EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 August 2014
EMA/337252/2014
Committee for Medicinal Products for Human Use (CHMP)/ Committee for Medicinal Products for Veterinary Use (CVMP)

Draft template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template"

Comments from:

Name of organisation or individual **Stakeholder Number 1**
AESGP contact: Christelle Anquez-Traxler, c.anquez@aesgp.be)
Name of organisation or individual **Stakeholder Number 2**
AOP Orphan Pharmaceuticals AG, contact: Agnes Schüller, agnes.schueller@aoporphan.com
Name of organisation or individual **Stakeholder Number 3**
APIC Contact: Pieter van der Hoeven ABO@cefic.be
Name of organisation or individual **Stakeholder Number 4**
AssICC (Associazione Italiana Commercio Chimico) contact Rinaldo Canofari rinaldo.canofari@unione.milano.it

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Name of organisation or individual **Stakeholder Number 5**
Laboratoire Biodim contact Cédric de Boysson cdeboysson@pharmaomnium.com
Name of organisation or individual Stakeholder Number 6
blue inspection body GmbH, Contact Dr. Stefan Kettelhoit, stefan.kettelhoit@blue-inspection.com
Name of organisation or individual Stakeholder Number 7
BPI German Pharmaceutical Industry Assosciation: Thomas Brückner tbrueckner@bpi.de
Name of organisation or individual Stakeholder Number 8
CHEMO Contact: Adolfo Gonzalez Adolfo.Gonzalez@chemogroup.net
Name of organisation or individual Stakeholder Number 9
EFPIA Contact: Isabelle Clamou isabelleclamou@efpia.org
Name of organisation or individual Stakeholder Number 10
EGA Contact: JULIE MARÉCHAL-JAMIL jmarechal@egagenerics.com
Name of organisation or individual Stakeholder Number 11
EPIG Contact: Jane Nicholson jane@nicholj.plus.com
Name of organisation or individual Stakeholder Number 12
EUCOPE Contact: Alexander Natz natz@eucope.org
Name of organisation or individual Stakeholder Number 13
GE Healthcare Contact: Claire Hill-Venning Claire.Hill-Venning@ge.com
Name of organisation or individual Stakeholder Number 14
PPF Hasco-Lek S.A Contact: Beata Biedroń b.biedron@hasco-lek.pl
Name of organisation or individual Stakeholder Number 15
INTeRACTIVE CONSULTING ASSOCIATES GmbH (ICA) Contact: Norman C. Franklin, Paul Scherer ps@interactive-consulting.ch
Name of organisation or individual Stakeholder Number 16
IFAH-Europe Contact: Sylvie Meillerais techsec@ifahsec.org

Name of organisation or individual Stakeholder Number 17
PHARMIG Austria Contact: Daniel Dangl Daniel.Dangl@pharmig.at
Name of organisation or individual Stakeholder Number 18
pharQcon - pharma Quality concepts Contact: Dr. Carl-Erich Bittes info@pharQcon.com
Name of organisation or individual Stakeholder Number 19
PPTA Europe Contact: Dr. Ilka von Hoegen Ilka@pptaglobal.eu
Name of organisation or individual Stakeholder Number 20
European QP Association Contact: Wolfgang Heimes info@qp-association.eu
Name of organisation or individual Stakeholder Number 21
STADA Arzneimittel AG Contact: Bettina Wendt Bettina.wendt@stada.de
Name of organisation or individual Stakeholder Number 22
STRAGEN PHARMA SA Contact: Dr Sophie NICOL **s.nicol@stragen.ch**
Name of organisation or individual Stakeholder Number 23
SYNTHON Contact: **Theo Vijn Theo.Vijn@synthon.com**
Name of organisation or individual Stakeholder Number 24
VAPI-UPIP (Professional Organisation for Pharmacists working in the Pharmaceutical Industry in Belgium) Contact: Bart De Greef upip-vapi@telenet.be

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	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
1	The principle of having a harmonised QP declaration is welcome. However, as currently proposed **it runs the risk of creating a lot of administrative burdens and duplication with the existing content of the Marketing Authorisation Application** (i.e. drug substance manufacture, CEP, ASMF). In addition, most of the detailed information on GMPs are of limited value for assessors. **The verification of the supply chain (starting with the introduction of the designated active substance starting material) is described in Eudralex GMP volume 4* and is part of the quality system which is checked by inspectors during inspections; it should not be included in the QP declaration.** **Applying the spirit of 'better regulation practices', we would hence propose to shorten the declaration and limit it to the essential.** We appreciate the acknowledgement of the particular situations where remote audit is made possible as well as the recognition of the specific characteristics of atypical actives. To allow smooth implementation of this document, we would request an appropriate transition period, i.e. 2 years. (*): notably chapter 5 GMP part I and introduction and chapter 7 of GMP part II	The objective of the QP Declaration Template is to emphasise the importance of providing a valid declaration, to harmonise the format for the declaration, to forestall questions during assessment, and to enhance the efficiency of the regulatory process, including the timely processing of relevant regulatory submissions. It is not mandatory, but applicants are strongly recommended to use the template to facilitate the validation of regulatory submissions and their review. The QP declaration links the MA, MIAH(s) sites and API sites and is valuable record for industry and regulators. The format has been simplified. The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken. Only in exceptional cases, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		(not the QP template) will need to be submitted according to the guidance document and considered on a case by case basis. Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
3	Given the well documented issues in recent years with API supply chain pedigree APIC acknowledges that improvements in compliance in this regard are warranted and understands what EMA are trying to achieve by means of the expanded QP Declaration template. That said we believe that because the QP Declaration forms part of the Module 1 of a Marketing Authorisation, the proposed template is not the appropriate mechanism to demonstrate GMP compliance. The extensive nature of this proposed Module 1 document has the potential to significantly increase the regulatory burden associated with submissions and subsequent maintenance of an authorisation. As stated above the QP Declaration is submitted in Module 1 of the dossier. The manufacturing supply chain (manufacturer name, address and outline description of activities at each site) is already included in Module 1 (in the Application Form) and is based on information submitted in Module 3. Much of the information being requested in the new template is therefore a repeat of what already is included in Module 1 and in some cases goes over and beyond information provided in Module 3. As an example the declaration template (line 331) requires the building number and function to be provided for each of the manufacturing operations in the API supply chain including the starting materials, intermediates and the final API. This level of detail is, reasonably, not required in the MAA. APIC is also of the opinion that most of information being requested in the template, such as the audit history of suppliers, risk assessments of the supplier sites and confirmation of the supply chain pedigree are more appropriate to a GMP inspection program rather than to inclusion in a regulatory dossier submission. As an alternative approach APIC suggests that EMA consider issuing a guidance document to API manufacturers and the QP to clarify expectations or amend the existing GMP regulations and then hold	Reference is made to Commission document C (2013) 2804 "Guidelines of 16.05.2013 on the details of the various categories of variations" See comments above. The detail should be sufficient to identify the site subject to audit. Building numbers may be necessary for some API super sites. The purpose of the QP Declaration is to confirm satisfactory GMP in place at the API site. This is required before assessment of the relevant regulatory submission. The text and template has been simplified. Supply chain traceability has been deleted.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	the manufacturing sites and the QP accountable for compliance with same in the course of a GMP inspection. The level of detail required in the template is in conflict with the spirit of the EU "Better Regulation of Pharmaceuticals" document which seeks to simplify the regulatory approval process. Furthermore the template is overly prescriptive in a number of places and lacks clarity in others (please see specific comments below	The Template is to enable a valid declaration to be submitted. The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken.
4	In general, we would suggest to clearly specify in the guidelines - when reference is made to "importation and certification of batches" – that this refers to finished medicinal products and not, in the contrary, for example, to API. This may be for example anticipated under par. 1 (see "Objectives/Scope" of the guidelines) and then specify along the text of the guidelines. Although we believe, indeed, that the above (i.e. reference to finished products) might be already inferred from the current text of the guidelines (e.g. "*The QP Declaration should be provided in support of an application for a new marketing authorisation, variation or renewal of a medicinal product(s) authorised in the Community*…"), a clear indication on that respect may only be advisable as it can help avoiding misinterpretation/ensure harmonization.	A QP Declaration is required for all Marketing Authorisations for medicinal products.
7	GMP compliance of the active substance is a general GMP requirement and subject to regulatory inspection during the life cycle of a product. Detailed requirements on the content of the QP declaration such as an on site audit not exceeding a three years interval therefore seem not justified. The responsibility of the finished product manufacturer and its Qualified Person to ensure GMP compliance is sufficiently defined in the national laws on medicinal products in the EEC. Part C The requirement to conduct an on-site audit prior to being granted the marketing authorization may cause different challenges: - The active ingredient manufacturer does not accept to be audited as long as there is no continuous business relationship - Applications for a marketing authorization via national procedure may be	A maximum three year period of audit is considered good practice The challenges are acknowledged,

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	pending for more than three years, a second audit would be necessary for the QP declaration At time of batch release the QP has to certify compliance with GMP, i.e. batch release implies the qualification of the active substance manufacturer at an adequate level normally including an on-site audit. Audits prior to starting routine manufacturing should not necessarily be required. Part D Supply chain traceability is an important element to ensure the quality and GMP compliance of an active substance. However a supply chain established at the time of compilation of the registration documentation may need to be modified at the time routine production starts. As the Qualified Person has to certify for each batch at time of release that the GMP requirements are complied with a declaration at time of application is not necessary. Part D should therefore be deleted.	but API GMP needs to be assured before MA or variation approval. Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
8	The published draft document should be revised to avoid disclosure of API confidential information that is normally compiled in the restricted part of DMF. See details below.	It is agreed that API confidential information is not disclosed. However, no revision is considered necessary. All relevant information is available in the Open Part of the DMF For EDQM CEPs, the MIAH should confirm with the active substance manufacturer, the names and addresses of all sites involved, including any intermediate manufacturing sites in case these are not openly declared on the CEP.
9	EFPIA welcomes the opportunity to comment on the EMA proposed QP declaration template and Questions & Answers document on the QP declaration template, and acknowledges the proposed Qualified Person Declaration template as a step towards harmonisation and clarification of regulatory expectations across EEA. We fully support the aim of the revised Declaration as described in the text in Lines 33 to 35 i.e. The Declaration provides ''a basis for demonstrating compliance of the API manufacturer with GMP requirements and that the manufacturer has relevant knowledge of the supply chain.'' However, some of the suggestions in the template go beyond this purpose and we believe there is an opportunity to	The template has been simplified.

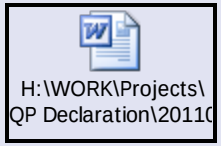
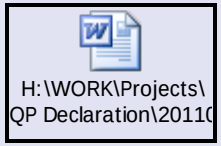
Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	simplify the template to reflect those core objectives of the template. The QP declaration is in many respects linked to chapter 5 and in some instances it is difficult to comment to this draft without understanding the final version of chapter 5 so our proposal is that the QP declaration is not finalized until the final text of chapter 5 has been published.	
9	REGULATORY FRAMEWORK EFPIA would like to highlight the following points to ensure consistency of the QP Declaration with EU regulatory guidance on related topics: The verification of the supply chain traceability and the GMP compliance of API are included in the EU GMP Part 1 Chapter 5 currently under revision: alignment of the QP Declaration template with this document is therefore recommended. The GMP compliance of all parties in the supply chain is managed and documented in the Quality systems of the relevant stakeholders of the supply chain and which are verified during periodical audits; furthermore APIs are supplied through qualified and approved sources according to a supplier qualification program. This ensures continuous control and a higher level of compliance rather than verifying all steps of the supply chain from the regulatory starting materials to the final API for each batch. The oversight and maintenance of the supply chain and any corresponding documentation referenced in the QP Declaration is considered to fall under GMP. It seems like part D of the template might go beyond the intended scope of the QP declaration as provided by article 8(3) of the Falsified Medicines Directive.	Confirmation of supply chain traceability has been deleted, to be addressed through GMP.
9	SCOPE OF QP DECLARATION EFPIA understands that the GMP related information referred to in the template (such as the audit history of suppliers, risk assessments of the supplier sites, contractual relationships along the supply chain and verification of the active substance supply chain traceability) is part of the GMP program governed by the Quality System relevant for GMP inspection and should not be included in the regulatory dossier submission. We suggest that this should be highlighted for clarification in the accompanying Questions and Answers document.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP. The Q&A has been replaced by updated guidance text. For Clinical Trials, a QP Declaration

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The scope of the QP Declaration is considered to refer to commercial finished products with respect to API and verification of the supply chain. The status of the declaration with respect to the sourcing and supply of investigational medicinal products should be clarified e.g. in Section 1 or in the Q&A document. It should be clarified if the QP declaration template applies to biologically derived products.	is required with respect to the finished product manufacturing site only. Existing Q&As address this. The QP Declaration applies to all human and veterinary medicinal products, including biologically derived products.
9	AUDIT CONSIDERATIONS The guidance is clear in the expectation to audit all API manufacturing sites mentioned in the regulatory dossier (as per part A of the declaration). There is some ambiguity however concerning the audit requirements of other actors in the supply chain. It is stated in Line 24 that the GMP compliance of 'all parties in the supply chain' need to be verified. According to 2.2, the supply chain includes API manufacturers, brokers, traders, repackagers ... The statement in Line 24 goes beyond the scope of the ''Declaration of GMP compliance'' described in Part B (Line 132) which refers only to the declaration of GMP compliance of active substance manufacturers. Furthermore Part C describes the auditing requirements for verifying GMP compliance of API manufacturers only. Whilst fully supporting the maintenance of traceability within the supply chain it is our understanding that GMP compliance verification of ''all parties'' by auditing is outside the scope of the QP declaration. It is stated in the template that tick boxes should be completed as confirmation that audit reports … are available. In Part C of the template e.g. Line 368 it is stated that audits have been carried out and ''all critical concerns have been rectified''. We suggest replacing this text by the Falsified Medicines declaration that the written confirmation shall contain "a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of GMP". Line 378 (Part C): The wording of the declaration is ''I have evaluated each of the named contract acceptors… …. Audit(s) was/were conducted by properly qualified and trained staff….'' This implies a	Confirmation of supply chain traceability has been deleted - to be addressed through GMP. Acknowledged, see revision. Acknowledged, see revision.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	personal check by the QP whereas the QP may have oversight for this verification e.g. through the auditing quality system. We would prefer the following statements in the template "Contract acceptor(s) have been evaluated'' etc. Any references to the availability of audit reports if requested for inspection by the competent authorities should be aligned with the requirements of revised chapter 5 of the EU GMP requirements.	 Acknowledged, see revision.
9	SUPPLY CHAIN CONSIDERATIONS It is requested in Line 333 (Part A) to list ''each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting materials''. This is not in line with Lines 69-73 which has as starting point the ''manufacturers of critical raw materials used in the manufacture of the API''. The starting point intended for the API supply chain for the purpose of the declaration therefore requires clarification. The Q and A wording (lines 65-66) is very precise regarding the API sites that are subject to the QP declaration, and this wording should be used in the template.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP.
9	DOCUMENT STRUCTURE AND CONSISTENCY EFPIA recommends that consideration should be given to simplifying the structure of the QP Declaration. For example: Compilation of Active Substance Manufacturing Sites, Finished Product Manufacturing Site(s) and Importation and/or Batch Certification Sites with or without linkage should only be required once, either in Part A or B. In cases where the Finished Product Manufacturing Site is the Releasing Site and a statement of every Releasing Site is provided, a compilation of the Active Substance Manufacturing Sites per Releasing Site should be sufficient. This (including Part C and E) is the main part of the declaration that should be signed by the QP. As multiple declarations are possible, it should be a separate document attached to a summary document (Part A), prepared by the MAH/DRA.	Acknowledged, see revision. Acknowledged, see revision. A MAH Cover Letter may be provided to address this.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Our understanding is that a QP Declaration is not required for all Variations but *only for the relevant variations* described in the Commission Regulation on Variations and the Guideline on Variations (2010/C17/01) (as stated in lines 79-82) but in the Introduction to the Template, (line 41), it is suggested that the QP Declaration should be provided in support of an application for a new marketing authorisation, variation or renewal…. The template needs to be clarified in this respect. We fully support the statement in Lines 78 and 79 that any changes to the supply chain outside the current scope of the existing Variations guidelines do not require notification. It should also be clarified that the QP declaration remains valid until further application, renewal or variation is submitted.	Acknowledged, see revision. Reference is made to Commission document C (2013) 2804 "Guidelines of 16.05.2013 on the details of the various categories of variations"
9	DEFINITIONS/TERMINOLOGY It is stated in Line 127 that sites that are considered redundant should be deleted from the MA. Although we understand and agree on the general principle, we underline that this may adversely affect medicines availability considering the complexity of existing supply chain. The definition of a ''redundant site'' should be clarified. The term ''direct audit'' should be clarified and used consistently throughout the Declaration. It is not clear whether this is the same as an ''on-site audit'' (line 217). In line 234 it is stated that a risk assessment is required for ''all sites'' in the supply chain. The word ''sites'' is confusing - Line 231 states that the supply chain should be defined for each of the active substance manufacturing sites listed in Part A (dossier) but in clause (ll) the ''sites'' may be broader and include the definition of ''sites'' used in Lines 71 and 72 (includes other parties in the supply chain). We suggest that caution is required when using the term 'sites' – to clarify whether ''API manufacturing site'' is intended. It is stated for audits conducted by the Manufacturing Authorisation Holder that ''all critical concerns have been rectified'' (Line 368). For audits conducted by a third party, it is a requirement that ''significant corrective actions have been completed'' (Line 374). It is not clear why these requirements are apparently different. Also the term ''significant corrective action'' is ambiguous. The statements should be aligned with respect to the follow up to audits that is necessary prior to completion of the QP Declaration. See also comments concerning the definition of ''Starting materials'' as above (under 'supply chain considerations').	Acknowledged, see revision. Acknowledged, see revision. Acknowledged, see revision. Note that Confirmation of supply chain traceability has been deleted - to be addressed through GMP. Acknowledged, see revision.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
10	We welcome the proposed EMA Qualified Person (QP) Declaration template as a positive step towards the harmonisation and clarification of regulatory expectations across the EEA. The future availability of an EU template for the QP declaration will provide the long awaited "EU harmonised approach" to ascertain and document GMP compliance of APIs used as starting materials for both regulatory quality review and GMP inspections. While discussions are still on going on the future format and contents of the EU QP declaration template (i.e. until a final EMA template is adopted), we would recommend that the current MS requirements in terms of QP declaration remain unchanged in order to limit the introduction of further heterogeneity in documenting API GMP compliance in regulatory applications.	Noted
10	The EGA believe the information listed in the QP declaration should be limited to the information requested in the regulatory dossier, i.e. application form (module 1.2) and in module 3.2.S, and should preferably not extend to GMP information which would prove of limited value to assessors. The EGA would like to further emphasise that it is the QP's responsibility to ensure compliance to 46f of Directive 2001/83 as amended. In addition, companies have quality organisations in place and rely on their quality systems to allow QPs to sign such declaration of compliance. Quality organisations, quality systems and QPs' competence and responsibility are subject to authorities' inspections and should be relied upon. These should be seen as adequate and sufficient safeguards and it should therefore comfort the idea that it is not necessary to include 'GMP information' neither in the QP declaration nor in the regulatory dossier in general. The EGA is fully supportive of : Rigorous inspections to ensure the quality organisations in place are adequately securing compliance with Article 46f and,	Acknowledged, see revision.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Strict regulatory actions in case the outcome of inspections would point out to any critical deficiencies/observations remaining unaddressed in a reasonable timeframe.	
10	The proposed template appears unnecessary long. The EGA would propose an alternative approach to the QP declaration template which consists in simplifying the proposed template so that information already present in the application form and in module 3.2.S. does not need repeated in the QP declaration. The necessary detailed GMP information will be available on request and for on-site inspections. An EGA proposal for a **"simplified" QP Declaration template** is accompanying this document. For clarity purposes, the EGA is also enclosing a proposal for a simplified version of the template. Both a clean and track changes versions are included. Clean Version:  Track Change Version: 	Acknowledged and the template has been simplified as much as considered practical. Much appreciated. The template should include sufficient information for the declaration to be considered valid.
10	The QP declaration is a regulatory document certifying that the GMP requirements are assessed, complied with and monitored. This is illustrated for instance by the fact that, as an annex to the application form, the QP declaration is not assessed per se by Quality assessors. In initial applications it will be reviewed by Quality Assessors but for variations, it will generally not be assessed (i.e. all but 2 variations described in the final variation classification guideline are either IA or IA_{IN}, i.e. Do and Tell notifications which are considered administrative and not reviewed by quality assessors). As such, we believe the QP declaration should remain a regulatory commitment by the QP which will then be confirmed by a GMP inspection and if not, challenged and sanctioned by the authorities.	This is incorrect – the declaration is not a commitment, but a

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Furthermore, the falsified medicines directive (yet to be adopted by Council) refers to a 'written declaration of compliance' for both the QP declaration and the future 'written declaration' to be issued by the API exporting 3rd countries. The EGA would call on a simple declaration which could be broadly and commonly understood and used by all. This reinforces the EGA's call for a comprehensive yet succinct regulatory QP declaration (template). Regarding the verification of the active substance supply chain traceability (Part D), the introductory text reads as follows: "The sites will include manufacturers of critical raw materials (as defined in Part II of the EU GMP Guide 7.11, 7.13), active substance manufacturers, brokers, traders, repackers, relabellers, micronisers and importers." The EGA notes the reference to the EU GMP Guide Part II but would like to highlight that it is of great importance to take into account who the actual contract giver for the designated outsourced GMP activities is (e.g. API manufacturer or FP manufacturer). In case the contract giver is the API manufacturer (i.e. no direct contract or technical between the contract acceptor and the FP manufacturer), a systematic audit of the subcontractor by the FP manufacturer should not be expected. However, the Technical Agreement (quality agreement) with the API supplier/manufacturer (if contract manufactured product) could possibly provide the Manufacturing Authorisation holder an authority to audit their subcontractors, including the API facility, if the QP of the Manufacturing Authorisation holder is not satisfied with those audits performed by them or a third party. Ideally, an appropriate, effective and efficient mechanism should be in place to ensure that the entire supply chain is identified at the time of the regulatory filing. This would limit the unnecessary workload and unexpected compliance issues during post filing stage.	confirmation – this needs to be in place before assessment of a relevant regulatory submission. See above. There is a concern here that there may be conflicts of interest. Audits should be by or on behalf of the MIAH, by suitably trained and experienced person(s), who may be a third party contractor
10	The introductory text reads "Competent authorities need not be notified of amendments to the supply chain that are outside the scope of the Commission Regulation on variations"	

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	It is important to note that by means of the adoption of the falsified medicines directive (adopted by the European Parliament on 16 Feb 2011, likely to be adopted by the Council either in Q2 or Q3 2011), the QP Declaration is now referred to under article 8.3 of the 2001/83/EC directive which in turn implies it is subject to the variations regulation. We strongly recommend further clarifying either in the Q&A or in the introductory note to the QP Declaration template that the QP declaration must not contain any piece of information NOT ALREADY present in the dossier (MA application form or M3S). Details relating to the API supply chain pedigree (Part D) should only be available for on-site inspections.	Reference is made to Commission document C (2013) 2804 "Guidelines of 16.05.2013 on the details of the various categories of variations" Not accepted. See above. The declaration needs to include relevant information. Accepted, confirmation of supply chain traceability has been deleted - to be addressed through GMP..
10	We are supportive of the clear statement reinforcing that although "GMP certificates from a relevant Competent Authority cannot replace direct audits", these may be used "in a risk based approach by the manufacturer in establishing priorities for its own audit programme of active substance supplier". Provided the risk based approach is well defined and documented in a company's Quality system, we believe reference to a recent EU GMP (or equivalent) certification can be used, among other elements, to adjust the date of the next scheduled audit and to justify exceeding a period of 3 years from the last satisfactory audit.	See European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP) EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances Q2: Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from an EEA member state and a valid GMP certificate is available?
11	The implementation of this QP Declaration Template will provide a harmonized format for a comprehensive declaration and is expected to facilitate the communications with the Competent Authorities. Indeed, the Declaration Template is strictly based on the duties and responsibilities of the QP, in agreement with the Directive 2001/83/EC, and helps clarify the position to be taken by the QP in facing different situations, with reference to API auditing, GMP compliance and supply chain verification. Indeed, this document could be considered an integration to the Annex 16 of EU-GMP, as it discusses extensively and in a more structured format most of the issues which were reported in the 2001 document on QP duties and responsibilities. However, the QP declaration already forms part of the Marketing Authorisation application and it is not believed the proposed template is the appropriate mechanism to demonstrate GMP compliance.	This comment is similar to those previously made.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Much of the information requested (eg manufacturer name, address and outline description of activities at each site) is already included in the application - thus the template represents duplication of information provision which is against the stated aims of the EU of Better Regulation On the other hand, some of the requirements of the proposal go beyond what is required in applications e.g. the building number and function to be provided for each of the manufacturing operations in the API supply chain including the starting materials, intermediates and the final API. Such information being requested in the template, such as the audit history of suppliers, risk assessments of the supplier sites and confirmation of the supply chain pedigree are more appropriate to a GMP inspection program rather than inclusion in a regulatory dossier submission.	See above.
12	As mentioned in the document the current version of Directive 2001/83/EC in Article 46 (f) provides that the marketing authorization holder shall "*comply with the principles and guidelines of good manufacturing practice for medicinal products and to use as starting materials only active substances, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.*" In practical terms the word starting material is however broader than the term active substance. It could be understood as "any substance used in the production of a medicinal product, but excluding packaging material". Therefore it can for example also cover raw materials or any intermediates gained in the manufacturing process of active substances. Since, however, "only" the manufacturing of active substances is subject to GMP requirements we recommend in the interest of clarity to replace the term "*active substances used as starting materials*" and the term "*starting material*" simply by "*active substance*" in the whole document. This clarification will be in line with the future amendments of Directive 2001/83/EC by the upcoming Directive concerning falsified medicinal products (COM (2008) 668). According to the current status of the legislative process the term active substance will be defined in the new Article 2b Directive 2001/83/EC as follows: "*Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended ...*".	The template applies to active substances used as starting materials in the manufacture of medicinal finished products. See revision.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Additionally, the amended Article 46 (f) of the amended Directive will refer to the good manufacturing practice for "*active substances*". Since raw materials or intermediate levels in the manufacturing process of active substances do not as such become an active ingredient of the final product, we recommend to work with the term "active substance" in the whole document and to generally avoid using the unprecise term of "starting material".	
15	The credibility the QP Declaration is absolutely dependent upon the quality of the report of the audit of the manufacturer of the active substance. The majority of users of active substances have these audits carried out by their own (often local) staff who, in the case of India and China are nationals of these countries with negligible experience of what it means to be "in compliance" with EU GMP Part II, as they have never seen a good European active substance manufacturer. These audit reports (usually after conducting a 1 day audit at the site) **may** be based on the "EMA GMP Inspection Report – Community format" (even though this format is not entirely suitable for the inspection of active substance manufacturers as the "headings to be used" on Page 2 are those related to EU-GMP Part I). The essential part of the report (which should be written for the use of a QP) may use the section "Headings to be used" to list the parts of EU GMP Part II used but usually consist of a table of the titles of the first 15 chapters of the EU GMP Part II guidance with the comment against each chapter "Complies". The report **may** list deviations from GMP observed but if so these are always of a minor nature. There is however, in such reports, never an explanation of **HOW** an active substance manufacturer is conducting his activities in order to meet the EU GMP Part II requirements, although this is exactly what a QP needs in order to judge himself (herself) whether the active substance manufacturer is in compliance with the majority of the requirements of EU GMP Part II. A recommendation will be made that audit reports of active substance manufacturers include descriptions of **how** the active substance manufacturer meet at least 75% of the EU GMP Part II requirements. Only with such detailed information can the QP truly assess the compliance of the active substance manufacturer with EU GMP Part II. Independent evidence for this view is found in the suspension of CEP certificates by the EDQM. Although the companies concerned had been audited by employees of the users of these active	The QP Declaration requires attestation that: Audit(s) are conducted by properly qualified and trained staff, in accordance with approved procedures. Acknowledged, but considered out of scope of the requirements of the QP Declaration. This is addressed by current GMP guidance.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	substances and were found to be "in compliance" (e.g. GLOCHEM in Hyderabad and CALYX in Mumbai, India or Tianjin Zhongan Pharmaceutical Co Ltd in Tianjin China) EDQM auditors have found in these (and other) cases serious GMP deficiencies at these sites and in the case of GLOCHEM this resulted in an immediate prohibition of the use of Clopidogrel besilate manufactured by GLOCHEM at MAHs in Europe. Publicly available FDA "Warning Letters", particularly after inspections in China, illustrate that many Chinese active substance manufacturers, (not yet inspected by EDQM) have serious GMP problems although they have been "certified" by local Chinese auditors employed by European generic manufacturers as being "in compliance" with EU GMP Part II It is also recommended that if any inspection by representatives of a competent authority or the EDQM of the manufacturer of an active substance results in either a determination that the company is not in compliance with EU GMP Part II or the Certificate of Suitability is suspended by the EDQM for the same reason the results of these assessments should overrule any assessment carried out by the representatives of the MAH or a third party as such inspections confirm that the company(ies) in question don NOT MEET the requirements of Article 46(f) of Directive 2001/83/EC (human medicinal products) and Article 50(f) of Directive 2001/82/EC (veterinary medicinal products) as amended.	This is already in place.
15 (additional)	WHEREAS: The recently approved amendment to Directive 2001/83/EC from March 2011[1], (which had not been approved when the original comments from this submitter were prepared) points out that (1) Falsified active substances and active substances that do not comply with applicable requirements pose a serious public health risk[2] (2) Manufacturing plants of active substances should be subjected not only to inspections carried out on the grounds of suspected non-compliance but also on the basis of risk analysis[3] (3) The manufacture of active substances should be subjected to good manufacturing practices regardless of whether those ingredients are manufactured in the Union or imported[4] (4) Article 1 is amended to have inserted under 2a the definition of a Falsified medicinal product[5]	

[1] DIRECTIVE of the EUROPEAN PARLIAMENT AND OF THE COUNCIL amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source (referred to later as"))
[2] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Preamble # 7
[3] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Preamble # 19
[4] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Preamble # 20

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	(5) The definition of a falsified medicinal products includes a false representation of (d) its history[6] (6) Article 8 paragraph 3 is amended to add after point h) the following text (ha) a written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conduction audits in accordance with Article 46(f)[7] (7) Article 46 (f) is amended to include "To this end the holder of a the manufacturing authorization shall either himself or, without prejudice to his responsibility as provided in this Directive, by an entity contracted by him, verify compliance by the manufacturer and distributor of active substances with GMP and GDP by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances"[8] (8) Article 47 (a) is amended to include, (under new (4)) ".....when a plant manufacturing an active substance for export and was found to comply with the principles and guidelines of GMP the requirement set out in point (b) of paragraph (2) may be waived[9] (9) Article 111 (a) is amended to include 1b The competent authorities shall have a system of supervision including inspection at appropriate frequency based on risk, at the premises of the manufacturers; importers or distributors of active substances located on their territory and effective follow up thereof. Wherever it considers there are grounds for suspecting non-compliance with the legal requirements of this directive, including the principles and guidelines of GMP referred to in Article 46(f) and 47 the competent authorities may carry out inspections at the premises of (a) manufacturers or distributors of active substances **located in third countries**[10] (10) And Article 111 (a) is amended to include 1c Inspections referred to in paragraphs 1 a and 1 b may also be carried out .....**in third countries** at the request of a Member States, the Commission or the Agency[11] (11) And Article 111 (a) is amended to include	

[5] Amendments to Directive 2001/83/EC regarding falsified medicinal products: 1) Article 1
[6] Amendments to Directive 2001/83/EC regarding falsified medicinal products: 1) Article 1, 2a Falsified medicinal product c)
[7] Amendments to Directive 2001/83/EC regarding falsified medicinal products: 1) Article 8, Paragraph 3 (ha)
[8] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Article 46 (f)
[9] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Article 47 a (4)
[10] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Article 111 (a) 1b
[11] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Article 111 (a) 1c

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	1e In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monograph of the European Pharmacopoeia, the standardisation body of the nomenclature and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia (EDQM) may ask the Commission or the Agency to request such an Inspection when the stating material concerned is the subject of a European Pharmacopoeia monograph[12] (12) And Article 111 (b) is amended to include 3 After each inspection as referred to in paragraph 1 the competent authorities shall report of whether the inspected entity complies with the principles and guidelines of GMP and GDP as referred to in Article 47 and 84 as applicable (13) And Article 111 (c) is amended to include 5 Within 90 days of an inspection as referred in paragraph 1, a certificate of good manufacturing practices or good distribution practices shall, when applicable, be issued to the inspected entity if the outcome of the inspection shows that it complies with the principles of GMP or GDP as provided for by the Union legislation If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up. **it is incompatible with the amended Directorate** that medicinal products are permitted to remain on the community market when these contain active substances which were not manufactured in compliance with the principles and guidelines of good manufacturing practice. If the competent authorities of the members states or the inspectors of the EDQM have refused to issue a certificate of good manufacturing practices to the inspected entity this confirms that the inspected entity is **NOT** following the principles and guidelines of GMP and thus the permission to market the products in the community **should be suspended until the deficiencies have been corrected.** A supplementary reason for suspending the Marketing Authorization, community wide, is that active substances which are not being manufactured under GMP now do not comply with the European Pharmacopoeia 7.0 onwards This is because to be in compliance with the monograph of the European Pharmacopoeia TWO criteria must be fulfilled:	Appropriate regulatory action in these cases is already in place.

[12] Amendments to Directive 2001/83/EC regarding falsified medicinal products: Article 111 (a) 1e

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	(a) analytical testing must have confirmed that the batch of active substance used complies with the monograph in the European Pharmacopoeia and (b) the batch in question has been manufactured in compliance with the principles and guidelines of good manufacturing practice. Should BOTH of these criteria not be met, then the batch of active substance does not comply with the requirements of the European Pharmacopoeia and thus if this batch of active substance is then used in a medicinal product, **this batch of medicinal product IS FALSIFIED.** Thus, as pointed out in the earlier submission, but now supported by the wording of the amended Directive 2001/83EC of March 2011, it cannot be that after the competent authorities of the members states or the inspectors of the EDQM have refused to issue a certificate of good manufacturing practices to the inspected entity products from this entity may continue to be marketed because the Qualified Person claims that they have the ultimate authority to determine whether the supplier of the active ingredients used in the products which are being certified are in compliance with principles and guidelines for GMP. Thus if any inspection by representatives of a competent authority or the EDQM of the manufacturer of an active substance results in a determination that the company is not in compliance with the principles and guidelines of GMP **the results of these assessments should overrule any assessment carried out by the representatives of the MAH or a third party**	Appropriate regulatory action in these cases is already in place.
16	IFAH-Europe welcomes the opportunity to provide feedback to the CHMP/CVMP/QWP initiative for a QP declaration template. As a general comment, we wish to express that this template goes beyond the legal requirements for marketing authorisation applications. 'Marketing', 'Manufacture and import' and 'Supervision and sanction' are described in separate sections of Directive 2001/82 as amended, respectively Titles III, IV and VIII, with their own requirements and control systems. The template, as currently drafted, will only increase regulatory burden without directly addressing GMP compliance and supply chain control. By becoming part of the marketing authorisation dossier, it will lead to a duplication of tasks between assessors and inspectors and will further create discrepancies	The objective of the QP Declaration Template is to emphasise the importance of providing a valid declaration, to harmonise the format for the declaration, to forestall questions during assessment, and to enhance the efficiency of the regulatory process, including the timely processing of relevant regulatory submissions.

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	between data systems (dossiers and QA documents). IFAH-Europe proposes a shortened template instead that will contain sufficient information to adequately address the authorities' concerns (a proposed revised template are given at the end of this document). Furthermore, the scope of the QP declaration should be limited to 'new marketing authorisation' and 'variation' applications (see specific comments overleaf with regard to the exclusion of 'renewals'). Additionally, we favour a system where all finished products' manufacturers are regularly inspected and in a consistent manner across the EU. We believe that inspections are the most efficient manner to guarantee GMP compliance and verification of the supply chain of the active substance. It is indeed on such occasions that manufacturers can appropriately present their API suppliers' audit programmes and outcomes. Furthermore, a sufficient transition period of 24 months minimum should be given for the implementation of the QP declaration. More specific comments to the draft template are given overleaf.	It is not mandatory, but applicants are strongly recommended to use the template to facilitate the validation of regulatory submissions and their review. The QP declaration links the MA, MIAH(s) sites and API sites and is valuable record for industry and regulators. The format has been simplified. The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken. For other exceptional case, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation (not the QP template) will need to be submitted according to the guidance document. Confirmation of supply chain traceability has been deleted - to be addressed through GMP. A transition period is not considered necessary.
16	Scope of the QP declaration template: it seems clear that the draft template has been designed for pharmaceutical products. Indeed, the manufacturing of active substances used in biological products is	Much appreciated, but some essential information, e.g. date of

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	an integrated part of the manufacturing of the final product, for which this template is of no added value. Thus, we suggest it is stated that the QP declaration will strictly apply to pharmaceutical products' applications and variations, where relevant. A revised template is proposed: Track changes QP_Declaration_IFAH_EU_TC.doc Clean Version: QP_Declaration_IFAH_EU_Clean.doc	audit, is missing. The template should include sufficient information for the declaration to be considered valid
17	PHARMIG – the association of the Austrian pharmaceutical industry – welcomes the opportunity to provide our comments on the draft template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template". We welcome the effort to harmonise the format for the declaration and to establish one standard template for the industry. Nevertheless we want to point out that such a standardised document has to be applicable in the daily life of our business and has to be adapted to the realities. Please find following a summary of some functional points we suggest to consider. Further details can be found in the comments on specific passages or lines in the text. First of all we would like to highlight the GMP certificate as a high level quality standard given to a manufacturer of medicinal products or active substances by a competent authority. The GMP certificate qualifies the manufacturer to produce according to one of the strictest regimentations. Listing of GMP certificates under "optional supplementary supportive information" (Part C, lines 394-397) would undermine the authority of widely recognised authorities. Therefore we strongly ask to accept GMP certificates together with risk-based audits as official documentation within this declaration. The manufacture of active substances usually is a very complex chemistry of synthesis or a complex production from purified extracts or fermentation. This information is owned by the manufacturer of the active substance and in most cases not known by the manufacturer of the finished medicinal product.	EU GMP certificates do not replace MIAH audits and the QP Declaration. GMP is necessary to be in place from the use of the designated starting material, as shown in the summary

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We strongly recommend to retain the current practise approved by EMA to refer to an Active Substance Master File (ASMF) in a submission. Certification should be limited to the active substance manufacturing site involved in the last quality relevant manufacturing step. It is not applicable to start with the introduction of the designated active substance starting material.	of the route of synthesis given in the DMF. Not agreed as discussed above.
18	The numbering of Part C (lines 354 to 397) is unclear. There are the sections (i), (ii), (iii) and (iv), however following section (ii) again subsections (i) and (ii) can be found (lines 378 to 383). (iii) is indented as the 2 subsections, but obviously it does not belong to the subsections which are headed by "I declare that:" The numbering of Part C should be revised and made unambiguous.	 Acknowledged. Accepted.
20	Will the Agency publish any comments or guidance on how to proceed in case the same API is independently used by different manufacturers and several finished products? Same requirements seem to be repeated at different paragraphs throughout the document. E.g. reference to Directives. Redundancies should be eliminated. Please provide guidance that and how API batches can be used, if requirements and GMP standards have been met at the date of manufacture, purchase or shipment. Often the required documentation can not be provided or updated, if manufacturer or supplier has left business after purchaser or site was closed in the meantime. After re-analyses according to current GMP APIs are often re-released based on updated analytical testing.	It is possible to share API audits, as discussed in the guidance, if supported by appropriate contract arrangements. The documents have been simplified. API GMP needs to be assessed and deemed satisfactory before purchase of material to be used for marketed products.
24	1. The template seems too long and complicated for small companies' e.g. Small pharmaceutical manufacturer of dry forms where active substances are used as starting material for productions. Only individual declarations are expected. Can the template be adapted/simplified in order to	The template has been simplified. The scope of the QP template has been limited - it can only be used

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	suppress all the irrelevant information? 2. As part C section (iii) mentions, it seems possible to assess remotely (based on questionnaires etc) in exceptional circumstances. Is it possible to give more details on these exceptional circumstances? 3. Would it be possible to have the name of the active substance in the header without repeating throughout the remainder of the template? 4. Recommendation to list all abbreviations to avoid misunderstanding/interpretation. 5. What does "on behalf of" mean, because for small companies there is not always a direct relationship with the manufacturer for 3rd party auditors (line 195) 6. In general too difficult/complex wording is used. Simplification is recommended. 7. The "control" of the supply chain, where starts and stops the liability. There is need for clear R&RQP and the supply chain. What can be delegated and covered under an effective quality system? 8. Listing all sites and buildings is a repetition of what is already listed in the submitted registration file/dossier (module 3). Reference should be made to the dossier; Otherwise, this would increase the possibility of inconsistencies. 9. For CP products, EMA already requests updated lists of manufacturing sites.. Will this be cancelled because it is a duplication of the same information? 10. What will be the validity of the QP declaration itself? Can one form/declaration be used for several medicinal products with same active substance? How long will the form/declaration be valid?	when an on-site audit has been undertaken. Only in exceptional cases, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation (not the QP template) will need to be submitted according to the guidance document and considered on a case by case basis. All acronyms are spelt out in full in the text. Supply chain traceability has been deleted. GMP guidance is available. The QP declaration links the MA, MIAH(s) sites and API sites and is valuable record for industry and regulators. Sufficient information is necessary for the declaration to be valid. No A QP Declaration may be shared across marketing authorisations, if appropriate and supported by necessary contractual arrangements. Audits of each site for GMP compliance should be undertaken at regular intervals, normally within

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
		three years.
	11 The QP declaration has to reflect the current status of the products life cycle, to avoid that there are different approaches and interpretations possible.	Agreed, but no revision required.

2. Specific comments on text

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part 1. Issue/Objective lines 17-19	**16**	At the start of the document, the QWP describes the objectives of this template as follows: 1. "To emphasise the importance of providing a comprehensive declaration, 2. To harmonise the format of the declaration, 3. To forestall questions during assessment and, 4. To enhance efficiency of the regulatory process." While IFAH-Europe greatly supports objectives 2 and 3, we question objectives 1 towards a "comprehensive declaration" and 4 that it will "enhance efficiency of the regulatory process". In fact, we believe it will have the opposite effect by generating administrative burden on industry (regulatory affairs' departments and QPs) and regulatory assessors alike, for providing information that already is available either in the dossier or covered by GMP obligations and regularly inspected. Indeed the proposed template does not introduce any new requirements (see also question 1 of the Q&A document) but mostly duplicates existing information; thus having to prepare and keep up to date such declaration will only generate administrative burden as illustrated below.	This is not accepted, as discussed above. The objective of the QP Declaration Template is to emphasise the importance of providing a valid declaration, to harmonise the format for the declaration, to forestall questions during assessment, and to enhance the efficiency of the regulatory process, including the timely processing of relevant regulatory submissions. It is not mandatory, but applicants are strongly recommended to use the template to facilitate the validation of regulatory submissions and their review. The QP declaration links the MA, MIAH(s) sites and API sites and is valuable record for industry and regulators. The format has been simplified.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken. Only for other exceptional case, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation (not the QP template) will need to be submitted according to the guidance document. Confirmation of supply chain traceability has been deleted - to be addressed through GMP.
Part 1. Issue/Objective lines 26-28	**1**	**Comment**: *"take steps to shorten the supply chain wherever possible"*. This recommendation is not really useful here. **Proposed change (if any):** Please delete the sentence: ~~*"take steps to shorten the supply chain wherever possible"*~~.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 1. Issue/Objective lines 26-28	**9**	Comment: '*... take steps to shorten the supply chain wherever possible'*. In practice this will likely be difficult. Companies use complex supply chains to manage supply and/or outsource certain steps, so the overall chain is likely to extend rather than to shorten. A potential concern is that inclusion of this statement will lead to shortening of the supply chain becoming a regulatory expectation.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 1. Issue/Objective lines 26	**24**	Comment: see general comment "control", Proposed change (if any): delete "and take steps..."	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 1	**15**	Comment: The assumption is made that the active substance is "accepted by them". This is	The active substance supply

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 29		now often not the case and the medicinal products are themselves manufactured outside the EU (e.g in India or China) and are certified and distributed in the EU by a MAH who is solely a marketing organisation of the Indian or Chinese MP manufacturer. Thus the wording of line 29 should be modified to reflect these facts. **Proposed change**: **…..** that each batch of active substance ~~accepted by them for use~~ **used** in the manufacture of medicinal products has been sourced through this supply chain	chain should be established, qualified and documented and addressed through GMP. The confirmation of supply chain traceability has been deleted from the template.
Part 1. Issue/Objective 29-30	**1**	**Comment:** The verification of GMP compliance of active pharmaceutical ingredients is described in chapter 5 and is ensured through the GMP programme controlled by the quality system. It is not appropriate to verify all steps of the supply chain from the regulatory starting materials to the final API for each batch. **Proposed change (if any):** *Clearly demonstrate that ~~each batch of~~ an active substance accepted by them for use in the manufacture of medicinal products has been sourced through **~~this~~ a validated** supply chain.*	Confirmation of supply chain traceability has been deleted - to be addressed through GMP.
Part 1 lines 29/30	**3**	Comment: Does this mean that QP will in future be required to certify as part of the release process of each drug product lot that each and every batch of API has been sourced through the verified supply chain? Moreover, various routes or service providers may be used. Furthermore, it is most relevant if a batch in fact was "used" but not necessarily if it has been "accepted by them" but not used at the end for whatever reasons. Proposed change: ….. that each batch of active substance ~~accepted by them for use~~ **used** in the manufacture of medicinal products has been sourced through ~~this~~ **a reliable and approved** supply chain	See above
Part 1 lines 29/30	**9**	Comment: Modify the requirement "Clearly demonstrate that each batch of active substance accepted by them for use in the manufacture of medicinal products has been sourced through this supply chain."	See above Confirmation of supply chain

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The GMP compliance of all parties in the supply chain is managed and documented in the Quality systems of the relevant stakeholders of the supply chain and which are verified during periodical audits; furthermore APIs are supplied through qualified and approved sources according to a supplier qualification program. This ensures continuous control and a higher level of compliance rather than verifying all steps of the supply chain from the regulatory starting materials to the final API for each batch. Proposed change (if any): (iii) "Clearly demonstrate that the supply chain of each batch of active substance accepted for use in the manufacture of medicinal products is documented in the relevant quality system"	traceability has been deleted - to be addressed through GMP
Part 1 lines 29/30	**10**	Comment: '*(iii) Clearly demonstrate that each batch of an active substance [...] has been sourced through this supply chain'* We would like to emphasise that it is not uncommon for multinational companies to have very complicated supply chains whereby, under one single MA, different supply chain scenarios could be foreseen. This 'adaptability' factor is part of the functioning of manufacturing operations. We believe the important aspect is that the Quality organisations are capable of documenting the actual supply chain and secure a continuous compliance rather than to demonstrate that each batch [...] has been sourced through a unique supply chain. Proposed change (if any): We would propose the following wording: "*(iii) Clearly demonstrate that* ***the supply chain of*** ~~***each batch of***~~ *an active substance [...]* ***is documented in the quality system***"	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 1 Issue/Objective Lines 40 -44	**10**	Comment: The current introductory text does not exclude explicitly IMPs and biotechnology medicinal products from the scope of applicability of the QP declaration. Proposed change (if any): The introductory text and the accompanying Q&A should clarify that the QP declaration	The QP Declaration of API GMP applies to all medicinal products, not IMPs see published Q&As.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		template does not apply to IMPs or biotechnology medicinal products.	
Part 1 Issue/Objective Line 41	**9**	Comment: Elsewhere in the guidance it is clarified for which variations the declaration is required (in line with the EU Variation guidance). Here however it could be understood that all variations should be accompanied by a declaration. Proposed change: ***relevant*** variation, renewal.....	Agreed
Part 1 Issue/Objective Line 41	**16**	Section 1 reads that the QP declaration will have to be provided "in support of an application for a new marketing authorisation, variation or renewal". We question the need for such document at renewal, where in case of a change to the information on the active substance, this would have been notified in the relevant variation application. Having to provide such template at renewal goes beyond the objective of the single renewal and creates additional administrative burden. Thus, the QP declaration should only be provided with a new marketing authorisation or a relevant variation application.	This is not accepted. By the time of renewal, an updated QP Declaration is required to confirm ongoing and active GMP oversight of active substance manufacture.
Part 1 Issue/Objective Line 43	**7**	Comment: "Regulation (EC) 1394/2007 builds up a tailor-made framework for advanced therapy medicinal products. Article 5 of this Regulation says that "the Commission shall, after consulting the Agency, draw up guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products." As Advanced Therapy Medicinal Products are very specific it is justified to exclude these products from the requirement of the declaration form. The declaration form is intended for classical pharmaceutical products. The proposals concerning the content of this form in the Draft are not specific enough to reflect the specificities of these products.	The QP Declaration applied to all medicinal products.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Should ATMP not be taken out of the scope of the Draft it would be necessary to work out the specificities of these products. One specificity is that donation, procurement and testing of the "sourcing material" tissue and cells for ATMP have to be in accordance with Directive 2004/23/EC and Directive 2007/16/EC. This means that GMP requirements do not have to be in place at this point of time independent of the fact if the cells or the tissue is intended to become starting material of a medicinal product at later stage or not. This has to be kept in mind concerning the responsibilities of the Qualified Person in this regard. The Qualified Person is not responsible for the donation, procurement and testing of tissue and cells being "sourcing material" for the manufacturing of ATMP as this is laid down in specific Directives outside pharmaceutical law. The main difference is that instead of GMP requirements the requirements of "good practice" according to Directive 2004/23/EC and Directive 2007/16/EC applies. If ATMP should be included in this Draft this has to be reflected when defining the responsibilities of the Qualified Person in case of ATMP. It would be necessary to consult the CAT in this regard." Proposed change: „ A declaration is not required for blood components; they are subject to the requirements of Directive 2002/98/EC. In addition, a declaration is not required for Advanced Therapy Medicinal Products according to Regulation (EC) 1394/2007 as the provisions for these products are very specific."	
Part 2. Regulatory	3	Comment: An audit of the active substance manufacturing site by or on behalf of the MAH without a	The comment is acknowledged, but addressed though GMP

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
basis line 62		detailed audit report is insufficient to make the signed declaration credible. The report should be sufficiently descriptive, and it must not only list the deficiencies observed during the audit. The report should explain in detail *how* an active substance manufacturer is conducting his activities to meet the EU GMP Part II requirements, in order to allow the QP to judge whether the API manufacturer is essentially in compliance with the EU GMP Part II. The requirement for a *detailed* report would also exclude "pseudo-audits" (e.g. 1-day "visits") that do not allow the QP an appropriate assessment of GMP compliance. This should be made clearer in the wording in line 62 as is given below. Proposed change: …based upon **a sufficiently detailed audit report resulting from** the direct audit of the active substance manufacturers....	guidance.
Part 2. Regulatory basis line 62	**7**	Direct audits may not always be possible, e.g. in case of applications for new marketing authorisations a supplier audit typically takes place after the authorisation is obtained	Compliance with API GMP is necessary before regulatory applications are submitted and should be by on-site audit.
Part 2. Regulatory basis line 62	**15**	Comment: An audit of the active substance manufacturing site by or on behalf of the MAH without a detailed audit report is insufficient to make the signed declaration credible. This should be made clearer in the wording on line 62 as is given below Proposed change: based upon a detailed audit report after the direct audit of the active substance manufacturers	Acknowledged, addressed by GMP guidance
Part 2. Regulatory basis line 62	**24**	Comment: MAH manufacturing authorisation holder or marketing authorisation holder Proposed change (if any): list all abbreviations	All abbreviations are first spelled out in the text.
Part 2. Regulatory basis line 63	**15**	Comment: The existing wording implies that an audit should be carried out by suitably trained and experienced person (SINGULAR) It is suggested that the wording here should reflect the fact that an audit may be carried out by more than one person	Agreed

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change **suitably trained and experienced person**(s)	
Part 2. Regulatory basis line 65	**15**	Comment: As has been explained in EMA Q & A guidance documents "GMP certificates from a relevant Competent Authority cannot replace direct audits, but the results of such inspections may be used …. in a risk-based approach". This statement however does not cover the situation where the representatives of a Competent Authority have refused to issue a GMP Certificate; on the contrary, they have determined that the site manufacturing the active substance is NOT in compliance with GMP, (e.g. GLOCHEM in India). Nevertheless MAHs, based in the fact that THEY have the responsibility to determine if the site is in compliance with GMP, are ignoring the findings of the authorities and are continuing to use active substances manufactured at the site in question (e.g. Amlodipine besilate from GLOCHEM). These findings by the Competent Authorities or the EDQM must have a greater weighting in the "risk-based approach" mentioned above Proposed change: GMP Certificates from a relevant Competent Authority cannot replace direct audits. But the results of such inspections may be used ……in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active substance suppliers. However if representatives of a Competent Authority or the EDQM have determined that the active substance manufacturer is NOT in compliance with EU GMP Part II then this alone is sufficient to overrule any audit findings made by the MAH holder or his representative(s) or any third party. Hence active substance from this site may not be used in any MP marketed in Europe until the Competent Authorities or the EDQM have determined that the site is now in compliance	API manufacturing sites, which have been inspected by an EU Competent Authority and found GMP non-compliant, should not be used as sources of API.
Part 2. Regulatory basis	**6**	Comment: It is still general and widespread practice, that audit reports provided by parties considered to exhibit a considerable conflict of interest such as brokers, traders, repackers, relabellers,	Conflicts of interest are addressed in GMP guidance.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 62-65		micronisers and importers are accepted to substantiate the QP GMP declaration. Proposed change (if any): **The QP Declaration should be based upon the direct audit of the active substance manufacturers, by or on behalf of the MAH, by a suitably trained and experienced person, which may be a third party contractor[5, 6].** **General principles applying for contracting such outsourced activities are laid down in Chapter 7 of the EU GMP guide.** **Parties involved in the supply chain of the active substance such as brokers, traders, repackers, relabellers, micronisers and importers are explicitly not considered as being suitable third party contractors.**	Simply put, auditors should either be first party or third party contractors.
Part 2. Regulatory basis line 65	**3**	Comment: As has been explained in EMA Q & A guidance documents "GMP certificates from a relevant Competent Authority cannot replace direct audits, but the results of such inspections may be used …. in a risk-based approach". This statement however does not cover the situation where the representatives of a Competent Authority have refused to issue a GMP Certificate; on the contrary, they have determined that the site manufacturing the active substance is NOT in compliance with GMP (e.g. GLOCHEM in India). Nevertheless MAHs, based on the fact that *they* have the responsibility to determine if the site is in compliance with GMP, are ignoring the findings of the authorities and are continuing to use active substances manufactured at the site in question (e.g. Amlodipine besilate from GLOCHEM). These findings by the Competent Authorities or the EDQM must have a greater weighting in the "risk-based approach" mentioned above. Proposed change: **Add** However, if representatives of a Competent Authority or the EDQM have determined that the active substance manufacturer is not in compliance with the EU GMP Part II then this alone is sufficient to overrule any audit findings made by the MAH or his representative(s) or	API manufacturing sites, which have been inspected by an EU Competent Authority and found GMP non-compliant, should not be used as sources of API.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		any third party. Hence active substances from this site may not be used in any medicinal product marketed in Europe until the Competent Authorities or the EDQM have determined that the site is now in compliance.	
Part 2. Regulatory basis line 65	24	Comment: GMP certificates from EMA/EU authorities audits should be sufficient for the QP to use and base its QP Declaration on. Proposed change (if any):	Not accepted. Compliance of API GMP is the responsibility of the MIAH and should be ongoing and by repeated audits – see GMP guidance
Part 2.1 GMP compliance Lines 62 & 65	17	Comment: - Proposed change: **A definition of the term "direct audit" should be given.**	"direct audit" to be replaced by "on-site audit"
Part 2. Regulatory basis lines 65-67	17	Comment: A GMP certificate is an internationally accepted quality standard for manufacturers of medicinal products and active substances. Therefore it should be allowed to be listed in the "official" documentation. Proposed change: GMP certificates from a relevant Competent Authority ~~cannot replace direct audits, but the results of such inspections~~ may be used, together with ~~other~~ supporting information, in a risk-based approach by the manufacturer in establishing priorities for its own audit programme of active substance suppliers	Not accepted, as discussed above.
Part 2. Regulatory basis lines 66	7	"together with other supporting information" To be deleted, a GMP certificate from an Authority should be sufficient without additional information/ justification	Not accepted, as discussed above.
Part 2. Regulatory	20	Comment: it should be clear that a risk based approach to audit priorities is acceptable in lieu of an	Not accepted – that the period of validity should be no longer

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
basis lines 65,66, 67		actual audit. Time periods in between audits may exceed the standard 3 years based on risk. Proposed change (if any):	than three years is a standard of good practice. Deviations from this should be exceptional, and on a case-by case basis.
Part 2. Regulatory basis lines 69-73	**17**	Comment: The reference made to the EU GMP Guide does not lead to a comprehensive definition of the term “critical raw material”. Proposed change: A definition of the term “critical raw materials” should be given.	With respect to API synthesis, GMP compliance should be in place from the designated starting material. The term “critical raw material” to be replaced with “designated starting material”. The following text has been included: *“It is acknowledged that the of suppliers of designated starting materials and other critical raw materials (as defined in Part II of the EU GMP Guide 7.11, 7.13) may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer’s quality system for starting materials.”*
Part 2. Regulatory basis lines 68 – 82 (and Part A of the template lines 333 – 334)	**9**	Comment: It is not fully clear what is the starting point of the API supply chain. In the introduction explanation section 2.2, it is specified that *"The supply chain is a ……tracing its history or supply chain from critical raw material(s) used in the manufacture of the active substance to the manufacturer of the dosage form. The sites will include manufacturers of critical raw materials (as defined in Part II of the EU GMP Guide 7.11, 7.13), active substance manufacturers, ……..and importers"* In the QP declaration itself, Part A, the GMP compliance is committed to check from the registered starting material for API manufacture *“List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material."* Proposed change (if any): The Q and A wording (lines 65-66) is very precise regarding the API sites that need to be subject to the QP declaration, and this wording should be used in the template itself	
Part 2. Regulatory basis lines 69 - 73	**3**	Comment: It may be rather difficult for the MAH to draw up such a supply chain if the manufacturer of the active substance holds a Certificate of Suitability from the EDQM as this was designed “to protect the commercial interest of the active substance manufacturer” who may thus be	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		unwilling to disclose certain information e.g. the sites where critical raw materials are manufactured. If the disclosure of such information by the API manufacturer would be mandatory in each case, this would also undermine the ASMF procedure where confidential information may be included in the restricted part at the API manufacturer's discretion. Furthermore, the raw materials themselves, whether critical or not, do not need to be manufactured under GMP. The GMP portion of the active substance synthesis starts with the introduction of the API starting material(s) in the process. Proposed change: The supply chain is a family tree for the active substance tracing its history or supply chain from **the introduction of the** critical raw material(s) ~~used~~ in the manufacture of the active substance to the manufacture~~r~~ of the dosage form. The sites will include ~~manufacturers of critical raw materials (as defined in Part II of the EU GMP Guide 7.11, 7.13),~~ active substance manufacturers, brokers, traders, repackers, relabellers, micronisers and importers.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 2. Regulatory basis lines 69 - 73	**7**	The demand to start the supply chain with critical raw materials of the active ingredients is not justified. Indeed, it is an important task for a dosage form manufacturer to evaluate the compliance of the active ingredient manufacturer with chapter 7.1 "general controls" (Part II of the EU GMP Guide) within audits. But this should remain a system check, instead of recording all suppliers of critical raw materials. One must consider that usually several raw materials are classified as critical, which can be supplied each by different approved suppliers again. The supply chain should start with active ingredients instead of critical raw materials.	Discussed above.
Part 2. Regulatory basis lines 69 - 73	**10**	Comment: *'[…] the supply chain from critical raw material used in the manufacture of the active substance to the manufacturer […]'* The term 'Critical raw materials' does not have a commonly agreed definition.	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The reference given to Part II of the EU GMP guide does not help clarifying the meaning. This sentence does not address who should be responsible for the determination and assessment of the criticality of a raw material or the expectation related to how the assessment should be performed. In order to avoid divergence in interpretation, we strongly recommend a harmonised definition of expectations upfront. In addition, although article 46a of Directive 2001/83/EC as amended foresees the need for API supply chain traceability, there exists no specific legal basis requiring systematic audits of critical API starting materials by the MAH/manufacturer of the final medicinal products. Proposed change (if any): We recommend that the text be changed to clarify that the risk assessment and criticality assessment of raw materials should be determined by the direct user/sourcer, e.g. the API manufacturer for critical API starting materials. The indirect user (eg FP manufacturer) should be responsible to audit and verify that the API manufacturer's quality system is able to ensure a continuous level of compliance of its sub-contractors.	Discussed above.
Part 2. Regulatory basis lines 69 – 75	**8**	Comment: Lines 71-73 cite the manufacturers of the critical raw materials (to be understood as DMF starting materials: restricted information) to be part of the supply chain. Lines 74-75 cite that verification of the availability of the supply chain form forms part of the QP Declaration. This means that names of the manufacturers of critical raw materials (API restricted information) would be disclosed to the QP. Lines 76-78 assign the MAH the responsibility to maintain the supply chain traceability available for inspection; so the restricted information would also be disclosed to the MAH.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Line 71-73: The sites will include active substance manufacturers *(excluding the manufacturers of the DMF starting materials)*, brokers, traders, repackers, relabellers, micronisers and importers. *Additional Comment: the proposed change will be in line with the wording of Lines 333-334.*	
Part 2. Regulatory basis Line 70	**1**	**Comment:** The term *"critical raw materials"* is not clearly defined. In lines 81 and 334, it is referred to the "active substance starting material". It would be preferred to use the wording "critical active substances starting material " throughout the document to be clearer. **Proposed change (if any):** "The supply chain is a family tree for the active substance tracing its history or supply chain from critical **active substance starting material(s)** ~~raw material(s)~~ used in the manufacture of the active substance to the manufacturer of the dosage form.	See discussion above
Regulatory basis Line 70-71	**9**	Comment: Although reference is given to Part II of the EU GMP guide, there is no common agreed definition of "critical Raw Material". Furthermore it is not clear whether *'critical raw material'* and *'active substance starting material'* should be considered as identical or whether these are different. Proposed change: Include definitions for *"critical raw material"* and *"active substance starting material"* in a glossary.	discussion above
Regulatory basis Line 70-71	**11**	Comment: The term "critical raw material", albeit in use in Part II of the GMP, gives rise to the issue of risk assessments to establish whether a raw material is critical or not. Proposed change (if any): The term "critical raw material" would be better replaced with "active ingredient starting material".	Discussed above.
Regulatory basis	**9**	Comment: Clarification is requested as to whether an audit would be required to cover the registered API manufacturing site and any 'part process' sites only, or also e.g. brokers, re-	Discussion above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 74-75		labellers and distributor storage sites. Proposed change (if any): Supplier chain traceability should be established and documented by QP of the medicinal product during audits performed at the API manufacturer. The QP relies on audits performed by the API manufacturer at its critical raw material suppliers. This should be documented in Quality systems and Quality agreements and available for GMP inspection.	
Regulatory basis Line 74-75	**15**	Comment: The requirement that the supply train should be established and documented is laudable requirement to ensure that the active substances used in MP in the EU are in compliance with the MA. However it may be rather difficult for the MAH to draw up such a supply chain if the manufacturer of the active substance possess a Certificate of Suitability from the EDQM as this was designed "to protect the commercial interest of the active substance manufacturer" who may thus be unwilling to divulge certain information e.g. the sites where critical raw materials are manufactured. It is also important that a check is made between the supply chain actually used by the active substance manufacturer and the supply chain as understood by the Qualified Person It is therefore suggested that the wording of lines 74 and 75 be amended to reflect these difficulties. Proposed change:This supply chain should be established**,** ~~and~~documented **and submitted as an Appendix to Part D of the "QP Declaration".** ~~Verification of the availablility of this forms part of the QP Declaration (Part D).~~ Comment: The last sentence can now be deleted as a submission with the QP Declaration is evidence that the supply chain is documented.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Regulatory basis Line 74-75	**17**	Comment: The verification of the supply chain should be part of the supplier qualification and be described in the EU GMP Guide, but should not be subject to the QP declaration. Proposed change: This supply chain traceability should be verified during direct audits ~~established and documented~~	Confirmation of supply chain traceability has been deleted - to be addressed through GMP

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Regulatory basis Line 74 and 233	**11**	Comment: It would be better to state more specifically that the traceability is to be extended backwards to the suppliers of the critical raw materials (active ingredients starting materials), in agreement with the requirements described in Par 6.30 of Part II of the GMP. Moreover, with regards to the supply chain verification and documentation, it is not clear whether an inspection is also to be extended to brokers, traders, repackers, relabellers, and importers. Finally, how is the supply chain traceability is expected to be documented. Would a presence of Technical Agreements (in compliance with GMP) with all sites (or actors) of the supply chain be sufficient ? Would a declaration of the QP on this basis be acceptable, as a documentation to be produced ?	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Regulatory basis Line 76	**7**	"Supply chain traceability is considered a matter of GMP": this kind of traceability is not defined in the EU-GMP guideline. The EMA document should not define GMP matters.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Regulatory basis Line 77	**15**	Comment: Supply chain traceability needs to be kept up to date in compliance with the Commissions Regulations or variations. Thus in spite of initially submitting the supply train as an appendix to Part D of the QP declaration it still should be made available for inspection including any changes to the supply chain since this was submitted as an Appendix to Part D of the QP Declaration Proposed change: This should be ~~made available~~ kept up to date and be maintained, together with the audit report(s), for inspection at the request of the competent authorities.	Confirmation of supply chain traceability has been deleted - to be addressed through GMP
Part 3 Format and	**8**	Comment: Lines 89-92: clarification should be given to the term "manufacturer" (e.g. Dosage Form	This is the MIAH, not the API manufacturer.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Guidance Line 89-92		manufacturer?) Proposed change (if any):	The text has been changed accordingly.
Part 3 Format and Guidance Line 94	**9**	Comment: As for line 41, indicate that not all variations require a declaration. Proposed change: ***relevant*** variation, renewal.....	Agreed
Part A General Lines 101-130 Lines 320-334	**17**	Comment: Requesting the QP declaration for the active substance beginning with the introduction of the designated active substance starting material would have following consequences: • The QP would have to assess complex chemistry of synthesis of Active Pharmaceutical Ingredients (APIs) or even more complex production in case of semi-synthetic substances from purified extracts or fermentation. There are very few experts that have such a broad knowledge. • For not in-house produced APIs, current practise approved by EMA is to refer to an ASMF in a submission. The MAA has only access to the open part. The information requested in the QP declaration, e.g. building numbers of API synthesis, is in most of the cases even not contained in many closed parts and is never found in the open part of an ASMF. Therefore, the proposed draft would request a complete change of the current ASMF system. • In many cases of out-sourced contract manufacturing & release of the drug product, the draft would mean that the QP of the contract manufacturer would have to control the client company (who supplies the API). Proposed change: • Certification should be limited to the active substance manufacturing site involved in the last quality relevant manufacturing step, but not beginning with the introduction of the designated active substance starting material. • It should be the responsibility of the active substance manufacturing site(s) to ensure that GMP is applied with the introduction of the designated active substance starting material.	This is not accepted – GMP should be in place from the introduction of the designated starting material in the API manufacture. This is not accepted. The open part gives a summary of the synthesis from the designated starting material. Building numbers can sometimes be essential to correctly identify the site of manufacture for large sites and the full address needs to be included in the DMF and application form. The API manufacturer is responsible for ensuring GMP is in place for all manufacturing

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The responsibility of the Manufacturing/ Importation/ Batch Certification States regarding supplier qualification should be limited to the Active Substance Manufacturing Site that is involved in the last quality relevant manufacturing step. • The description of the manufacturing and distribution route of the active substance from the first starting material to the final active substance as delivered to the Marketing Authorization Holder should be part of the ASMF. • Compilation of Active Substance Manufacturing Sites, Finished Product Manufacturing Site(s) and Importation and/or Batch Certification Sites with or without linkage should only be required once, either in Part A or B. In cases where the Finished Product Manufacturing Site is the Releasing Site and a statement of every Releasing Site is provided, a compilation of the Active Substance Manufacturing Sites per Releasing Site should be sufficient.	steps. The MIAH is responsible for confirming this is the case by on-site audit of all steps. Incorrect – the description should be from the designated starting material. The template has been simplified. It is possible for the declaration to be signed by a lead QP.
Part A lines 107-108 and throughout document	**9**	Comment: “All proposed active substance/……..sites” (Plural) whereas in the Q&A document (lines 69 – 70) is stated “Only those manufacturing sites to be registered and used as sources of the API need be subject to the QP declaration. Proposed change: Please change wording in the Q&A document.	Agreed, the text to be revised as necessary
Part A lines 105, 324, 331	**18**	Comment: The word "function" is not defined. Proposed change (if any): It should be made clear what the meaning of "function" is. What are the expectations on the description of "function"? Maybe examples should be given.	Accepted – “function” has the same as meaning as that seen in the MAA form – it is the manufacturing activity of that site. The term will be revised to “manufacturing activity/function.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A lines 107-108 and throughout document	**10**	Comment: "All proposed active substance/……..sites" (Plural) whereas in the Q&A document (lines 69 – 70) is stated "Only those manufacturing sites to be registered and used as sources of the API need be subject to the QP declaration. It is to be noted that in the normal course of manufacturing operations, the industry generally needs a back-up solution for API sourcing to guarantee and secure continuous supply of the medicinal product and limit the risk of shortages (i.e. in the event of a supply of quality issue with a single API source, any new source would need first to be registered – Type IB or II – and only after approval would medicines be available). We strongly recommend that this flexibility should be kept provided the necessary auditing of GMP compliance has been performed and documented. Proposed change (if any): Please change the wording in the Q&A document so that the notion of "alternative/back-up supplier" is kept under the express condition that the necessary audit has been performed.	Accepted. All registered API sites should be subject to QP on-site audit and supported by a QP Declaration.
Part A lines 107-116	**24**	Comment: Can the text be simplified because the decision tree is clear. Can the repetitions be deleted? Is batch certification site the batch release site or not? Can this be clarified? Proposed change (if any): Simplify the text.	Template has been simplified.
Part A lines 117-119	**3**	Comment: Reference is made to our comments on line 65. Proposed change: These lines should either be deleted entirely or re-written as follows: "Note: According to the variation classification guideline, currently approved active substance manufacturing site(s) **which have not been refused a GMP certificate by a Competent Authority or have not had their Certificates of Suitability suspended by the EDQM and** for which valid QP declaration(s)…"	See comment under line 65
Part A lines 117-119	**15**	Comment: It is recommended that these 3 lines be deleted completely. If the manufacturing site is not listed this would condone the continuing use of an active	The concern is acknowledged, but Competent Authorities

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		substance manufacturing site even after the authorities had determined this site was not in compliance with GMP and no one (apart from the QP) would know that a new active substance was being obtained from this suspended or even deleted site Proposed change: **DELETE COMPLETELY** ~~**"Note: According to the variation classification guideline currently approved active substance manufacturing site(s) for with a valid QP declarations are in place need not be listed in the table provided**~~ **ALTERNATELY MODIFY THE WORDING as BELOW**: "Note: According to the variation classification guideline, currently approved active substance manufacturing site(s) which have not been refused a GMP certificate by a Competent Authority or have not had their Certificates of Suitability suspended by the EDQM and for which valid QP declaration(s) are in place need not be listed in the table provided.	would be aware of all previously approved sites and their GMP status if subject to inspection. For variations, a Declaration would be required only for the new site. Discussed above, proposed amendments not accepted.
Part A lines 120- 127	**10**	Comment: Line 120 states that all currently registered active substance manufacturing sites may be added …then in line 127 it states all 'redundant' sites should be deleted from the MA. See also "Line 107-108" comment above. It is important to clarify upfront the meaning of "redundant sites". Impact on medicines availability should not be underestimated and the common existence of complicated supply strategies acknowledged. Proposed change (if any): Please define 'redundant site'. Please ensure that the notion of "alternative/back-up supplier" is kept under the express condition that the necessary GMP audit has been performed	All registered API sites should be subject to QP on-site audit and supported by a QP Declaration.
Part A line 127	**24**	Comment: Can this line be deleted? It seems to have no added value? This is covered by the variations process and has no value related to the QP declaration form. Proposed change (if any):	Discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A lines 127-129	**9**	Comment: 'Sites that are considered redundant should be deleted from the MA'. Although we understand and agree on the general principle, we underline that this may cause practical issues on medicines availability considering complexity of existing supply chain Proposed change (if any): Definition of "redundant" site. Suggest adding: "Sites that are considered redundant should be deleted from the MA, unless a justification is provided in the QP declaration." It is recommended to introduce the notion of alternative supplier providing that the required regulatory and GMP conditions are met.	Text has been simplified.
Part A lines 129	**3**	Comment: "Should" could be misinterpreted as optional which is not at all desirable in this case. Proposed change: Replace "should" by "**must**".	The term "should" has sufficient imperative force.
Part A lines 129	**15**	Comment: The use of the word "should" suggests almost that this requirement may be optional. This should not be the case. Proposed change: DELETE "~~should~~" and replace with "must	The term "should" has sufficient imperative force.
Part A i.e. lines 101- 130 and lines 333-334	**1**	**Comment:** Requesting the QP declaration for the active substance *beginning with the introduction of the designated active substance starting material* exceeds GMP requirements and would have the following consequences: • For not in-house produced APIs, current practice approved by EMA is to refer to an ASMF in a submission. The applicant only has access to the open part. The information requested in the QP declaration, e.g. building numbers of API synthesis, is in most of the cases even not contained in many closed parts and is never found in the open part of an ASMF.	The comment is incorrect, and has been discussed above. See earlier discussion above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		• In many cases of outsourced contract manufacturing & release of the drug product, the draft would mean that the QP of the contract manufacturer would have to control the client company (who supplies the API) and beyond. • For atypical actives, which are substances used in greater quantities in industrial sectors other than the pharmaceutical ones, it is close to impossible to obtain the manufacturing details of the substance. • For herbal substances and preparations (and in particular essential oils), it is extremely difficult to risk assess the whole supply chain. In addition, it should be borne in mind that the cultivation, collection and post-harvesting treatment fall under GACP guideline, not GMP. • Certification should be limited to the active substance manufacturing site involved in the last quality relevant manufacturing step, but not beginning with the introduction of the designated active substance starting material. • It should be the responsibility of the active substance manufacturing site(s) to ensure that GMP is applied with the introduction of the designated active substance starting material. The responsibility of the manufacturing/importation/batch certification sites regarding	This is not accepted. The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken. Only in exceptional cases, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation (not the QP template) will need to be submitted according to the guidance document and considered on a case by case basis. Risk assessment is necessary nonetheless – see GMP guidance Not accepted as discussed above Discussed above Not accepted as discussed above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		supplier qualification should be limited to the active substance manufacturing site that is involved in the last quality relevant manufacturing step. **Proposed change (if any):** - Line 331 contains some information that is not considered essential to confirm GMP compliance and should be deleted: o For Active Manufacturing Sites: Address details such as building numbers o "Finished Product Manufacturing Sites: Function(s)" This should hence read: 2 State the site name and address ~~in detail, including the building numbers and function~~ - Lines 333 and 334 should be deleted or modified as follows: "list ~~each~~ **the** site involved in the **last quality relevant manufacturing step** ~~synthesis of the active substance beginning with the introduction of the designated active substance starting material~~" -Lines 321-353: compilation of Active Substance Manufacturing Sites, Finished Product Manufacturing Site(s) and Importation and/or Batch Certification Sites with or without linkage should only be required once, either in Part A or B. In cases where the Finished Product Manufacturing Site is the Releasing Site and a statement of every Releasing Site is provided, a compilation of the Active Substance Manufacturing Sites per Releasing Site should be sufficient. **Overall we very much feel that part A unnecessarily duplicates information already provided in the regulatory dossier and in part B of the QP declaration and hence we apply for shortening part A i.e. keeping the section from line 320 to 324 and deleting the remainder.**	Not accepted as discussed above
Part A line 127 – 128	**7**	"Sites that are considered redundant.." To be deleted, redundancies should be avoided anyhow	Discussed above
Part B 131-174, 335-353	**9**	Comment: - Proposed change (if any): This (including Part C and E) is the main part of the declaration that should be signed by the QP. As multiple declarations are possible, it should be a separate document attached to a	No change is made, but it is accepted that an appropriate

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 171		summary document (Part A), prepared by the MAH/DRA. Comment: "The Applicant is responsible for ensuring that <u>that</u> additional QP declaration forms …Correct typo Proposed change (if any):"The Applicant is responsible for ensuring that additional QP declaration forms …	supplementary MAH cover letter may aid regulatory administration
Part B lines 132	**3**	Comment: Reference is made to our comment on line 62; it should be reiterated here as follows. Proposed change: In this section the QP declares, **based upon a sufficiently detailed audit report in his/her possession,** GMP compliance of the active substance manufacturer(s) and indicates…	Not accepted, discussed above.
Part B lines 132	**15**	<u>Comment</u>: As stated in the general comments the QP declaration should only be made when the QP has in his/her possession a detailed report(s) of the audit carried out at the site(s) of the manufacturer of the active substance(s). This should be emphasised in line 132 as is given below: <u>Proposed change</u>: in this section the QP declares GMP compliance of the active substance manufacturer(s) **based upon a detailed audit report in his/her possession after an audit of the active substance manufacturer(s)** and indicates……..	Not accepted, discussed above.
Part B lines 140-143	**4**	Comment: Is the QP of each MAH responsible of importation and/ or batch certification site(s) of API or of finished product or both? It should be convenient specify this point. Proposed change (if any): for instance if referred to API: The QP of each Manufacturing Authorisation holder responsible for importation / batch	A QP Declaration is only required from each EU MIAH site that use the API to manufacture a drug product or the batch release site.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		certification *of active substance* when the importation / batch certification site is a different site from the above. This is because the QP responsible for importation / batch certification takes overall responsibility for each batch.	
Part B lines 142	**10**	Comment: This section addresses the QP responsible for importation and batch certification taking overall responsibility. There is a distinction between importation and batch certification and this should be made clear in the text. It can well happen that a site is not currently a batch certification site as certification of imported product takes place in a different site. Accordingly, the QP named on the import license is distinct from the certifying QP. We would like to refer to the EMA questions and answers on annex 16 as it makes this distinction clear: *"However, as before, the Qualified Person performing final certification before release holds overall responsibility for manufacture of the batch in accordance with GMP and the Marketing Authorisation."* Proposed change (if any): Please amend this section to ensure consistency with existing Q&A.	A QP Declaration is only required for each EU MIAH site that use the API to manufacture a drug product or the batch release site. A lead QP is possible, in the case of multiple MIAH(s) it should be declared that : The declaration is made on behalf of all the involved QPs and that a documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.
Part B i.e. lines 131-174 and lines 335-353	**17**	Proposed change: This (including Part C and E) is the main part of the declaration that should be signed by the QP. As multiple declarations are possible, it should be a separate document attached to a summary document (Part A), prepared by the Marketing Authorisation Holder (MAH)/Drug Regulatory Affairs (DRA).	No change is made, but it is accepted that an appropriate supplementary MAH cover letter may aid regulatory administration
Part B Line 156	**13**	Comment: In the case of a drug product which is manufactured under contract by several third party manufacturers, each with their own QP who releases product from that site, a separate QP, acting on behalf of the MAH, may be named on a Manufacturing Licence of a site not involved with the manufacture of that particular product.	Yes, as discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Is it permissible for that QP to provide the single declaration covering all relevant sites? Proposed change (if any):	
Part B ii 2 **Lines 171 - 173**	**9**	In case of multi Drug Product manufacturing sites, including sub-contractors, the MAH may sign the QP declaration on behalf of its manufacturing sites. This is very important when a Drug Product is manufactured by a sub-contractor, and the API is purchased by the MAH. As the MAH audit report is not normally communicated to sub-contractors due to confidentiality agreements with the API supplier, this paragraph may allow the MAH to endorse the responsibility of API GMP compliance, without communicating full audit report and corrective action to the QP of the sub contractor drug product manufacturing site who releases drug product batches. Proposed change (if any): This should be described as an acceptable practice in the Q&A section	For the MAH to act as the lead QP, it will need be a MIAH and be a registered site.
Part C **lines 175-229** **Lines 354-397**	**17**	Comment: A Quality Assurance Agreement (QAA) between the finished product manufacturer and its API supplier gives the finished product manufacturer a right to audit the API supplier. However, in most of the cases the API supplier is not carrying out the full synthesis, but is sourcing advanced intermediates from other chemical companies. To our knowledge in the real world industry there are no reach-through clauses in any contracts with API suppliers and therefore the product manufacturer has no right to audit the suppliers of API suppliers. In the draft it is asked to establish such contractual relationships along the supply chain which would tenfold increase the number of contracts. As already stated above GMP certificate(s) issued by European Economic Area (EEA), Mutual Recognition Agreement (MRA) partners or other recognised authority should not be listed as optional supplementary information. These internationally accepted quality standards should	This has been discussed above. GMP needs to be in place from the designated starting material to the finished API. It this involves more than one API

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		be part of the "official" documentation. Proposed change: • As described above, qualification incl. audits should be limited to the active substance manufacturing site involved in the last quality relevant manufacturing step. • Another section (v) should be introduced so that the content of section (iv) can be split into the new sections (iv) and (v). Section (iv) should contain documentation on GMP certificate(s) issued by EEA, MRA partners or other recognised authority as "official" part of the documentation and section (v) should be in place for other supplementary supportive information	site, then all will require to be subject to an on-site GMP audit by the QP and supported by a QP Declaration. Not accepted. Not accepted as EU GMP certificates are supportive, as discussed above.
Part C lines 178-179	**3**	Comments: Reference is made to our comments on lines 62 and 132; this should be emphasized here as follows. Proposed change: ….substance(s) used are manufactured in accordance with GMP through **sufficiently detailed audit reports resulting from** direct audit of the active substance manufacturer(s)[5]	Discussed above.
Part C lines 178	**15**	Comment: As stated above, the required assurance that the active substance(s) used are manufactured in accordance GMP is only available after a direct audit of the active ingredient manufacturer together with a detailed audit report This should be emphasised in line 178 as is given below: Proposed change: …. are manufactured in accordance with GMP though a detailed audit report drawn up after a direct audit of the active substance manufacturers(s).	Addressed through GMP guidance
Part C i.e. lines 175-229 and lines 354-397	**1**	**Comment:** A Quality Assurance Agreement between the finished product manufacturer and its API supplier gives the finished product manufacturer a right to audit the API supplier.	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		However, in most of the cases, the API supplier is not carrying out the full synthesis, but is sourcing advanced intermediates from other chemical companies. There is no statutory obligation for the supplier of API to reveal its own pre-suppliers hence there are no reach-through clauses in any contracts with API suppliers and therefore the product manufacturer has no right to audit the suppliers of API suppliers. In the draft it is asked to establish such contractual relationships along the supply chain which would tenfold increase the number of contracts and may not be possible in all cases. **Proposed change (if any):** - As described above, a note should be added to indicate that qualification including audits should be limited to the active substance manufacturing site involved in the last quality relevant manufacturing step. - "audit report(s) and other documentation" should be summarised by "documentation" on lines 186-187 and 360-361 to read: - Lines 186-187: "*part C includes tick boxes that should be completed as confirmation that ~~audit reports and other~~ documentation pertaining to the audit ~~are~~ **is** available for inspection by the Competent Authorities*". - Lines 360-361: "*~~Audit reports and other~~ documentation relating to the audit(s) of the active substance manufacturers(s) listed in Part A ~~are~~ **is** in place and will be made available for inspection by the Competent Authorities if requested."*	This has been previously discussed. This has been previously discussed. Not accepted, as discussed above.
Part C Line 186	**15**	Comment: The confirmation requiring that audit reports are available should be strengthened to state that the audit reports explains how the site audited site complies with more than 75% of the requirements of the EU GMP Guide Part II. Proposed change: PART C includes tick boxes that should be completed as confirmation that **detailed** audit reports **explaining how the audited site is in compliance with more than 75% of the requirements of EU GMP Part II** and other documentation pertaining to the audit are	Addressed through GMP Guidance The template has been revised such that the QP is to declare that: manufacture of the API is in accordance with the detailed guideline on good

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		available …….	manufacturing practice, based on an audit of the active substance manufacturer(s), and that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice
Part C General Line 186-193	**17**	Comment: "Group audits" are not mentioned, although they are included in the table of Part C below line 368. Proposed change:"Group audits" should be explicitly included in lines 186-193.	Text has been significantly revised to improve clarity.
Part C Lines 186/187	**2**	**Comment:** these lines confirming that audit reports and other documentation pertaining to the audit are available for inspection by the Competent Authorities should be deleted. Internal audit reports are not routinely made available during inspections by the authorities. Even if this will not be done on a routine basis according to the "*Draft Q&A on the template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template*" question 13, it should not be implemented as a standard requirement in the QP declaration template. There might be situations where it is appropriate to show an audit report to an authority, but it should not be requested as a standard requirement	This is not accepted – all reports should be available for inspection, if requested to support claims of a satisfactory quality system and GMP compliance
Part C Lines 186/187	**17**	Comment: It is common agreed practice not to routinely make internal audit reports available during inspections by the authorities. Therefore this statement should be changed here and in lines 361/362 as well. Proposed change: PART C includes tick boxes that should be completed as confirmation that ~~audit reports and other~~ documentation pertaining to the audit ~~are~~ is in place. ~~available for inspection by the Competent Authorities.~~	see above Not accepted.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part C Lines 186/187	**19**	Comment: It is a commonly agreed practice not to routinely make internal audit reports available during inspections by the authorities. Proposed change (if any): The statement should be deleted here and in lines 361/362 as well.	see above
Part C Lines 186/187	**20**	Comment: The statement should be deleted: It is common agreed practice not to routinely make internal audit reports available during inspections by the authorities. Therefore this statement should be deleted here and in lines 361/362 as well. ***Rationale:*** Otherwise such requirement might trigger a process of parallel audit reports: one for the official part to show during inspection and in parallel a second one used internally, something that would not add any value for any involved party. Proposed change: Documented evidence and summary reports must be on hand for conformation that audits have been conducted. Detailed reports must not be made accessible during inspections by the Competent Authority.	see above Not accepted.
Part C Lines 175-229 and lines 354-397	**1**	**Comment:** Audits are the most effective tool for verifying GMP compliance of manufacturers and suppliers; however, it should be sufficient to have any information related to audits conducted by the MAH available on site (i.e. the site which is responsible for the qualification of the material manufacturer and supplier). In addition, audits are conducted regularly, whereas the QP declaration would only refer to the last audit conducted before issuance of the declaration. The requirement to conduct periodical audits can only be verified during authority inspections. This is in line with the requirements drafted in the update of chapter 5 of the EU GMP requirements. The required documents include audit reports, qualification of auditors, qualification of third	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		party auditors, where applicable, contracts, justification of audit frequencies, etc. The submission of these detailed documents would represent an unnecessary regulatory burden for both the applicant and the authority. Most of Part C should be held internally and be available for review by competent authorities during inspections. **Proposed change (if any):** Requirements should be described in the document for the basis of the declaration, but not be submitted with the declaration hence **this part should be limited to the first paragraph (line 355 to 362), the remainder (i.e. line 363 to 397) should be deleted.**	Not accepted.
Part C lines 188-193	**7**	***Section (i) audit conducted by Manufacturing Authorisation holder(s)*** In the early phase of the registration procedure this requirement will cause a significant delay of the process. 1. An audit of the active substance manufacturer may not possible during this early phase because · only small amounts of the active substance are being produced; therefore, the used equipment may be different (pilot batch) the production of the pilot batch(es) may be carried out in other manufacturers sites 2. It is rather unlikely that the active substance manufacturer will accept audits at this early stage.	Discussed above, not accepted. The requirement to submit a QP Declaration is not new.
Part C lines 188-193	**10**	Comment: The acceptance of Group audits is mentioned in part C of the template however it is not fixed in the text. This is a particularly important approach for Quality organisations operating on a global scale. Proposed change (if any): "…that have been audited by the Manufacturing Authorisation holder **or corporate representative, within the same group of companies** and the date…."	The guidance text has been significantly changed.
Part C line 193	**20**	Proposed change: Such as risk based approach in case the audit frequency exceeds 3 years.	Not accepted, this should be on a case by case basis that

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			cannot be generalised.
Part C lines 188 and 369,375	**9**	Comment: A fixed audit frequency of three years does not consider the principles of ICH Q 9. The audit frequency should be defined on a risk-based approach. Proposed change (if any): …….The table provided is completed to state those active substance manufacturing sites that have been audited by the Manufacturing Authorisation holder and the date of the last audit. The audit frequency or extension beyond 3 years between audits should be defined on a risk-based approach.	Not accepted, this should be on a case by case basis that cannot be generalised.
Part C Line 188	**13**	Comment: Some manufacturers will manufacture both drug substance and drug product at the same facility. Therefore the audit of API manufacturer by the manufacturing authorisation holder will be a self inspection. The structure and language used would imply that this would typically be an external audit.	The guidance text has been significantly amended. In the case where the API manufacturer and the MIAH are within the same group of companies then Chapter 9 of the GMP Guideline "Self Inspection" should be followed.
Part C lines 189-190	**3**	Comment: Reference is made to our comments on lines 62, 132, and 178-179. Proposed change: …has conducted a direct audit of the active substance manufacturer(s) **and has written a sufficiently detailed report describing/explaining the active substance manufacturer's activities and processes to ensure compliance with the EU GMP Guide Part II.**	This is addressed in GMP guidance
Part C lines 189-190	**15**	Comment: The fact that the MAH (or corporate representative(s) of the MAH within the same group of companies) has conducted a direct audit of the active substance manufacturer should be strengthened with the requirement that there is a detailed written audit report of the site. This requirement would eliminate one day "visits" to the site by a QP (or local "corporate	Discussed above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		representatives") as in one day it is impossible to determine if the site truly is in compliance with a majority of the EU GMP Part II requirements Proposed change: Section (i) indicates that the MAH (or corporate representative(s) of the MAH**)** has (have) conducted a direct audit of the active substance manufacturer(s) and has written a detailed report explaining how the active substance manufacturer has demonstrated that it is in compliance with EU GMP Part II	
Part C lines 189-193	**9**	Comment: The acceptance of "corporate representative" audit function is mentioned in Part C of the template but not in the text Proposed change (if any):"…that have been audited by the Manufacturing Authorisation holder or corporate representative, within the same group of companies and the date…."	See discussion above.
Part C Lines 192-193	**1**	**Comment**: The justification of the audit frequency should be available at the Manufacturing Authorisation Holder's site. Three years can only be a recommendation, as it is not defined by any GMP regulation. In addition, as outlined in lines 65-67, prioritisation of audits may be done following a risk-based approach. Detailed documents should be available for review during authority inspections at the MAH, but not submitted with the QP declaration. **Proposed change (if any):** Delete this mention	Not accepted, as discussed above
Part C line 192	**11**	Comment: Although one can easily find in the document "Compilation of Community Procedures on Inspections and Exchange of Information" (EMA/INS/GMP/459921/2010 Rev 12 Corr) a reference to a re-inspection frequency of 2 to 3 years, it would be better to mention that re-inspection should also be based on a risk assessment, as per emerging practices in the field. Proposed change (if any):	Not accepted, as discussed above
Part C Lines 192-193	**14**	Comment: The introduction of a 3-year deadline for the re-audit of the manufacturer of the active substance in order to verify compliance with Good Manufacturing Practice seems to be too short term. Taking into account the fact that manufacturers of active substances often have GMP certificates and report any changes in the certificate it must be noted that there is no	Not accepted, as discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		rational justification for the need to audit every 3 years. This period could be extended to at least five years, which would correlate with the adopted state regulations. Proposed change (if any): (…) to be within the last 5 years. Suitable justification should be provided in case the audit frequency 5 years.	
Part C line 195 - 199	**7**	Furthermore, if the a GMP inspection conducted by EEA, MRA partners or other recognised authority was only focussing on the relevant active substance or on active substances manufactured by similar chemical synthesis pathways, this inspection should be regarded as completely equivalent to an audit conducted by a third party. EEA, MRA partners or other recognised authorities are adopting a neutral position and have properly qualified personnel. Therefore we see no reason to downgrade the value of the outcome of such kind of inspection. This circumstance should be described and implemented in section (ii) audit conducted by third party", part C, lines 195 – 199: "Section (ii) indicates that an audit …has been conducted on behalf of the MAH by a suitably qualified third party (contractor) or an inspection by an EEA, MRA partners of other recognised authority has been performed for the relevant active substance and/or for its derivates produced in a similar chemical pathway."	This is not accepted, a GMP inspection is not an ongoing commitment and is usually triggered Discussed above
Part C line 197	**3**	Comment: Reference is made to our comments on lines 62, 132, and 178-179. Proposed change: …by a suitably qualified third party (contractor), **and that the third party has written a sufficiently detailed report describing / explaining the active substance manufacturer's activities and processes to ensure compliance with the EU GMP Guide Part II.** …	Discussed above
Part C	**24**	Comment: what means suitably qualified"?	Having sufficient competence,

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 197		Proposed change (if any):Please clarify	training and experience in the conduct of audits for conclusions to be valid. See GMP guidance
Part C **line 199**	**15**	Comment: As explained in the comments relevant to line 189 & 190, the fact that a third party has conducted a direct audit of the active substance manufacturer should be strengthened with the requirement that this third party has prepared and delivered to the QP of the MAH a detailed written audit report of the site. This requirement would eliminate one day "visits" to the site by local third party "auditors" (as is in fact happening in India and China) because in one day it is impossible to determine if the site truly is in compliance with a majority of the EU GMP Part II requirements. Proposed change: …. relationship to Manufacturing Authorization holders and that the third party has written a detailed audit report explaining how the active substance manufacturer complies with more that 75% of the EU GMP Part II requirements	This has been previously discussed above.
Part C Lines 194-201	**1**	**Comment:** for the purpose of the QP declaration it is irrelevant whether the audit has been conducted by the manufacturing authorisation holder itself or a third party, if the third party has been appropriately qualified. Relevant documentation should be available for review during authority inspections, but not submitted with the QP declaration. **Proposed change (if any):** Delete (ii) and merge with section (i) as follows (new text underlined): **"Section (i) audit(s) of API manufacturer(s) ~~by Manufacturing Authorisation holder(s)~~** Section (i) indicates that the Manufacturing Authorisation holder has ~~conducted a direct~~ audit report(s) of the active substance manufacturer(s) in place. The table provided is completed to state those active substance manufacturing sites that have been audited ~~by the Manufacturing Authorisation holder~~ and the date of the last audit ~~which is expected to be within the last 3 years. Suitable justification should be provided in case the audit frequency exceeds 3 years.~~	The QP Declaration should state who has undertaken the audit The QP Declaration should not include the audit report

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		~~Section (ii) audit conducted by third party~~ ~~Section (ii) indicates that an audit of the active substance manufacturing sites listed in the table provided has been conducted on behalf of the Manufacturing Authorisation holder by a suitably qualified third party (contractor). In this case, information should be provided as to who has conducted any audit(s) as appropriate e.g. third party including their relationships to Manufacturing Authorisation holder.~~ Tick boxes are completed to certify that the contract acceptors are properly qualified and that appropriate technical agreements are in place between the contract giver and acceptor."	
Part C Lines 198	**9**	Suggest to put "*e.g. third party*" between brackets: "*(e.g. third party)*"	This text has been significantly revised
Part C Lines 205	**10**	Comment: Although in principle the provision of "evidence in lieu of audit" seems an excellent idea it appears to contradict the legislation. This approach would definitely be useful in the particular case of periodic re-evaluation of manufacturers (which fits with one of the examples about current travel advice or warnings) but the legislation states the QP declaration (at least initially) is based on audit by the QP /or authorised designate. Line 205 contains the statement that this 'may be acceptable' and therefore individual health authorities 'may' interpret this differently and lead to critical deficiencies. Considering the typically large number of sites in which the generic medicines sector has a presence this could become a major issue. Please see hereafter an extract from EMA questions and answers section: *"The EEA inspectorates are not generally in favour of "paper-based audits" per se as they do not provide the same level of assurance as on-site assessments, but do accept that they have a part to play in a risk-based strategy. They may be particularly applicable when recent positive inspection information is available and where satisfactory audits have been concluded in the past. They cannot replace on-site audits of active substance suppliers but can be a useful interim and temporary measure within the manufacturers audit programme"* The grounds for justification for remote assessment should be left for the applicant to justify.	Acknowledged. The scope of the QP template has been limited - it can only be used when an on-site audit has been undertaken. Only for other exceptional case, e.g. atypical actives, where the QP Declaration is not based on an on-site audit, then other documentation (not the QP template) will need to be submitted according to the guidance document and considered on a case by case basis.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part C Lines 202- 220	**1**	**Comment:** We very much appreciate the reflection of the particular case of atypical actives and other circumstances where remote assessment is made possible.	See above discussion
Part C Lines 202- 220	**7**	Section (iii) evidence provided in lieu of audit This section should be reformulated. In general, a remote assessment should be possible if plausible.	See above discussion
Part C Lines 202-209	**1**	**Comment:** Section (iii): The second sentence of the first bullet point is written as if the given example (travel advice) is the only one to draw on. **Proposed change (if any):** Therefore we recommend to change this bullet point as follows (new text underlined): "remote assessment e.g. based on questionnaires and review of relevant documentation. This may be justified **on specific** ~~on~~ grounds **to be explained by the applicant** ~~of current travel advice provided by the local authorities of the EEA member States.~~	See above discussion
Part C Lines 208	**7**	**"**This may be justified...." This may be**, for example**, justified....	See above discussion
Part C **Line 210**	**13**	Comment: The definition of atypical API is considered to be ambiguous. In the guidance given it indicates that atypical APIs are where dosage form manufacturers are using as active substances materials that are not true API's and where there is difficulty in getting the manufacturer of these starting materials to comply fully with Part II of the GMP Guide. In the manufacture of certain drug products, the drug substance is manufactured in-situ i.e.	See above discussion

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		in a continuous process from the starting materials of the drug substance to the drug product. Clarification is requested in that- would such manufacturing processes be considered atypical. There is an API manufactured but due to the nature of the manufacturing process and short shelf-life of the product the API is not isolated.	
Part C Line 210	**20**	Comment: Does this approach also refer to APIs for advanced therapies?	A QP Declaration is required for all medicinal products.
Part C Line 210	**24**	Comment: "atypical" and "non-traditional" can it be defined or at least some examples to clarify Proposed change (if any):	See above discussion.
Part C Line 211-212	**1**	**Comment:** We appreciate that in special other situations which are applicable to Atypical Actives (e.g. essential oils), evidence in lieu of an audit can be provided. **Proposed change (if any):** In order to take the specific situation of Atypical Actives fully into account, we propose the following change: *"**Depending on the specific manufacturing conditions of atypical active substances**, ~~A~~**a**ppropriate elements of the EU GMP guide Part II are nevertheless expected to be applied by the active substance and finished product manufacturers **to the extent possible.**"*	See above discussion
Part C line 221-229	**7**	***Section (iv) supplementary supportive information (optional)*** A GMP inspection, GMP report or certificate issued by EEA, MRA partners or other recognised authority can not only be regarded as a so called "Supplementary supportive information (optional)", but rather should be an integrative part of QP's risk assessment and supplier evaluation/qualification. Therefore this section IV of part C should be moved to section III, part C, "Evidence provided	This is not accepted, as discussed above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		in lieu of audit". The sentence in lines 206 – 207 should be changed into: "The relevant tick box is completed to indicate the following possible scenarios, as applicable:" Lines 222 – 229 should be moved behind line 209. The line 394 of Part C: Basis of Declaration, should be omitted and lines 391 – 397 should be adjusted accordingly.	
Part C **Line 229**	**15**	Comment: It is an envisagable situation that the active substance manufacturer, after an inspection by representatives of the Competent Authorities or the EDQM, has been found to be so far out of compliance with EU GMP Part II that a GMP Certificate has been refused (or a Certificate of Suitability suspended). This situation should result in active substance from the site being automatically disqualified for use in a MP being marketed in the EU. The MAH may however take immediate action to correct this situation including sending consultant to the site to advise on suitable immediate corrective measures. These actions could be explained under (iv) in order to justify the use of active substance(s) manufactured at this site. This could be made clearer in the wording in line 229 as is given below. Proposed change: section 5.25 of the GMP. The table provided may also be used to explain why the MAH is justified in using an active substance(s) from a manufacturing site that has been found by representatives of the Competent Authorities or the EDQM to be so far out of compliance with EU GMP Part II that a GMP Certificate has been refused (or a Certificate of Suitability suspended).	Discussed above.
Part C	**14**	Comment:	The QP is described in Directive

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
After the sections "iv", after the line 229		Taking into account the competence of Qualified Persons, as well as its role in the placing of medicinal products on the market, manifested in its responsibility for ensuring before the product launch to the market that each batch of medicinal product has been manufactured and checked in accordance with applicable law (in particular with Good Manufacturing Practice), there should be no doubt that the statements made by Qualified Person are credible. Therefore, if the manufacturer of medicinal products acquires QP declaration from the manufacturer of the active substance (API) which manufacturer employs the QP, then the declaration should be accepted by the product manufacturer which used the active ingredient in the manufacture of the final product. Proposed change (if any): Adding a new section as follows: "Declaration of acceptance issued by QP of API manufacturer , shall be acceptable."	2001/83/EC Article 49 in the context of MIAHs only. API sites are not the subject of MIAHs and therefore do not have a legal QP. Not accepted
Part C After the sections "iv", after the line 229	**14**	Comment: The international organization of the PIC / S associates state-level governmental authorities (pharmaceutical inspections), entitled under Article 111 (5) of Directive 2001/83/EC, as amended, to issue GMP certificates, after prior manufacturer inspection carried in accordance with Article. 40 of Directive 2001/83/EC. In view of the status of these entities, as well as the structural independence and, above all actions of these entities carried out within the limits imposed by law, it is clear that GMP certificates issued by the authorities affiliated to the PIC / S while confirming compliance with the principles of Good Manufacturing Practice, shall also certificate and ensure that the manufacturer of the active substance complies with the GMP requirements and has the appropriate experience & knowledge in the supply chain. Proposed change (if any): Adding a new section as follows: „Certificates issued by authorities affiliated with PIC / S shall be acceptable. "	Discussed above. Certificates of CAs can only be supportive of the QP Declaration and cannot replace the basis of the QP Declaration. Not accepted.
Part C Line 361/362	**2**	**Comment:** The last part of the sentence "and will be made available for inspection by the competent authorities if requested" should be deleted see comment relating to lines 186/197	This is considered incorrect. Discussed above Not accepted.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part D line 230-235	**7**	PART D Verification of the active substance supply chain traceability For Atypical Actives there should be an distinction. Due to the special nature of these products it is very unlikely that pharmaceutical manufacturer will ever have the complete knowledge about the whole of the supply chain. Instead, alternative means for achieving an adequate level of safety should be accepted and/ or listed.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Lines 230-235 Lines 398-406	**17**	Comment: The expectations for "documented risk assessment for all sites in the supply chain" are not clear. Proposed change: The verification of the supply chain should be part of the supplier qualification and be described in the EU GMP Guide, but should not be subject to the QP declaration.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Line 233 (and 74)	**11**	Comment: It would be better to state more specifically that the traceability is to be extended backwards to the suppliers of the critical raw materials (active ingredients starting materials), in agreement with the requirements described in Par 6.30 of Part II of the GMP. Moreover, with regards to the supply chain verification and documentation, it is not clear whether an inspection is also to be extended to brokers, traders, repackers, relabellers, and importers. Finally, how is the supply chain traceability is expected to be documented. Would a presence of Technical Agreements (in compliance with GMP) with all sites (or actors) of the supply chain be sufficient ? Would a declaration of the QP on this basis be acceptable, as a documentation to be produced ?	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D	**15**	Comment: It has already be explained why it is recommended that the supply chain be	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Line 233		submitted as an Appendix to Part D. The recommended wording below brings line 233 in to agreement with this proposal. Proposed change: …….the supply chain has been established, ~~and is~~ documented and is submitted as an Appendix to Part D of the "QP Declaration".	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D line 234	**3**	Comment: APIC is not clear as to what is meant by risk assessment in this context and what the scope of such an assessment is. Clarification on EMA's expectations is requested.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Line 234	**1**	**Comment:** The expectations for "documented risk assessment for all sites in the supply chain" are not clear. With reference to our comments in lines 29-30, the assessment of the supply chain is done comprehensively and globally and as outlined in lines 65-67, the manufacturer may establish priorities for its audits following a risk-based approach. **Proposed change (if any):** We would find the following clearer: "There exists a documented risk assessment for ~~all sites in~~ the supply chain."	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Line 234	**10**	Comment: This section refers to a "documented risk assessment for all sites in the supply chain". The EGA believes more clarity is needed on: - the basis of the risk assessment is and, - the risk allocation supply chain vs individual sites (i.e. whether the risk assessment results in a cumulative risk 'value' for the entire supply chain or whether 'risk' is assessed for each site) The overall accountability lies with the QP for completing these assessments but without clear guidance on what risks are being assessed this could lead to inspection findings and non compliances. Proposed change (if any): Please define expectations as far as - the type of risks to be part of the risk assessment (basis of the risk assessment) clarifies and	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the risk allocation (supply chain vs individual sites)	
Part D Line 234	**17**	Comment: A documented risk assessment only makes sense in case of GMP related activities. Not every site involved in the supply chain is automatically involved into GMP related activities. Proposed change: (ii) there exists a documented risk assessment for all sites performing GMP related activities in the supply chain of the active substance	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Line 234	**24**	Comment: Not clear what is the scope Proposed change (if any): Replace “site” by “manufacturing site”	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Lines 230 -235 & Lines 398- 406	**1**	**Comment**: We refer to our comments concerning traceability made under the general part.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Lines 234 (and 403-404)	**7**	“There exists a documented risk assessment for all sites in the supply chain of the active substance” Not feasible.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Lines 234	**7**	Comment: A documented risk assessment only makes sense in case of GMP related activities. Not every site involved in the supply chain is automatically involved into GMP related activities.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D Lines 230-235 (and 398-406)	**9**	Comment: The expectations for "documented risk assessment for all sites in the supply chain" are not clear. Proposed change (if any):	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		The documented risk assessment should be further explained in a Q&A	
Part E Lines 236-252 & lines 407-422	**1**	**Proposed change (if any):** For (b) there should be a tick box, as this may apply or not. (c) to (e) should be covered under one bullet point.	Text revised to list a series of relevant declaration statements
Part E Lines 236-252 & lines 407-422	**9**	Comment: - Proposed change (if any): For (b) there should be a tick box, as this may apply or not. (c) to (e) should be covered under one bullet point.	Text revised to list a series of relevant declaration statements
Part E Lines 241-243	**9**	Comment: MRA partners should have a special status as they have in Annex 16 already. Proposed change (if any): Declarations from persons employed by manufactures located in MRA partner countries WILL BE ACCEPTABLE if specified in the agreement (as per Annex 16).	Not accepted – a QP Declaration is required from each registered MIAH that uses the active substance as a starting material and/or is responsible for QP certification of the finished batch of a medicinal product
Part E Lines 244-246	**9**	Comment: In early phases when a new API manufacturer is introduced in the dossier, signed technical agreement is sometimes not in place as long as no commercial supply takes place. Proposed change (if any): "This section also sets out the requirements in situations where a declaration covers multiple sites listed in PART A and the QP confirms that appropriate technical agreements are in place between sites/companies concerning GMP compliance **once the API is used for marketed batches."**	Not accepted, discussed above
Part E	**10**	Comment:	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Lines 244-246		In early phases when a new API manufacturer is introduced in the regulatory dossier, the availability of a signed technical agreement might not be readily achievable as long as no commercial supply takes place. Proposed change (if any): Please amend the paragraph as follows: "This section also sets out the requirements in situations where a declaration covers multiple sites and the QP confirms that appropriate technical agreements are in place between sites/companies concerning GMP compliance **once the API is produced at commercial scale (commercial batches)**	Not accepted, discussed above

3. QP Template Form

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A and C	**16**	These two parts ask to provide names of the active substance manufacturer, which is a duplication of information already available in Part 2. Also the animal health industry deals with many more active substances and suppliers that may change more frequently, than its human counterpart. All these elements will generate more variations.	Template simplified
Part A, B and C Lines 321, 336 and 356	**16**	PARTS A, B and C: these parts should avoid being substance specific and the template could be simplified as follows: "… the active substances ~~***[insert name of active substance]***~~ …", i.e. those (there could be several) referred in the application form.	Template simplified, as much as possible.
Part A lines 313- 315	**22**	Comment: The variation regulation EC 1234/2008 required a QP declaration as supportive documentation of a variation B.III.1.a)2.: updated Ph.Eur. Certificate of suitability from an already approved manufacturer. In annex 1 of the QP declaration template, the only variation on API for which a QP declaration has to be submitted is the addition of a new site. It seems there is a discrepancy between both texts.	Annex 1 deleted.
Part A lines 313- 315 Tree	**24**	Comment: Merge bloc part A, so the history is always captured and the actual situation is reflected. To simplify the process and have clarity in one QP declaration. Proposed change (if any):	Template simplified
Part A line 317	**9**	Add a space between "Active" and "Substance"	Accepted

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A line 320	**9**	Comment: Multiple copies of the QP declaration may be required depending on the application (see line 323 - MA application/ renewal or variation) - but also depending on what is registered in different countries. Proposed change (if any): Clarification for expectations of how complex supply chains would be covered (e.g. One QP declaration for each step) e.g. in a Q&A	The proposal is possible, but in the case where one QP is making the declaration on behalf of others, a documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.
Part A line 320	**24**	Comment: Should micronisation be mentioned only if this step is done under the responsibility of the API manufacture, only if under responsibility of the finished product manufacturer (FPM) or in both cases? Can this be clarified? Proposed change (if any):	Assurance that GMP is in place at the site of micronisation is necessary, so a QP Declaration is required for the site of micronisation If the site is considered part of finished product manufacture then it should be subject to EU GMP inspection, which should be requested.
Part A line 320-334	**10**	Comment: Part A of the QP declaration template proposed requires repeating the information already present in the regulatory dossier application form. In order to ensure a full alignment between the regulatory dossier and the QP oversight, we suggest streamlining the information and only inserting the unique regulatory procedure/application reference number in the first paragraph and not repeating the information related to the manufacturing sites. Proposed change (if any): A “simplified” EGA QP Declaration Template is accompanying this response document with a proposal for an amended Part A.	The template is simplified, with restricted scope of on-site audit only.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A line 321	**5**	Comment: **site QP' manufacturer can not audit all the sites of the supplier (if any) if only one site provides the active used, according to Part B: Declaration of GMP Compliance. An audit in general corresponds to one site.** Proposed change (if any): I confirm that all sites concerned **and just quoted below** with manufacture…	This is not necessarily the case. All sites involved in the synthesis of the API from the designated starting material should be registered, subject to on-site audit and included in the QP declaration.
Part A line 324 325	**4**	Comment: in part A, it is not so clear if in the third column "importation and/ or batch certification site" should be mentioned the importer and/or batch certification site of API or of finished product or both. It should be convenient specify this point.	The template to be simplified.
Part A line 329	**5**	Comment: same comment as above in line 321	
Part A line 330	**15**	Comment: Bearing in mind the answer given to Question 10 in the Q & A document on this template it is necessary that "up-stream" sites, where different manufacturing sites are used sequentially to the manufacture / synthesise the API, be included. The text of line 330 should be modified to make this clear. Proposed change: All sites concerned with part processing should be listed including those manufacturing sites which are used sequentially to the manufacture/synthesis of the active substance such as for micronisation, etc.	The guidance text has been revised to state: The manufacturing operation / activity of each site should be stated e.g. complete synthesis, intermediate synthesis, micronisation.
Part A line 330	**21**	Comment: Are upstream processes of the finished API such as coating with stabiliser (as with ascorbic acid) defined as Finished Product Manufacturing or Active Substance Manufacturing? Proposed change (if any):	Finished product manufacture. See also published QWP Q&As for further information

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A line 331	**3**	Comment: APIC is of the opinion that the requirement to include the building number is overly prescriptive. Proposed change: .name and address in detail ~~**including the building number and function**~~	This is not accepted, as discussed above.
Part A line 331	**7**	The demand to state also the building numbers and function is not justified. Even in CEPs of the EDQM only the site of production is noted in general. It is proposed to delete the part ", including the building numbers and function." Or "... building numbers, **if applicable"**	Agreed
Part A line 331	**9**	Comment: Requiring building numbers and function is additional detail to what is generally listed in Sections S.2.1 and P.3.1 and should not be required here. Proposed change (if any): Delete 'including building numbers and function'.	Not accepted, as discussed above.
Part A line 331	**17**	Comment: The words "in detail, including the building numbers and function" should be deleted. Stating the address and contact information is sufficient according to the requirements for the preparation of a Site Master File (SMF), which has now been included in Part III of EU-GMP-Guide. In order to harmonize the requirements this document should not require additional information beyond the details as required per the SMF. Proposed change: State the site name and address. ~~in detail, including the building numbers and function.~~	Not accepted, as discussed above
Part A line 331	**15**	Comment: It is recommended that it is not required that the building number be include in the detailed information to be given about the manufacturing site of the active substance. Although in some countries, because facilities dedicated to just one product are often used in other countries production flexibility has lead to a number of companies having almost	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		identical production facilities in more than one building and depending on product demand or even batch size either the one or the other or both (or all three) facilities might be used. The building used for production is only one part of a site which needs to be in compliance with GMP and one could just as well require the number of the building used for incoming goods, packaging or quality control be included. It is recommended that the building number be deleted. Proposed change: …..name and address in detail ~~including the building number and function~~	Not accepted, as discussed above
Part A line 331	**18**	Comment: The requirement to include building numbers goes too far. It will result in endless discussion which buildings to include and which not (e. g. water treatment, waste treatment, HVAC, warehouses etc. pp.). Proposed change (if any): Delete the requirement to include building numbers.	Not accepted, as discussed above
Part A line 331	**19**	Comment: Stating the address and contact information should be sufficient according to the requirements for the preparation of a Site Master File (SMF), which has now been included in Part III of the EU-GMP-Guide. For the sake of harmonisation the QP declaration template should not require additional information beyond the details as required per the SMF. Proposed change (if any): The words "in detail, including the building numbers and function" should be deleted.	Not accepted, as discussed above
Part A line 331	**20**	Comment: The words “in detail, including the building numbers and function” should be deleted. Stating the address and contact information is sufficient according to the requirements for the preparation of a Site Master File (SMF), which has now been included in Part III of EU-GMP-Guide. In order to harmonize the requirements this document should not require additional information beyond the details as required per the SMF.	Not accepted, as discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part A line 331	**21**	Comment: Does this mean that all buildings involved in manufacturing of API should be listed, e.g. manufacturing, storage, testing, or only buildings or plots being part of the official manufacturing (site) address? Proposed change (if any):	Not accepted, as discussed above
Part A line 334	**16**	PART A goes further into details, asking for the following information: Line 331 (note 2): a list of all sites, including building numbers and functions; this is far too detailed information that brings no added value to this declaration. Lines 333-334 (note 3): a list of each site involved in the synthesis of the active substance, beginning with the introduction of the designated active substance starting material; we believe that the latter is out of the scope of GMP and that such requirement should be deleted	Not accepted, as discussed above This is incorrect, as discussed above, GMP is required to be in place from the introduction of the designated starting material.
Part A line 334	**7**	It will be impossible to list all sites for all starting materials. It should be sufficient to list the sites which produce the final intermediate(s). Not feasible	Manufacturing sites of starting materials are not required.
Part B line 338	**5**	Comment: Proposed change (if any):… is manufactured **on the basis of the audit**, in accordance …… (**see part C)**	Not accepted – please note that the template declarations include the following- The manufacture of the named active substance is in accordance with the detailed guideline on GMP and that this is based upon an audit of the active substance manufacturer(s) and that the outcome of the audit confirms that the manufacturing

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			complies with the principles and guidelines of good manufacturing practice.
Part B line 340	**3**	Comment: Reference is made to our comments on lines 62, 132, and 178-179. Proposed change: This declaration is **based upon a detailed audit report in my possession resulting from an audit of the active substance manufacturer(s) and is** underpinned by requirements as set out in PART E and is provided as follows	Not accepted, as discussed above
Part B line 340	**15**	Comment: As stated in the comment to line 132 the QP declaration should only be made when the QP has in his/her possession a detailed report(s) of the audit carried out at the site(s) of the manufacturer of the active substance(s). This should be emphasised in line 340 as is given below: Proposed change: This declaration is based upon a detailed audit report in my possession after an audit of the active substance manufacturer(s) and is underpinned by requirements as set out in PART E and is provided as follows	Not accepted, as discussed above
Part B line 352-353	**4**	Comment: As above, in part B, is the second column “importation and/ or batch certification site(s)” referred to API or to finished product or both? It should be convenient specify this point.	It refers to the relevant MIAH
Part B line 353	**5**	Comment: to complete the Declaration of GMP Compliance (according to the audit performed) : to add the following sentence : Proposed change (if any):**The manufacturing plant at …… has the facilities, systems**	Not accepted Not accepted, as discussed above. Addressed by GMP guidance.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		and capacities to manufacture the API (*see line 336*) according to GMP standards.	
Part C	**16**	PART C further asks to provide the dates when the active substance manufacturers were last audited; this should remain under the remit of inspectors and not be part of such declaration.	Not accepted.
Part C line 354-397	**10**	Comment: Part C of the QP declaration template is very detailed and the EGA suggests that this section focuses on its declaration parts and on listing the API sites at stake along with the date of the last audit. Indeed, the name of who did carry the audit does not bring any regulatory added value as the key aspect associated with who performed the audit is his/her qualification to do so. This is ensured by the QP and documented in the Quality system as a GMP matter. In addition, the future Falsified medicines directive reads as follows: *"Article 8.3* *(ha) A written confirmation that the manufacturer of the medicinal product has verified compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practice by conducting audits, in accordance with point (f) of Article 46.* ***The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice****."* This comforts the idea that a shorter version of part C could be satisfactory. Proposed change (if any): A "simplified" EGA QP Declaration Template is accompanying this response document with a proposal for an amended Part C.	Some simplification has taken place.
Part C line 354	**24**	Comment: Can this be simplified? Proposed change (if any):	The template has been simplified
Part C line 357	**5**	Comment: according to GMP Proposed change (if any): …has been verified on the basis of (i) or (ii) or (iii**)**, or (i) and (ii)	Not accepted.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		or (i) and (iii) if audits > 3 years – one of these sections should be completed……	
Part C line 357	**15**	Comment: If the declaration is being signed by the QP this signifies that he/she is taking personal responsibility for this declaration. This should be made clearer in the wording in line 357 as is given below: Proposed change: "….has been verified by me on the basis of (i)…."	Not considered necessary
Part C line 357	**15**	Comment: As stated above, the required assurance that the active substance(s) used are manufactured in accordance GMP is only available after a direct audit of the active ingredient manufacturer together with a detailed audit report This should be emphasised in line 357 as is given below: Proposed change: …. has been verified by me on the basis of a detailed audit report in my possession drawn up after a direct audit of the active substance manufacturers(s) and on the basis of (i) or (ii) or (iii).	Not accepted, as discussed above
Part C line 359	**15**	Comment: To ensure that the QP has personally judged whether the site at which the active substance is manufacturer is in compliance with EU GMP Part II (and not just been verbally informed that the site "is in compliance") the declaration should confirm that he/she actually has a copy of the audit report. The proposed change in line 359 is given below: Proposed change: "……..and I have in my possession**…."**	Not accepted, as discussed above
Part C line 360	**3**	Comment: Reference is made to our comments on lines 62, 132, 178-179, and 340. Proposed change: Detailed audit report(s) describing/explaining the active substance manufacturer's activities and processes to ensure compliance with the EU GMP Guide Part II and other documentation…	Not accepted, as discussed above
Part C	**15**	Comment: To ensure that the QP can personally judge whether the site at which the active	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 360		substance is manufactured is in compliance with EU GMP Part II a change in line 360 is proposed: Proposed change: Audit report(s) which describe(s) how the manufacturer of the active substance meets, at the manufacturing site of the active substance, at least 75% of the individual requirements listed in the relevant chapters of the EU GMP Part II guide and other documentation	Not accepted –discussed above. Addressed in GMP guidance.
Part C line 361-2	**19**	Comment: Proposed change (if any): The words "and will be made available for inspection by the competent authorities if requested" should be deleted. For reason and explanation please see comments on lines 186 - 187.	Not accepted. Discussed above
Part C line 362	**5**	Comment: to add the following sentence according to the new chapter 7 (7.15) : outsourced activities whose public consultation was until Feb 28th 2011 Proposed change (if any): **Conclusion of the report and CAPA if any will be made available for MAH and/or company commercialising the product (fyi: so called "exploitant" in France) if requested**	This is not accepted, outside the objective of the Declaration this has to be addressed by the MAH / MIAH contract.
Part C line 362-362	**17**	Comment: See for Lines 186-187 Proposed change: ~~Audit report(s) and other documentation~~ Documentation relating to the audit(s) of the active substance	Not accepted, as discussed above
Part C line 363	**15**	Comment: The confirmation requiring that audit reports are available should be strengthened to state that the audit reports explains how the site audited site complies with more than 75% of the requirements of the EU GMP Guide Part II. Proposed change: Please tick and complete each section as confirmation that detailed audit reports explaining how the audited site is in compliance with more than 75 % of the	Not accepted. Discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		requirements of EU GMP Part II are available to the QP, as applicable	
Part C line 367	**15**	Comment: The fact that the MAH (or corporate representative(s) of the MAH within the same group of companies) has (have) conducted a direct audit of the active substance manufacturer should be strengthened with the requirement that there is a detailed written audit report of the site. Proposed change: ……have been completed by the MAH (or corporate representatives of the MAH) as listed below and there is a written detailed report in my possession explaining how the active substance manufacturer has demonstrated that it is in compliance with EU GMP Part II.	Not accepted, as discussed above
Part C line 368	**3**	Comment: The term "critical concerns" is not used in other EU guidance documents. It is recommended to use the wording "critical deficiency" instead, in accordance with the language of the "Compilation of Community procedures on inspections and exchange of information". While "critical" deficiencies should, of course, be in the focus, major and other deficiencies should not be ignored. Proposed change: …critical ~~concerns~~ **deficiencies** have been rectified**, and an appropriate corrective action plan for major and other deficiencies has been implemented**:	Not accepted. Discussed above.
Part C line 368	**15**	Comment: The wording "critical concerns" is not used in the definition of SIGNIFICANT DEFICIENCIES included in the GMP Inspection Report – Community Format document. It is suggested that the terminology to be used is consistent with this document. Proposed change: ……and all critical ~~concerns~~ deficiencies have been rectified	Not accepted. Discussed above
Part C line 369	**23**	Comment: The draft template indicates that a justification should be provided if the date of last inspection exceeds 3 years. If a vendor has a continuous good track record this period should be allowed to be extended to 5 years without further specification. This decision is to be assessed yearly. If required the	An audit frequency of 3 years is considered a good standard. Exceptions to this standard can only would be on a case by

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		audit frequency is increased. Synthon thinks that a risk based approach is justifiable. Does the EMA agree? Proposed change (if any): For vendors with a proven good track record the date of last inspection should not exceed 5 years.	case basis, that cannot be generalised.
Part C line 369 and 375	**5**	Comment: Proposed change (if any): 3 years:**check (iii)**	Not accepted, discussed above
Part C line 371-374	**3**	Comment: The term "significant corrective action" is not clearly defined, so disputes over interpretation will be the consequence. It is recommended to use the same language as in line 368. Proposed change: …critical ~~concerns~~ **deficiencies** have been rectified**, and an appropriate corrective action plan for major and other deficiencies has been implemented**:	Text revised. The following declaration phrase is included: "that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice"
Part C line 371-374	**6**	Comment: The audit burden for manufacturers of APIs and certain excipients has constantly increased with resulting considerable workload to all involved parties and sometimes questionable repetition of standard audit procedures. At the same time, many QPs have neither the time nor are they qualified to audit often highly sophisticated processes of API and excipient manufacturing. Measures should thus be taken to decrease the overall audit burden to manufacturers and to increase the audit quality level at the same time. Consequently, truly independent, accredited audit bodies should be accepted also to be contracted from all parties involved (including API and excipient manufacturers) in order to cope with the outlined current deficiency. The same approach is currently being favoured for excipients manufacturers with the EXIPACT project.	Only third party auditors are acceptable to act on behalf of the QP.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Audit(s) of the active substance manufacturer(s) listed in PART A relative to the product(s) stated i this declaration has/have been completed by the third party auditing body(ies) i.e. contract acceptor(on behalf of the Manufacturing Authorisation holder(s) i.e. contract giver(s) as listed below and all significant corrective actions have been completed: *Table content first row:* Name of active substance manufacturer (contract giver)[5] [5] In some cases (e.g. independent, accredited auditing bodies) the active substance manufacturer may also be the contract giver. In such cases evidence has to be provided that the auditing body is accredited for such purpose and has been formally qualified and accepted by the Manufacturing Authorisation holder(s) in line with the requirements laid down in Chapter 7 of the EU GMP guide	Not accepted, as discussed above
Part C line 373	**15**	Comment: The fact that a third party has conducted a direct audit of the active substance manufacturer should be strengthened with the requirement that this third party has prepared and delivered to the QP of the MAH a detailed written audit report of the site. Proposed change: …. has been completed by the third party auditing body(ies) i.e. contract acceptor on behalf of the MAH i.e. contract giver and that the third party auditing body (ies) has written a detailed audit report explaining how the active substance manufacturer complies with more that 75% of the EU GMP Part II requirements as listed below.	Not accepted. Addressed by GMP guidance. Discussed above.
Part C	**17**	Comment:	Not accepted. Discussed above.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 373 - 374		Only critical observations are subject to immediate corrective actions. It is common practice for contract acceptor and contract giver to agree for a time frame to establish other corrective actions. Proposed change: ... on behalf of the Manufacturing Authorisation holder(s) i.e. contract giver(s) as listed below and all ~~significant~~ immediate corrective actions on critical observations have been completed:	
Part C line 374	**7**	It cannot be expected from a API manufacturer that all corrective actions have been completed months or years ahead of the marketing authorisation. Not feasible	The QP Declaration requires confirmation that the outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice
Part C line 374	**15**	Comment: The wording "significant corrective actions could mean that all SIGNIFICANT DEFICIENCIES included in the GMP Inspection Report – Community Format document should have been corrected. This is not in line with the idea expressed in line 368 where only "critical concerns" need to be rectified. It is suggested that the terminology to be used is consistent within this document. Proposed change: .....and all critical ~~significant corrective actions~~ deficiencies have been ~~completed~~ rectified	Discussed above
Part C line 374	**18**	Comment: "... and all significant corrective actions have been completed" goes too far. A site may be acceptable even if not all significant corrective actions have been completed. This phrase should be brought in line with line 368. Proposed change (if any): change to: "... and all critical concerns have been rectified" Comment: The title of the right column in the table should be the same as in the table in line 368. Proposed change (if any): The title of the right column should be changed to "Date of last audit".	Discussed above Not accepted
Part C	**9**	Comment:	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 377-383		Clarification is requested for understanding the specific necessity to include the declaration (lines 377-383) on the form in relation to audit by Third Party. Those obligations are stated in the guidance / existing GMPs - and are also presumably relevant to audits conducted internally by i) the MA Holder? The requirement to include "undertaking by the auditor(s)" is not appropriate; this is the responsibility of the API manufacturer to correct their gaps that are of relevance to the manufacturer. Proposed change (if any): Clarification requested. Delete (ii)	Not accepted. See revised template
Part C line 380	**5**	Comment: precision to add Proposed change (if any): ….approved procedures **<u>of the manufacturer</u>**	See revised text.
Part C line 382	**18**	Comment: To be 100 % clear, it should be made clear between which parties the contracts should exist. The word "Technical" should be deleted. Proposed change (if any): change to: "Contractual arrangements between auditing body and marketing authorisation holder are in place."	The template has been revised with the following required declaration: "In the case of third party audit(s), I have evaluated each of the named contract acceptor(s) given in Part C and that technical contractual arrangements are in place and that any measures taken by the contract giver(s) are documented e.g. signed undertakings by the auditor(s). In all cases, the audit(s) was/were conducted by properly qualified and trained staff, in accordance with approved procedures."

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
Part C line 383	**18**	Comment: It is absolutely unclear what the meaning of the phrase " ... and that any measures taken by the contract giver(s) are documented e.g. signed undertakings by the auditor(s)." is. Proposed change (if any): Rephrase this part or delete it.	See above
Part C line 384	**5**	Comment: Proposed change (if any): (iii) Evidence …..of audit **/ or if last audit > 3 years.**	Not accepted. Discussed above
Part C line 384	**21**	Comment: If the MAH have reliable control instruments for assuring that an API manufacturer will be audited prior to use, will a remote assessment be accepted? There is no risk to the patients as long as the API is not used. Proposed change (if any):	Not accepted .Discussed above
Part C lines 385-386	**23**	Comment: The draft template indicates exceptionally, and if satisfactorily justified, other supporting evidence in lieu of an on-site audit. Synthon considers a paper based audit (vendor questionnaire) in combination with a GMP certificate to be acceptable for a new submission or the addition of a new active substance manufacturer, as long as an on-site audit is performed before the first API batch is released for use in commercial product. Proposed change (if any):	Not accepted. As discussed above, the audit, which should be an on-site audit, cannot be replaced by GMP certificates from a relevant Competent Authority.
Part C line 387	**7**	A tick box for “GMP certificate from a relevant competent authority” (as mentioned in line 66) is missing	The template has now been revised.
Part C line 397	**15**	Comment: It is an envisagable situation that the active substance manufacturer after an inspection by representatives of the Competent Authorities or the EDQM has been found to be so far out of compliance with EU GMP Part II that a GMP Certificate has been refused (or a Certificate of	Not accepted, as discussed above

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Suitability suspended). This situation should result in active substance from the site being automatically disqualified for use in a MP being marketed in the EU The MAH may however take immediate action to correct this situation including sending consultants to the site to advise on suitable immediate corrective measures. These actions could be explained under (iv) in order to justify the use of active substance(s) manufactured at this site. This could be pointed out by adding boxes to be ticked below line 397 Proposed change: (add below line 397) ☐ The active substance manufacturing site has been inspected by representatives of a Competent Authority or the EDQM who determined that, at the time of the inspection of the site, this was not in compliance with EU GMP Part II and no GMP Certificate was issued. ☐ Since the time of this (these) inspections measures have been taken to correct the deficiencies and it is my belief that the site now complies with EU GMP Part II. ☐ There is thus adequate justification for using the active substance(s) manufactured at this site in a MP to be marketed within the EU and this justification is included as an attachment to Part C (iv).	
Part C III	**20**	Comment: For traditional active substances risk assessments should not be requested to be set-up by the QP, Risk Assessments should be made available to the QP. QP should be aware and accept it	Please note that the QP is responsible for the declaration.
Part D **Lines 398-406**	**23**	Comment: Part D template (supply chain traceability) indicates that there exists a documented risk assessment for all sites in the supply chain of the active substance and that these documents are available for inspection. Could the EMA elaborate on the requirements for the documentation of the supply chain and	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		the risk assessment of site in the supply chain? For example: How far down the manufacturing supply chain (finished API –final intermediate – starting materials) should the QP consider when preparing a declaration.?	
Part D line 401	**5**	Comment: precision to add Proposed change (if any): … established and documented **on the basis of the audit,**	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D line 401	**15**	Comment: It is recommended that the supply chain be submitted as an Appendix to Part D. The recommended wording below brings line 401 into agreement with this proposal. Proposed change: "The active substance supply chain of each of the active substance manufacturing sites listed in PART A has been established, ~~and~~ documented and is submitted as an Appendix to Part D of the "QP Declaration."	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D line 403	**5**	Comment: precision to add Proposed change (if any): …. for all sites **listed in Part A,** in the supply chain…	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D line 403	**17**	Comment: See for Line 234 Proposed change: (ii) there exists a documented risk assessment for all active substance manufacturing sites in the supply chain ~~of the active substance~~.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D line 403	**18**	Comment: The requirement that a documented risk assessment for all sites in the supply chain of the active substance has to exist is new. This is not based on any legal framework or GMP Guidelines. Proposed change (if any): Delete this requirement.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D	**3**	Comment:	Confirmation of supply chain

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
line 406		Supply chain traceability and risk assessment documents should be well maintained and kept up-to-date throughout the use of a certain API. Proposed change: (iii) the above documents ~~are~~ will be updated as necessary and the current versions will be made available for inspection.	traceability has been deleted. To be addressed through GMP.
Part D line 406	**15**	Comment: In addition to the statement that the MAH is willing to make the documents available for inspection, it is recommended that this statement be supplemented by a statement of maintaining the documents up-to-date (even if the changes do not warrant the submission of a variation). Proposed change: (iii) the above documents ~~are~~ will be updated as necessary and the current versions will be made available for inspection if requested.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part D	**20**	Comment: Please clarify that supply chain risk assessments should cover all sites of the API supply chain only. Supply chain to be defined as where GMP activities start for manufacturing an API – key starting materials - until the API is used for pharmaceutical manufacturing. Clarification is requested that physical flows are covered by transport validation or monitoring and excluded from the scope of such assessments.	Confirmation of supply chain traceability has been deleted. To be addressed through GMP.
Part E line 415	**18**	Comment: It is not clear what is meant by "the arrangements". Proposed change (if any): Rephrase (c).	The template declaration text has been revised to state: "In the case of third party audit(s), I have evaluated each of the named contract acceptor(s) and that technical contractual arrangements are in place and that any measures taken by the contract giver(s)

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
			are documented e.g. signed undertakings by the auditor(s). In all cases, the audit(s) was/were conducted by properly qualified and trained staff, in accordance with approved procedures.
Part E line 415-416	**5**	Comment: precision to add Proposed change (if any): …by a technical **and quality** agreement ….of the GMP ~~Guide~~ **current guidelines and in accordance with the MA and other legal requirements,** as applicable;	Not accepted. Addressed by GMP guidance.
Part E line 417	**18**	Comment: Point (d) is not clear - Maybe it is redundant to point (c)? Are there requirements beyond Chapter 7 of the GMP Guide? Additional remark:A contract between MAH and API supplier is NOT mandatory. Proposed change (if any): Rephrase point (d) or delete it.	See above
Part E line 417	**5**	Comment: precision to add Proposed change (if any): …defining GMP responsibilities **since responsibilities are usually detailed in table(s) at the end of / as an annex, of the technical and quality agreement.**	See above
Part E line 420	**5**	Comment: a question raised: which procedures ? the ones of the QP's facility or the ones of API manufacturer ?	This relates to contract giver and acceptor for multiple MIAH sites
Part E line 420-421	**10**	Comment: In early phases when a new API manufacturer is introduced in the regulatory dossier, the availability of a signed technical agreement might not be readily achievable as long as no commercial supply takes place.	

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change (if any): "the relevant technical agreements are available for inspection by competent authorities **once the API is produced at commercial scale (commercial batches).**"	Not accepted. Discussed above.
Part E line 407-422	**17**	Comment: - Proposed change (if any): • For (b) there should be a tick box, as this may apply or not. • (c) to (e) should be covered under one bullet point.	Text completely revised.
Part E line 422	**18**	Comment: The word "Holder" is missing in the table text "Manufacturing Authorisation name". Proposed change (if any): change to "Manufacturing Authorisation Holder name"	Agreed

4. QP Q&As

NOTE: The Q&As have been replaced by updated guidance text

Line number(s) of the relevant text	Stake-holder No	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
	1	A Question and answer should be added to clarify that this document does not apply to investigational medicinal products.	This is addressed by existing Q&As.
	17	PHARMIG – the association of the Austrian pharmaceutical industry – welcomes the opportunity to provide our comments on the Questions & Answers on the draft template for the Qualified Person's declaration concerning GMP compliance of the active substance used as starting material and verification of its supply chain "The QP declaration template".	
NEW	17	Comment: Does the QP Declaration Template also apply for Investigational Medicinal Products? Proposed change: Clarification through a Q&A would be helpful. We ask for adding another Q&A on this topic.	No This is addressed by existing Q&As.