EUROPEAN GENERIC MEDICINES ASSOCIATION (EU)
&
GENERIC PHARMACEUTICAL ASSOCIATION (USA)

JOINT EGA & GPHA RESPONSE TO THE EU-US HIGH LEVEL WORKING GROUP ON JOBS AND GROWTH ON REGULATORY ISSUES

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The European Generic medicines Association (EGA) and the US Generic Pharmaceutical Association (GPhA) greatly support the initiative for setting up a High Level Working Group on Growth and Jobs aimed at creating opportunities for the European and American industries in the globalised economy. We are in favour of measures that seek to increase EU-US trade and investment, to support mutually beneficial job creation, economic growth and international competitiveness.

In this context, the EGA and the GPhA would like to put forward five practical priority measures for our respective industries that we trust will improve the regulatory environment for generic and biosimilar medicines in Europe and in the US and facilitate business on both sides of the Atlantic.

These are 1) global development and harmonisation of data requirements for approval of biosimilar medicinal products, 2) a single development programme and harmonisation of data requirements for approval of generic medicinal products, 3) mutual recognition of compliance inspections 4) the different regulatory IP systems between Europe and the US support the fact that the systems do not need to be harmonised in all aspects and 5) an advanced manufacturing provision.

1. Global Development and Harmonisation of Data Requirements for Approval of Biosimilar Medicinal Products

The EGA and the GPhA call on the newly established High-Level Working Group on Jobs and Growth to support a regulatory framework which allows a single development programme for biosimilar medicinal products for the European Union (EU) and the United States of America (USA). Such a programme would substantially reduce the development costs of biosimilar medicines and therefore enable the European as well as the American biosimilar industry to considerably increase patient access to high quality biopharmaceuticals, while at the same time boost their competitiveness and support the sustainability of their respective healthcare systems.

The EU was the first worldwide to put in place a legal and regulatory framework for the registration of biosimilar medicines and is consistently developing general and product-specific scientific guidelines. But the cost of development of a biosimilar for one region ranges between EUR 100 and 220 million / USD 120 and 266 million depending on the molecule. Duplication of trials for other regions involving the biosimilar and the same reference product is unethical, unnecessary and definitely uneconomical. The moment has come for this young industry to capitalise on its very high investments and increase its competitiveness and growth.

The three draft guidance documents on biosimilar medicines issued by the US Food and Drug Administration (FDA) on 15 February 2012 as part of the implementation by the FDA of the new abbreviated biosimilar pathway created in the US Biologics Price Competition and Innovation Act of 2009 now provide an excellent opportunity to work together on avoiding the unethical conduct of duplicative trials and on moving towards a harmonised approach in regulating this new category of medicines. The EU (EC/EMA) and the US FDA have identified biosimilars as a topic area of mutual interest for the two agencies. A new 'cluster on biosimilar medicines' was created in June 2011 which provides a framework for the regular exchange of information and collaborative meetings.

Therefore, the EGA and the GPhA hereby call for continued support for these very important regulatory developments between the EU and the US and for formal recognition by the EU-US High Level Working Group of the importance of this sector. Putting in place a scientific framework supporting the development of a single biosimilar development

programme for the EU and the US will boost the competitiveness and growth of the biosimilar medicines industry on both sides of the Atlantic.

Biologicals indeed represent the fastest growing pharmaceutical market worldwide and patents have expired or are about to. Creating together a competitive regulatory framework for biosimilar medicines, based on sound science, will enhance growth, jobs and health in the EU and the US and consequently enhance the global competiveness of this industry.

	RECOMMENDATIONS – BIOSIMILAR MEDICINES
1	Increase the EU /US FDA 'biosimilars cluster' interactions;
2	In the EU, adapt the so-called overarching EMA biosimilar guideline allowing global development for biosimilars (revision of CHMP/BMWP/572643/2011 ongoing);
3	In the US, achieve a firm and definite commitment from the FDA regarding the use of non US sourced reference products in comparative clinical trials for proving biosimilarity;
4	Organise a yearly EU/US regulators' workshop on biosimilars around the biosimilars cluster face to face annual meetings.

2. A Single Development Programme and Harmonisation of Data Requirements for Approval of Generic Medicinal Products

With the globalisation of markets, an increasing number of generic medicines manufacturers are keen on introducing their products on both the EU and the US markets. In view of this trend, and given the pressing need to boost competitiveness in both Europe and the USA, as well as in response to the challenges of globalisation, the EGA and the GPhA call on the EU-US High Level Working Group on Jobs and Growth to consider among its priorities and deliverables with substantial impact the need for simplification and stimulation of the recognition of assessments of generic medicinal products between the EU and the US, in order to avoid duplications and to ensure faster access to pharmaceuticals for patients in both markets.

A Single Development Programme for Generic Medicines instead of the duplication of studies (coherent with the idea of a Global Development Programme for Biosimilars outlined above) is an area where the EGA and the GPhA see potential for cutting inefficiencies, responding to the needs of patients and gaining from larger markets. A Single Development Programme for Generic Medicines would entail three key elements:

- A more harmonised approach with regard to which studies are requested to support generic and hybrid applications;
- More harmonised criteria that have to be met for an application to be successful;
- Sourcing the same reference product from the EU and the US markets for the purpose of trials and studies mutually accepted by the EU and the US.

A more harmonised approach will be particularly beneficial for more complex generic products (e.g. pre-filled syringes, inhalers, patches, modified release products) for which an abridged clinical programme is requested for marketing authorisation application in the EU and the US. Such a programme would substantially reduce the development costs and an unethical duplication of studies. This would allow increasing patient access to high quality and more affordable generic medicines, while at the same time boost their competitiveness and support the sustainability of the respective healthcare systems.

Accelerating harmonisation of pharmacopoeia (USP-NF and Ph Eur) for further achieving the above point is another concrete element which would contribute to the simplification and harmonisation of the two systems. Based on the history of initiatives such as the ICH (International Conference on Harmonisation) topic Q4B 'Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH regions' and the Pharmacopoeial Discussion Group[1] (PDG), the EGA and the GPhA call for a pragmatic approach to:

- The recognition of monographs which do not exist in one of the pharmacopoeia, and
- The joint and collaborative elaboration of new monographs.

This would greatly streamline and simplify the way industry operates in the two regions.

It is important that the EU and the US further enhance mutual trust and confidence building through initiatives (such as the pilot parallel assessment of Quality by Design applications[2]).

Another area where industry and regulators in both the EU and the US could create more effective collaboration relates to the filing and review of Drug Master Files (DMF), also called Active Substance Master File (ASMF) in the EU, for active substances used in medicinal products.

The generic medicines sector operates on a multisource model where several manufacturers produce a medicine with the same active substance. They often use external suppliers for the active substance. Consequently, the exact same DMF (or ASMF) ends up being submitted, assessed and reviewed multiple times by both the EU and the US authorities.

The mutualisation of assessment efforts by the EU and the US could help optimise authorities' resource allocations but also potentially reduce the overall abridged application review procedure timelines.

Such collaborative efforts will help identify and resolve potential gaps (e.g. interpretation, approach) even in situations where in theory, regulatory concepts and approaches are harmonised (e.g. via ICH).

In this regard, we would recommend the setting up of a new 'cluster' between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) dedicated to abridged applications. The clusters are topic areas of mutual interest for the two agencies, which they have identified as benefiting from the regular exchange of information and collaborative meetings. The current experience shows that the EMA-FDA clusters are a very useful discussion platform between the competent authorities from both sides of the Atlantic. The creation of the new biosimilar medicines cluster in 2011 only confirms this experience. A new cluster dedicated to generic medicines would be a perfect platform to discuss all possible aspects of greater harmonisation of the development and assessment of generic medicines based on scientific criteria.

RECOMMENDATIONS – GENERIC MEDICINES

[1] Pharmacopoeial Discussion Group (PDG) Achievements, EDQM Press Release, 20 June 2012, http://www.edqm.eu/site/pharmacopoeial_discussion_group_achievementspdf-en-30955-2.html, July 2012

[2] EMA-FDA pilot program for parallel assessment of Quality by Design applications - http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103621.pdf

1	Create an EU/US 'generics cluster' which would specifically support optimisation of - approach with regard to which studies are requested to support generic and hybrid applications and the use of the same reference product sourced from both the US and EU markets; - criteria that have to be met for an application to be successful; - DMF (or ASFM) review process and recognition of assessment.
2	Foster pragmatic evolution of pharmacopoeia (USP and Ph Eur) through: - the recognition of monographs which do not exist in one of the pharmacopoeia; and - the joint and collaborative elaboration of new monographs.

3. Mutual Recognition of Compliance Inspections between Europe and the USA

To establish a true level playing field, particularly in the area of pharmaceutical Good Practice (GxP) inspections, supporting fair global competition while overcoming the issue of limited resources in both the EU and the USA, there is a need for the full utilisation of the regulatory relief offered by the EU/US Mutual Recognition Agreement (MRA), complemented by the development of alternative, less formal collaborative schemes and a more centralised coordination of inspection activities.

The EGA and the GPhA recognise the efforts put into initiatives such as the pilot international collaboration programme on good manufacturing practice inspections for active substances between the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and Australia's Therapeutic Goods Administration (TGA) that was carried out in 2010. The scheme has fostered greater collaboration and trust between regulators from the participating regions. This project has allowed a better prioritisation of inspections through information-sharing on inspections, including planning, policy and reports, for manufacturers of active pharmaceutical ingredients that are located outside the participating countries. The EGA and the GPhA welcome the fact that the scheme has now been extended beyond its pilot phase to become permanent and that it is open to new participating regions/countries. The EGA and the GPhA commend the boost of cross-border collaboration and the increased number of joint inspections or alternatively, reliance on partner regulators' reports. We believe that regulators as well as pharmaceutical and API manufacturers would benefit from reduced redundant inspections and increased partnerships in the field (e.g. mutualisation of database, intelligence, IT and human resources). As the EMA noted, the cooperation has shown that "there is a need for an improved shared inventory of sites of common interest and supporting software applications and a need for longer planning lead times to arrange joint inspections"[3].

In this regard, the European Generic medicines Association (EGA) and the Generic Pharmaceutical Association (GPhA) welcome the joint initiative of the EMA and the FDA from 7 December 2011 for enhancing GMP inspection collaboration, not only focusing on information sharing, but also ultimately relying upon that information to meet inspectional obligations, including confidentiality arrangements, participation in joint inspection and information-sharing projects. The EGA and the GPhA see major opportunities for gaining inspection resource efficiencies from moving on beyond existing collaborative projects towards reliance on each other's inspection outcomes. The joint efforts towards applying a mutual recognition approach are of high importance given the large number of inspections carried out by the FDA in the EU and vice versa, and especially in view of the shift of manufacturing base away from Europe and the USA and towards other regions.

[3] "Joint API inspection pilot a success, says EMA", by Gareth Macdonald, In Pharma Technologist, 8 November 2010

This is particularly important in view of the 1999 signed EU/US Mutual Recognition Agreement (MRA) and the unfortunate situation through which it never became operational. An operational entry into force would clearly lead to a relief of unnecessary administrative and regulatory burden while safeguarding the quality of medicinal products and the safety of EU and US patients.

Mutualisation of inspection efforts will also contribute to bringing a level playing field to all pharmaceutical supply chain operators through the headroom provided for more manufacturing sites to be visited in countries / regions outside the EU and USA. This will help the competitiveness of all US and EU operators with these of third countries where operators are, today, less subject to such inspections.

Finally, the proposed mutual recognition initiative will bring relief to manufacturers who also put substantial resources into hosting inspections, sometimes with intervals of only weeks.

	RECOMMENDATIONS – INSPECTIONS
1	Further develop collaborative approaches in the field of GMP in order to achieve: - the centralisation of data related to manufacturing sites of interest; - the planning and prioritisation of inspections,
2	Re-engage the process to render the EU/US MRA fully operational to bring substantial regulatory and administrative relief through recognition of inspections outcomes.

4. The Different Regulatory IP Systems between Europe and the US Support the Fact that the Systems Do Not Need to be Harmonised in All Aspects

The EGA and the GPhA recognise that the EU and the US operate different regulatory IP rights / data/ market exclusivity systems for pharmaceuticals, although with some areas of overlap. These differences are illustrated in the table below:

IP Elements	EU	USA
Data Exclusivity (DE), Market Exclusivity (ME) (years) and Filing Moratorium (FM)	Generics and Biosimilars: 8 (DE) +2 (ME) +1 (New Indication) No DE for line extensions (part of the so called Global Marketing Authorisation)	Generics: 5 years (FM), 3 years for changes to an application that are supported by a clinical study Biologics: 12 years (ME)
Bolar	Restricted Bolar (only since 2004)	Broad Bolar (since 1987)
Patent Linkage	NO	YES
First Mover Incentive	NO	YES (6 months exclusivity)
Supplementary Protection Certificate (SPC)	YES (up to 15 years)	YES (up to 14 years)
Pediatric	YES (+ 6 months SPC)	YES (6 months of DE)

Extension		
Market Share (volume)	50 %	80%
Advanced Manufacturing	NO	NO

Therefore it will be more constructive to keep intellectual property / data protection rights out of the scope of this exercise. For this reason we recommend to not attempt to create harmonisation in this area but to recognise the different approaches, as the intentions and history behind them are different.

	RECOMMENDATION – IP RIGHTS
1	Do not try to harmonise the European and the American Intellectual Property Rights / Data/ Market Exclusivity systems, but recognise the wide differences between them.

5. Advanced Manufacturing Provision

A concrete way in which the EU and the US can support their generic and biosimilar medicines industries' competitiveness globally is by adopting a provision for advanced manufacturing of generic and biosimilar medicines, which currently is not available in either of the two regions. This provision would allow European and American companies to manufacture and stockpile generic and biosimilar medicines in Europe and the USA respectively during the Supplementary Protection Certificate / patent extension period, without considering this as a patent infringement, in order to be ready to launch their products immediately on their markets after patent expiry or to export to countries where no patent /SPC is in place. Such a provision would provide a boost for jobs and growth in the manufacturing sector of both the USA and the EU with no negative consequences for patent holders[4].

	RECOMMENDATION – ADVANCED MANUFACTURING
1	Introduce an advanced manufacturing provision for generic and biosimilar medicines in both the EU and the USA

6. Conclusion

In conclusion, the EGA and the GPhA are confident that if implemented the five proposed measures: 1) global development and harmonisation of data requirements for approval of biosimilar medicinal products, 2) a single development programme and harmonisation of data requirements for approval of generic medicinal products between the EU and the US, 3) mutual recognition of compliance inspections, 4) the different regulatory IP systems

[4] An advanced manufacturing provision would enable the European and American generic and biosimilar industries to become more competitive as compared to local producers from emerging markets. Over the next decade, an opportunity of 90 billion Euro globally is opening up due to the patent expiries of biopharmaceuticals. At the same time, the global generic medicines market is set to experience a predicted 10% annual net growth, reaching 92 billion Euro in 2012. Countries such as India and South Korea have already established task forces in order to promote strategies that would see them evolve into important hubs for medicine development and manufacturing, particularly in the generic and biosimilar medicines sectors. We call on the EU and the US to do the same by adopting an advanced manufacturing provision, to remain globally competitive and save jobs within their territories.

between Europe and the US support the fact that the systems do not need to be harmonised in all aspects, and 5) an advanced manufacturing provision, would bring a substantial improvement to the regulatory environments in both the EU and the US, which in turn would stimulate competitiveness and foster growth and jobs in both regions during these critical times of austerity.

7. Full List of Recommendations

Therefore to achieve the above, we recommend:

	FULL LIST OF RECOMMENDATIONS
	Global Development and Harmonisation of Data Requirements for Approval of Biosimilar Medicinal Products
1	Increase the EU /US FDA 'biosimilars cluster' interactions;
2	In the EU, adapt the so-called overarching EMA biosimilar guideline allowing global development for biosimilars (revision of CHMP/BMWP/572643/2011 ongoing);
3	In the US, achieve a firm and definite commitment from the FDA regarding the use of non US sourced reference products in comparative clinical trials for proving biosimilarity;
4	Organise a yearly EU/US regulators' workshop on biosimilars around the biosimilars cluster face to face annual meetings.
	A Single Development Programme and Harmonisation of Data Requirements for Approval of Generic Medicinal Products
5	Create an EU/US 'generics cluster' which would specifically support optimisation of - approach with regard to which studies are requested to support generic and hybrid applications and the use of the same reference product sourced from both the US and EU markets ; - criteria that have to be met for an application to be successful; - DMF (or ASFM) review process and recognition of assessment.
6	Foster pragmatic evolution of pharmacopoeia (USP and Ph Eur) through: - the recognition of monographs which do not exist in one of the pharmacopoeia; and - the joint and collaborative elaboration of new monographs.
	Mutual Recognition of Compliance Inspections between Europe and the USA
7	Further develop collaborative approaches in the field of GMP in order to achieve: - the centralisation of data related to manufacturing sites of interest; - the planning and prioritisation of inspections.
8	Re-engage the process to render the EU/US MRA fully operational to bring substantial regulatory and administrative relief through recognition of inspections outcomes.
	IP Rights
9	Do not try to harmonise the European and the American Intellectual Property Rights / Data/ Market Exclusivity systems, but recognise the wide differences between them.
	Advanced Manufacturing Provision
10	Introduce an advanced manufacturing provision for generic and biosimilar medicines in both the EU and the USA.