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Comments to

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION On the IMPLEMENTING ACT ON THE REQUIREMENTS FOR THE ASSEMENT OF THE REGULATORY FRAMEWORK APPLICABLE TO THE MANUFACTURING OF ACTIVE SUBSTANCES OF MEDICINAL PRODUCTS FOR HUMAN USE (7 Dec 2011, SANCO/D3/(2011)ddg1.d3. 1438409)

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Introduction			
		4. to be listed, the Commission shall, at the request of a third country, assess whether the regulatory framework applicable to active substances and the respective control and enforcement activities in the third country ensure a level of protection of public health equivalent to that of the Union (hereinafter: ' the equivalence assessment').	**The EU equivalence Assessment should focus on 3rd countries' manufacturing sites exporting to the EU.** **A list of concerned sites within a country on the EC list would therefore be needed.** The current wording omits an important aspect. Article 111b is actually limiting the regulatory framework (and the respective control and enforcement activities) applicable to active substances '**exported to the Union'**. This is an important nuance in terms of implementation as it delimits the actual scope of the equivalence in 3rd countries to only those sites exporting to the EU. It appears necessary that the EC implementing act addresses the need for the request of a 3rd country to be on the EC list to include the list of concerned manufacturing facilities exporting to the EU and under the necessary 'equivalent' scrutiny by local authorities.

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		9. the adoption of the implementing act is scheduled for 2013.	**The date of entry into force of the implementing act (after adoption) and the date from which countries can send requests for equivalence assessment need to be confirmed.** This is required in order to have optimal preparedness and readiness among stakeholders.
1. EQUIVALENCE ASSESSMENT OF THE RULES FOR GMP			
	1	*11. In this context, and pending the adoption of a delegated act on the principles and guidelines of good manufacturing practice for active substances[6], the EU rules to be taken into account are contained in Part II of the good manufacturing practice guideline of the EU (Eudralex Volume 4).[7]*	**An explicit reference to equivalent international standards (non-exhaustive) for API GMP should be made (e.g. ICH Q7).**
2. EQUIVALENCE ASSESSMENT OF THE REGULARITY OF INSPECTIONS TO VERIFY COMPLIANCE WITH GMP AND THE EFFECTIVENESS OF ENFORCEMENT OF GMP			
		13. In the equivalence assessment, the regulatory framework for inspections of manufacturing plants of active substances is taken into account. […]	Same comment as for point 4 of the introduction above. **The EU equivalence Assessment should focus on 3rd countries' manufacturing sites exporting to the EU.** **A list of concerned sites within a country on the EC list would therefore be needed.** The current wording omits an important aspect. Article 111b is actually limiting the regulatory framework applicable to APIs (and the respective control and enforcement activities) to active substances '**exported to the Union'**.
		13. […] This regulatory framework is set out in Article 52a(4) and Article 111(1b) of Directive 2001/83/EC.	**To allow efficient border checks, a list of authorised 3rd countries API exporters would be needed to complement the EU list of registered API importers/manufacturers/distributers.** Article 52a(4) relates to the new EU scheme for EU-based API

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			related activities (import, manufacture and distribution). This article foresees the storage of the data in a Union database. The EC implementing act on equivalence assessment should introduce a “mirror” requirement for exporters of APIs to enable EU based importers to assess the need for administrative steps to complete prior to importation into the EU. Non-EU API exporters will also need to check whether the recipient (EU importer) is registered in the Union database. Finally, the border/customs officials will have the necessary tools to allow or prevent entry of shipments. This is relevant in both the context of written declarations and in a listed country where only the manufacturing sites involved in exportation will be covered by the assessment and these might evolve with time (even within the 3 years period between listing and verification). It therefore appears necessary that a list of authorised exporting sites be drawn and maintained up-to-date similarly to the Union database on EU based API-related activities.
	2	**Audit checklist in the Annex**	**The audit checklist presented is an internationally recognised tool which is suitable to undertake the equivalence assessment as required under the FMD.** The EGA supports the use of the audit check list in annex. It is comprehensive and addresses all critical areas. The EMA website highlights the broad international consensus around this document ‘*The EEA JAP (Joint Audit Programme) and the PIC/S (Pharmaceutical Inspection Cooperation Scheme) have agreed to use the Evaluation Guides developed by Health Canada as the basic auditing tool. This guide has been adapted to the EU legislation. EEA, PIC/S and MRA audit programmes now use the same evaluation guide and this has paved the way for mutual acceptance of audit results. EEA,*

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			PIC/S and MRA partners agreed on sharing outcome from visits[1]*.'*
			The EU should organize practical information/training sessions prior to 2 July 2013 (and as early as Q2-Q3 2012) on the EU regulatory framework, the Compilation of Community Procedures and the audit check list in order to ensure timely readiness of 3rd countries' competent authorities. The EC implementing act should address (directly, through reference to existing guidelines or preferably through complementary guidelines) the detailed expectations for each section by beginning 2013 at the very latest.
3. REGULARITY AND RAPIDITY OF INFORMATION PROVIDED BY THE THIRD COUNTRY RELATING TO NON-COMPLIANT PRODUCERS OF ACTIVE SUBSTANCES			
	3	To ensure equivalence, it could be considered that the third country • participates in and contributes to the '*Community information and rapid alert system*';11 and	**To achieve a worldwide level playing field, access, participation and contribution to the EU rapid alert system by countries outside the EU is highly desirable and would provide an extremely important tool of information to regulators.** **The EU should organize practical information/training sessions in 2012 and 2013 on the Access to EU Community information and rapid alert system.** A prerequisite for non-EU countries participation will be the overall understanding of the system, its interoperability with 3rd countries systems, etc. The EU consequences of rapid alerts on industry are serious and the information input and trigger of

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/joint_audit_programme.jsp&mid=WC0b01ac058006e06f

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			the mechanism in place should be of high quality.
		• communicates any suspension or withdrawal of an authorisation granted, based on non-compliance with GMP, to the EU.	**The communication of non-compliance information available in 3rd countries should be considered as a means to achieve greater awareness of regulators.** It is welcome and desirable that non-compliance information is exchanged among regulators in a centralised fashion. This contributes to achieving a level playing field.
4. OTHER ISSUES			
	4	**Form of assessment** 18. According to Article 111b(1) of Directive 2001/83/EC, the equivalence assessment shall take the form of: • a review of relevant documentation; • an on-site review of the third country's regulatory system, unless a mutual recognition agreement ('MRA') is in place that covers the manufacturing of active substances; and • if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.	**The EC implementing act must introduce 'categories' for 3rd country applicants allowing to allocate resources where greater assessment needs are identified** (for now except for Switzerland, all countries would require and on-site assessment, regardless of the existence of other comparable assessments). According to publicly available information, out of the 6 EU MRAs, only Switzerland is covering APIs. Consequently, all remaining 3rd countries (i.e. the rest of the world except EU MSs and Switzerland) would fall into the category where on-site inspectorate review and, if necessary, observed inspection of at least one API manufacturing site would be required. Please see below the EGA's interpretation of article 111b(1).

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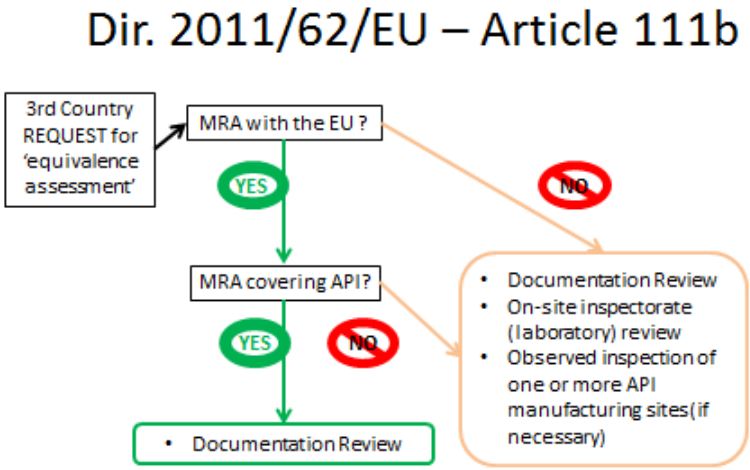
		Form of assessment (Continued) 18. According to Article 111b(1) of Directive 2001/83/EC, the equivalence assessment shall take the form of: • a review of relevant documentation; • an on-site review of the third country's regulatory system, unless a mutual recognition agreement ('MRA') is in place that covers the manufacturing of active substances; and if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.	 This seems highly resource intensive, unfocused and undesirable particularly when noting the existence of collaborative efforts in the area of GMP supervision which are also based on an 'equivalence assessment' and have a track record of quality information exchange, understanding and confidence.

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		Form of assessment (Continued) 18. According to Article 111b(1) of Directive 2001/83/EC, the equivalence assessment shall take the form of: • a review of relevant documentation; • an on-site review of the third country's regulatory system, unless a mutual recognition agreement ('MRA') is in place that covers the manufacturing of active substances; and if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.	**The exact meaning of 'documentation review' should be clarified (directly or through the adoption of guidelines) available at the time of adoption of the implementing act.** Ideally, in order to save time and resources, the EC should refer to a similar approach as for instance the PIC/S and its membership questionnaire[2] preliminary to an application. *"The purpose of this document is to provide guidance on the information and documentation to be submitted in order to ensure (i) equivalency in the way Authorities are assessed and (ii) consistency in the way the information and documentation is presented and evaluated."*
		Interface with existing mechanisms • MRAs on GMP for medicinal products which cover also the manufacturing of active substances; • Regulatory alignment with applicable guidance of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ('ICH');[13] • Existing assessment programs such as o The Joint Audit Programme used for assessing European Union's authorities and MRA partners; and o The Assessment and Reassessment Programmes of the Pharmaceutical	**Building on existing cooperation platforms is necessary and highly desirable.** The EGA welcomes the EC considerations to limit and avoid unnecessary duplication of work and its willingness to build on existing mechanisms of cooperation and exchange of expertise. **The implementing act should clearly define the scope and extent of the assessment of equivalence (i.e. categories) to be envisaged for 3rd country applicants pertaining to one or several of the listed initiatives.** From a resource perspective, it will be extremely resource intensive if all countries (except Switzerland) have to undergo

[2] Questionnaire for Competent Authorities to be used for assessment, re-assessment and self evaluation. http://www.picscheme.org/documents/PSW012011QuestionnaireforAssessment.pdf

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		Inspection Convention and Pharmaceutical Inspection Co-operation Scheme ('PIC/S').[14]	similar EC/EMA on-site inspectorate review and if necessary one or more observed inspections. The benefit for patients will not be proportional when resources are focuses on well-known partners. Countries active in one or more of the listed initiatives: • Should be waived the need for observed inspections. • On-site inspectorate review should ideally be (waived as well but if not possible under the current legislation wording) kept to a very minimum duration. The objective being to focus resources on the categories of 3rd country applicants where less knowledge is available and therefore where a potential risk of uneven public protection lies. **EU assessment of non-EU countries also members of PIC/S should be expedited and ideally should constitute a mere recognition of the assessment of equivalence undertaken by PIC/S.** We support the reference to PIC/S as the principles of equivalent regulatory systems (the existence of GMP legislation), the existence of inspections and effective enforcement form the basis of membership applications and have already been assessed and validated[3].

[3] PIC-S Accession procedure is described on the following website http://www.picscheme.org/accession.php : "*The main conditions are to have a law on medicinal products, a GMP Guide equivalent to that of PIC/S (or the EU GMP Guide), a GMP inspectorate, which fulfils PIC/S quality system requirements, and experienced GMP inspectors.*"

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			The existence of a Cooperation Agreement[4] between the EMA and PIC/S should facilitate the recognition by the EU of assessments performed by PIC/S and allow an expedite assessment procedure for the concerned countries to be listed. We highlight here that the fact that PIC/S assessment does not yet formally cover API GMP should not be regarded as a limitation *per se*, as recognition of equivalence of GMP for finished products already gives a clear sense of the regulatory system, the regulatory supervision and enforcement, and as such of public health protection. **The API GMP inspection cooperation scheme (Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers) should be added to the list of initiatives on which to build now that it is opening for more participants**. In addition to the already listed schemes referred to in the concept paper, the EGA would like to add: • The API GMP inspection cooperation scheme (Programme to rationalise international GMP inspections of active pharmaceutical ingredients/active substances manufacturers) which completed its pilot phase in Dec 2010 and has now published its terms of reference with a view to have more partners cooperating. *"The World Health Organization (WHO) has already become a new partner in this collaboration, through its Prequalification of Medicines Programme. WHO's*

[4] Co-operation between the Pharmaceutical Inspection Co-operation Scheme and the European Medicines Agency.http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000470.jsp&mid=WC0b01ac05801f0a08#

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			membership will contribute to its objective of there being safe and effective medicines for all."[5] This programme highlights that beyond the defined scope of MRAs (not covering APIs), the mere fact of having an MRA in the area of GMP has led to greater exchange, understanding and finally confidence between certain regions. This is illustrated by the pragmatic approach laid out in the EMA GMP/GDP IWG Work Plan 2011[6].
		Regular verification According to the Article 111b(3) of Directive 2001/83/EC, the Commission shall verify regularly whether the conditions of the GMP equivalence are fulfilled. The first verification shall take place no later than three years after the country has been included in the list.	**Re-assement of EC listed 3rd countries (and the list of exporting manufacturing facilities) for equivalence is required on a regular basis.** This is a basic principle of Good Practices and it is used in other collaborative schemes on GMP. It ensures that all listed 3rd countries fulfil the same up-to-date GMP requirements. The extent and frequency of verification should be adapted based on risk and performance indicators.
		Date of application	Same as point 9, Introduction above. **The date of entry into force of the implementing act (after adoption) and the date from which countries can send requests for equivalence assessment need to be confirmed.** The EC should clarify whether 3rd countries' request can be sent from 2 July 2013 or earlier.

[5] EMA Press release – 6 Mar 2012 - International collaboration on good manufacturing practice inspections expanded http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/02/news_detail_001456.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

[6] "*To include active substances in the operational phase of the current scope of MRAs where possible and to liaise with MRA partners on information exchange and collaboration on inspections performed outside of the respective territories.*", Work Plan for GMP/GDP Inspectors Working Group for 2011 and 2012 - EMA/INS/GMP/678698/2010 corr1 and EMA/INS/GMP/43493/2012

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			The implementing act should detail equivalence assessment procedure timelines (for the various categories of 3rd country applicants) in order to have a better predictability of when administrative relief surrounding API importation could potentially be foreseen. A prerequisite for 3rd countries requests is the availability of the implementing act and all complementary procedural guidance documents.
		Date of application **TRANSITIONAL MEASURES**	**Need for transitional measures (6 years) for operators with a track record of equivalent GMP compliance** For countries having requested an assessment, a list of facilities exporting to the EU complying with equivalent GMP standards should be temporarily waived the need for a written declaration. Countries/companies would have to establish the history of GMP compliance of the concerned site for at least the last 6 years. A good track record of GMP compliance could potentially be defined as having had 2 successful inspections (by any EU inspector or PIC/S or MRA country or EDQM or equivalent) and the absence of any unaddressed/unresolved critical deficiencies highlighted in the last 6 years. This would prevent GMP compliant 3rd country manufacturers from being 'administratively' disfavoured for being established in a 3rd country. This would also allow 3rd countries' competent authorities that cannot be considered equivalent today to have sufficient time to progressively adapt resources, processes and practices to new requirements. An alternative and shorter transition period could be envisaged

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			if the provision was limited to new API manufacturers (ie, new manufacturer or new API for a known manufacturer) and that existing GMP compliant API suppliers to the EU would be temporarily exempted (so called 'grandfathering' approach).
	5	**Any other issue or comment** **- AWARENESS RAISING - PREPARDNESS**	**Early awareness raising of key non-EU API exporting 3rd countries (prioritisation list):** • **industry mailing to API manufacturers and,** • **joint regulatory/industry information sessions.** Awareness raising is required as early as possible and for 3rd countries, both for local competent authorities and for industry. To ensure readiness, information sessions by EU officials/regulatory authorities should be foreseen on all API aspects of the FMD taking advantages of existing gatherings e.g. International Conference of Drug Regulatory Agencies, CPhI China, Europe, India Latin America. EGA member companies have initiated an outreach campaign to their non-EU API suppliers, disseminating information on new obligations, timelines and upcoming steps. **Preliminary feedback from API manufacturers in 3rd country is concerning and indicates a very poor level of awareness and understanding of the new obligations for a written confirmation whereas this is the default situation on 2nd of July 2013.** The most frequent misunderstanding is that an EU GMP certificate will be sufficient to support exportation to the EU.
	5	**Any other issue or comment** **- LEVERAGING ON OTHER REGULATED SECTORS' EXPERIENCE**	**Other regulated sectors such the Food and Feed sector have similar import rules as those introduced in the FMD**. **Countries should be considered for inclusion on the basis of the API exporting facilities they list and commit to supervise according to EU standards.**

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			Other sectors can provide a good source of hands-on experience to help establish and maintain a list of manufacturing sites within a country on the EC list allowed to export API to the EU. Mirroring the Food and Feed scheme, the EC implementing act should introduced a staged approach for accepting, for a defined period, API exports from GMP compliant facilities within a country rather than awaiting all facilities within the country to reach EU equivalent GMP. The latter would indeed go beyond the legal provision which specifically refers to the regulatory framework (and the respective control and enforcement activities) applicable to active substances '**exported to the Union'**.
	5	**Any other issue or comment** **- STAGED APPROACH to an EU LIST OF EQUIVALENT COUNTRIES**	**The EC Implementing Act needs to identify means of acknowledging the long history of GMP compliance of non-EU operators and maintaining their ability to supply the EU market.** Based on the well-known fact that a vast majority of imported APIs are primarily manufactured in countries where the overall current GMP status cannot be readily deemed equivalent to those in the EU, their inclusion as "country" in the EC list of equivalent countries might require some time. The Food and Veterinary Office, referred to above, established a staged approach to compliance to food safety standards by means of drawing up a provisional list of third country establishments from which imports of certain products are permitted. This should be used as a positive experience for the supervision of the importation of regulated goods. In this context, the EC/EMA/MSs should foresee provisions: • To acknowledge the long history of compliance to

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			GMP for APIs (EU GMP Guide part II or ICH Q7A) of certain manufacturing facilities located in those countries • To guarantee GMP compliant API supply continuity from key non-EU API exporting countries
	5	**Any other issue or comment** **- EU INSPECTORATE DEDICATED TO NON-EU API INSPECTIONS**	**The EC implementing act should consider the creation of an EU inspectorate with dedicated resources which would be responsible for undertaking, among other tasks, the planning, audit and periodic re-evaluation of foreign inspectorates.** This was already proposed in the EGA Vision 2015[7] (released in 2010). Making a parallel with the food and feed sector, the Food and Veterinary Office (FVO), a directorate of the Directorate-General for Health and Consumers of the European Commission, works to ensure effective control systems and to evaluate compliance with EU standards in the areas of food and feed safety, animal health, animal welfare and plant health. It does this mainly by carrying out inspections and audits in Member States and third countries. It has its own dedicated expert resources (175 inspectors) working on an EU central inspection programme (involving re-assessment inspections) covering food producing establishments in the EU and in third countries.
	5	**Any other issue or comment** **- NEW OBLIGATIONS ON API IMPORTATION and THREATS TO (GMP**	In addition to the 'equivalence assessment', a number of other API importation related provisions and obligations are introduced with an implementation date of 2nd of July 2013.

[7] *www.egagenerics.com/doc/**EGA_Vision_2015**.pdf*

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		Compliant) API SUPPLY CONTINUITY	These are listed in the main act and no further act or guidance (public consultation) is explicitly foreseen to address their practical implementation. The EGA anticipates **the industry will be facing huge challenges to secure the continuity of API supply chain** from 2 July 2013 onward and **MSs will need to address the question of patients' access to medicines**. This should be addressed as a matter of urgency.
	5	**Any other issue or comment** - **SAFEGUARDING (GMP Compliant) API SUPPLY CONTINUITY - Summary**	The EGA proposes the following pragmatic approaches to achieve a seamless implementation in the given timeframe: • **Adopt transitional measures** and proceed with a **'grandfathering' approach** for long existing, well-known and GMP compliant pharmaceutical supply chain operators by **temporarily waiving administrative requirements** • Integrate the necessary and realistic **transition periods** to accommodate substantial organisational changes and process elaboration (both in the EU and in 3rd countries) while securing GMP compliance • **Raise awareness** among all stakeholders who will have an active role to play in the implementation (i.e. non EU based supply chain operators, key non EU API exporting 3rd countries) by means of regulatory dialogue or joint competent authorities-industry information sessions • **Leverage on positive experience from other sectors** (import of high quality regulated goods, involvement of customs, EU inspectorate) • **Foster collaboration with equivalent countries** (optimise inspections resources allocation)

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			• **Enhance the use of IT/electronic interfaces** as enabler for efficient collaboration
	5	**Any other issue or comment** - **ASSESSING (GMP Compliant) API AVAILABILITY - General**	**The EC/EMA/MSs should establish and maintain an EU priority list of substances or medicines 'at risk' of supply discontinuity.** This list would among other aspects help prioritise those substances for which the EU supply is highly dependent on non-EU supply and those for which the existing number of manufacturing sites is restricted. According to artice 46b(4), Member States are responsible for assessing the scarcity of GMP compliant API supply and the risk of supply discontinuation, to waive the need for a written confirmation of GMP compliance issued by a third country exporting API to the EU and to inform the EC of their decision. Industry operates in a global environment and would favour a transparent and central repository where supply availability trends for the whole EU appear. Other EGA Recommendations on the implementation of waiver 2 for the written confirmation: 'Exceptionally and where necessary' circumstances (article 46b(4)) • A **single EU process to** assess the state of supply of GMP compliant API would be needed for all MSs. • A single EU decision-making process for waiver granting would be needed. • Risk-based inspection prioritisation should ensure that GMP compliant API manufacturers based in third countries are not at a disadvantage: as the EU GMP certification is a key condition for obtaining this waiver, there should be a

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			'contingency' mechanism: o The EC (through the EMA or an EU inspectorate dedicated to APIs) should secure a sufficient number of 'contingency' GMP inspections to maintain the incoming API supply and patients access to high quality medicines o As a complementary approach, the EC should consider establishing an expedite process for paper based GMP certification based on a manufacturing site 'history of compliance' • The above EU processes, decisions and EU priority list should be published on EC and/or EMA websites.
	5	**Any other issue or comment** **- ASSESSING (GMP Compliant) API AVAILABILITY - EU Incident Network**	**The EC/EMA/MSs should expand the scope of the EU Incident Network to cover emerging issues such as API or medicines shortages.** The EU regulatory network already has in place crisis management cooperation mechanisms, such as the EU Incident Network and its EU Regulatory System Incident Management Plan, for medicines for human use. Although the scope of activities of the EU Incident Network is currently limited to 'quality defects resulting in safety concerns', the perspective of potential shortages could also fall in the category of emerging safety issues for medicines for human use as some treatments might end up being interrupted and cause issues for patients.
	5	**Any other issue or comment** **REGULATORY and COMPLIANCE RESOURCES**	**Considerations for expedited regulatory procedures and inspections timeframe should be made in the light of the supply trends from 2 July 2013.** In order to secure API supply, the EC/EMA/MSs should take into consideration the likely increase in:

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			- Variations submissions: API source (towards EU or listed country source), Dosage Form production (towards non-EU facilities), removal of API source (e.g. which cannot be imported for failure to provide a written confirmation) - API GMP inspections requests (or need in ,exceptional circumstances) And the consequences on MSs resources.
	5	**Any other issue or comment** **REGULATORY and COMPLIANCE RESOURCES – EDQM Attestations**	**The EC/EMA/MSs should take the opportunity of the EC implementing act on 'equivalence assessment' to reconsider the EDQM attestations as equivalent to EU GMP certificates.** Although the number of EDQM inspections carried out annually is limited, this measure would allow to expand the pool of inpectors and the number of yearly inspected sites. Today, EDQM inspectors are very often accompanied by an EU or Swiss inspector in their foreign inspections. This has been the case for many years and one would say that in light of other cooperation schemes, confidence has been build, reinforced and well illustrated by a recent FDA decision to rely on EDQM inspections findings and conclusions to place an API manufacturer under Import Alert[8]. Recognising EDQM attestations as equivalent to EU GMP certificates would allow EU inspectors to visit other sites leading to a greater supervision. This might be meaningful considering valid EU GMP

[8] FDA's Hamburg declares no one can "inspect world on its own" for poor quality medicines, Scrip 17 June 2011, Elizabeth Sukkar © - Link: http://www.google.be/url?sa=t&rct=j&q=edqm%20fda%20relies%20on%20edqm%20for%20import%20decision&source=web&cd=6&ved=0CGIQFjAF&url=http%3A%2F%2Fwww.picscheme.org%2Fbo%2Fcommun%2Fupload%2Fdocument%2Fscrip-fdas-hamburg-declares-no-one-can-inspect-world-on-its-own--elizabeth-sukkar.pdf&ei=lptoT9LIIIvJ8gPjkuykCQ&usg=AFQjCNFBwZvGUf_AKj0OVXiXnAf3iSt9Yg

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			certificates are a prerequisite to the waiver granted in exceptional circumstances.
	5	**Any other issue or comment** **- BORDER CONTROLS of API IMPORTATION**	**The EC should consider the need for a separate legal act which would complement Dir. 2001/83/EC, as amended, to secure harmonised Member States implementation of new API importation rules by customs at their border.** On the model of Council Directive 90/675/EEC laying down the principles governing the organisation of veterinary checks on products entering the Community from third countries, the EC should consider a separate legal act which would complement Dir. 2001/83/EC, as amended, as far as API import from 3rd countries is concerned in order to secure harmonised Member States implementation by customs at their border and prevent the creation of uneven ports of entry into the EU (i.e. absence of level playing field).
	5	**Any other issue or comment** **- WRITTEN CONFIRMATION – Summary**	**Joint EU Member States guidelines** are necessary to align and harmonise requirements (template) and processes to elaborate, verify and accept the written confirmation of API GMP compliance. These guidelines would concomitantly benefit non-EU API 3rd countries, helping them understand expectations, timelines as well as to set up national systems/procedures allowing issuance of the necessary written confirmation. **Involvement of customs/border officials in the drafting process** is essential given the role they will play in allowing or preventing the entry of the shipment onto EU territory. **Transition period of 6 years** from the date the EU requirements and processes are laid out to allow 3rd countries

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			to adapt.
	5	**Any other issue or comment** **- WRITTEN CONFIRMATION – Shipment document**	**The written confirmation is a shipment/customs document not a regulatory document.** Consequently, the written confirmation issued by third countries should remain distinct from any existing import licensing process and should not be cross-referred to in the QP declaration template.
	5	**Any other issue or comment** **- WRITTEN CONFIRMATION – Template**	**The EU should develop a template for 'written confirmation' in order to clearly identify the necessary elements required.** The co-existence of multiple formats for the written declaration to be issued by the various non-EU API exporting country would be a great source of highly undesirable administrative work and possibly a great source of delays and misunderstanding. The EU should also include discussions on the written confirmation template when engaging with competent authorities from key non-EU API exporting countries in order to ensure clear wording and appropriate understanding, while resolving potential legal issues. It should be made available early enough (very latest Q4-2012) to allow preparedness of 3rd countries.
	5	**Any other issue or comment** **- WRITTEN CONFIRMATION – Scope and Validity**	**The written confirmation should be issued for a manufacturing facility. Ideally, the handling of the written confirmation should mimic 'site' GMP certificate.** The issuance of written confirmation at any of the following levels would prove counter-productive as it would trigger massive administrative bottlenecks in key exporting countries in greater proportion than the increase in public health protection). e.g.: active substance, active substance batch,

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			active substance batch shipment (i.e. several shipped parcels/drums for a given batch).
	5	**Any other issue or comment** - **WRITTEN CONFIRMATION – Issuance-retrieval**	**API manufacturers exporting to the EU should be identified as the primary responsible operators for obtaining the written confirmation from their local competent authorities.** They have direct interactions with their local competent authorities and are responsible for exporting API to the EU. This aspect could be cross-referred in the delegated act on API GMP. **The EC/EMA/MSs in cooperation with 3rd countries should establish and maintain a central list of 'authorised signatories'** (i.e. API exporting 3rd countries local competent authorities responsible for the issuance of the written confirmation - according to the model of the EU Commission's single and central lists of approved food establishments published by each Member State[9]). This will facilitate the verification of the validity of the 'written confirmation' by border/customs officials and manufacturing authorisation holders or importers. **The written confirmation should be stored in a central and public EU repository for easy access by the EU and 3rd countries' Competent Authorities, Manufacturing Authorisation holders, as well as border/customs officers.** The EudraGMP database already contains information related to importation (e.g. Import Licenses). It is already used for cross-referencing the latest available certificates and licenses

[9] http://ec.europa.eu/food/food/biosafety/establishments/list_en.htm

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			and would allow manufacturing authorisation holders to ensure compliance with the requirements of article 46b of the Falsified medicines directive. **The management of 'copies' of a written confirmation to be accompanying each shipment deserves early consideration.** The necessary safeguard should be in place so that only genuine 'copies' are in circulation.
	5	**Any other issue or comment** - **WRITTEN CONFIRMATION –** Role of EU border/customs officials	**A written confirmation template needs to be developed in conjunction with customs and border officers.** EU borders/customs officials will be responsible for validating or allowing import. The HMA Working Group of Enforcement Officers is an existing platform where the network between regulatory authorities and customs is already established and would provide an adequate forum to initiate such discussions.
	5	**Any other issue or comment** - **WRITTEN CONFIRMATION – TRANSITIONAL MEASURES**	**Need for transitional measures (6 years) for operators with a track record of equivalent GMP compliance** Only after EU Member States have clarified their expectations/requirements and processes, will API exporting 3rd countries competent authorities be in a position to develop their own implementation action plan, procedures and processes. • EU Member States (and EMA guidelines) should therefore o Aim at a harmonised approach to minimise unnecessary complexity o Consider the necessity of a transition period after having clarified requirements allowing industry and API exporting 3rd countries to prepare for their entry into

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			force • Non-EU API 3rd countries would then have to o Develop request and issuance mechanisms for the written confirmation (signatories) as well as o Organise the necessary GMP supervision (where needed) o Establish a rapid alert mechanism with the EU (where needed) o Notify the EMA of the 'authorised signatories' from the local competent authorities, responsible for the issuance of the written confirmation • The transition period (from the date the requirements and expectations are made clear) should be **6 years** provided GMP compliance is evidenced.
	5	**Any other issue or comment** **- WRITTEN CONFIRMATION – OPEN QUESTIONS**	**- Are Investigational Medicinal Products (IMPs) in the scope of the applicability of the 'written confirmation' for API imports?** **- Would pre-treated APIs (i.e. manufacturing intermediates) be considered in the scope of applicability of the written declaration? e.g. API plus Aerosil for better flowability, direct compressible API (granulated)** **- Will the EC extend the 'operational' implementation of the FMD that 'active substance import' shall be understood as both bulk API and API within a finished dosage form in order to fulfil the objective of harmonisation of GMP for APIs?** Taking into account the definition of active substance as introduced in Dir. 2011/62/EU, it implies that article 46b would apply only to "bulk non-EU API import" ('*any substance […] intended to be used in the manufacture of a medicinal*

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			product'). Understanding that the intentions of the FMD are to create a level playing field for API quality, the mere fact of not including the import of a non-EU API already within a finished dosage form would create a legal gap by which a difference in GMP/GDP supervision requirements and in the administrative steps would be required. This could likely trigger a shift from "bulk non-EU API import" to import of finished dosage forms (implying a shift of EU based production outside the EU) to circumvent the additional administrative burden. - **Are there considerations regarding the temporary acceptance of locally issued GMP certificates by a local inspectorate during the transition period where the 'written confirmation' might not be readily available?** Certain Member States currently require locally issued GMP certificates provided they specifically refer to the standards against which the certification was made e.g. WHO GMP. This would however not work for all countries (e.g. China), where some APIs can be produced for export only (and not for the local market, because of patent reasons) consequently they are not yet under scrutiny by the local authorities. - **What will be the consequences and processes in place in situations where following an EU GMP inspection or a company audit, a site already benefiting from a 'written confirmation' is found to be out of compliance with EU GMP?**

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<tr><th>Paragraph</th><th>Consultation Item No.</th><th>Question/Topic</th><th>Comment</th></tr>
<tr><td></td><td>5</td><td>Any other issue or comment
INTERNATIONAL COOPERATION</td><td>The EGA is a strong supporter of increased international cooperation as a key manner to meet the challenges of a globalised pharmaceutical industry and the need for global supervision schemes.
The EGA encourages the exchange of information among competent authorities as well as intensified recognition of inspection outcomes to limit redundant inspections and enhance overall regulatory supervision (e.g. of API manufacturers not inspected to date). We acknowledge that mutual recognition is a complicated step to achieve outside the EU however we believe that the integration of 3rd country inspection outcomes in the risk-based assessment and prioritisation of inspections could already provide a significant relief for collaborating competent authorities worldwide.</td></tr>
<tr><td></td><td>5</td><td>Any other issue or comment
MEDICINES SHORTAGES – Lessons learnt</td><td>Scarcity of supply is a well-known driver for criminal and fraudulent activities. They need to be prevented and when effective they deserve immediate and maximum attention.

The USA are undergoing an unprecedented number of medicines shortages.

For each of 127 shortages in 2010-11, the US FDA took one of several approaches below:

<table>
<tr><th>Action</th><th>Shortages</th></tr>
<tr><td>Asked other companies to boost production</td><td>31%</td></tr>
<tr><td>Exercised regulatory discretion</td><td>28%</td></tr>
<tr><td>Expedited review of other sources</td><td>26%</td></tr>
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Took no action	6%
Exercised discretion on importation	5%
Asked sole source to boost production	3%
Other	1%
Total	**100%**

Source: "A Review of FDA's Approach to Medical Product Shortages," Food and Drug Administration, October 2011 (**www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/ucm277755.pdf**)

It is interesting to note that in almost 60% of the cases, the US FDA had to take measures to ensure supply chain continuity. In a very recent situation, the US FDA had to use its "*regulatory authority to temporarily permit Indian drug maker Sun Pharma to import its ovarian cancer and multiple myeloma medicine Lipodox (doxorubicin hydrochloride liposome injection) into the US, even though the product is not approved for marketing by the agency, to fill the shortage of Janssen Products' Doxil, which contains the same active ingredient.*" *Source | Scrip, 22 Feb 2012* *http://www.scripintelligence.com/home/Shortage-crisis-drives-temporary-importation-quick-OK-of-cancer-drugs-327235*

The EGA proposals made in the present document:

- **Echo the 'emergency' measures taken by other authorities in crisis situations and**
- **Are intended to support early identification of**

Paragraph	Consultation Item No.	Question/Topic	Comment
			solutions before the problem of shortages actually occurs.