23 October 2015

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

Comments from:

| Name of organisation or individual |
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*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).*

1. General comments

| Stakeholder number*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)*(To be completed by the Agency)* |
| --- | --- | --- |
| **EFPIA** | EFPIA welcomes the effort made to combine the 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. |  |
| **EFPIA** | **Scope - Investigational Medicinal Products (IMPs):**Efpia recommends that Investigational medicinal products (IMPs) are clearly excluded. |  |
| **EFPIA** | **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.  |  |
| **EFPIA** | **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. |  |
| **EFPIA** | **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 reference standards). |  |
| **EFPIA** | **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). |  |
| **EFPIA** | **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.  |  |
| **EFPIA** | **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.  |  |
| **EFPIA** | **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.  |  |
| **EFPIA** | **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. |  |
| **EFPIA** | **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. |  |

1. 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)* |
| --- | --- | --- | --- |
| 52 - 54 | **EFPIA** | 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). |  |
| 65 | **EFPIA** | 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 other relevant guidelines.”**  |  |
| 76-79 | **EFPIA** | **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.  |  |
| Line 82 | **EFPIA** | Comment: The term ‘identity’ in this context could be omitted.Proposed change: ‘This section deals with the ~~identity,~~ nomenclature and chemical structure …’ etc. |  |
| 87 | **EFPIA** | **Proposed change** (if any): “The following information on the … should be provided, if applicable, to an existing or new active substance: …” |  |
| 91 | **EFPIA** | **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
 |  |
| 97 - 102 | **EFPIA** | **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.
 |  |
| 98 | **EFPIA** | 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 |  |
| 107 | **EFPIA** | **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…” |  |
| 110 | **EFPIA** | Suggest to change "contractors" to contract manufacturers" |  |
| 111 | **EFPIA** | Suggest to change "introduction of" to "should be provided for the productions steps after" |  |
| 110-112 | **EFPIA** | **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.” |  |
| 111 | **EFPIA** | Is update of approved CMC/DMF documentation needed to fulfill this requirement? Should we include also testing sites? Please clarify. |  |
| 114 | **EFPIA** | 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?)  |  |
| Line 116 | **EFPIA** | 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) |  |
| 116-117 | **EFPIA** | 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. |  |
| Lines 118-120, 130-132 | **EFPIA** | 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. In the sequential procedural narrative of the manufacturing process, critical process parameters and in-process controls could for example be **bolded** and underlined to emphasize them against the non-critical ones. We suggest to adapt the current wording in the guideline accordingly. |  |
| Lines 121-125 | **EFPIA** | 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: ‘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’. |  |
| 128 | **EFPIA** | 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. |  |
| 129 | **EFPIA** | Criteria for distinguishing between pilot, commercial and production batches should be provided |  |
| 129 | **EFPIA** | Suggest to change "scale commercial" to commercial scale" |  |
| Line 129 | **EFPIA** | “…solvents, catalysts and reagents used in manufacture of a representative scale commercial batch.”Is this referring to a representative-scale? |  |
| Lines 129-132 | **EFPIA** | 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](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004694.pdf)):“*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 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 | **EFPIA** | 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’ |  |
| 130 | **EFPIA** | Also consider some reference to CPPs in addition to critical steps L130, L133, L229. |  |
| 134 | **EFPIA** | Comment: It seems unusual to include a section on Manufacture, range and yield in Section S2.4 |  |
| 134 | **EFPIA** | Generally a ±10-fold variation in the quantities is considered to be acceptable in the field of purely synthetic API technology. |  |
| 134-137 | **EFPIA** | 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): 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 |  |
| 136-137 | **EFPIA** | Yield should only apply to intermediates if they are isolated. **Suggestion:** Add qualification …”for isolated intermediates only”… |  |
| 137 | **EFPIA** | 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. |  |
| Lines 138-142 | **EFPIA** | 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? |  |
| Line 142 | **EFPIA** | “…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?  |  |
| 143 | **EFPIA** | 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. |  |
| 145 | **EFPIA** | 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**. |  |
| 147 | **EFPIA** | 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 providedProposed change (if any):Delete solvents: “Recovery (…) of reactants, intermediates or the active substance |  |
| 155 | **EFPIA** | 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: |  |
| 155 | **EFPIA** | 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. |  |
| 156-157 | **EFPIA** | 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 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.”*  |  |
| 161-162 | **EFPIA** | Minor clarification of scope of ‘biological’**Suggestion:** rephrase to…”biological (animal and human) origin”… |  |
| 163 | **EFPIA** | 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. |  |
| 163 | **EFPIA** | 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.]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). |  |
| 165 - 166 | **EFPIA** | Since the reflection paper is not a guideline it should not be referenced. Instead reference the new ICHQ11 Q&A. |  |
| Line 168 | **EFPIA** | 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 critical non-isolated intermediate, and ultimately to the active substance.” |  |
| Line 170-171 | **EFPIA** | 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 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 | **EFPIA** | 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.* |  |
| 187-195 | **EFPIA** | 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). |  |
| 194-196 | **EFPIA** | 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?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 | **EFPIA** | please specify: ...registered as intermediate manufacturing sites in chapter 3.2.S.2.1 Manufacturer(s) of the marketing authorisation application |  |
| 196 | **EFPIA** | 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. |  |
| 197 | **EFPIA** | Comment: What is “fully” characterized? What is “complete” specification ?Proposed Change: Remove “fully” and “complete”. |  |
| 197 - 201 | **EFPIA** | 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 approaches may be appropriate (e.g. demonstrate peak purity, track impurities backwards in synthesis). |  |
| Line 198 | **EFPIA** | 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 |  |
| 198 | **EFPIA** | **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. |  |
| 207 | **EFPIA** | 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 drug substances or intermediates / starting materials’) of plant origin….” |  |
| 218 | **EFPIA** | Need for consistency with line 156.**Suggestion:** rephrase to…” Specifications for all materials (e.g. raw materials, catalysts, solvents, reagents, processing aids) used”… |  |
| 220 | **EFPIA** | 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’* |  |
| 223 | **EFPIA** | 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 ChangeThis 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 ChangeConsider including the wording from ICHQ11:*“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 | **EFPIA** | 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). |  |
| 227-228 | **EFPIA** | 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 specification”… |  |
| 233 | **EFPIA** | "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 |  |
| 233-234 | **EFPIA** | 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" |  |
| Lines 233-234 | **EFPIA** | Comment: formatting error “Transformation” belongs to line 233, following lines are sub-bullets to line 233? |  |
| Lines 239-240 | **EFPIA** | “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. |  |
| 240 | **EFPIA** | Remove ‘always’ since it would not be critical for a solution or IV drug product. |  |
| 243 | **EFPIA** | It is unclear what "characterisation" of isolated intermediates refers to. Please replace "characterisation" with specification. 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 | **EFPIA** | 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.  |  |
| 244 | **EFPIA** | 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 how this all works together and can be extremely important/ valuable for enhanced submissions.]  |  |
| Line 245 | **EFPIA** | Comment: “which are those” is a copy paste error from former guideline.Proposed change (if any):Delete “which are those” |  |
| 246-247 | **EFPIA** | 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. |  |
| 247 | **EFPIA** | Can the phrase ‘information on the characterisation of these intermediates’ be clarified. What is expected to be included? |  |
| 248 | **EFPIA** | Does not address expectation that reprocessing data are included here (per line 145). However, suggest that S.2.6 is a better location. |  |
| 248-252 | **EFPIA** | 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.” |  |
| 249 | **EFPIA** | 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 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 anexception 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 | **EFPIA** | 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.”… |  |
| Line 253 | **EFPIA** | Comment: The heading should read ‘Manufacturing Process **Development**’ 3.2.S.2.6 |  |
| 253-261 | **EFPIA** | **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. |  |
| Line 254-261 | **EFPIA** | Comment: Please clarify whether the current wording applies to both, a ‘traditional’ as well as an ‘enhanced’ development programme. |  |
| 258-260 | **EFPIA** | Please clarify what “ Existing active substances” means. |  |
| 264-265 | **EFPIA** | 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? |  |
| 266 | **EFPIA** | **Comment**: we understand “official standard” as referring to a compendial API source, if this can be confirmed. |  |
| Line 268 | **EFPIA** | 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” |  |
| 268-269 | **EFPIA** | Not all the tests performed for characterization of a material are needed for routine testing**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 | **EFPIA** | 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 beencarried out on material from a synthetic process other than the one covered in the application” |  |
| 283 | **EFPIA** | Potential to misunderstand what is meant by ‘origin’ referred to here and preferable to explain what is meant with respect to different synthetic routes. |  |
| 286 | **EFPIA** | 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 – ”  |  |
| 286 | **EFPIA** | 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. |  |
| 292-293 | **EFPIA** | Comment: Line 292 and 293 belongs to the section of key intermediates, not to elucidation of structure.Proposed change (if any): Transfer accordingly. |  |
| 294 | **EFPIA** | Comment: Line 294 is only important if the other information cannot be obtained.Proposed change (if any): Explain further or omit. |  |
| 295 | **EFPIA** | Reference to S.2.3 adds no value**Suggestion:** Delete reference |  |
| 298 | **EFPIA** | Seems redundant to MS data referenced above**Suggestion:** Delete line |  |
| 298 | **EFPIA** | Comment: Line 298 is not clear and should be explained further or omitted.Proposed change (if any): Explain further or omit. |  |
| 299-300 | **EFPIA** | Appears to be an impurity topic**Suggestion:** Move to Item S3.2 |  |
| 301-343 | **EFPIA** | **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. |  |
| 307-308 | **EFPIA** | Use ICH term of “drug substance” not API.  Propose typographical change for clarity of following sentence.Proposed change: ...of said ~~API~~ drug substance.  Information on the ~~proposed commercial~~ solid state form of the proposed commercial drug substance should be provided.... |  |
| 307-308 | **EFPIA** | 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? |  |
| 311 | **EFPIA** | Comment: The term "chemistry" can be a very vague term eg it can be used to describe reactivity - others the biological activity |  |
| 323 | **EFPIA** | Proposed editorial change: “Solid state NMR spectroscopy” |  |
| 324-326 | **EFPIA** | **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.  |  |
| 325-326 | **EFPIA** | 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”… |  |
| 327 | **EFPIA** | Much of lines 327 – 243 are also listed in S.1.3 |  |
| 327-334 | **EFPIA** | 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. |  |
| 328 | **EFPIA** | 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.Proposed change (if any): Please clarify what is important to the selection of these temperatures and make this text more specific. |  |
| 328 | **EFPIA** | This should be part of the FDF dossier and should be excluded from ASMF requirements.  |  |
| 332 | **EFPIA** | Physical characteristics: These parameters are also mentioned in S.1.3 “general properties”. It should be kept in mind that 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 |  |
| Lines 333-334 | **EFPIA** | 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. |  |
| 341 | **EFPIA** | 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 |  |
| Line 345 | **EFPIA** | 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. |  |
| 345 | **EFPIA** | 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? |  |
| 345 – 350 | **EFPIA** | 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.  |  |
| 348 | **EFPIA** | 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” |  |
| 349 | **EFPIA** | 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 whether the impurity was isolated by e.g. chromatography or independent synthesis.Proposed change (if any): Please remove /amend this expectation. |  |
| 349 | **EFPIA** | 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. |  |
| 350 | **EFPIA** | 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 |  |
| Line 350 | **EFPIA** | 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 substanceProposed change (if any):Please replace “identified impurities” by “specified impurities in the drug substance”Please further clarify what type of data is expected and in which format (tabular summary for each specified impurity?). |  |
| 350 | **EFPIA** | Please clarify what characterization data are needed if the drug substance is covered by a PhEur monograph. |  |
| 350 | **EFPIA** | 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. |  |
| 351 | **EFPIA** | 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.” |  |
| Line 354 | **EFPIA** | 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. |  |
| 356-358 | **EFPIA** | 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 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 | **EFPIA** | This section should mention genotoxic impurities an include the reference to ICHM7 (ref 21) |  |
| 358 | **EFPIA** | 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). |  |
| 361-367 | **EFPIA** | **Comment**: Residual solvents are missing from this list of potential specifications and from the ‘additional tests’ (lines 368-370).**Proposed change**: add to the list* Residual solvents
 |  |
| Line 364 | **EFPIA** | 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 addressedProposed change (if any): Description (of note: acceptance criterion for appearance should be defined if relevant)  |  |
| 368-369 | **EFPIA** | Please provide clarity in which specific cases these additional tests are required. |  |
| 368-370 | **EFPIA** | **Comment**: Water content should be listed also. |  |
| 370 | **EFPIA** | Ref 21 should also be included (now only have CHMP guidance on genotoxins). |  |
| 372 | **EFPIA** | 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.  |  |
| 372 | **EFPIA** | 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. |  |
| 376 | **EFPIA** | 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. |  |
| 379 | **EFPIA** | **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). |  |
| 383 | **EFPIA** | **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  |  |
| 384 | **EFPIA** | **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? |  |
| 387 | **EFPIA** | development of controls throughout the development should be included here |  |
| 387-409 | **EFPIA** | **Comment**: Should it be described to include historical analytical methods used during development in the batch analyses section? |  |
| 389 | **EFPIA** | 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 needed. |  |
| Lines 391-396 | **EFPIA** | 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 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 | **EFPIA** | 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. |  |
| 392 | **EFPIA** | Generally a ±10-fold variation in the quantities is considered to be acceptable in the field of purely synthetic API technology. |  |
| Line 392 and line 400 | **EFPIA** | Comment: There is some ambiguity in the language.Proposed change (if any): Change to read: ‘Recent consecutive batches (at least 3 from each manufacturing site) which ….’ |  |
| 395-396 | **EFPIA** | 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 onproduction size batches should be provided, if necessary on an on-going basis, after approval.” |  |
| Lines 404-406 | **EFPIA** | Comment: The draft uses the undefined term ‘relatively wide’. Everybody may understand that in a different way.Proposed change (if any): Delete to say: ‘Results which merely state that the material “complies” with the test are insufficient.’ |  |
| Lines 410-412 | **EFPIA** | 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….’ |  |
| 411-413 | **EFPIA** | 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 takinginto 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?”… |  |
| 411 - 413 | **EFPIA** | 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. |  |
| 420 | **EFPIA** | Ref 21 should also be included (now only have CHMP guidance on genotoxins). |  |
| 421 | **EFPIA** | 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. |  |
| 415 | **EFPIA** | **Comment**: the general monograph referred to here is ‘2014’ not ‘2034’. |  |
| 423 | **EFPIA** | **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 |  |
| 424 | **EFPIA** | 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 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 |  |
| 424-427  | **EFPIA** | 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 |  |
| 425 | **EFPIA** | 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. |  |
| Lines 431-433 | **EFPIA** | 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.” |  |
| Lines 437-438 | **EFPIA** | 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 applicable regulatory requirements (e.g. food grade materials) should be provided, where relevant. |  |
| 446-449 | **EFPIA** | Forced degradation and photo stability for existing drug substances, monograph and old monographs should not be required. |  |
| 451-453 | **EFPIA** | **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. |  |
| 452 | **EFPIA** | Please clarify that an S.7.2 is not needed when data covering the full proposed retest is provided. |  |
| 453 | **EFPIA** | 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 for production batches covering the full proposed retest period or shelf-life is not available**.** |  |
| 458 | **EFPIA** | 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 |  |
| 461 | **EFPIA** | Clear definitions should be provided for the optional process, alternative process, pilot, production, commercial scale... |  |

Please add more rows if needed.