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Transatlantic Administrative Simplification Action Plan – Final Report on implementation

Under the auspices of the Transatlantic Economic Council, on 28 November 2007 the European Commission hosted the Transatlantic Administrative Simplification (TAS) Workshop which was co-chaired by the European Commission and the United States (U.S.) Food and Drug Administration (FDA) and organised in collaboration with the European Medicines Agency (EMA) and the Heads of the EU National Medicines Agencies (HMA). The key objective was to identify opportunities for administrative simplification through transatlantic cooperation at the level of administrative practices and guidelines.

As a follow up of the workshop, a "Medicines Regulation Transatlantic Administrative Simplification Action Plan" was published in June 2008, outlining 15 administrative simplification projects to be taken forward.

A progress report on the implementation of the TAS Action Plan was published in September 2009.

During the annual EC/EMA-FDA bilateral meeting in September 2010, the parties updated on the progress with implementation of the administrative simplification projects as outlined in the table below. In addition, since the most of the TAS projects have now been completed, it was agreed that ongoing developments in these areas and/or new transatlantic administrative simplification initiatives will be included in the annual report on EMA-FDA interactions. Reports on EMA-FDA interactions will be regularly discussed at annual EC/EMA-FDA bilateral meetings and published on a yearly basis on the international webpages of the agencies' websites:

- FDA International Programs webpage;
- EMA Partners and networks webpage.

#	Project title	Note in 2008 Action Plan	Update 2010
1	Collaboration on inspections	The European Commission/European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) will pilot joint inspections of companies manufacturing pharmaceuticals in the US and in the EU and of companies manufacturing active pharmaceutical ingredients in third countries.	Two joint inspections of manufacturing sites in the EU were successfully completed in April (Ireland) and July 2009 (UK). The initial scope of this collaboration focused on pre-approval inspections of finished products, for which marking authorisation applications had been submitted around the same time to both the FDA and EMA. Since the number of such 'parallel' submissions in 2010 was limited, and since the need for a pre-approval inspection had not been identified by either the FDA or EMA for any of those submissions, no joint finished product inspection under this pilot took place in 2010. In order to increase the opportunities for joint inspections, the FDA and EMA have agreed to extend the scope of the pilot to include routine post-authorisation (surveillance) inspections of manufacturing sites for which an inspection is planned around the same timeframes by both regulators. Inspection plans are being exchanged and planning for possible joint routine/surveillance inspections is currently ongoing. A reminder about the inspection collaboration was published on the EMA's website in August 2010, inviting companies to participate in the pilot program for upcoming FDA or EMA pre-approval or routine/surveillance inspections.

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2	Collaboration on 3rd-country inspections	The Commission/EMA and the FDA will pilot the exchange of inspection schedules, results and information on inspected manufacturing sites in order to attain more GMP inspection coverage collectively and to better identify manufacturing sites producing active pharmaceutical ingredients in third countries.	Following publication of the pilot project for exchange of API inspection information, the operational phase of the project started in December 2008 with the sharing of inspection plans and information on inspections carried out by the FDA, EMA/EU and TGA in the last 24-36 months. As the setting-up of the practical details to implement the project took more time than expected, it was decided in November 2009 at a meeting of the regulatory authorities participating in the pilot, in Washington DC, to extend the pilot until the end of 2010. An interim report on progress to June 2010 (the original end-date of the pilot), has been published by the EMA and TGA in October 2010 and by the FDA in January 2011, and a final report will be published in July 2011. The reports illustrate the extensive exchange of API inspection plans and inspection reports, leading to increased transparency in inspections performed by participating authorities, as well as to an increase in number of inspections which are of value to more than one authority. The 9 joint API inspections conducted under the pilot (5 in India, 1 in Croatia, 1 in Mexico, 1 in Japan and 1 in China) have helped to build up confidence between the participants, and have facilitated better use of EU/FDA combined inspection resources. The GMP inspection collaboration reports can be found here.
3	Dedicated facilities for high-risk products	The Commission/EMA and the FDA will step up collaboration to determine to what extent dedicated production facilities are necessary for certain drugs, taking into account a risk-based approach.	Following extensive preparatory discussions in the EU GMP Inspectors Working Party in 2009 and 2010, drafting of the revised EU guideline started in June 2010 and early drafts were shared with the FDA in order to explore the best international risk-based approach to address this issue. In addition, further work on developing a toxicological tool is required, to enable implementation of the guideline.

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4	Biomarkers	The EMA and FDA have recently announced successes in their transatlantic work on biomarker development and joint validation for various product development purposes. Both parties will continue to work on this initiative with a view to further biomarker development and joint validation.	In addition to the initial joint qualification in 2009 of 7 nephrotoxicity biomarkers submitted by the C-Path Predictive Safety Testing Consortium (PSTC), the EMA and FDA continued their transatlantic work on biomarker development and joint qualification for various product development purposes. One common EMA-FDA procedure (ILSI/HESI nephrotoxicity biomarker qualification), which was started in 2009, has been finalised and three new qualification procedures are ongoing or in the pre-submission phase. In addition, at the quarterly FDA-EMA pharmacogenomics 'cluster' teleconferences, joint FDA-EMA briefing meetings were held with several companies developing new biomarkers (e.g. for liver toxicity and for patient selection in cancer treatment). Product-specific biomarkers were also discussed, as well as 1 FDA and 3 EMA draft guidelines in the area of pharmacogenomics.
5	Regulatory collaboration on the outputs of the Critical Path and Innovative Medicines Initiatives	The EMA and FDA will exchange assessments of the outputs of the Critical Path and Innovative Medicines Initiatives relevant to medicines regulation and will report findings to the 2009 EC/EMA-FDA bilateral meeting.	The FDA and EMA are collaborating in a number of Critical Path (CP) and Innovative Medicines Initiative (IMI) topics which are of common interest. Information-sharing and collaboration are ensured by representation of both the EMA and FDA on project steering/advisory boards. In addition, the EMA and FDA are discussing specific validation or qualification requests from CP or IMI consortia that have been submitted to both agencies (e.g. for patient-reported outcomes).
6	Combating counterfeit / falsified medicines	In addition to the collaborative work with the WHO IMPACT initiative, the FDA and Commission will exchange information on future requirements for track-and-trace and authentication systems. The Commission/EMA and FDA will exchange information on specific cases of counterfeits.	In addition to the collaborative work with the WHO IMPACT initiative, exchange of information on specific counterfeit cases detected in the legitimate supply chain occurs through the international rapid alert systems. The Commission and the FDA continuously update each other on regulatory changes, including those related to the new EU legislation on 'falsified medicines' (Directive 2011/62/EU), such as requirements for track-and-trace features.

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7	Collaboration on product-specific risk management	Under the EC/EMA-FDA confidentiality arrangements, the EMA and FDA will intensify bilateral discussion on proposed specific risk-management initiatives for specific new medicinal products and report to the 2009 EC/EMA-FDA bilateral meeting.	Discussions on product-specific RMPs/REMS have taken place as part of the 2-monthly Pharmacovigilance Videoconferences that take place between the FDA and the EMA's Pharmacovigilance Working Party. In addition, further to the extensive discussions between the FDA and EMA on Tysabri and risk-minimisation measures to prevent development of progressive multifocal leukoencephalopathy (PML), which took place at the end of 2009/early 2010, a need to look at collaboration in this area was identified. Consequently, a 'Progressive Multifocal Leukoencephalopathy (PML) Research Agenda' is being developed in collaboration with the FDA. The project addresses drug-related PML as an adverse event of different immunosuppressive drugs (especially monoclonal antibodies). The agenda is not product specific and aims at stimulating JC virus (JCV) and PML research. The main objective is to improve public health by accelerating the delivery of answers to JCV and PML knowledge gaps that could impact on the prevention or treatment of drug-induced PML. A joint EMA/FDA scientific paper and a scientific workshop on JCV and PML research will take place in London on 25-26 July 2011. Information on the workshop can be found here.
8	Convergence of risk-management formats	The EU and US pharmaceutical industries are invited to conduct a study to compare EU and US approaches to risk-management formats (e.g. E2E, Volume 9a RMP guidance, REMS, etc.) and to identify opportunities for convergence.	Informal discussions between the FDA and EMA took place in 2010 and the review of the EU risk-management guideline is ongoing. The draft revised guideline will be shared with the FDA before public consultation. The current revision of the EU risk-management guideline will require RMP information to be presented in a modular format, which will allow using the 'common' parts of RMPs for submissions to other regulatory authorities. The EMA and FDA area also collaborating as part of CIOMS IX, which is looking at harmonisation of risk-management tools. CIOMS IX activities started in March 2010. Feedback from the industry study/survey on EU & US risk-management formats and opportunities for convergence is still awaited.

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9	Increasing the uptake of parallel transatlantic scientific advice	Voluntary industry parallel scientific advice for human medicines to be opened to all medicinal products covered by clusters (e.g. paediatrics, oncology, vaccines, orphans, pharmacogenomics). Review of industry uptake and recommendations on procedures by end of 2009.	Following a rather slow uptake in previous years, in 2010, the EMA and FDA discussed 7 new parallel scientific advice (PSA) procedures. WHO experts were involved in two of these, due to the therapeutic area covered by the request. In addition to the formal parallel scientific advice exchanges between the FDA and EMA, ad-hoc informal scientific advice teleconferences between the agencies took place for five products in 2010. In addition, information on EU and FDA scientific advice procedures is routinely exchanged as part of the oncology FDA-EMA 'cluster' interaction. To increase transparency in this area and to further increase awareness of the possibility of PSA, statistics on the number of PSA procedures are now included in the CHMP monthly report.
10	Exchange of information on herbal medicines	The EMA Committee on Herbal Medicinal Products to provide draft and final monographs to FDA.	Transmission of final Community herbal monographs from the EMA's Committee on Herbal Medicinal Products to the FDA has taken place and continues on a 6-monthly basis. The FDA has also been invited to provide comments on draft monographs that are published on the EMA's website for consultation. Ad-hoc information requests on the (medicinal) use of a specific plant in the EU or US may also take place between the two agencies.
11	Collaboration on biosimilar medicinal products / follow-on biologicals	The EMA and FDA will compare their experience of biosimilar medicinal products / follow-on biologicals and will report to the EC/EMA-FDA bilateral meeting by end of 2009.	Initial FDA-EMA discussions took place at the end of 2008. A teleconference in the context of a Biosimilar Working Party (BMWP) meeting was held at the end of February 2009, and FDA experts attended the EMA workshop on biosimilar monoclonal antibodies in July 2009. Following adoption of the US health care reform bill, HR 3590 'Patient protection and affordable care act' in 2010, which gives the FDA the authority and responsibility to regulate biosimilar biological products, the EMA and FDA are exploring further enhanced collaboration in the area of biosimilars (e.g. under the form of a new 'cluster').

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12 and 13	Collaboration on development of medicinal products for children	Under the EC/EMA/FDA confidentiality arrangements, the EMA and FDA will intensify bilateral discussion on the development of specific medicinal products for children and will report to the 2009 EC/EMA-FDA bilateral meeting.	Bilateral discussions via monthly teleconferences at which selected paediatric development plans are discussed continued in 2010, in addition to a number of ad-hoc teleconferences. Paediatric information on 50 products was discussed during the paediatric teleconferences from October 2009–Dec 2010. FDA experts have participated in the meetings of the PDCO's Non-Clinical Working Group and the Formulation Working Group since the end of 2009. The EMA has provided access to FDA colleagues to its internal database that includes scientific details of all PIPs. Staff exchanges and agency visits continued in 2010: 3 EMA staff members visited FDA OPT in 2010, including being given the opportunity to listen in to the PERC. Visits of FDA staff to observe some of the activities of the EMA, including PDCO meetings, also took place.
14	Advanced therapy medicinal products	Under the EC/EMA-FDA confidentiality arrangements, by end 2008, establish a 'cluster' on advanced therapy medicinal products. The cluster to strive for scientific excellence and harmonisation of terminology for new technologies, and to make recommendations for transatlantic convergence in the administration of regulations for these medicinal products.	Four bilateral FDA-EMA 'cluster' teleconferences took place in 2010, in the margins of the EMA CAT meetings. The agendas of such teleconferences are agreed jointly between FDA/CBER/OCGT and the EMA on the basis of discussions at the CAT (CAT table of decisions shared with FDA) and FDA regulatory activities (overview document received from FDA). Staff exchanges and agency visits continued in 2010. FDA colleagues participated in an EMA-organised workshop on stem-cell medicinal products in May 2010, and subsequently attended the CAT meeting which took place on the following day. An EMA staff member from the CAT secretariat visited FDA/CBER/OCGT in November 2010.

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15	Safety-reporting from clinical trials	EU/FDA reconfirm their commitment to pursue these topics through ICH.	ICH E2F Guideline on Development Safety Update Report (DSUR) reached Step 4 in August 2010. In November 2010, a pharmacovigilance brainstorming session was held for an overarching discussion on safety-update reporting in view of DSURs and periodic safety update reports (PSURs) aimed at optimising the lifecycle benefit/risk of medicines for the promotion and protection of public health.
	Harmonisation of business rules for single case reports		The E2B(R3) expert working group 'Revision of the Electronic Submission in Individual Case Safety Reports', a pilot process that involved work in parallel with standards development organisations, progressed the E2B(R3) Implementation Guide (IG) to Step 2, which will be released for regulatory public consultation in summer 2011.
	Maintenance and updating of the ICH CTD		The M2/M8 expert working group, in collaboration with the CTD-Quality IWG, has completed the first set of Q&As based on change requests processed by the M2 (now M8) EWG. The second and third sets of questions are under discussion by the CTD-Quality IWG.
	Electronic CTD		In November 2010, the ICH Steering Committee endorsed the creation of a new expert working group (M8), tasked with producing a Step 4 implementation guide for the next major version of the electronic common technical document (eCTD NMV), while continuing to support the current ICH eCTD v3.2.2 and STF v2.6.1 standards as the eCTD IWG.