APIC Active Pharmaceutical Ingredients Committee

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POSITION PAPER

APIC POSITION PAPER ON THE DEFINITION OF ACTIVE SUBSTANCE

September 27, 2013

Executive Summary

1. What is at stake?

The EMA/EDQM and some national health authorities[1] have recently started a move to exclude API/auxiliary substances mixture(s)* from the scope of the "API" definition. As a consequence, APIC members in several EU member states have received adverse findings from inspections or deficiency letters. In some cases production of these mixtures has been halted. Additionally, several members report that it is no longer possible to obtain a CEP or that the ASMF is no longer accepted by the health authorities. The recommendation from authorities was to include such API/auxiliary substances mixture(s) into the MAH dossier which causes confidentiality issues. Furthermore, some member states are now requiring these mixtures to be manufactured to EU GMP Guide Part I.

This is causing confusion and difficulties for both the supplier and Marketing Authorisation Holder (MAH) as EU GMP Guide Part I was never envisaged for API/auxiliary substances mixture(s). Indeed, before the implementation of the EMA Q&A[2] such mixtures have been accepted by the authorities as Active Pharmaceutical Ingredients (APIs) produced under GMP for APIs (EU GMP Guide Part II).

APIC is very concerned about this recent development and the resulting increased regulatory burden for both enforcement authorities and MAHs during the authorization of the finished product. If this interpretation by EMA, EDQM and national health authorities prevails, API-MIX manufacturers would be regarded as intermediate drug product manufacturers with several risks and issues like shelf-life impact.

Conversely, there is no significant or tangibly increased benefit for the quality of the finished drug product, safety or efficacy for the patient to be gained by moving these mixtures into the category of EU GMP Guide I.

2. Industry's point of view

The APIC position paper describes the APIC members' harmonized understanding on the definition of an API, including certain API/auxiliary substances mixture(s), and addresses the current unsatisfactory trend of exclusion of such mixtures from the definition of an "API". Indeed, in some cases (such as safety, stability, workability/handling when processed in final dosage form) it is technically necessary to have API/auxiliary substances mixture(s). In these justified circumstances we consider the strict implementation of the EU GMP Guide Part I and the non-availability of an ASMF/CEP for these blends unduly restrictive whilst adding no benefit to patient safety. In this regard, this is creating a situation in which many approved and well-established "APIs" are no longer legally defined as APIs. This may lead to even the withdrawal of API-MIX from the market and removing them from patient availability.

3. Conclusion

We believe that certain API/auxiliary substances mixture(s) (for safety, stability, workability/handling) should *not* be treated as drug product intermediates but rather as "APIs" with all relevant regulatory and quality aspects applicable to them, particularly given that the situation prior to the enforcement of the EMA Q&A[2] has ensured patient safety and product quality.
In order to achieve this, there is a need for harmonization and clarification of the API definition. APIC would very much appreciate contributing to discussions with regulators and other relevant stakeholders and for them to adopt our views for such APIs. First and foremost, existing API/auxiliary substances mixture(s) should be permitted to be manufactured and supplied as APIs. Ideally, the API definition should be clarified in order to guarantee that API manufacturers can continue to develop and design such mixtures using sound science instead of being hampered by the implementation of GMP Guide Part I that was not designed for such substances.

*Examples of API/auxiliary substances mixtures for safety, stability and workability reasons are Potassium clavulanate (EP 07/2010:1653) or Cholecalciferol concentrate (powder form) (EP 01/2008:0574)

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1. PURPOSE

This APIC position paper describes the APIC members' harmonized understanding on the definition of an API including certain API-auxiliary substance(s) mixtures (herein denoted API-MIX) (ANNEX 1). APIC makes a recommendation for extending the EMA definition of API to include API-MIX. This also forms the basis for addressing current risks and issues observed by APIC members arising from the current narrow definition of "active pharmaceutical substance" (ANNEX 2).

APIC "Active Pharmaceutical Ingredients (API) Committee" as a Sector Group within Cefic (the European Chemical Industry Council) consists of companies from different pharmaceutical industry sectors, all involved in the manufacture of APIs. This provides a basis for developing and communicating a balanced, holistic view on API-related regulatory and quality regulations and guidelines. To represent the interests of pharmaceutical and chemical companies producing APIs and intermediates in Europe, **APIC promotes the use of compliant APIs in medicinal products to ensure patient safety.**

In order to fulfill this mission, there is a need for a harmonization and clarification of the API definition related to regulatory and GMP compliance.

2. EXISTING DEFINITIONS API/API-MIX

Regulated API definition:

In "The rules governing medicinal products in the European Union", Volume 4[3] Part II on Basic Requirements for Active Substances used as Starting Materials, a list is made next to the API definition describing the application of this Guide to steps used in this type of manufacturing wherein physical processing and packaging are applicable to EU GMP Guide Part II.

Physical processing of active substances, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronising), should be conducted at least to the standards of these guidelines.[3]

API mixtures manufactured as e.g. beadlets, granulates or within a spray drying process are physically processed. Physical processing can involve auxiliary substance(s) (e.g. coating agent) and therefore such API mixtures fall under the definition of an API. It is important to distinguish between auxiliary substances as used here, and the term "excipient". Whilst "excipient" has been used in connection with examples of API-MIX, confusion arises because it is also used to describe other ingredients specifically used as aids for finished product manufacture. An example of the distinction between API and API-MIX, and the distinction between auxiliary ingredients and excipients (in the latter sense) is shown in ANNEX 3. API-MIX are not finished products used directly by patients, but mixtures used as active substance.

The legislation (Falsified Medicine Directive FMD[4]) as well as GMP guidelines (Part II Basic Requirements for Active Substances used as Starting Materials)[3] clearly define Active Pharmaceutical Ingredient (API) (or Drug Substance) as a substance or **mixture of substances**.

Generally, this definition of an API has been well recognized by the licensing authorities within Europe as demonstrated by numerous approvals of MA where the API-MIX is registered in the drug substance section (3.2.S as e.g. ASMF) of the medicinal product's dossier.

Consequently API-MIX falls under the definition of API. The APIC position described herein is in full accordance with the above definitions.

3. CURRENT AMBIGUITIES

The interpretation and enforcement by the MS health authorities of the API definition (including mixtures of substances) are not currently harmonized, and subject to ambiguity. This may have serious negative implications for the European API industry in terms of manufacturing complexity, legislative barriers, control of intellectual property, quality control, supply chain, without any improvement for patient safety (ANNEX 1 and 2).

Up to now API industry in Europe was selling API-MIX as active substances, in compliance with the EU GMP Guide II.

The EMA (European Medicines Agency) published several positions on the definition of an API under the Quality of medicines questions and answers (Q&A) section, which aimed for clarification on certain issues, nevertheless these are in some way contradictory, without explanation of the reasons for the change of opinion.

- In the Q&A 2007 EMA excludes mixtures of APIs with excipients[2] and mixtures of API with API[5] from the definition of an API. The only exceptions can be made where the active substance cannot exist on its own, for example, due to insufficient stability without a stabilising agent, or in the case of herbal dry extracts if it is not possible to produce a solid extract without excipients.[2]

- Q&A 2011 says that the mixing of active substances that can exist and are produced on their own should be considered as the first step of the manufacture of the finished product. Exemption: when active substances are not single chemically defined substances (e.g. herbal extracts).[5] It is not meant to allow a mixture of chemically defined active substances to be considered as a single active substance.[5]

In these cases the Q&A consider mixtures as falling within the first step in the manufacture of the medicinal product and hence GMP compliance with EU GMP Guide Part I (finished products) is required. Furthermore Active Substance Master File for the mixtures is excluded.

However, this interpretation is contradictory to another EMA position on this topic in Q&A document (CPMP/ICH/4680/02)[6] which is still available and therefore not repealed. It states that:

- *Question: If a drug substance is used in the form of a preparation (e.g. a [commercially available] vitamin trituration) in which module/ section should the excipient(s) included in the preparation be described? Should the relevant information be given for example in Section 3.2.S Drug Substance or in Section 3.2.P.4 Drug Product - Control of Excipients?*

  Answer: If the drug substance is defined as two or more materials, the manufacturing information would be described in 3.2.S.2.2 and the control of the additional material(s) (e.g., excipient(s)) would be described in 3.2.S.2.3.

In this case "drug substance" can be defined as two or more materials. Drug substances containing auxiliary substance(s) are defined as APIs and to be described in the drug substance part of the MA (Marketing authorization) dossier.
The above described EMA position generates ambiguities by virtue of uncertainty over the API definition, use of the terms "mixtures" and "excipients" and as such is inconsistent with API definition as described elsewhere and opinions of health authorities, accepting API-MIX as APIs.

The consequences of these ambiguities are:

- EDQM[7] and some regulatory authorities[1] are starting to follow the EMA's Q&A[2,5] and exclude mixtures from the definition of an API, despite the fact that in the past API-MIX were fully accepted as APIs. EP monographs exist for several API-MIX and CEPs are valid (e.g. Glyceryl trinitrate solution (01/2008:1331), Isosorbide dinitrate, diluted (01/2008:1118), Potassium clavulanate (07/2010:1653), Benzylpenicillin, Benzathine (01/2008:0373) or Cholecalciferol concentrate (oily form) (01/2008:0575))

- Although mixtures are included in the FMD's definition of an API, mixtures are excluded from the import requirements from outside EU countries into EU. Such partial manufacturing of the finished product is not included in the rules on the written confirmation.[8] If API-MIX are to excluded from the written confirmation, it would raise the question of which import rules should apply. API-MIX manufacturer normally do not have a QP and an importation authorization for finished drug.

The WHO has ongoing discussions on the definition of an API with proposals to exclude API mixtures from the API definition.[9]

4. RATIONALE FOR CONTINUED INCLUSION OF "API-MIX" (API/auxiliary substance(s) mixtures) UNDER API DEFINITION

APIC identified the above mentioned ambiguities (section 2 and 3) as well as the linked issues and seeks for a harmonized position and a level playing field for the definition of an API.

In some justified cases it is scientifically and technically necessary to have certain API mixtures (API-MIX) included within the definition of an API (ANNEX 1):

1) Safety
2) Stability of the API itself and in the target application, and safe and accurate incorporation in the final dosage form
3) Workability/Handling when processed in final dosage form

In such scientifically and technically justified circumstances APIC considers that the strict implementation of EU GMP Guide Part I and the non-availability of an ASMF or CEP for the API-MIX blend is unduly restrictive and adds no benefit to patient safety nor quality of the final product (see also ANNEX 1).

The exclusion of API-MIX from the definition of API leads to several risks and issues (ANNEX 2) for the API-MIX industry, the final drug producer/MAH holder as well as to regulatory authorities related to regulatory and GMP compliance of these special mixtures. Some examples are as follows:

- Exclusion of ASMFs, CEPs for API-MIX with associated impact on intellectual property for API-MIX industry. The regulatory workload for licensing authorities and MAH would increase dramatically during the marketing authorization process of the finished product.

- Other implications would be more stringent GMP (EU GMP Guide Part I for finished products), jeopardize the existing production due to higher hurdles or even banning API-MIX. APIC notes that EU GMP Guide Part I was not designed nor intended for the preparation of API-MIX, and where it is to be applied to API-MIX a number of ancillary complications and confusions also arise: would a QP declaration be needed to release batches of API-MIX to the end pharmaceutical manufacturer for example?

- Supply chain implications – *de facto* decrease in current shelf life and impact on the final drug producer. According to 'Note for Guidance on start of shelf-life of the finished dosage form' the date of production of a batch is defined as the date as the first step is performed combining the active ingredient with other ingredients.[10] Day 0 for the shelf-life of finished product would therefore start with the production of API-MIX at the API premises: In this case, if a medicinal product which has a verified 36 months shelf life of the final form would be produced with an API-MIX with a remaining shelf life of 2 months, the medicinal product shelf life of 36 months would no longer be valid. This would have massive implications for the entire supply chain and in certain markets importation of such a medicinal product would no longer be feasible. Optimizing production planning of multi DP manufacturers together with one/several API-MIX manufacturer(s), involving contract manufacturer(s) is practically not feasible.

5. CONCLUSION & RECOMMENDATION

Based on the foregoing, APIC draws the following conclusions:

1. Certain API-MIX (for safety, stability and workability reasons) should be considered as APIs with all relevant regulatory and quality aspects applicable to APIs (such as ASMF and CEP allowance, GMP Guide Part II, (FMD/Eudralex Vol 4 part II). [4, 3]

2. This is in line with the way EU and MS authorities have always worked (there are numerous examples of MA granted with API-MIX in module 3.2.S drug substance part). The situation prior to the enforcement of the EMA Q&A[2] has ensured patient safety and product quality across Europe.

3. There is ambiguity in the current use of the API definition, which is fueling a shift in policy making (EMA Q&A[2]/EDQM, MS challenges in policy making) to exclude API-MIX from the API definition. This would have a high impact for API-MIX manufacturers and MA holders, without improving the quality or safety of the API-MIX or the final drug product, meaning without any improvements for patient safety.

APIC therefore proposes the following measures to clarify the API definition and harmonize the legislative landscape for use of APIs and API-MIXs in medicinal products:

1. Amendment of the question and answer[2] 2007 (EMA QWP Quality of Medicines part 1 Q&A) **"on Active Substance - Active-substance-master-file procedure"** to allow certain API-MIX, according to additional clearly defined exemptions, such that the Q&A would read as follows:

   > "…Exceptions can be made where the active substance cannot practically exist on its own during storage, transport or processing into the finished dosage form for reasons of safety, stability and/or workability such that it needs to be mixed with one or more auxiliary substances or, in the case of herbal dry extracts, if it is not possible to produce a solid extract without auxiliary ingredients. Such mixtures (API-MIX) shall fall under the definition of API..."

2. Amendment of the question and answers[5] of 2011 (EMA QWP Quality of Medicines part 2 Q&A) on Definition of 'active substance' in relation to mixtures by also taking over the exemptions as mentioned above.

3. Amendment of EP monograph 2034 on substances for pharmaceutical use[7] by taking into account above mentioned points such that the related paragraph would read as follows:
   Where active substances have been processed with auxiliary substances to produce, for example, coated or granulated substances due to safety, stability or workability reasons, the processing is carried out under conditions of good manufacturing practice and the processed substances are regarded as APIs.

4. FMD import requirements from outside EU countries into EU should apply also to API-MIX.
   Amendment of EC Q&A question 11 accordingly[8].

5. The QP of the MAH should take the responsibility with regard to determining the GMP used to manufacture API-MIX as already required for pure APIs.

These adaptations will result in several advantages for the API industry, EMA and the EDQM and national authorities. These include a harmonized and hence more efficient legislative landscape, fewer exception requests, continued ability to rely on an efficient, productive and cost effective CEP certification procedure for API-MIX, reduced administrative and cost burden arising from reduced need for inspection of API-MIX facilities under EU GMP Guide Part II, substantial cost savings across the industry due to maintenance of existing supply chain and manufacturing processes. Ultimately this will ensure continued socio-economic competitiveness for the current API industry.

6. ANNEX 1

API and API-MIX definition: rationale for considering specific API-MIX as APIs

6a. EU GMP Guide Part II for API-MIX sufficiently protects patient safety EU GMP Guide Part I would not result in added value for patient safety, quality or efficacy of final drug product

EU GMP Guide Part II is intended to help ensure that all APIs (including API-MIX) meet the requirements for quality and purity that they purport or are represented to possess. The guideline requires API Industry to put in place systems, equipment and facilities that will ensure the API and/or API mixture when defined as an API is of the appropriate quality, efficacy and safety and requires the manufacturer to implement such necessary controls. For the relevant requirements of EU GMP Guide Part I that are related to receipt, storage, control and manufacture of an API with an excipient there is adequate controls for GMP within EU GMP Guide Part II.

The table below shows a risk assessment comparing EU GMP Guide Part I with EU GMP Guide Part II with regards to the API mixture blending step. The defined risk is patient safety.

Based on the analysis APIC concludes that:

1. Some parts from EU GMP Guide Part I would not be applicable for the API mixture (marked as not applicable in the table = n.a).

2. Other parts would not result in added value for the patient safety (marked as NO in the table) but would have negative implication on competitiveness of API mixture manufacturer which would result in higher costs during manufacture and higher prices of medicine. Therefore upgrading the production of API mixture to EU GMP Guide Part I would have negative socio-economic implications.

The table demonstrates that GMP applicable for DP does not fit for API mixture manufacturing. EU GMP Guide Part I consists of some very prescriptive requirements originally designed for Final Dosage Form Manufacturing which applied to API mixtures will have either negative impact in terms of cost without increasing product or patient safety or generate liabilities which are not in line with entire supply chain. This would end up in a situation where such requirements are not feasible to implement.

CONCLUSION:

The current established practice of applying EU GMP Guide Part II for the API mixture has ensured patient safety. Quality assurance systems to manufacture bulk APIs and API mixtures are sufficiently described in EU GMP Guide Part II.

	Drug Product EU GMP Guide Part I	API/auxiliary substances mixtures(s) EU GMP Guide Part II (ICHQ7)	Applying EU GMP Guide Part I for the mixing step improves assurance of patient safety? YES/NO/n.a	Arguments Inclusion of ICHQ9 risk management principles in EU GMP Guide Part II ensures the control and practices for API-MIX which do not impact on the quality, safety and efficacy of the final Drug Product
Additional resources needed	Qualified person required for batch release etc. GMP Part I, 2.4* *Article 48, 49, 51 of Directive 2001/83/EC	No qualified person needed (except biosimilar) GMP Part II, 2.32	NO	Currently the EU GMP Guide Part II does not require a QP to release the APIs but it is the responsibility of the Quality Unit. This requirement and the other requirements of ICH Q7 ensure APIs are released only when they have the appropriate quality. The same applies to API mixtures when the API Quality Unit releases such products. QPs need to certify release of batches to the markets and as such typically delegate to the rest of the drug product quality unit (QA) for the release of incoming APIs and incoming excipients and batch record review of the bulk drug product manufacture. The latter activities are those similar to those of the manufacture of an API mixture showing the same systems are followed. Release of an API mixture by a QP would not increase the assurance of patient safety. Additionally in both parts of the EU GMP Guide there is a need to ensure regulatory compliance is maintained for the products being released. Employing a QP at the API manufacturing site is unlikely to increase the assurance of patient safety as the QP. Additionally the QP should only release APIs that have been demonstrated to meet the appropriate GMP requirements via an audit of the API manufacturer/facility as a minimum. If API mixtures are classed as APIs then the QP would have the visibility and knowledge that such products have been manufactured to the appropriate GMP standard
	PQRs including starting materials, packaging, MA parameter (customer registration), contracts in place GMP Part I, 1.4	Annual PQR without these elements GMP Part II, 2.6	NO	It is common practice to also consider these items (except the MAH registration) in the PQR. The annual PQR covers all elements to ensure product quality including safety. It does not include any registration information which is requested in a PQR done by MAH. This makes sense since MAH is in charge of the proper application of the final drug and not the API-MIX manufacturer. By including these details into the annual PQR, the API-MIX manufacturer would interfere in the operational freedom and ownership of the MAH. This could even lead to confidentiality issues.

	Drug Product EU GMP Guide Part I	API/auxiliary substances mixtures(s) EU GMP Guide Part II (ICHQ7)	Applying EU GMP Guide Part I for the mixing step improves assurance of patient safety? YES/NO/n.a	Arguments Inclusion of ICHQ9 risk management principles in EU GMP Guide Part II ensures the control and practices for API-MIX which do not impact on the quality, safety and efficacy of the final Drug Product
	Release of intermediates by QU GMP Part I, 1.9, 5.31, 5.6	Release of intermediates by QU or production GMP Part II, 6.73 and 6.71	n.a	The API-MIX would be the final manufacturing stage and so would be released by the QU. The definition of intermediate is different; therefore this scenario is not applicable. So no difference in this instance.
	Process validation for critical steps GMP Part I, 5.37	Validation for critical steps GMP Part II, 12.2 and 12.51	n.a	No difference. Due to the fact that the mixing operation is the final step before filling/packaging, all steps are critical and therefore validated according to EU GMP Guide part II.
	Import of outside EU produced materials by authorized EU site plus testing GMP Part I, 2.4	No additional requirements for APIs produced outside EU	n.a	If API-MIX is classified as API, then the QP declaration by MAH and supportive data would ensure GMP compliance of an API-MIX. Additional Note: APIC's position is: API mixtures should fall under the Falsified Medicines Directive and therefore have to meet the import requirements as outlined in the directive and corresponding guidelines.
	Cleaning validation GMP Part I, chapter 3, 4.29, 5.19 Annex 15	Cleaning validation for critical steps only GMP Part II, 12.70	n.a	EU GMP Guide Part II recognizes that the final step is critical. Therefore in the mixture, made according to GMP II, cleaning will be validated. No difference.
Reduced productivity	Dedicated weighing room for starting materials GMP Part I, 3.13	Not defined	NO	Having a dedicated weighing room is too prescriptive. Controlled conditions to avoid cross contamination are justified. According to EU GMP Guide Part II critical weighing need to be checked and documented anyway.
	Outdoor equipment not allowed including storage of material GMP Part I, 3, 3.18	Outdoor equipment & material storage possible GMP Part II, 4.12	NO	According to EU GMP Guide Part II, outdoor equipment like e.g. storage tanks need to be allowed in case of API-MIX.Solvent storage, hazards good require sometimes outside storage. Outdoor equipment should be possible as long as it is closed.

	Drug Product EU GMP Guide Part I	API/auxiliary substances mixtures(s) EU GMP Guide Part II (ICHQ7)	Applying EU GMP Guide Part I for the mixing step improves assurance of patient safety? YES/NO/n.a	Arguments Inclusion of ICHQ9 risk management principles in EU GMP Guide Part II ensures the control and practices for API-MIX which do not impact on the quality, safety and efficacy of the final Drug Product
	Limited access to production unit GMP Part I, 5.16	Not required	n.a	The restriction does already apply where open product is handled.
	Use of purified water Water for pharmaceuticals use CPMP/QWP/158/01	Intended use & potable water, compliant to API GMP Part II, 4.30	NO	Relevance should be checked. Need for purified water should be determined from product/application risk. It is one possibility but not the only one for ensuring quality of API-MIX. The Note for guidance on quality of water for pharmaceutical use includes a requirement for relevant water quality and controls. The impact to the drug product would be assessed as part of that evaluation.
	Rejected material in restricted area (physical segregation) GMP Part I, 5.61	Identification & quarantine system, logical segregation sufficient GMP Part II, 7.44 and 10.11, 4.14	NO	Buildings and facilities have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination (4.1 EU GMP Guide Part II). Section 4.14. of the EU GMP Guide Part II requires defined areas or other control systems for certain activities including holding rejected materials. Although the wording is not exactly the same in the two guidelines the API Industry does place reject materials in separate locations to that of other material or other control systems which allow logical separation are in place. Such systems and practices are evaluated via audits and Inspections for their appropriateness. Part I is focused on finished products where the consequences of mix-ups are higher – little or no chance of rectifying it or spotting it later in the supply chain. An API mixture goes to the MAH next and they have to check its quality on receipt therefore possible to spot errors and minimise threats to patient safety.
	Reference samples for, starting materials & final products, packaging GMP Part I, 1.9, 6.12, 6.14 plus annex 19	Retain samples for API(API-mix) only GMP Part II, 11.7	NO	GMP Guide Part II covers this point. It is good industry practice that everything patient is exposed to is retained.

	Drug Product EU GMP Guide Part I	API/auxiliary substances mixtures(s) EU GMP Guide Part II (ICHQ7)	Applying EU GMP Guide Part I for the mixing step improves assurance of patient safety? YES/NO/n.a	Arguments Inclusion of ICHQ9 risk management principles in EU GMP Guide Part II ensures the control and practices for API-MIX which do not impact on the quality, safety and efficacy of the final Drug Product
	Restricted blending & recovery of batches GMP part I, 5.62	Typical & allowed GMP part II, 8.4, 14.4	NO	No differences in case of non-conformity product handling. Restricted blending of batches is current practice e.g. to assure homogeneity. Need to be reflected in the Batch Record.
	Residual material restricted to same product GMP part I, 5.63	Residual material allowed GMP part II, 8.50	NO	Minimal carry over in a controlled manner could be acceptable for different product campaigns to minimize risks (risk assessment). Need to be reflected in the Batch Record and Cleaning Record.
	Rework allowed GMP Part I, 6.30, 8.4	Rework allowed GMP Part II, 14.3	n.a	No difference.
	Reprocessing only in exceptional cases GMP Part I, 5.62	Reprocessing acceptable but not standard procedure GMP Part II, 14.2	n.a	No difference. Risk assessment regarding mixing: should be possible in case that reason for deviation is clarified and no quality or safety risk occurs in the blend. Need to be reflected in the batch record. Reprocessing of final API-MIX is not applicable.
Increased liability	No GMP Part I requirement	Material & solvent recovery allowed GMP Part II, 14.4	n.a	No clarification according to EU GMP Guide Part I. Adding costs without value if solvent needs to be replaced.
	GMP from beginning GMP Part I, 1.2, 1.4 and 5.0	GMP from declared starting material of API GMP Part II, 1.2	n.a	The reference starting material for the DP irrespective of API or API-MIX is adequately covered by EU GMP Guide Part II.
	Detailed Personal hygiene programs GMP Part I, from 2.13 to 2.20	Personal Hygiene GMP Part II, 3.2	NO	The whole API mixture production should be run under such conditions that any environmental impact on the product is excluded as there is no purification anymore. Conditions like for the last (physical) steps of the API production apply here. The sliding scale in EU GMP Guide Part II ensures the last part e.g. API-MIX is comparable to the corresponding parts of GMP Part I. Personal hygiene as described in EU GMP Guide Part II is appropriate for API-MIX.

	Drug Product EU GMP Guide Part I	API/auxiliary substances mixtures(s) EU GMP Guide Part II (ICHQ7)	Applying EU GMP Guide Part I for the mixing step improves assurance of patient safety? YES/NO/n.a	Arguments Inclusion of ICHQ9 risk management principles in EU GMP Guide Part II ensures the control and practices for API-MIX which do not impact on the quality, safety and efficacy of the final Drug Product
	Batch packaging record GMP Part I, 4.21	Batch record GMP Part II, 6.7	n.a	Not relevant for API-MIX.
	Certificate of compliance with MA & regulations GMP Part I,2.4, Annex 16	CoA GMP Part II, 11.4	n.a	API-MIX documents like e.g. Certificate of Analysis normally also include compliance statement in case reference to a monograph can be given. The API-MIX producer is not the MAH and therefore cannot certify compliance with a MA.
	Legal liability for patient safety GMP Part I, Chapter 1	General product quality GMP Part II, 1.1	n.a	API-MIX manufacturer can only be responsible for general product quality as the product does not go directly to the patient.
	Mandatory authority inspections & registrations GMP Part I, Introduction	Notification according to FMD Art. 52a and inspections by responsible authorities according to Art. 46b.1 and 111.1b with frequency based on risk	n.a	FMD Art. 111 (a): API inspections: API manufacturer may be inspected. General note: APIC fully agrees with mandatory inspections of APIs and API-MIX.

6b. API-MIX in food applications
Existing principal considerations on safety and hygiene sufficiently protects public health

Several API-MIX (like e.g. vitamin and mineral powders) are not used only in pharmaceutical products. Vitamin formulations are also widely used in food applications like in food supplements (FS). The finished product forms (tablet or capsule) of FS are largely identical to those for finished pharmaceutical products, although the regulatory framework for their commercialization follows food regulations11 rather than pharma regulations. The exposure can hence be considered a lifetime exposure.
European regulatory authorities deemed these manufacturing and hygiene regulations as sufficient to protect the consumer health.

Upgrading even EU GMP Guide Part II produced API-MIX to EU GMP Guide Part I would not result in added value for consumer's safety.

In conclusion the API-MIX used in food and in pharmaceutical products are frequently identical.
Industry would consider the implementation for EU GMP Guide Part I for vitamin mixtures as an unwarranted measure from a risk assessment point of view. In the case of vitamins, the measure would also disproportionally impact vitamin manufacturers supplying pharma and food industry.

6c. API-MIX for safety, stability and workability/ handling reasons

In some cases it is scientifically and technologically necessary to employ API-MIX because the APIs need to be a blend with auxiliary substance(s) (which may be preservatives, antioxidants as well as a diluent) to allow for more accurate dispensing of particularly concentrated pure (potent) APIs etc.
Sometimes the properties of the „pure" APIs are such that an API-MIX adds benefits both to product quality, stability and to dispensing by the drug product manufacturer. For the following cases the pure API needs to be mixed with auxiliary substance(s) (API-MIX):

i. Safety
ii. Stability of the API itself and stability for safe and accurate incorporation in the final dosage form
iii. Workability/Handling when processed in final dosage form

i. Safety

Pure APIs can have hazard profiles. For safety reasons they are mixed with auxiliary substance(s) in a number of cases, as illustrated in the following examples:

Vitamin D: As stated on Material Safety Data Sheet from suppliers, crystalline Vitamin D3 is a powder with high hazard profile (Dust explosion class St (H)2, Hazard statements H330, H311, H300, H372)). Typical preparations with auxiliary substances (API-MIX), in this example a vitamin D powder, are much less hazardous (Dust explosion class St1, not a hazardous substance according to Regulation EC 1272/2008).

Nitroglycerine/Nitro-ester derivates (EP Glyceryl trinitrate, solution): Nitroglycerin is an explosive API. It needs to be diluted in auxiliary substance in order to be sold, transported and used at final dosage form manufacturer's production side.

Potassium clavulanate: Alone this substance is not stable enough to transport and handle. It is even explosive and therefor needs auxiliary substances to render it practicable.

Strong Cetrimide Solution 40 % BP, with alcohol: Auxiliary substances can be added to preserve against microbial contamination, e.g. alcohol in solutions. Although the API has antimicrobial properties, a solution of less than 50 % active presents risks of microbial contamination.

ii. Stability of the API itself and stability for safe and accurate incorporation in the final dosage form

Vitamin A Palmitate and Vitamin A acetate are both extremely sensitive to oxidation and decomposition by light (see Vitamin A, A.B. Hanck, C.C.Kuenzle, W.F. Rehm, 1991 and Vitamin A, J.A. Olson in Handbook of Vitamins, third edition, 2001) and therefore invariably necessitate mixing with auxiliary ingredients for stability.

iii. Workability/Handling

a) Appropriate handling of the API and stability in final dosage form (e.g. direct compressing)

Some pure APIs are not manageable for use in final dosage form. Such APIs could be for example oily or fatty substances, hygroscopic, not flowable, water-insoluble, or very high viscosity liquids which could be in addition sensitive to oxidation or other degradation.

To add an oily ingredient into a tablet formulation is highly challenging, because an adsorption step is needed. API-MIX can provide a mean for avoiding an exudation issue and sticking during the compression step. Hygroscopic APIs also make the weighing step particularly difficult.
Neat APIs would be difficult to dispense accurately then also have issues with homogeneity and dosage when mixed together in the final dosage form.

Dilution of an API in solution may be difficult and requires additional equipment for the drug product manufacturer. The easiest and safest solution (GMP/clean room process) is that the API manufacturer performs the dilution, so the API is ready for direct use for the drug product manufacturer.

Strong Cetrimide Solution 40 % BP, with alcohol: The API-MIX contains water for workability reasons as the product would otherwise be too thick and would require additional dilution steps for the drug product manufacturer.

Benzalkonium Chloride Solution 50 % Ph. Eur., USP/NF, JP: Water is present for workability reasons, where the concentrated version (95 % and more) is very thick and requires additional dilution steps before mixed into the drug.

b) Dilution of a potent API and homogeneity

Dilution in a spray dried matrix helps to achieve a compliant homogeneity in the finished product. Mere µg amounts of pure API are difficult to be mixed homogenously, with all the associated technical and safety implications. Conversely a formulated API-MIX helps to achieve reliable and safe content and homogeneity, as well as satisfactory protection of the sensitive APIs.
As an example, Vitamin D3 crystalline powder contains 40 000 000 IU vitamin D per gram. Medicinal products registered in France contain between 200 IU to 5800 IU per tablets (source: affsaps, consulted on August 7th, 2012). This means that on the basis of pure crystalline material, the inclusion rate would be between 5 µg and 145 µg per tablet. The Vitamin D3 API-MIX (Cholecalciferol concentrated powder) would be dosed at 2 mg and this has been shown to be sufficient to achieve homogeneity.
Homogeneity can only be achieved via predilution in an API-MIX.

For many pharmaceutical applications the pure substance API is not suitable for large scale preparation of the drug product and the active molecule (e.g. vitamin) has to be protected in order remain intact during the operations of manufacturing the drug product. This was the rational leading to the development and commercialization of powder concentrates, as tableting process generating heating or pressure would destroy API (physical property).

Another example of such a potent API is Ethinylestradiol.

c) Protection of the API within final dosage form

An API-MIX can assist in limiting the interactions between several APIs contained in the final drug product with impact on stability of the finished medicinal product.

d) Transport

API-MIX may be necessary to ensure requirements can be achieved for transport in pipeline, in cases where a sticky pure form of the API cannot be unloaded. Also for safety reasons during transport API need to be mixed with auxiliary substance(s)

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7. ANNEX 2 - Risk analysis in case API-MIX fall outside API definition

Risk analysis and impact if API-MIX is excluded from API definition

Enforcement of excluding API-MIX from the API definition would result in blocking this business by European API-MIX producers as the hurdles would be too high. Possible implications include drug shortage. The regulatory system will increase in complexity.

1. Manufacturing implications

In most cases all, or part, of an API manufacturing site has dedicated equipment for the production of API-MIX (blender, granulator, spray drier) with design and process compatible with the current EU GMP Guide Part II practice. If the preparation of the API-MIX would now be considered as the first step of the finished product, this may lead to the necessity of transferring this process step to the finished product manufacturing site in order to be covered by the pharmaceutical licenses. Possible patents need to be checked. In such case, the issues are the following:

a) Increasing risk of cross contamination since equipment will be shared between different formulations (with obvious safety risk for the final customers)
b) Increasing workload for the cleaning validation to cover the additional cross contamination risk
c) Increasing risk for the operators since highly potent products will be handled when API-MIX is not available (such as vitamin D3) such that plant layout would need to be redesigned
d) Mismatching of the production capacities requested for the first step (e.g. dilution of API) and the finished product
e) Manufacturing process cost impact (including for the final customers)

2. Regulatory implications and impact on confidentiality of API-MIX

Exclusion of ASMFs, CEPs for API-MIX:

Obtaining CEP for API-MIX would benefit both the applicant and the medicinal authority in EU/CEP accepting authorities outside EU by reducing the administrative burden for both parts while still ensuring that quality and safety level of the preparation is adequate for the intended use.
The regulatory workload for licensing authorities and MAH would increase dramatically during the marketing authorization process of the finished product resulting in:

f) Uncertain status of approved MA containing existing ASMFs, CEPs, documentation on API-MIX in 3.2 part of dossier
g) Update of MAH dossiers impacted by the withdrawal of the API-MIX and their re-approval High additional barrier for new registrations or renewals/variations

<u>Further impact:</u>
Cessation of production of API-MIX due to too high hurdles related to EU GMP Guide Part I, Provision of information on the API-MIX to all affected MAHs and the associated impact on intellectual property and change control. Possible drug shortage could be the consequence.

3. Dossier related implications linked to increased complexity

Move from documentation of the API-MIX from 3.2.S to 3.2.P:

All the ingredients compounding the mixtures should be registered in 3.2.P.4., their quality control (monographs and methods) should comply with Ph. Eur. Monograph when possible; if not it should be justified showing equivalence of methods. To ensure this new location in the CTD dossier, this quality control would have to be under MAH responsibility instead of supplier (API-MIX manufacturer) responsibility.
All the API-MIX manufacturing sites should be registered in 3.2.P.3 of dossier as a manufacturing site for the finished product, in addition to the site manufacturing the final tablets for example. This means, API-MIX manufacturer would be often contacted and requested to provide a large amount of information about manufacturing and control, plus all the GMP statements.

All the manufacturing steps for API-MIX and validation of manufacturing have to be described in dossier in 3.2.P.3 in addition to the description of the tablets manufacturing for example. This is a confidential issue for the API-MIX industry.

In order to still use the API-MIX under the mixture form, all the methods to control the mixtures and stability data under ICH conditions should be described in 3.2.P.3 as well (declared as intermediates).

Section 3.2.P of marketing authorizations applications/variations dossiers would be very detailed and difficult to build as often many APIs, API-MIX are used in finished products (like for instance OTC vitamin/mineral tablets).

In conclusion, many human resources and time would be needed to re-organise the quality and format of existing already approved dossiers, for API-MIX producers as well as final drug producers. The cost of such a potential change would then be very high.

4. Resource Implications at MS authorities

Authorities need to have resources to assess such materials registered as drug products. Authorities would need to inspect API-MIX sites and grant manufacturing license. On this point, there are contradictory opinions within member states[12].

5. Supply Chain Implications

Implication on shelf-life of finished product resulting in a *de facto* decrease in current shelf life and impact on the final drug producer related to period of availability for marketing. Therefore, this would dramatically impact the supply chain.[10]

6. Importation implications

FMD "Falsified Medicine" related implication on written confirmation: According to "Question and Answers" document (version 4 – April 2013) of European's Commission[8]: partial manufacturing of the finished product is not included in the rules on the written confirmation (Q11).
Q&A Number 10 says: Regarding finished medicinal products, the rules for importation of finished medicinal products (importation authorization and batch release by a qualified person, see Articles 40(3) and 51 of Directive 2001/83/EC) apply. These rules remain unchanged.

If API-MIX are to be excluded from the written confirmation, which import rules apply?
API-MIX manufacturer normally do not have a QP and an importation authorization for finished drug products. API-MIX are considered to be APIs, therefore the rules for written confirmation according to the FMD should apply.

7. Uncertainties

If EU GMP Guide Part I is to apply to API-MIX which additional implications do apply?

a) Marketing Authorisation?
b) Registration of API-MIX as a drug product?
c) Mandatory Inspections according to EU GMP Guide Part I?

8. ANNEX 3

Figure 1a: Practical example of API and API-MIX
Figure 1b: Distinction between API, API-MIX, auxiliary ingredient and excipient

Figure 1a: Practical example of API and API-MIX

Active Substance	Safety	Stability	Workability/Handling
API D3 cryst (EP0072)	High hazard powder Dust explosion class St (H)2, Hazard statements H330, H311, H300, H372	To be stored at 2-8 °C under inert gas	**Not suitable for large scale preparation** High potency: Homogeneity in DP is only possible to achieve via predilution Very fine powder makes dosing, mixing, etc. more difficult during the production of pharmaceutical application Solubility: insoluble in water
API-MIX Cholecalciferol concentrate powder (EP0574)	Not a hazardous substance according to Regulation EC 1272/2008 Dust explosion class St1	To be stored below 15 °C, Stability for safe and accurate incorporation in the final dosage form given Matrix protects D3 cryst	**Suitable for large scale preparation** Homogeneity in DP Direct compression possible Dispersibility: in water

Figure 1b: Distinction between API, API-MIX, auxiliary ingredient and excipient

Denomination	Ingredient	Definition	Applied GMP standard
Vitamin D crystalline	Vitamin D	API	EU GMP Guide Part II
Vitamin D powder	Vitamin D + auxiliary substance*	API-MIX	EU GMP Guide Part II
Vitamin D tablet	[Vitamin D + auxiliary substance*] + Tablet excipients**	drug-product	EU GMP Guide Part I

*e.g. antioxidant, matrix element, flowing agent, solvent which are necessary for physical processing[13] of API-MIX

** e.g. Sodium Stearate

9. ANNEX 4

References and Remarks

Foot-note	References and Remarks
1	The following exemplarily mentioned licensing authorities start to exclude API-MIX from the definition of an API: Austria, Belgium, Estonia, Ireland, Portugal, Spain, United Kingdom
2	**EMA Q&A 2007 Part I - Active Substance - Active-substance-master-file procedure**
	Can a mixture of an active substance with an excipient be submitted through an active-substance-master-file (ASMF) procedure? H+V August 2007 No. A mixture of an active substance with an excipient cannot be submitted through an ASMF procedure. The blending of an active substance and an excipient is considered as the first step in the manufacture of the medicinal product, and therefore does not fall under the definition of an active substance. The only exceptions can be made where the active substance cannot exist on its own, for example, due to insufficient stability without a stabilising agent, or in the case of herbal dry extracts if it is not possible to produce a solid extract without excipients.
	Ref 2: CHMP/CVMP Quality Working Party, Quality of medicines Q&A: Part 1: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000071.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002c2af&jsenabled=true#section1
3	**EudraLex - Volume 4 Good manufacturing practice - EU GMP Guide Part II (ICHQ7): Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients section - 1.2 Scope**
	…Physical processing of active substances, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronising), should be conducted at least to the standards of these guidelines.
	EudraLex - Volume 4 Good manufacturing practice - EU GMP Guide Part II (ICHQ7): Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients section - Glossary
	Active Pharmaceutical Ingredient (API) (or Drug Substance): Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.
	http://ec.europa.eu/health/files/eudralex/vol-4/2007_09_gmp_part2_en.pdf
4	**DIRECTIVE 2011/62/EU - Falsified Medicine Directive - Article 1**
	3a. Active substance: 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 to exert a pharmacological, immunological or

Foot-note	References and Remarks
4	metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.
	http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:174:0074:0087:EN:PDF
5	**EMA Q&A 2011 Part 2 Definition of 'active substance' in relation to mixtures**
	In case more than one active substance produced at different manufacturing sites is mixed together at a different manufacturing site, is it possible to consider the mixing as active substance manufacture? H+V June 2011 No. The mixing of active substances that can exist and are produced on their own should be considered as the first step of the manufacture of the finished product. It should be noted that the definition of active substance given in part II of the European Union (EU) good-manufacturing-practice (GMP) guide (active substances) states that an active substance is a substance or a 'mixture of substances', but this definition takes into account cases when active substances are not single chemically defined substances (e.g. herbal extracts) and it is not meant to allow a mixture of chemically defined active substances to be considered as a single active substance. As a consequence of what is stated above, the mixing of active substances is subject to compliance with part I of the EU GMP Guide (finished products) and it is not possible to present a single active substance master file for the mixture.
	CHMP/CVMP Quality Working Party, Quality of medicines Q&A: Part 2: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000072.jsp&mid=WC0b01ac058002c2b0#section2 APIC recognizes that mixing an API with an API is already first step of finished product and therefore does not fall under the API definition any more.
6	**EMEA CPMP/ICH/4680/02 from 2003 Quality/Questions and Answers on Location issues for Common Technical Document for the Registration of Pharmaceuticals for Human Use**
	If a drug substance is used in the form of a preparation (e.g. a [commercially available] vitamin trituration) in which module/ section should the excipient(s) included in the preparation be described? Should the relevant information be given for example in Section 3.2.S Drug Substance or in Section 3.2.P.4 Drug Product - Control of Excipients? If the drug substance is defined as two or more materials, the manufacturing information would be described in 3.2.S.2.2 and the control of the additional material(s) (e.g., excipient(s)) would be described in 3.2.S.2.3.

Foot-note	References and Remarks
7	**The Monograph 2034 (04/2013) on substances for pharmaceutical use in the European Pharmacopoeia (EP) 7.7 - section production**
	Powdered substances may be processed to obtain a certain degree of fineness (2.9.35). Compacted substances are processed to increase the particle size or to obtain particles of a specific form and/or to obtain a substance with a higher bulk density. Coated active substances consist of particles of the active substance coated with one or more suitable excipients. Granulated active substances are particles of a specified size and/or form produced from the active substance by granulation directly or with one or more suitable excipients. If substances are processed with excipients, these excipients comply with the requirements of the relevant monograph or, where no such monograph exists, the approved specification. Where active substances have been processed with excipients to produce, for example, coated or granulated substances, the processing is carried out under conditions of good manufacturing practice and the processed substances are regarded as intermediates in the manufacture of a medicinal product.
	Nevertheless, there exist valid CEP certificates of API-MIX and EU GMP Guide Part II standard has been accepted by MS health authorities.
8	**EC Q&A on IMPORTATION OF ACTIVE SUBSTANCES FOR MEDICINAL PRODUCTS FOR HUMAN USE VERSION 4.1 - Question 11**
	IS THE WRITTEN CONFIRMATION ALSO REQUIRED FOR IMPORTED ACTIVE SUBSTANCES WHICH HAVE ALREADY BEEN MIXED WITH EXCIPIENTS, WITHOUT YET BEING THE FINISHED MEDICINAL PRODUCT? No. Such partial manufacturing of the finished product is not included in the rules on the written confirmation.
	http://ec.europa.eu/health/files/gmp/2013_04_12_qa_en.pdf
9	The WHO requested input from experts, industry and regulators in order to agree on a definition of an API for the WHO. (Working Documents QAS/11.426/Rev1, QAS/13.522)
10	**Note for guidance on start of shelf-life of the finished dosage form**
	…The date of production of a batch is defined as the date as the first step is performed involving combining the active ingredient with other ingredients. For medicinal products consisting of a single active ingredient filled into a container, the initial date of the filling operation is taken as the date of production…
	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002917.pdf
11	**Applicable food regulations:** Regulation (EC) 852/2004 on the hygiene of foodstuffs, 29 April 2004 Regulation (EC) 853/2004 laying down specific hygiene rules for food of animal origin, 29 April 2004 Regulation (EC) 854/2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption, 29 April 2004 Directive 2004/41/EC repealing certain Directives concerning food hygiene and health

Foot-note	References and Remarks
11	conditions for the production and placing on the market of certain products of animal origin intended for human consumption and amending Council Directives 89/662/EEC and 92/118/EEC and Council Decision 95/408/EC, 21 April 2004.
12	ANSM issues GMP certificates based on inspection of API-MIX towards EU GMP Guide Part II (ICHQ7).
13	Physical processes such as: Solubilisation, Homogenization or mixing, emulsification, spray drying, etc.

10. GLOSSARY

API	Active Pharmaceutical Ingredient or drug substance
API-MIX	API/auxiliary substance(s) mixtures Not a mixture of API plus API
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the European Pharmacopoeia
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
DP	Drug Product
EEA	European Economic Area competent authorities
EMA	European Medicines Agency
EP	European Pharmacopoeia
FMD	Falsified Medicine Directive
FS	Food Supplement
GMP	Good Manufacturing Practice, Part II, Part I EU GMP Guide Part II (ICHQ7): Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients EU GMP Guide Part I: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	European Member States
PQR	Product Quality Review
QP	Qualified Person as defined in Directive in Article 48, 49, 51 of Directive 2001/83/EC
QU	Quality Unit