and strategy to establish retest date are managed by internal SOPs and should not be considered regulatory binding information to be provided into registration submissions, hence it is suggested to amend the text, as per the below.* Proposed change (if any): *Information on the drug substance reference standards or reference materials used for testing of the active substance should be provided: Specifications, full analytical and physico-chemical characterizations, impurities profile, etc. The criteria for establishing the reference substances (primary and secondary) for routine analysis should be given with full analytical profiles. An expiration date*	Plus according to other comments (see below): The expiration date is deleted also. The brackets “(primary and secondary)” are deleted. “The source of future secondary…” will change to “The procedure to establish future secondary.” New text: ***Reference Standards or Materials 3.2.S.5*** Information on the reference standards or reference materials used for testing of the

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		should be described if critical for the reference standards/materials. The source of future secondary reference standards or materials should be stated4,10.	active substance should be provided: specifications, full analytical and physico-chemical characterisations, impurities profile, etc. Chemical reference substances (Ph. Eur. CRS) are qualified as primary reference standards and do not need to be further qualified. The criteria for establishing the reference substances for routine analysis should be given with full analytical profiles. The procedure for establishing future secondary reference standards or materials should be stated[4,10].
423	5	**Comment:** In some cases (e.g due to hygroscopic nature of the AS), a different salt form of API may be selected as the reference standard. Since the reference standard is not intended for human use, impurity profile should not be critical. Some of the physical-chemical characterization may not be necessary	Agreed, however no change in text is necessary.
423-427	4	**Information on the reference standards or reference materials used for testing of the active substance should be provided: Specifications, full analytical and physico-chemical characterizations, impurities profile, etc.**	This does not appear to be a relevant comment so has been disregarded.
424	5	Comment: According to ICH Q7 secondary reference standards should be determined prior first use by comparing against the primary reference standard and each batch of a	Agreed. The brackets “(primary and

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		secondary reference standard should be periodically re-qualified in accordance with a written protocol. The qualification and requalification of a secondary standard should therefore be handled under GMP. Therefore full analytical profiles of a secondary reference standard should not be part of a registration dossier. Proposed change (if any): Delete secondary standard	secondary)" will be deleted.
424-427	5	Clarification of the various regulations (ICH Q6A, ICH Q12 in planning, etc.) on the information to be provided in support of reference standard would be useful, as well as the possible role of reference standard test protocols in lieu of Certificates of Analysis (for reference standard updates). Also, Sstandards normally have a retest date. This should be considered in the text accordingly: expiration/retest date	Agreed. To avoid overlapping with GMP requirements the statements concerning expiry date will be deleted.
425	5	Can EP 5.12 be referenced in section S.5 as basis of the definition of the aliquotation, of the storage, of the handling and of the strategy to establish an expiration date of reference standards? However, it should be noted that aliquotation is already part of GMP, there is no need for it to be part of the dossier.	Agreed. To avoid overlapping with GMP requirements the statements will be deleted.
425-426	8	Comment: For many reference standard materials no special aliquotation, storage or handling procedures are required. The requirement for this discussion should be focussed on cases where the aliquotation, storage or handling procedures impact the performance of the reference standard.	Agreed. To avoid overlapping with GMP requirements the statements will be deleted.

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		Proposed change (if any): Aliquotation, storage, **and** handling **procedures should be described in cases where these procedures impact the performance of the reference standard.**	
425-427	1	The following text *"Aliquotation, storage, handling and the strategy to establish an expiration date should be described. The source of future secondary reference standards or materials should be stated."* , should be deleted because these requirements are covered by GMP requirements. As long as future reference standards comply with the specification provided in the dossier, their source should not be relevant for inclusion in 3.2.S.	Agreed. To avoid overlapping with GMP requirements the statements will be deleted – however the procedure (not the source) to establish secondary standards should be part of the documentation.
425 – 427	2	Aliquotation, storage, handling, the strategy to establish an expiration date and a future source for reference standards are subject of internal standard operation procedures as required by the established quality management system at level of ICH Q7. Therefore, it is deemed not to be necessary to repeated this procedures in a dossier for a MAA. The dossier should consistently show the quality of reference standard that had been applied for the presented analytical data. Proposed change: Please remove this requirement. ""	Partly Agreed. To avoid overlapping with GMP requirements many of the statements will be deleted – however the procedure (not the source) to establish secondary standards should be part of the documentation.
425-427	8	Comment: How is aliquotation being defined? Does it refer to how bulk is subdivided into smaller packaging or how packaged reference standard material is being divided for	Since the text has been reformulated, the aliquotation is not mentioned any more to

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		multiple use? In both cases, aliquotation should be considered the responsibility of the user, and be handled in accordance with prudent laboratory procedures. The requirement to provide aliquotation information in regulatory dossier is considered unnecessary. Proposed change (if any): Define aliquotation.	avoid overlapping with GMP requirements.
426	1	Standards normally have a retest date. This should be considered in the text accordingly: expiration/retest date	Since the text has been reformulated, the expiry date is not mentioned any more to avoid overlapping with GMP requirements.
429-430	1	~~bulk~~ storage container closure system	Agreed. The word “bulk” will be deleted.
429 - 430	2	Identity testing is obsolete for describing the suitable quality of packaging material. See also comment to lines 155 – 156. Proposed change: “A brief description of the bulk storage container closure system (s), including specifications and details of materials of construction should be provided.”	Not agreed. Identity testing is essential.
429-430	3	Comment: F*ocus on control of specifications and associated analytical method testings to primary packaging. Hence it is suggested to amend the text, as per the below.* Proposed change (if any): *A brief description of the bulk storage container closure system (s), including for primary packaging: specifications with suitable identity test (s).*	Agreed.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Details of materials of construction should be provided.	
430-433	7	Comment: Studies required for the packaging materials are proposed to be dependent on the nature of the active substance. Proposed change: If the bulk storage container closure system is critical for assuring the quality of the active substance, its suitability should be justified. Depending on nature of the active substance, aspects that may need justification include e.g. ~~with respect to~~ choice of the primary packaging materials, protection from light and/or moisture, compatibility with the active substance including sorption to material and leaching and/or any safety aspects.	Fully agreed. New text reads: A brief description of the storage container closure system (s), including specifications with suitable identity test (s) and details of materials of construction should be provided. If the storage container closure system is critical for assuring the quality of the active substance, its suitability should be justified. Depending on nature of the active substance, aspects that may need justification include e.g. choice of the primary packaging materials, protection from light and/or moisture, compatibility with the active substance including sorption to material and leaching and/or any safety aspects. Reference to stability data can be additional supportive information to justify suitability of the proposed container closure system. The information should cover the whole packaging including the primary packaging material (e.g.: polyethylene bag) and secondary packaging (e.g. fibre or metal drum). Compliance of the primary packaging with any current applicable regulatory requirements

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			(e.g. food grade materials) should be provided].
431-433	5	Comment: Not all items mentioned to justify the suitability of the packaging material might need to be assessed even if the container is critical for assuring the quality of the active substance. However, the current wording seems to determine that all aspects need to be addressed in the justification. Focus should be on primary packaging and not packaging in general. Proposed change (if any): rephrase to …" The information should cover the whole packaging including the primary packaging material (e.g.: polyethylene bag) and secondary packaging if functional"… and/or "… its suitability should be justified with respect to all relevant aspects, e.g. choice of materials, protection from light and/or moisture, with the active substance including sorption to material and leaching and/ or any safety aspects."	This may be justified on a case by case basis – no changes of the text.
437-438	5	Additional Comment: According to section 3.1 and Appendix I of the *Guideline on plastic immediate packaging materials CPMP/QWP/4359/03* for solid active substances there is no need to provide evidence that the material complies with any regulatory requirements such as food stuff legislation. Proposed change (if any): Compliance of the primary packaging with any current	No change.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		applicable regulatory requirements (e.g. food grade materials) should be provided, where relevant.	
446-449	5	Forced degradation and photo stability for existing drug substances, monograph and old monographs should not be required.	Not understood what is meant by stability of a monograph and/or “old monograph”? No change. Nonetheless, an amendment is proposed.
451-453	5	**Comment**: Because such a commitment is routine, and the expectations should be well established, it would be more helpful if the specifics of such expectations were stated here.	The comment is noted. Requirements on the stability commitment are described in ICH Q1A. No need to amend.
452	5	Please clarify that an S.7.2 is not needed when data covering the full proposed retest is provided.	This is clearly stated – no need for changes.
453	5	A stability commitment may be required to provide for production batches as well as data for the full proposed retest period (or also for the full proposed “shelf-life”). **Proposed change:** A post-approval stability protocol and stability commitment should be provided if data <u>for production batches</u> covering the full proposed retest period <u>or shelf-life</u> is not available**.**	Proposed change: A post-approval stability protocol and stability commitment should be provided if data <u>for production batches</u> covering the full proposed retest period <u>or expiry date</u> is not available**.**
453 (and analogously 458)	7	Proposed change: A post-approval stability protocol and stability commitment should be provided if data covering the full proposed re-test period <u>or expiry date</u> ~~is~~ <u>are</u> not available.	Agreed and amended accordingly.
455	9	**Comment:** For existing APIs, no forced degradation studies or studies under stress conditions may be available. As already mentioned before in the general comments section, such	Amended as above.

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		requirements should not be mandatory for existing APIs. **Proposed change:** Please modify this paragraph in order to clarify that only new APIs are concerned.	
458	5	The statement "The major degradation pathways of the active substance, the storage conditions and the retest period should be defined." does not belong in this Module, some clarification is needed. Proposed change: The major degradation pathways should be comprehensively discussed in the section S.3.2 rather than in section S.7	Agreed. Up to the applicant to decide whether to discuss under 4.3, 4.4 or 4.7. The major degradation pathways of the active substance should be discussed. The storage conditions and the retest period should be defined.
461	5	Clear definitions should be provided for the optional process, alternative process, pilot, production, commercial scale...	These have been clarified in the guideline text. Reference to commercial scale has been removed.
483	8	Comment: ICH M7 should be the definitive reference for assessment and control of potentially mutagenic impurities. All locations of the document that refer to CPMP/SWP/5199/02 should instead refer to ICH M7. Proposed change (if any): Removal of text: *'15. Guideline on the limits of genotoxic impurities CPMP/SWP/5199/02'*	Agreed. Reference added.

Please add more rows if needed.