EFPIA and PhRMA Joint Submission to the Call for Proposals for EU-US Regulatory Cooperation Activities

Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) appreciates the opportunity to provide input to the European Commission's public consultation regarding proposals for EU-US regulatory cooperation activities. The proposals outlined in this submission have been developed jointly with EFPIA's sister association in the US, the Pharmaceutical Research & Manufacturing Association (PhRMA), and were also submitted to the US authorities.

The pharmaceutical industry, both larger companies and small- and medium sized ones, as well as regulatory authorities, see great benefits stemming from the Mutual Recognition Agreement (MRA) completed in 2017 (and under ratification currently) between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Under the existing MRA, the EU and US are able to avoid unnecessary duplicate inspections and thereby realise savings of the order of €350,000 ($380,000) per average inspection[1]. We strongly call for all steps to be taken to ensure that the current MRA is complete by July 2019. We are confident that building on this experience, tackling further mutually important and beneficial areas can contribute to delivering life-saving innovative medicines quicker to patients, and result in significant cost-savings for both the regulators and the industry.

To build on the success of this MRA, this paper contains four detailed assessments in areas, where our industry believes that further regulatory cooperation is possible on both sides of the Atlantic:

1. Expansion of the Mutual Recognition Agreement of Good Manufacturing Practice (GMP);
2. Creation of a Mutual Recognition Agreement in the area of Good Clinical Practice (GCP);
3. Closer alignment in the area of paediatric medicines;
4. Ensuring regulatory support for innovation.

We believe the regulatory alignment is possible through process and policy adaptions and do not require legislative changes.

In addition, we also included a fifth point on tariffs for industrial goods:

5. Tariffs on industrial goods.

Broader scope for EU-US relations in pharmaceuticals

EFPIA and PhRMA welcome the European Commission's efforts to forge closer ties with the US through regulatory cooperation and the commitment to reduce tariffs on industrial goods. We also believe there is a need for, and are committed to, further engagement in areas beyond the current regulatory sphere, especially with respect to intellectual property, transparency, and market access. EFPIA remains ready to put forward further proposals in these areas that are of vital importance for our industry. We strongly believe that addressing these areas as well in the future is needed to complete a more encompassing EU-US work programme and a strong transatlantic economic partnership.

[1] http://trade.ec.europa.eu/doclib/docs/2019/january/tradoc_157651.pdf

1. Expansion of the Mutual Recognition Agreement of Good Manufacturing Practice (GMP)

Executive Summary

Good Manufacturing Practice (GMP) principles and related concepts in the US and the EU are comparable, and the implementation of the EU-US Mutual Recognition Agreement (MRA) is starting to prove successful already in its current scope. Therefore, we encourage both parties to proceed with the full implementation and thereupon extension of the MRA to optimize the use of inspectorates' resources and to save costs for industry while maintaining the high standards we know the EU and US to uphold.

Thus, EFPIA invites the relevant parties to especially consider opportunities to maximise the utilisation of resources by:

1. Implementing all the provisions of the current MRA regarding:
   a. Inspections called pre-approval inspections (PAI) in the US (Art. 3.1 and Art. 11);
   b. Recognition of inspections of manufacturing sites in 3rd countries (Art. 8.3);
   c. Biological products, if registered by Center for Biologics Evaluation and Research (CBER) (Art. 4.1);
   d. Medicinal Products with a Medical Device registered as 'Combination Products' in the US by the Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER).
2. Accelerating the joint inspection program of manufacturing facilities for Human vaccines and plasma-derived pharmaceuticals (Art. 20.2) and including Veterinary products (Art. 20.1).
3. Initiating efforts towards expanding the MRA to include:
   a. Waiving of import testing after inspection of manufacturing sites in a 3rd country;
   b. GMPs for Advanced Therapy Medicinal Products (ATMPs) / Cell and Gene Therapies (CGTs).

Finally, we strongly call for all steps to be taken to ensure that the current MRA is complete by July 2019.

Introduction

The current EU-US Mutual Recognition Agreement recognises the equivalence of the inspections and testing process applicable to both active pharmaceutical ingredients and finished medicinal products across regulatory agencies for commercial products. The ongoing implementation of the current MRA industry shows that the number of routine inspections from EU in US and vice versa will be decreasing[2]. This focus of inspection resources arises from the efficiency of avoiding duplication and does not increase any risks for patients. Regulatory expectations in the US and EU during the MRA were adopted to align with the status of innovation. This leads to the opportunity to review and improve the current scope of the MRA.

[2] See also additional clarifications by a Q&A: https://www.ema.europa.eu/en/documents/other/questions-answers-impact-european-union-united-states-mutual-recognition-agreement-marketing_en.pdf (accessed: 03. March 2019)

1. Opportunities to implement all provisions in the current MRA

EFPIA is asking both parties to consider securing progress to implement the recognition of inspections of manufacturing sites in third countries (Art 8.3) and include US recognition of inspections performed by an EU member state inspectorate when they have already inspected processes associated with a new product submitted for authorization, thus avoiding the need for FDA pre-approval inspections (PAI). Further considerations include biological products, where authorised by the Center for Biologics Evaluation and Research (CBER), and clarification around medicinal products containing medical devices (EU) / combination products (US).

Recognizing inspections performed by FDA/EMA outside US/EU territory (3rd countries)

Building on the confidence gained from inspections performed on their own territories, EFPIA would encourage both FDA and EMA to make full use of the Art 8.3 of the MRA and accept each other's inspection outcomes at sites located in third countries building further on recognition. In this way, the agencies will gain additional flexibility and be able to cover more manufacturing sites between them. Furthermore, the level of risk, if any, is further reduced, if this third country is member PIC/S, which can provide an additional layer of confidence. To further elaborate on the avoidance of duplication of inspections and associated GMP certificates of inspections, similar provisions are established and implemented e.g. for the MRA between the EU and Switzerland[3]. Here, the inspection results are also entered into the EU GMDP database (*Community database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing-practice (GMP) and good-distribution-practice (GDP) certificates*). Switzerland has received full access to the database, and all licenses granted for sites based on inspections performed by Swiss inspectors will be entered into the database. Inspectors from the EU and Switzerland have access and recognise the GMP status of manufacturing sites inspected by the other party including those in third countries. Furthermore, the MRA between the EU and Israel[3] includes also "manufacturers in third countries inspected by the regulatory authority of either party if the product also undergoes re-control in one of the parties". EFPIA member companies see this provision successfully implemented.

Pragmatic approach to Pre-Approval Inspections (PAIs)

Both jurisdictions might address specific questions relevant to the dossier on how the GMP processes are executed. As the dossiers are similar, EFPIA member companies do not experience any significant differences between the US' and EU's outcomes of manufacturing sites inspections, if targeted for the registration of a new product. We understand the MRA already allows recognition of PAI (Art. 3.1 of the MRA), and believe that this should now be fully implemented.

Biological products, if registered by CBER

EFPIA member companies report that biological products registered as medicinal products in the EU and as biologicals products with CBER in the US are still subjected to inspection, even if the product/drug is in the scope for the country inspections (Art. 4.1 of the MRA)[4]. As this is not aligned with the current scope of the MRA, we encourage scheduling of inspections of such products to be included in a more systematic manner.

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[3] See for the MRA EU/Switzerland and EU/Israel https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra (accessed: 03. March 2019)

[4] Question 5 of the Q&A on the impact of Mutual Recognition Agreement between the European Union and the United States as of 1 December 2018, 29 November 2018, EMA/752292/2018

Clarifying the scope on Medicinal Products with a Medical Device

EFPIA is confident that inspections of all medicinal products are in the scope of the current MRA, if classified as such. Consequently, it is our understanding that products regulated as 'medicinal products' in the EU, with a device part falling under the EU Medical Device Regulation (No. 2017/745), and as 'drug products' with CDER or CBER, following the US requirements for 'combination products' (21 CFR part 4, which are unfortunately not listed explicitly in the MRA) are also in scope of the current MRA[5].

2. Inspections of manufacturing facilities for Human vaccines, plasma-derived pharmaceuticals and Veterinary products

EFPIA supports the next steps and wants to re-confirm its ask to accelerate the joint inspection program of manufacturing facilities for **human vaccines** and **plasma-derived pharmaceuticals** (Art. 20.2) paving the way for the extension of the MRA to these areas by no later than 2022[6]. Furthermore, inclusion of **veterinary medicinal products** in the scope of the MRA (Art. 20.1) should be confirmed by no later than July 2019.

3. Considerations to expand the scope of the MRA

Waiving of import testing after inspection of manufacturing sites in a 3rd country

EFPIA believes as next step, the waiver should include retesting on import from third countries, if the site was inspected under the MRA. The MRA between the United Kingdom and US has such a waiver for re-testing on import established without restrictions on territories. In this case, our call is not a precedent, neither for the EU Member States, nor the US side.

Opportunity to include GMPs for ATMPs/CGTs

The regulatory and GMP requirements for Advanced Therapeutic Medicinal Products (ATMP) / Cell and Gene Therapeutic products (CGTs) products are still evolving globally. However, EFPIA would like to ensure that the regulatory expectations in the different jurisdictions are based on the basic GMPs adopted to the specific product needs and techniques used. As part of this, we would urge to start considerations on expanding the scope of the MRA to include recognition of inspections of GMP for ATMPs and CGTs.

Progress has already been made by implementing the updated regulatory requirements regarding GMP for ATMPs in the EU[7]. ATMPs are defined in the EU as medicinal products which are either: 'a gene therapy medicinal product or a somatic cell therapy medicinal product or a tissue engineered product'. They hold much promise for major advances in treatment of several diseases, including many that have limited or no other treatment options. The EU has a single regulation (EC 1394/2007, guideline C(2017) 8179) and the US regulates specific elements separately e.g. on Good Tissue Practice (21 CFR part CFR 1271.145 - 1271.320). Further inspection requirements (21 CFR 1271.400) highlight that an inspection needs to be performed, and if the ATMP is considered a 'drug / biologic' in US, 21 CFR Part 11 (Electronic records), 21 CFR Part 50 (Protection human subjects), 21 CFR Parts 210/211 (cGMP), 21 CFR Part 312 (IND) and 21 CFR Parts 600-680 (Biological Products) apply. For

[5] Question 7 of the Q&A on the impact of Mutual Recognition Agreement between the European Union and the United States as of 1 December 2018, 29 November 2018, EMA/752292/2018

[6] See interim report from EC http://trade.ec.europa.eu/doclib/docs/2019/january/tradoc_157651.pdf

[7] EU Directive: Advanced Therapy Medicinal Products, Regulation EC 1394/2007); New Commission Guideline: GMP for ATMPs, EUDRA-Lex Vol.4 (EU-GMP), Part IV, guideline C(2017) 7694.)

ATMPs used as part of a device, the Medical Device Regulation (Regulation 2017/745, 05. April 2017) and ISO 13845 standards apply in the EU and 21 CFR 820 (Quality System Regulations for combination products) in the US. An element of complexity is that ATMPs are covered by CBER at the FDA and handled at an equivalent level to vaccines. We do not predict nor anticipate regulatory hurdles or risks to patients if ATMPs/GCTs are included.

Annex

About the Inspection Process

Appropriate manufacturing and distribution are essential for drug (medicinal) products quality and supply chain security. The regulatory commitments are described in the format of the Common Technical Document (CTD, ICH M4) in both the US and the EU. As such, the inspections of Good Manufacturing Practices have the primary objectives of assessing the

a. Capability of manufacturing process - aligned with regulatory commitments;
b. Adequacy of production and control procedures;
c. Suitability of equipment and facilities; and
d. Effectiveness of the quality management system.

The inspection process is based on the commitments in the CTD and regulations, on which equivalency is demonstrated by both jurisdictions. The current MRA already recognizes the similarity of the different administrative processes for conducting inspections in US and EU.

Difference in the need for inspections as part of the registration process

EFPIA is aware that there can be cases caused due to the difference between the two registration processes in EU and US. Part of the application validation in the EU requires a valid GMP certificate before the EU can accept the application for review. In case a company want to apply for approval in both EU and US at the same time, they would be the need to ask FDA to perform the inspection before it would be scheduled as PAI by FDA.

In the EU, certification of the compliance status of a manufacturing site is performed according to the operation following a 'system approach'. During these types of inspections, the manufacturing process description of new or existing products is taken into consideration. Although the regulatory pathway and terminologies used are different in EU and US, the description of the manufacturing process cannot be significantly different as the product from the same production line at the same manufacturing site is supplied to patients in both the US and EU. If further clarification is required, reviewers, inspectors or investigators may contact the inspectorate of the respective jurisdiction and potentially conduct a joint inspection.

2. Mutual Recognition Agreement in the area of Good Clinical Practice (GCP)

Executive Summary

Clinical research is global. Differences in standards or interpretations of Good Clinical Practice (GCP) increase unnecessarily burdens and bureaucracy, and present a risk of error and confusion.

EMA and FDA conducted GCP inspections are extremely resource intensive for both the applicant and regulatory authorities.

In September 2009, the EU EMA and US FTA launched an 18 months GCP pilot initiative under the framework of their confidentiality arrangements.
During the pilot and subsequent collaborative arrangement, EMA and FDA conduct periodic information exchanges, streamline sharing of GCP inspection planning information, communicate on inspection outcomes in a timely manner, and cooperate in the conduct of on-site inspections[8].

However, there remains a high level of redundancy and duplicity in the GCP inspection-related activities of the EMA and FDA even within a joint onsite sponsor inspection.

Since clinical research is global in nature, **a mutual recognition agreement (MRA) in the area of Good Clinical Practice (GCP)** would reduce duplication of inspections and focus both regulatory authority and industry resources that could be used in other ways to oversee or reduce risk where needs are higher. As both Agencies operate under harmonized ICH GCP standards and have already significant experience in collaboration, the agreement of a formal MRA would be a logical next step.

Background

- Regulators define GCP Inspection as the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect[9,10].
- GCP inspections may be routine or may be triggered by issues arising during the assessment of the dossier or by other information such as previous inspection

[8] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice
[9] EMA GCP SOP; https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-co-ordination-gcp-inspections_en.pdf
[10] FDA GCP Regulations https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#FDARegulations

experience. They are routinely requested during the initial review of a Marketing Authorisation Application (MAA), but could arise post-authorisation as well[11].

- Based on standard practices by EU and US regulatory authorities, Marketing Authorization Application (MAA) GCP-related inspections typically include authority inspection activities at several of the clinical trial sites located worldwide as well as at the sponsor companies' office facilities.
- Over the last 7 years, the number of EMA GCP inspections[12] has more than doubled while also the number of FDA GCP inspections[13] has increased, but to a lesser extent, as listed in Table 1 below. For 2017, EMA and FDA conducted 209 inspections jointly.

Table 1: EU EMA and US FDA GCP inspections (2011 – 2017)

	2011	2012	2013	2014	2015	2016	2017
EMA	65	72	70	66	86	121	136
FDA	50	65	74	60	59	66	73

- EMA and FDA conducted GCP inspections are extremely resource intensive for both the applicant and regulatory authorities, as well as the clinical trial site(s). Moreover, they typically occur during an extremely active phase of the product development lifecycle – i.e. during the regulatory assessment phase to inform the approval decision.
- EFPIA is currently carrying out a survey among members to determine the average company costs associated with new product related GCP inspections. This information will be provided to the European Commission once finalized.

We note that the EMA and FDA are already collaborating:

- In September 2009, the EU EMA and US FTA launched a GCP pilot initiative under the framework of their confidentiality arrangements. The main objectives of the initiative were to share information on inspections and GCP-related documents of common interest and to conduct collaborative inspections. The 18-month pilot concluded in 2011[14];
- The EMA and FDA stated that the GCP pilot was "*judged by both agencies to be extremely successful and very productive, and it has further strengthened the confidence in inspections between the partner organizations*"[15].
- Based on the experience with the pilot, FDA and EMA agreed to continue with the initiative with the broader aim of moving from "confidence building" to "confidence in," with "*mutual acceptance of inspectional findings in the near future*"[emphasis added][15].
- During the pilot and subsequent collaborative arrangement, EMA and FDA conduct periodic information exchanges, streamline sharing of GCP inspection planning

[11] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/inspections-procedure
[12] https://www.ema.europa.eu/documents/report/annual-activity-report-2017_en.pdf; https://www.ema.europa.eu/documents/annual-report/annual-report-european-medicines-agency-2013_en.pdf
[13]https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf
[14] https://www.ema.europa.eu/en/documents/other/questions-answers-european-medicines-agency-food-drug-administration-good-clinical-practice_en.pdf
[15] See footnote 11

information, communicate on inspection outcomes in a timely manner, and cooperate in the conduct of onsite inspections[16]. From 2009 to 2017, EMA-FDA collaborative initiative had jointly inspected approximately 48 entities[17].

- However, there remains a high level of redundancy and duplicity in the GCP inspection-related activities of the EMA and FDA even within a joint onsite sponsor inspection.
- Nearly a decade after the pilot was first initiated, formal mutual acceptance of inspection results has not been achieved, which would conserve further authority and applicant resources.
- The similar example of the recently agreed *MRA for GMP inspections* is considered as highly positive. According to an EU Commission report, "(U)nder the existing MRA, the EU and US are able to avoid unnecessary duplicate inspections and thereby realise savings of the order of € 350,000 ($380,000) per average inspection, as well as ensuring an improved allocation of resources by regulators"[18].

Conclusion

Since clinical research is global in nature, **a mutual recognition agreement (MRA) in the area of Good Clinical Practice (GCP)** would reduce duplication of inspections and focus both regulatory authority and industry resources that could be used in other ways to oversee or reduce risk. As both Agencies operate under harmonized ICH GCP standards and have already significant experience in collaboration, the agreement of a formal MRA would be a logical next step. Varying levels of convergence and sharing are possible with an MRA, as has been shown, for example, by the recent MRA for GMP inspections between the US and EU.

[16] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice

[17] https://www.diaglobal.org/en/conference-listing/meetings/2017/06/dia-2017/agenda/20/comparison-of-inspection-findings-and-recommendations-of-registration-trials-submitted-in-support-of-marketing-applications-of-new-drug-products-to-ema-and-fda?ref=ComparisonofInspectionFindingsandRecommendationsofRegistrationTrialsSubmittedinSupportofMarketingApplicationsofNewDrugProductstoEMAandFDA

[18]http://trade.ec.europa.eu/doclib/docs/2019/january/tradoc_157651.pdf?utm_source=POLITICO.EU&utm_campaign=5de58489aa-EMAIL_CAMPAIGN_2019_01_30_12_32&utm_medium=email&utm_term=0_10959edeb5-5de58489aa-189664017

3. Closer alignment in the area of paediatric medicines

Executive summary

This section is intended to progress alignment for further EU-US regulatory cooperation on paediatric development and specifically, the concept of **mutual reliance on required regulatory assessments of the paediatric development planning document** (Paediatric Investigational Plans (PIP) in the EU or Paediatric Study Plans (PSP) in the US). As such, it does not propose details on how this would be operationalized, does not include or suggest changes to the US proposed paediatric plans for work required to obtain an incentive, and does not introduce detailed suggestions for funding approaches, dispute resolution, or timing of paediatric plan submission.

The EMA and FDA have demonstrated their commitment to harmonization of scientific issues and convergence of approaches with a view toward a more global approach to the effective and efficient development of medicines for paediatric patients.

Paediatric medicines development is carried out globally, as the affected population is usually smaller in number than in adult diseases.

The feasibility of efficiently carrying out global paediatric development programmes is greatly facilitated when the regulatory authorities' requirements, scientific standards, approaches and processes for approval of the paediatric development plans are aligned.

Further significant benefits and savings are achievable if the regulatory cooperation between EU and US in paediatrics could be intensified, with an eventual goal of a concept of **mutual reliance on required regulatory assessments of PIP applications in the EU or PSP applications in the US**. This would lead to faster paediatric medicines development and reduce unnecessary testing on children.

EMA and FDA are committed to global paediatric cooperation

The EMA and FDA have demonstrated their commitment to harmonization of scientific issues and convergence of approaches with a view toward a more global approach to the effective and efficient development of medicines for paediatric patients. Despite several differences in legislation and processes, both regulatory approaches are aligned on common scientific principles as outlined in ICH E11 and are designed to require the timely, ethical, and scientifically sound development of products for children.
The EU and US have declared "Achieving a Global Paediatric Approach" a joint goal[19] and have implemented many basic requirements and enablers for intensified EU-US cooperation:

1. Regular cluster calls between regulators to discuss global paediatric development issues have been established between FDA and EMA since 2007[20].
2. Paediatric medicine development and scientific development guidelines have already been harmonised under ICH E11 since 2000[21]. Those standards are implemented by EMA and FDA.

[19] https://www.ema.europa.eu/en/documents/presentation/presentation-session-42-global-collaboration-between-regulatory-agencies-paediatric-research_en.pdf

[20] https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm

3. Both agencies have similar approaches and requirements[22] as reflected in the PIP and PSP documents, which have very similar content components (see Annex 1).

The regulatory approaches of both agencies are designed to yield timely, ethical, and scientifically sound development of products for children with the goal of global development of more safe and effective therapeutics labelled for paediatric use[23] and that paediatric cluster discussions are leading to global alignment[24].

Data also show that the outcomes of waiver assessment on both sides of the Atlantic are in most cases congruent[25].

Although these data show promising results, the efforts and resource investment to achieve global alignment are significant. Product-specific Common Commentaries[26] to align on specific development plans between EMA and FDA to resolve differing viewpoints cannot be expanded to involve the applicant in a tripartite manner due to resource bottlenecks at both agencies. This leads to complex regulatory procedures and unnecessary R&D activity.

Global paediatric development is an important public health goal

Innovative, safe and effective medicines should be developed and made available to paediatric patients without unnecessary burden on the children or their families through unnecessary clinical trials. The affected population is usually smaller in number than in adult diseases and enrolment of sufficient patients requires a broader outreach. Hence, paediatric medicines development is carried out globally and usually only one global paediatric development program is planned to satisfy both EU and US requirements.

The feasibility of efficiently carrying out global paediatric development programmes is greatly facilitated when the regulatory authorities' requirements, scientific standards, approaches and processes for approval of the paediatric development plans are aligned. The

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[21] https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

[22] https://www.ema.europa.eu/documents/presentation/presentation-multiregional-regulatory-considerations-pediatric-drug-development-lyao-us-fda_en.pdf

[23] D Penkov et al, Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States, TIRS 2017, Vol. 51(3) 360-371

[24] Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States, and the EMA presentation on 16 May 2017- Global collaboration: between regulatory agencies with paediatric research networks: *"FDA and EMA continue to harmonize on scientific issues pertaining to pediatric product development through at least monthly discussions of the Pediatric Cluster. FDA and EMA have converged approaches for 73% of the issues discussed (368/507) with respect to the development of over 100 products in the past 3 years*."

[25] A Comparative Review of Waivers Granted in Pediatric Drug Development by FDA and EMA from 2007-2013. It found that for single active substance products, PDCO and PeRC (FDA's closest counterpart to EMA's PDCO) adopted similar opinions (for waiver) in 42 of 49 indications (86%). The conclusion is that despite the different legal frameworks, criteria, and processes of determination, the waiver decisions of the 2 agencies were similar in the majority of cases.

[26] https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106621.htm

importance of international cooperation and harmonisation has already been recognised by the EU Commission in its recent report[27].

Mutual reliance can provide further significant benefits and resource savings

Further significant benefits and savings are achievable if the regulatory cooperation between EU and US in paediatrics could be intensified, with an eventual goal of a concept of **mutual reliance on required regulatory assessments of PIP applications in the EU or PSP applications in the US**.

Mutual reliance is the act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision[28]. This means that intensified cooperation through the establishment of an optional reliance scheme would allow for respect of each agency's regulatory autonomy based on respective legal frameworks and agreed international guidelines such as ICH.

Regulatory reliance is widely recognised and promoted by WHO. An example is the WHO Good Review Practices – guideline for national and regional regulatory authorities[29] which recognises that the use of reviews and decisions reached by other Regulatory Authorities is expected to become increasingly important in making the review process more efficient in the face of pressures on resources.

In the EU, for example, the regulatory resources for paediatric assessments are specifically constrained, because as part of the policy goals, the assessment activities are exempted from fees and the Regulation stipulates that EU funding should be provided to cover all aspects of the work of the Paediatric Committee (PDCO) and of the Agency. This includes, for example, the assessment of PIPs, scientific advice, and information and transparency measures, including the database of paediatric studies and the network of paediatric academic networks (EnprEMA)[30,31].

Simplifying the regulatory process will likewise help economic operators, and specifically pharmaceutical (and other industry) small and medium size enterprises (SMEs), to reduce their overall resource investment and potentially free up funds for more paediatric or other research.

It should be noted that mutual reliance can be a step towards but is different from mutual recognition, which is the routine and potentially even mandatory acceptance of the regulatory decisions of another regulator or other trusted institution (see Annex 2). Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B[28]. The concept of

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[27] https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf

[28] Source: Mike Ward, WHO, Why is Reliance Important?, DIA EuroMeeting 2019, Vienna (see Annex)

[29] https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex9-TRS992.pdf?ua=1

[30] https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

[31] https://www.ema.europa.eu/documents/report/european-medicines-agency-budget-2019_.pdf

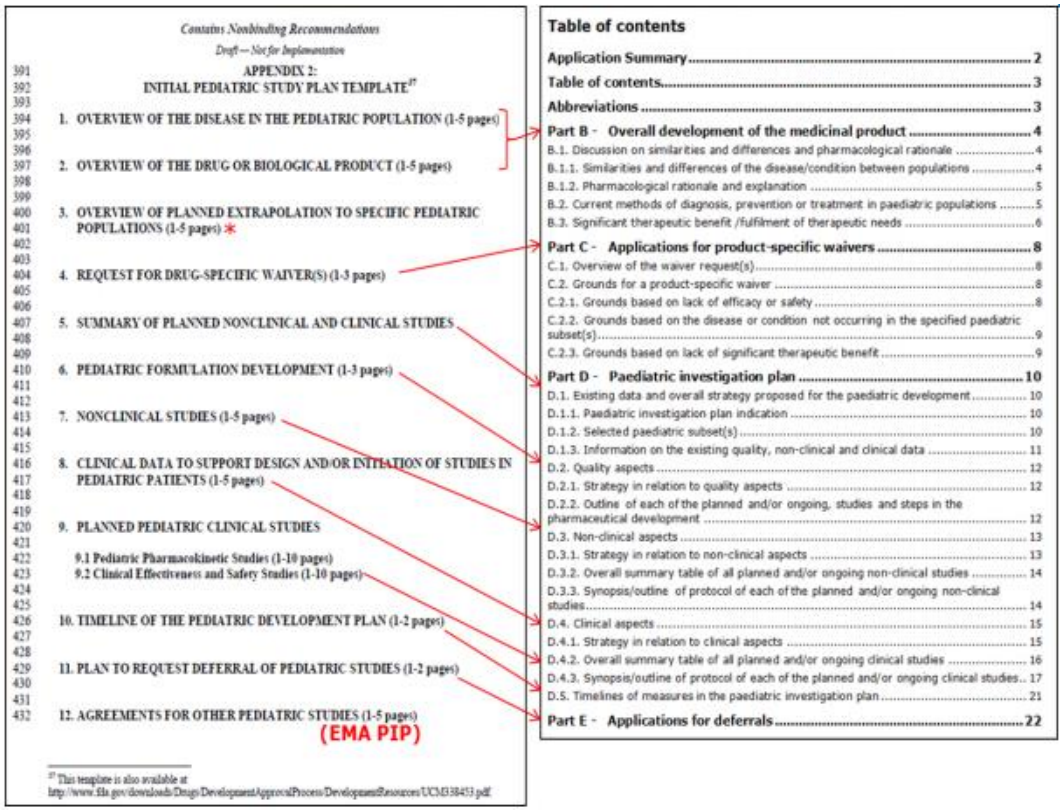
mutual recognition between EMA and FDA is for example already being applied in the field of GMP inspections.

Recently introduced legislation in Switzerland is implementing the concept of mutual recognition in paediatric medicine regulation. It requires the submission of a paediatric investigation plan. However, applicants can submit either a EU PIP or US PSP that has already been approved. PIPs that have already been approved are accepted by Swissmedic without a separate review. Alternatively, a new PIP (CH-PIP) can be developed[32].

Conclusion

Regulatory cooperation between the US and EU has already been implemented in many aspects and further global harmonisation is a policy goal for more effective implementation[10]. Increasing and intensifying this cooperation, to further build mutual understanding and trust, could lead to the establishment of a mutual reliance concept in the context of the assessment of paediatric development planning documents (EU PIPs and US PSPs). This would be a valuable opportunity under the new US-EU regulatory cooperation dialogue to focus resources for assessment of global development plans while supporting an important public health imperative. It could help regulators and economic operators to free up resources for other value adding activities. Moreover, it would lead to faster paediatric medicines development and reduce unnecessary testing on children.

Annex 1: Comparison between PSP and PIP templates



Contains Nonbinding Recommendations
Draft—Not for Implementation

APPENDIX 2:
INITIAL PEDIATRIC STUDY PLAN TEMPLATE[37]

1. OVERVIEW OF THE DISEASE IN THE PEDIATRIC POPULATION (1-5 pages)
2. OVERVIEW OF THE DRUG OR BIOLOGICAL PRODUCT (1-5 pages)
3. OVERVIEW OF PLANNED EXTRAPOLATION TO SPECIFIC PEDIATRIC POPULATIONS (1-5 pages) *
4. REQUEST FOR DRUG-SPECIFIC WAIVER(S) (1-3 pages)
5. SUMMARY OF PLANNED NONCLINICAL AND CLINICAL STUDIES
6. PEDIATRIC FORMULATION DEVELOPMENT (1-3 pages)
7. NONCLINICAL STUDIES (1-5 pages)
8. CLINICAL DATA TO SUPPORT DESIGN AND/OR INITIATION OF STUDIES IN PEDIATRIC PATIENTS (1-5 pages)
9. PLANNED PEDIATRIC CLINICAL STUDIES
   9.1 Pediatric Pharmacokinetic Studies (1-10 pages)
   9.2 Clinical Effectiveness and Safety Studies (1-10 pages)
10. TIMELINE OF THE PEDIATRIC DEVELOPMENT PLAN (1-2 pages)
11. PLAN TO REQUEST DEFERRAL OF PEDIATRIC STUDIES (1-2 pages)
12. AGREEMENTS FOR OTHER PEDIATRIC STUDIES (1-5 pages)

(EMA PIP)

[37] This template is also available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM338453.pdf

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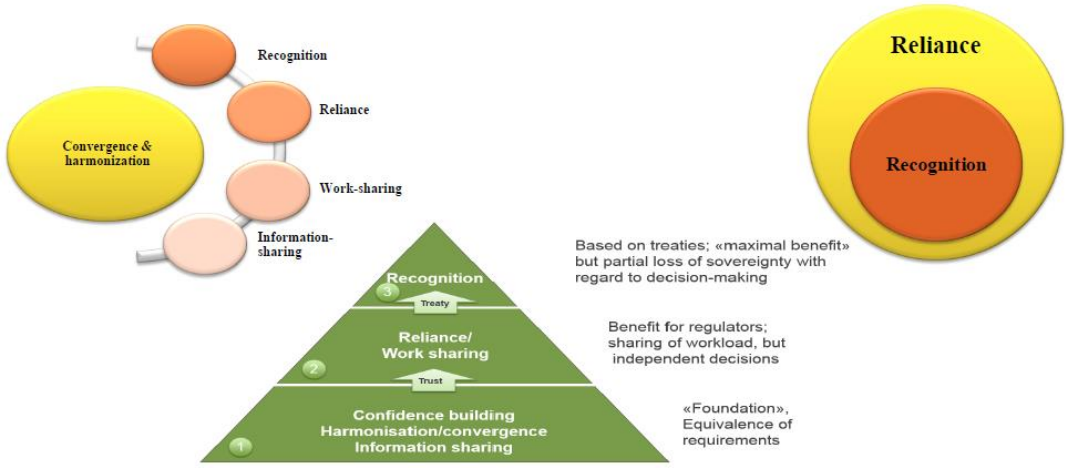
Source: FDA

32 https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/zl_hmv_iv/zl000_00_023d_wlpaediatirschespruefkonzept.pdf.download.pdf/zl000_00_023e_wlpaediatricinvestigationplan.pdf

Annex 2: Reliance and recognition



Source: WHO

4. Regulatory support for innovation

Executive summary

Science and technology is rapidly presenting new opportunities in the development and use of medicines, and aligned regulatory approaches are important to avoid duplicative or inconsistent regulatory requirements that may inhibit patient access to new medicines. Therefore, it is important to prioritise upstream discussions between the EU and US on evolving science and technology (e.g. for new sources of evidence) to support the development of medicines and their assessment.

The US and the EU should pursue a joint horizon scanning on evolving science and technology at the interface of medicines, medical devices and diagnostics.

Background

Science and technology is rapidly presenting new opportunities in the development of healthcare. Medicines are increasingly developed and applied in combination with diagnostics (e.g. genomic sequencing) and medical devices (e.g. monitoring apps) for a safer and more efficient use in the interest of patients. In addition, patient data from clinical trial sources other than randomized controlled trials and electronic health records have the potential to play an important role in the development and monitoring of medicines in the future but will only do so if data from different sources and geographies can be compiled and analysed based on common standards. Moreover, aligned regulatory approaches in these areas and at their mutual interface are important to avoid duplicative or inconsistent regulatory requirements that may inhibit patient access to these new healthcare solutions.

The following proposals lay out areas for increased upstream regulatory collaboration with the potential of facilitating trade.

EU and US Regulatory Collaboration needs

Horizon scanning in regulatory context

The US and the EU should pursue a joint horizon scanning on evolving science and technology at the interface of medicines, medical devices and diagnostics. Given the ongoing digitalization in healthcare, a particular focus should be on the integration of data sources from clinical trials and electronic health records and the evolution of supporting technical regulatory and structural conditions.

To advance this work, EU and US should commit to closely collaborate with other international organisations and cooperation frameworks, such as WHO, the International Coalition of Medicines Regulatory Authorities (ICMRA), the International Council for Harmonisation (ICH), International Medical Device Regulatory Forum (IMDRF).

Regulatory collaboration

The key objectives of the aforementioned horizon scanning are

- Identifying areas for potential synergies;
- Identifying areas for a more structured regulatory and inter-disciplinary collaboration between the EU and US on emerging topics deemed mutual priorities;

- Establish mechanisms for such collaboration, including early upstream mutual consultation on planned standards in support of regulatory provisions;
- Leveraging existing initiatives/enablers and resources wherever possible.

Regulatory provisions and standards

We propose to prioritize the following areas for this activity:

- Processes for designation of medicines, diagnostics and medical devices for accelerated and prioritized development and assessment;
- Evolution of a learning regulatory system, including aspects such as:
    - Integration of real world data/ real world evidence in regulatory assessment and monitoring;
    - Infrastructure and capacity building for access and analysis of healthcare data;
    - Interoperability of health data (formats):
        - Exchange of digital health information systems such as electronic health records (EHR);
        - Standards for genomic data and other health data;
    - Applications of digital technology, artificial intelligence, cognitive computing to support data-driven decisions.
- Development of methodologies to reinforce patient relevance in evidence generation:
    - Collection and use patient data from the wider patient community;
    - Core health-related quality-of-life (HRQOL; e.g. via patient reported outcomes (PRO)).
- Development of standards for software as a medical device;
- Development of standards for validation of biomarkers;
- Development standards for genome profiling.

Aspects of collaboration

To achieve the above objectives, EU and US should:

- Establish or reinforce mechanisms of joint and inter-disciplinary collaboration and information exchange;
- Invite each other to take part in existing relevant mechanisms of information exchange (also to foster mutual learning on decision making);
- Notify each other of relevant proposed and actual regulatory provisions and standards and exchange information concerning their implementation;
- Agree on how to best collaborate in other international fora.

Upstream collaboration with stakeholders

In preparing for the above discussions, upstream collaboration with stakeholders should be established. This could happen, amongst others, through the Center for Innovation in Regulatory Science (CIRS), with EU and US industry associations, academia, private partnerships (e.g. Transcelerate), public private partnerships (e.g. IMI).

Resources

It will be important that both parties support and contribute to this activity with the appropriate experts and resources. Given that in the EU, certain topics touch upon responsibilities in the EU Member States, a strong commitment not only from the EU but also from EU Member States will be needed.

5. Tariffs on industrial goods

Executive summary

The WTO Pharmaceutical Tariff Elimination Agreement ("Zero for Zero")[33] exempts pharmaceutical products in all forms from the chemical compound up to the drug product for retail sale from duties. The agreement has not been updated since 2011. Therefore, we are urging the EU and US to update the WTO agreement, and as starting point, eliminate tariffs on at least the products exchanged between the US and the EU.

Overall, we are calling for tariff-free trade of pharmaceuticals in all forms between EU and US.

The WTO Pharmaceutical Tariff Elimination Agreement ("Zero for Zero")[34] exempts pharmaceutical products in all forms from the chemical compound up to the drug product for retail sale from duties. Some tariff headings of the tariff schedules, dedicated to pharmaceutical industry, are duty exempted (2936 vitamins, 2937 hormones, 2939 alkaloids, 2941 Antibiotics), as well as chapter 30 for pharmaceutical products (extract of organs, blood, antisera, toxins, vaccines, biotechnological products, formulated products and product for retail sale).

In addition to these headings and chapter, other active ingredients and chemical intermediates for use in the production of active ingredients only, classified in the HS section VI of chemical products, are listed per products in annexes to the tariff schedule. These lists require updates to cover new products. The last update accepted by all parties was enforced the 1st of January 2011 (one year after for Japan).

Since then no update has been approved even though lists of products have been presented by Intercept (International Committee for Elimination of Pharmaceutical Tariffs), an informal body representing pharmaceutical and chemical industry for the elimination of tariff duties, to all signatory parties.

We therefore urge for the zero-for-zero agreement to be included in the discussion between EU and US to eliminate tariffs on at least the products exchanged between the US and the EU. Ultimately, we are calling for an update of the zero-for-zero agreement.

WHO INN proposed lists from 2011 (INN list 105 to 120) have not been included in the pharmaceutical agreement, unless products in the lists are exempted due to their HS classification mentioned above. An approval of automatic incorporation in the exempted list of all INN should be part of the discussion to eliminate duties, elimination of duties being part of the reduction of global medical costs targeted by all states.

Finally, given the nature of pharmaceuticals and related inputs in supporting public health, we strongly emphasise that relevant headings should be excluded from any measures to increase tariff rates by either the EU or the US. Overall, we are calling for tariff-free trade of pharmaceuticals in all forms between EU and US.

[33] http://trade.ec.europa.eu/doclib/docs/2016/july/tradoc_154828.pdf
[34] http://trade.ec.europa.eu/doclib/docs/2016/july/tradoc_154828.pdf