Report of the Paediatric Regulatory Network meeting, 14-15 April 2021
### Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>AMA</td>
<td>African Medicines Agency</td>
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<td>AMRH</td>
<td>African Medicines Regulatory Harmonization</td>
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<td>BCS</td>
<td>Biopharmaceutics Classification System</td>
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<td>BPCA</td>
<td>Best Pharmaceuticals for Children Act</td>
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<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>CRP</td>
<td>WHO Collaborative Registration Procedure</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<td>GAP-f</td>
<td>Global Accelerator for Paediatric Formulations</td>
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<td>ICH</td>
<td>International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<td>iPSP</td>
<td>initial pediatric study plan</td>
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<td>PIP</td>
<td>paediatric investigational plan</td>
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<td>PREA</td>
<td>Pediatric Research Equity Act</td>
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<td>RACE</td>
<td>Research to Accelerate Cures and Equity</td>
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<td>TB</td>
<td>tuberculosis</td>
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<td>WHA</td>
<td>World Health Assembly</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Background
The Paediatric Regulatory Network was initially created as a global paediatric working group in February 2010 in response to a recommendation from the 2008 International Conference on Drug Regulatory Authorities and as part of the WHO Better Medicines for Children Project in collaboration with the Bill & Melinda Gates Foundation, to offer a platform for discussion on paediatric regulatory considerations for national regulatory authorities.

The Network was reactivated in December 2019 as a global paediatric network supporting the availability of quality-assured medical products for children, by facilitating communication, collaboration, training and regulatory harmonization across the development, registration and pharmacovigilance of paediatric medical products. The Network’s activities contribute efficiently to the implementation of World Health Assembly (WHA) resolutions WHA60.20 (2007) on better medicines for children, WHA69.20 (2016) on promoting innovation and access to quality, safe, efficacious and affordable medicines for children, WHA67.20 (2014) on regulatory system strengthening for medical products and WHA67.22 (2014) on access to essential medicines.

The Network held a virtual meeting on 14 and 15 April 2021, chaired by Professor Moji Christianah Adeyeye, Director-General, National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria and co-chaired by Dr Alysha Croker, Manager, Office of Paediatrics and Patient Involvement Centre for Regulatory Excellence, Statistics and Trials, Health Canada. For the agenda, see Annex 1, and for the list of participants, see Annex 2.

2. Meeting objectives
The aim of the meeting was to share updates and experience among Network members:

- give a platform to members to share paediatric regulatory information, updates and achievements;
- present the results of the survey conducted among Network members in 2020 and discuss areas in which interactions within the Network can help national regulatory authorities;
- discuss how to optimize the use of reliance on other regulators’ work for paediatric medicines;
- present the experience of WHO prequalification for paediatric medicines and promote the use of the WHO collaborative registration procedure;
- give examples in which joint efforts and working towards the same goals have achieved results (commitments from the Rome Action Plan initiative and the Global Accelerator for Paediatric formulations (GAP-f));
- promote good practices and inventive solutions to overcome regulatory challenges.

3. Opening of the meeting
Dr Mariângela Simão, Assistant Director-General, Access to Medicines and Health Products, World Health Organization (WHO), delivered opening remarks, with a warm welcome to all participants in the second meeting of the Network, which gave regulators and other stakeholders the opportunity to discuss and exchange information on paediatric-specific regulatory issues. The pandemic of coronavirus disease 2019 (COVID-19) has dramatically changed the lives of all and provided many lessons, including the need to collaborate and work
together more than ever. On 29 March 2021, WHO published the Good Reliance Practices (1) and Good Regulatory Practices (2), documents that were prepared with and for Member States to promote a more efficient global regulatory oversight and make best use of resources. Reliance approaches are essential tools, given the limited resources to facilitate access to high-quality paediatric medicines. A great deal of progress has been made for paediatric medicines in the last 20 years, but much still needs to be done to give children access to the same quality of health technologies as adults; all stakeholders have to work together towards equitable access to paediatric medicines. Experience has shown that prioritization, focusing efforts and working together can achieve great results. Dr Simão strongly encouraged the collaboration within the Network and joint efforts to facilitate development and registration of quality paediatric medicines and promote good practices and inventive solutions to overcome regulatory challenges.

4. Presentations

4.1 United States Food and Drug Administration Reauthorization Act

Dr Lynne Yao, Director of the Division of Pediatric and Maternal Health, United States Food and Drug Administration (FDA), gave an update on the Research to Accelerate Cures and Equity (RACE) for Children Act, which was passed as part of the FDA Reauthorization Act of 2017. Over the last 20 years, the FDA has worked to advance drug development for children, largely through the Pediatric Research Equity Act (PREA) of 2003 and the Best Pharmaceuticals for Children Act (BPCA) of 2002. These two laws have worked well to advance the labelling of paediatric information and drug products for over 800 drug products in the last 19 years in the United States of America. Both PREA and BPCA requirements were based on the correlation between adult and paediatric indications. In the oncology field, this meant that, if the specific adult indication did not occur in children, the FDA had no authority to request paediatric studies (e.g. in breast cancer, lung cancer, colon cancer). The RACE changed the PREA to require that new molecular entities intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a paediatric cancer should apply under the PREA. Accordingly, the FDA can require sponsors to develop drugs for paediatric cancers, if the molecular target is similar for adults and children. Sponsors are required to collect clinical data on dosing, safety and preliminary efficacy, using appropriate formulations, so that paediatric labelling can be informed.

A lot of preparation was undertaken between the issuing of the RACE Act in 2017 and its entry into effect in August 2020, notably in terms of collaboration between regulators, early planning of relevant studies for sponsors and the preparation of a list of molecular targets in a multistakeholder discussion involving industry, academia, patient advocates, professional societies and regulators (3). The FDA offers sponsors the possibility of discussing and holding early advice meetings (referred to as “type F meetings”) as early as the end of phase I of their clinical development programme. It is important to highlight that these early interaction (type F) meetings are not limited to oncology drugs, but are available to sponsors for all drugs for serious and life-threatening diseases that occur in children. Between 2017 and 2019, 15 type F meetings had already been convened to discuss earlier plans for oncology drug development in children. An oncology subcommittee was created for the paediatric review committee, which includes multidisciplinary committee members (clinical, clinical pharmacology, toxicology, biostatistics, ethics, regulatory policy, expertise in paediatric oncology) to review the oncology paediatric study plans.

Between August 2019 and December 2020, 151 initial paediatric study plans were reviewed by the oncology subcommittee of the paediatric review committee, of which 38 related to new
active ingredients leading to 21 planned paediatric studies (for the remaining 17, they are not being developed because that molecular target is not relevant in children).

One of the most important coordinating activities between regulators is to discuss early alignment on paediatric oncology development plans in the paediatric cluster. A mechanism exists to provide informal feedback from the paediatric cluster discussions to sponsors under the “common commentary”, consisting of bilateral non-binding advice to sponsors (4). There is also a call for simultaneous submission of paediatric investigational plans (PIPs) and initial paediatric study plans (iPSPs). The FDA and the European Medicines Agency (EMA) are working towards an early collaborative and aligned PIP and iPSPS in the cancer paediatric cancer space. In her closing remarks, Dr Yao highlighted the need for a global developmental collaboration in terms of designation of relevance, prioritization and decision-making for paediatric medicines.

4.2 EMA: ongoing paediatric work in the European Union

Dr Ralph Bax, Head of Paediatric Medicines, Scientific Evidence Generation Department, European Medicines Agency, gave a progress update on the EMA–European Commission action plan on pediatrics, citing the 10-year report on the Paediatric Regulation (5) and the EMA/EC multistakeholder workshop in March 2018 (6). An interim progress report was published in December 2020 (7). The EMA’s progress in the implementation of the action plan has been guided by business continuity considerations; many lessons can be learned from the regulatory activities undertaken in response to the COVID-19 pandemic, where a high level of global interaction, reliance and collaboration was applied. The report covers the different activities on medical needs, cooperation on the part of decision-makers, work on timely completion of PIPs, improving handling of PIP applications and transparency. In respect of paediatric medical needs, particularly in the field of oncology, PIP activities have been refined to take more account of the currently unmet medical needs. The close international collaboration in the field of paediatric oncology, for example as part of the ACCELERATE initiative (8), has been very positive, as it gives the opportunity for a multistakeholder platform (including academia) to discuss pre-submission activities in the non-competitive space and help in the area of prioritization and, ultimately, regulatory decision-making. For the handling of PIP applications, the EMA is working on a model based on a gradual level of evidence, for example only to agree on the high-level principles (i.e. important key elements) at the start of the planning and to develop a more detailed plan once more evidence is available, to avoid multiple modifications of the plan where possible; this facilitates submission and focuses on key elements of the PIPs. In the European Union, the requirements for developing medicines in children are also driven by the adult indication. However, in view of the change in legislation in the United States for oncology products, the EMA Paediatric Committee has received PIPs that have been triggered by the new RACE requirements from the United States.

The European Commission is currently reviewing orphan and paediatric regulations (9). The paediatric regulation has brought many new medicines for children, but development still remains mainly driven by adult needs. Discussions are taking place to consider an approach looking at the mode of action in order to trigger the need for a paediatric plan for oncology products but also other disease areas. One important and challenging topic is how to better define paediatric medical needs and how to incentivize drug developers to develop paediatric medicines. Prioritization is essential for paediatric medicines and the experience gained on prioritization, for example from WHO and other stakeholders, will be essential in the context of the discussion for the revision of paediatric legislation in the European Union.
### 4.3 Access Consortium

Dr Alysha Croker, Network Co-Chair and Manager, Office of Paediatrics and Patient Involvement Centre for Regulatory Excellence, Statistics and Trials, Health Canada, presented the work of the Access Consortium as an example of successful work-sharing activities across five jurisdictions: Australia, Canada, Singapore, Switzerland and the United Kingdom of Great Britain and Northern Ireland, as of January 2021. The Consortium’s work focuses on regulatory work and information-sharing between the five regulatory authorities including, but not limited to, biosimilars, generic medicines, new active substances, complementary medicines and information technology. For new active substances, the idea behind the Access Consortium is that one submission is made to five different jurisdictions with a combined population of about 150 million people. An evaluation plan is tailored to each submission, which is done well in advance of the filing of the application. The Access partners will determine whether they will participate in a particular submission and which regulatory authority will be responsible for leading the review of the different modules (Module 3 on quality, Module 4 on non-clinical and Module 5 clinical modules). Modules 3 and 5 can be split: for example, for Module 5 if there are multiple indications. In addition to the common review, some country-specific evaluations take place (for example product monographs, labels, stability, etc.). Once the review is completed, each Access partner makes its own separate sovereign decision about whether to authorize the product in its jurisdiction.

International work-sharing requires trust. For Access, the process started with information-sharing followed by confidence-building; the first work-sharing took place in 2018. Dr Croker illustrated the success of the procedure with the recent examples of seven medicinal products authorized through Access work-sharing in 2020–2021 and mentioned that 11 applications were currently under review at the time of the meeting. The Access Consortium has a great potential. For example, it reduces duplication of effort and reduces the workload for the partners involved, which can lead to more efficiency in the regulatory system. It also increases collaboration among jurisdictions, leading to more robust regulatory decisions and better access to medicines across the different Access countries. Challenges include the large coordination effort needed and national specificities (e.g. each jurisdiction has its own different review processes, which may include expert committees or specific review teams). The Consortium’s efforts in the COVID-19 response is a great example of the benefits of working together. Access partners were able to leverage their strong relationships to collaborate on the relevant guidance and submissions, and have also published various documents and statements related to the regulatory oversight of COVID-19 commodities.

Specifically in terms of paediatrics, two medicinal products were under review by the Consortium at the time of the meeting. The Consortium has been discussing specific paediatric issues in terms of activities ongoing in the different jurisdiction and how they could collaboratively address the challenges. The Consortium is perceived as an interesting platform to develop collaboration on regulatory paediatric activities.

### 4.4 WHO good regulatory practices and good reliance practices

Dr Samvel Azatyan, Regulatory Convergence and Network Team Lead, WHO, presented WHO’s recent activities in good regulatory practices and good reliance practices. Infectious (preventable) diseases remain a leading cause of death among children under the age of 5 years, according to the United Nations Inter-agency Group for Child Mortality Estimation (10). It is acknowledged that good health is not possible without access to medical products and that universal health coverage depends on the availability of quality-assured, affordable health technologies in sufficient quantities. An estimated 2 billion people have no access to essential
medicines, effectively shutting them off from the benefits of advances in modern science and medicine. WHO promotes good governance and transparency in the medical products sector through the WHO Good Regulatory Practices process; promotes and facilitates the building of strong national regulatory systems through the Global Benchmarking Process; supports regulatory workforce development via the Global Regulatory Curriculum; and promotes reliance and work-sharing through regulatory cooperation, convergence and harmonization. Good Regulatory Practices is a set of principles and practices that are applied to the development, implementation and maintenance of controls – including laws, regulations and guidelines – in order to achieve public policy objectives. These practices are robust and relevant to all regulators, irrespective of their level of resources. If consistently and effectively implemented, they can lead to higher-quality regulation, improved regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. The nine principles are: legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency. The WHO Good Reliance Practices and Good Regulatory Practices were adopted by the WHO Expert Committee on Specification for Pharmaceutical Products in October 2020 (1, 2).

International cooperation and reliance are essential to ensure the safety, quality and efficacy/performance of locally used medical products. At present, no regulatory authority, even the best resourced, can ensure the required regulatory oversight alone. The aim of reliance is to make best use of available resources and expertise, avoid duplication and concentrate regulatory efforts and resources where most needed in order to promote a more efficient approach to regulatory oversight, thereby improving access to quality-assured, effective and safe medical products over the entire life cycle. The definition of reliance in the Good Reliance Practices document is as follows: “The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision”. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others. The nature of the paediatric market (small and fragmented market) calls for international collaboration and the use of work-sharing and reliance in terms of setting up the paediatric development plans and for registration.

4.5 Results of the Network survey: where can the Network help?

Professor Moji Christianah Adeyeye, Dr Alysha Croker and Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Network Team, WHO, presented the results of the survey conducted among Network members in 2020.

The survey was developed after the initial meeting of the revived Network (December 2019) and the discussions on the Network workplan. The aim was to understand the paediatric regulatory landscape in each jurisdiction. The survey covered five main aspects: the current legal and regulatory framework in the country and/or region; paediatric roadblocks and current challenges; information regarding regional harmonization and joint assessment initiatives that could facilitate the registration of paediatric medicines; suggestions on best practices or inventive approaches for tackling challenges related to paediatric medicines; and the main paediatric medicine priorities at national level.

Responses were received from six national and one regional regulatory authorities (geographical distribution: one from the WHO African Region, four from the European Region and two from the Region of the Americas).
Regarding the existence of legal provisions required to request submission of paediatric data and/or grant incentives or rewards for paediatric drug development, four of the seven respondents reported having such provisions in place. Similarly, four of the seven respondents indicated that specific obligations to submit paediatric data exist in their country/jurisdiction (mainly the requirement to develop and agree with the authority on a plan for development of the medicinal product in the paediatric population in order to submit marketing authorization applications and certain post-authorization changes, e.g. new indication, new formulation, new method of administration).

Regarding incentives, six of the seven respondents offer incentives for paediatric development. The main incentives are extension of data exclusivity, market or patent protection, free scientific advice, exemption of registration fees, specific data/market protection for paediatric-only developments and disease priority review vouchers to encourage development of paediatric medicines for the prevention and treatment of certain rare paediatric diseases.

The legal and regulatory frameworks for paediatric medicines are usually based on a mixture of incentives and obligations, in order to promote the development of medicines for the paediatric population. Global experience has shown that mandatory requirements bring more results than incentives alone.

The paediatric plan describes the entire development (including quality-related studies for paediatric formulations, non-clinical and clinical studies and modelling and simulation measures) in order to assess the benefits versus risks of authorizing a medicine in the paediatric population. Plans are binding on companies and changes have to be agreed with authorities. A waiver system exists for cases where there is no need for a paediatric development, i.e. if the indication that does not occur in children (e.g. Alzheimer disease), or for a specific product, or justified for a specific subset of the paediatric population. There is the possibility to postpone certain studies and measures (deferral), for example if further adult data are needed before starting studies in children or in order not to postpone an authorization in adults. The overall goal of paediatric plans is to have more information available on appropriate use of the medicines in children on the labelling and in the product information. The timing of the requests relating to paediatric plans varies slightly between the United States and the European Union (end of phase II in the United States versus end of phase I of clinical trials in adults in the European Union). Reliance may be used in the terms of the PIP; for example, in Switzerland, applicants may submit to Swissmedic a PIP that has already been approved by a foreign medicines agency with comparable medicinal product control, without the need for a separate review.

Regarding the use of foreign data, all respondents indicated that data from clinical trials in children conducted in other countries are accepted for submission in their own countries (reference is made to the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E5, Ethnic Factors in the Acceptability of Foreign Clinical Data (11)).

In terms of challenges and road blocks, three of the seven respondents referred to the unattractive market (small volumes/margins, low return on investment, absence of applications for registration, lack of incentives to develop such products, market withdrawal of paediatric medicines with no alternatives). Two respondents mentioned the fact that paediatric data are not submitted to the regulatory authority or the unavailability of clinical trial data to local manufacturers to guide the formulation of paediatric medicines.

Two respondents highlighted that the development is driven by adult needs and that the access to treatment for paediatric patients is delayed (long delay in completion of paediatric plans,
especially for the youngest subset of infants and neonates). Other challenges include the reimburse...age-appropriate formulations; absence of early planning for pediatric studies; high degree of off-label use; difficulties of conducting clinical trials in children; and incomplete understanding of pediatric extrapolation. Flexibilities exist in some countries, and some national regulatory authorities offer a fee waiver for pediatric medicines. Although not pediatric-specific, other fee reduction options are available in other countries (e.g. small and medium-sized enterprises, reduced registration/application fees on request, fee reductions or incentives for the development of orphan medicines, etc.). Many countries/regions offer free scientific advice for pediatric development. Regional harmonization, joint assessment initiatives and international collaboration are essential tools to facilitate access to quality pediatric medicines. In addition, many facilitated regulatory pathways were suggested as part of the responses to the survey, for example reliance and the use of foreign reviews/decisions; “early approvals” to address an unmet medical need in the treatment of serious or life-threatening conditions; accelerated review; specific product-enhanced interactions with regulators to optimize development and access; special/temporary authorization; alignment of efforts with health technologies assessments; and use of real-world evidence. In terms of proposed solutions to the challenges identified, respondents suggested prioritizing pediatric formulation submissions, to train manufacturers of pediatric medicines, work-sharing with international partners (e.g. ACCESS), international regulatory project focused on the standardization of pediatric data from patient registries and other real-world evidence for regulatory purposes, new drug submissions relying on literature and market experience to support clinical safety and efficacy, the possibility of importing some unauthorized medicinal products for specific patient groups and the value added by pediatric forms when deciding on price/reimbursement. The areas where the Network can help were highlighted in terms of sharing information, experience and best practices between members and promoting work-sharing, reliance approaches and facilitated regulatory pathways for pediatric medicines (e.g. WHO CRP).

4.6 Reliance for pediatric development plans – the Swissmedic example

Dr Cornelia Bigler, Regulatory Manager, Sector Authorisation, Swissmedic, presented the experience from Swissmedic in terms of reliance for PIPs. These became mandatory in Switzerland in 2019 with the revision of the Swiss Therapeutic Products Ordinance. The requirements are based on European Union requirements. Companies have to submit a PIP for regular new authorizations of medicinal products containing a new active substance, for new authorizations of orphan drug products containing a new active substance and for extensions of indications, additional pharmaceutical forms and additional administration routes. The incentive for the complete fulfilment of PIP conditions is a six-month extension of an existing supplementary protection certificate. The applicant can submit to Swissmedic a PIP approved by a foreign authority, for example a PIP approved by EMA or a pediatric study plan approved by the FDA. The decisions of foreign authorities on pediatric plans are accepted by Swissmedic, provided that the medicinal products are comparable (e.g. same indication, same dosage recommendation or same pharmaceutical form). Applicants also have the possibility of submitting a PIP newly produced for Switzerland. Reliance is part of Swissmedic strategic goals (2019–2022) as Swissmedic is a relatively small regulatory authority, it uses a risk-based approach in order to use its resources more efficiently.

The experience since 2019 is that the procedure is well established, fully implemented and well received by the industry (since it presents a minimal additional burden). The majority of plans
were received from the European Union, and so far there have been no disagreements with the submitted PIPs. Two Swiss PIPs have been received so far. A few medicinal products have already obtained the incentives through complete fulfilment of PIP conditions.

4.7 Project Orbis

Dr Angelo de Claro, FDA, presented the experience gained so far with Project Orbis. The Project Orbis Global Collaborative Oncology Review Program was launched in May 2019. There is a long history of global collaboration between the FDA oncology programme and other international regulators. The countries currently participating (Project Orbis partners) are Australia, Brazil, Canada, Singapore, Switzerland and the United Kingdom. The criteria considered for an application to Project Orbis are medicinal products with high-impact, clinically significant applications with oncology indications that would generally qualify for priority review in the United States. The FDA serves as primary coordinator, and there should be a plan from the applicant for concurrent or near-concurrent submissions across participating countries.

This programme makes use of the assessment aid document that is a primary review document for the FDA and the core reference document for Project Orbis countries. The review is conducted according to the standard FDA review process, with the addition of multicountry teleconferences (2–3 per application) to discuss key aspects of the evaluation. Each country performs its regular reviews and retains full independence in regulatory decision and labelling negotiations. The FDA takes the lead review role of verifying the data, verifying the results and conducting additional analyses as needed.

The Project Orbis one-year update shows that, at the time of the presentation, the FDA had approved 21 products through the Project (seven authorizations for the Australian Therapeutic Goods Administration, eight for Health Canada, one for Swissmedic, and four for Health Sciences Authority Singapore) (12). Initially, the Orbis procedure was for supplemental applications, i.e. new indications for previously approved products. Subsequently, the project has expanded to include new molecular entities, also known as new active substances or new drug substances, in various regions. The median time gap between FDA and Orbis submission dates is 0.6 months (range –0.8 to 9.0 months) and the median time gap for approval is 1.1 months (range 0.0 to 3.8 months), which are very notable results compared to the situation before the introduction of this project, when differences of 12 months between submissions could be observed. Regarding paediatric oncology, there was no product with a paediatric oncology indication in year 1 of Project Orbis but, in year 2, multiple applications with paediatric indications are under review. Regarding the challenges, the project represents a resource-intensive activity in terms of involvement of regulatory authorities (review coordination and logistics) and concurrent submission and management of applications. In addition, translation requirements and operational considerations, for example in terms of clock stops in review management, may also present some challenges.

4.8 African Medicines Regulatory Harmonization work-sharing activities

Ms Sybil Ossei Agyeman Yeboah, West Africa Medicines Regulatory Harmonization, presented the work-sharing activities of the African Medicines Regulatory Harmonization (AMRH) initiative. The AMRH is a partnership initiative formalized in 2009. The partnership includes African countries (regulatory authorities) and regional blocs, the New Partnership for Africa's Development, the African Union Commission, the Pan-African Parliament, WHO, the Bill & Melinda Gates Foundation, the United Kingdom Department for International Development, the United States President’s Emergency Plan for AIDS Relief, the Global Alliance for Vaccines and Immunization and the World Bank. The project aims to improve the
fragmented regulatory system of product registration in Africa by changing from a country-focused approach to a collaborative regional and simplified approach. The process used a stepwise approach, starting with harmonizing and streamlining technical requirements for product registration, leading to increased and timely product access. It also creates a platform for building African regulatory capacity by region. The project started with generics and then moved over to in-vitro diagnostics. Currently, more than 85% of sub-Saharan Africa is covered by medicines registration harmonization projects at different levels. The objective of the AMRH is to ensure that African people have access to essential medical products and technologies. All regional economic communities have started, or are preparing the launch of, regional harmonization for medicines. From the regional bases (the eight regional economic communities) the African Union envisions the establishment of a single African Medicines Agency (AMA). The AMA is expected to provide an enabling environment for the development of the pharmaceutical and related medical products industries and lead to better coordination between the different partners and stakeholders involved in regulatory strengthening and harmonization efforts for medical products and health technologies on the continent. At the time of the presentation, 18 African Union Member States had signed the Treaty for the Establishment of the African Medicines Agency, and eight African Union Member States had ratified it. Ms Ossei Agyeman Yeboah presented the example of the ECOWAS-MRH Initiative launched in February 2015. Regarding the AMRH achievements, she indicated, for example, that 15 medicines have been reviewed under the joint medicine assessment procedure, 329 national regulatory authority staff have been trained, 105 local manufacturers have been trained on CTD and 190 manufacturers in nine Member States have been assessed. Some of the AMRH projects included paediatric indications.

4.9 Experience of WHO prequalification with paediatric medicines

Dr Ray Corrin, WHO prequalification team, presented some recent experiences of WHO prequalification for paediatric medicines. WHO prequalification for medicines, which began in 2001, aims to ensure that medicines supplied to low- and middle-income countries are quality-assured, safe, effective and accessible. The WHO prequalification team works with stakeholders and joint initiatives (e.g. the pharmaceutical industry and the Drugs for Neglected Diseases initiative/Medicines for Malaria Venture) to facilitate prequalification of unique paediatric products (e.g. rectal artesunate for severe malaria, fixed-dose combinations for HIV therapy) by providing the relevant advice on scientific aspects. Bioequivalence evaluation is a major and important task for assessing paediatric products, since many products are generic products. In the absence of paediatric strengths, the prequalification team issued specific guidance for the design of bioequivalence studies to assist manufacturers, for example adaptation of bioequivalence study designs to account for differences between paediatric strength and adult strength, adaptation of bioequivalence study designs to account for differences in the method of administration between paediatric and adult patients (for example, dispersion of paediatric strength product in a small volume of liquid (e.g. 50 ml) versus administration of adult strength product whole with 240 ml water). The prequalification team also gives advice to companies regarding the identification of an appropriate comparator product when an originator product is not available in paediatric strength (very common occurrence) and reviews the final draft study protocol to assess compliance with medicines prequalification team guidelines and ensure appropriateness of study design with ICH E6. Sometimes waivers are possible for the sponsors, for example no new clinical efficacy/safety data are needed for first-time fixed-dose combinations of existing drug substances if bioequivalent to a combination of the mono-component products. Biopharmaceutics Classification System (BCS) biowaivers are possible through application of BCS biowaiver principles for products containing BCS class I or III products, even if a pharmaceutically
equivalent comparator product does not exist (includes consideration of biowaiver criteria appropriate for the paediatric situation, e.g. demonstration of high solubility in volumes relevant for administration to the paediatric population).

The prequalification team implemented innovations in terms of paediatric bioequivalence; for example, they accepted BCS biowaivers for products containing BCS class III drug substances prior to any stringent regulatory authorities, they applied BCS biowaiver principles to paediatric strengths of products for which there is no equivalent comparator strength, but for which the adult strength(s) meet the BCS biowaiver eligibility criteria. They also provided advice on comparative bioavailability studies that could be used to establish the safety and efficacy of paediatric mono-component products and paediatric fixed-dose combinations that have not been previously approved by a stringent regulatory authority. Other prequalification support on paediatric medicines include the Collaborative Procedure for Accelerated Registration (CRP) to facilitate national registration of prequalified products, the expert review panel mechanism to enable procurement of products not yet prequalified or approved by a stringent regulatory authority (the advice from the expert review panel is time-limited to one year, renewable). In addition, increased visibility of invited paediatric formulations has been achieved in the prequalification expression of interest, inviting manufacturers to submit specific products with score lines and dispersibility as required. Pre-submission guidance meetings take place with sponsors to facilitate the prequalification process.

Dr Corrin also mentioned the ongoing pilot with the United States of the CRP-Lite procedure, whereby FDA shares minimally redacted assessment reports with the prequalification team to facilitate prequalification and national registration (via CRP) of FDA-approved products. Other ongoing initiatives include involvement in ICH working groups (recently E6 and M9), giving input to the European paediatric formulary initiative to develop a list of excipients acceptable for use in paediatrics and continuing development of prequalification product-specific guidance (e.g. insulin). Recent paediatric prequalification accomplishments include dolutegravir paediatric fixed-dose combination advice for two companies, rectal artesunate 100 mg prequalified in 2018 in severe malaria for children up to 6 years, zinc for diarrhoea where acceptability/palatability is required, for all manufacturers, and the inclusion of specific instructions in WHO public assessment report labelling in case of “extemporaneous formulations”.

4.10 CRP: a useful tool for paediatric medicines

Dr Luther Gwaza, Technical Officer, Facilitated Product Introduction Regulatory Systems Strengthening, WHO headquarters, presented the CRP and its use for paediatric medicines. The principle of the CRP is for national regulatory authorities to rely on the assessment and inspection conducted by the WHO prequalification team, or by stringent regulatory authorities, to facilitate in-country registration. Each national regulatory authority keeps its own sovereignty in terms of decision-making for marketing authorizations in its own countries. Dr Gwaza referred to the published guidelines for CRP based on prequalification (see Annex 8 (13)) and on stringent regulatory authorities (see Annex 11 (14)), and additional tools, for example Good practices of national regulatory authorities in implementing the CRP for medical products (see Annex 6 (15)) and Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions (see Annex 9 (16)). CRP is a voluntary procedure on the part of both the national regulatory authority and the manufacturer. Importantly, the product and registration dossier in countries are “the same”, as prequalified by WHO, and confidential information is shared to support national regulatory authorities’ decision-making in exchange
for an accelerated registration process. The “harmonized product status” is monitored and maintained throughout the life cycle of the product.

The CRP allows for best use of available resources by using reliance on regulatory decisions performed by other competent and trusted agencies and/or cooperation or collaboration with other regulators to reduce the workload, with independent final decision-making. The added value of the WHO prequalification CRP is that it considers the benefit/risk evaluation in the intended population and the relevant stability data (climatic zone IV). Approval by stringent regulatory authorities usually considers the benefit/risk for their populations, except for the global mechanisms such as EU-M4all (EU Article 58) (17) or the Swissmedic marketing authorization for global health products. Resources saved from using reliance approaches where possible (example of prequalified and stringent regulatory authority-approved products) can be redirected to assess products that have not yet been evaluated by any regulatory authority.

At the time of the presentation, 45 national regulatory authorities and one regional economic community in Africa had joined CRP. Dr Gwaza presented some statistics on registration of paediatric formulations through the CRP. As of 22 February 2021, 88 paediatric formulations had been registered through CRP: mainly in tuberculosis (TB) (41%) and malaria (27%). The data show an uneven distribution of the use of CRP between regions. As for the timelines for the CRP, the statistics show that, in most cases, the timeline of 90 days is met.

4.11 Joining forces and working towards the same goals: examples of GAP-f and the Rome Action Plan initiative

Dr Martina Penazzato presented the recent activities of GAP-f. This is a WHO network that was set up to facilitate collaboration between different partners across the product life cycle of paediatric medicines from prioritization and evaluation of new products, all the way through development, introduction and delivery. The platform also works to unlock some of the barriers and to mobilize the relevant resources to do so to facilitate access to paediatric medicines. The key principles of GAP-f are to promote coordination and synergies across multiple stakeholders to achieve common goals, to think innovatively to find solutions to shared problems, to avoid duplication through promoting transparency and dialogue, to share resources and information to keep abreast of the latest developments and to use agility in responding to change. GAP-f interacts with a big variety of stakeholders in order to achieve its mission (for example governments, funders, affected communities, innovators, regulators and other sectors). GAP-f is growing and, at the time of the meeting, 30 organizations had joined the network¹ and were participating in one or more working groups (the four GAP-f working groups are as follows prioritization; clinical research; product development and regulatory affairs; and product access and treatment delivery). GAP-f also works with financial and technical partners: ELMA; Unitaid, the Global Fund to Fight AIDS, TB and Malaria, the Bill & Melinda Gates Foundation and United States Government agencies.

The GAP-f working groups promote best practices and address common challenges for the different steps: prioritize, evaluate, develop and deliver. Regulatory activities by GAP-f include facilitation of in-country registration of GAP-f portfolio products (e.g. dolutegravir 5 mg and 10 mg), the collaborative review of new guidance (e.g. FDA anti-infective paediatric guidance, European Union parallel marketing authorization application and Article 58 procedure) and carrying work on identifying innovative and facilitated regulatory pathways. A project is ongoing to explore the use of bitter-blockers to eliminate the bitterness of medicines as one of the causes of poor adherence. The GAP-f portfolio was presented (18); it initially covered HIV, TB and malaria, but is now expanding to other disease areas (e.g. childhood cancer, neglected...
tropical diseases). A project is currently ongoing in collaboration with the Bill & Melinda Gates Foundation to identify and prioritize paediatric formulations missing from the WHO Model List of Essential Medicines for Children. This scoping exercise will allow an assessment of the appropriateness of existing paediatric formulations and identification of overall gaps. The dolutegravir case study is a good example of coordinated efforts that greatly facilitate the early availability of the two dolutegravir 10 mg generic paediatric formulations. Finally, Dr Penazzato shared the experience of the Vatican Platform for High-Level Dialogues and the Paediatric HIV & TB: Rome Action Plan (19) that has helped greatly to elevate technical work to a political level, with strong commitments from the different key stakeholders.

4.12 COVID-19 no child left behind: update from the United States FDA and EMA

Dr John Alexander, Deputy Director of the Division of Pediatric and Maternal Health, Center for Drug Evaluation and Research, FDA, gave a presentation on the United States paediatric regulations for COVID-19 products. The FDA Guidance on COVID-19: developing drugs and biological products for treatment and prevention was published on 11 May 2020 (20). The Guidance states that children should not be categorically excluded from clinical trials of investigational COVID-19 products in which there is a prospect for direct benefit. It also indicates that there is a potential for the use of paediatric extrapolation of adult efficacy data. In addition, if dosing recommendations for a drug are the same for adults and adolescents and there is sufficient prospect of benefit to justify the risks, then it may be appropriate to include adolescents in the initial phase III clinical trials. Sponsors are encouraged to submit an iPSP as soon as practicable. FDA intends to work with sponsors to reach agreement on the iPSP and any paediatric trial protocols as quickly as possible, to avoid any unnecessary delays in the initiation of trials or submission of a marketing application.

On the same day as the publishing of the Guidance for COVID-19, the FDA announced its Coronavirus Treatment Acceleration Program. The programme provides for a rapid, coordinated response to drug developers, a contact point for individuals seeking information about COVID-19 expanded access programmes for single patients and for drug development input and protocol review for sponsors to be conducted in a rapid fashion (21). As of 28 February 2021, the Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research had discussed over 590 drug developments in the planning stage, more than 430 trials had been reviewed, nine different treatments had received emergency use authorization (for either direct treatment or supportive care of patients with COVID-19) (22) and one product had been approved by FDA for use in COVID-19.

Veklury (remdesivir) was approved on 22 October 2020 for adults and paediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. This authorization includes a post-marketing requirement to conduct a study to evaluate the safety, tolerability, pharmacokinetics and treatment response to remdesivir in paediatric subjects from birth to under 18 years of age, including neonates, with COVID-19. This trial is intended mainly to provide pharmacokinetics and safety information for paediatric patients hospitalized with COVID-19, as paediatric extrapolation was considered appropriate in this case. There was good collaboration with the EMA on paediatric matters for the development of COVID-19 therapeutics, since the PIP and PSP were submitted in parallel to both the EMA and the FDA. Interactions took place through the paediatric cluster, and several ad-hoc meetings were held to coordinate an international paediatric development as far as possible.

Regarding the six treatments with emergency use authorization for treatment of COVID-19, most of the products are monoclonal antibody products that are authorized for use in paediatric
patients 12 years and older and weighing at least 40 kg. For one of the products, baricitinib, the FDA was able to rely on paediatric information, including pharmacokinetics and multiple dose safety information already available from another study, to support authorization down to 2 years of age. The safety and dosing information available in children and extrapolation of the efficacy data in adults allowed the FDA to support the emergency use authorization in children aged 2 years or older. Three COVID-19 vaccines had received emergency use authorization at the time of the meeting, namely Pfizer-BioNTech COVID-19 vaccine (for the prevention of COVID-19 in individuals aged 16 years and older), Moderna COVID-19 vaccine and Janssen COVID-19 vaccine (both indicated for the prevention of COVID-19 in individuals aged 18 years and older). On 31 March 2021, Pfizer announced the results of their study of 2260 adolescents aged 12–15 years. Close collaboration between the FDA and the EMA regarding the development of paediatric plans for vaccines was also observed.

Dr Laura Fregonese presented EMA initiatives and collaboration with international regulators for COVID-19. She referred to the EMA plan for emerging health threats that foresees a flexible, streamlined and rapid case-by-case PIP approach in full respect of legislative requirements in times of emergency (23). In addition to the provision already foreseen in the emergency plan, the EMA implemented a number of activities, including the preparation of a short- to medium-range forecast of expected PIPs, early engagement with developers (including proactively) in the PIP pre-submission phase, no specific submission deadlines, applications for PIPs/waivers for therapeutics and vaccines for COVID-19 reviewed in an expedited manner (triage) with a rapid and flexible approach while preserving the scientific robustness of the outcome. A rapid agreement on PIPs was put in place with target fast-track timelines of 20 days (compared with a standard timeline of 120 days). For marketing authorization, the EMA introduced a rolling review, with a review cycle of ~14 days. The EMA created a specific EMA task force for the COVID-19 response, including infectious disease experts from across the European Union. Close collaboration with the United States and other regulatory authorities was managed through the paediatric clusters. Early in the pandemic, in June 2020, the United States/EMA published a common commentary on submitting iPSP and PIP for the prevention and treatment of COVID-19 (24). This document guides applicants through the PSP and PIP templates to help them for the preparation of their applications for both agencies. At the time of the meeting, the EMA had so far agreed six PIPs for vaccines (three ongoing) and three PIPs/waivers were agreed for therapeutics (eight ongoing). The PIP assessment time, in practice, was between 20 and 60 days. Positive feedback has been received from applicants on rapid PIPs. All therapeutics PIPS were discussed in the paediatric clusters. The common guidance with FDA on PSP/PIP templates was considered useful by several applicants. Occasionally, the EMA, with the United States, also produces common commentaries on important aspects discussed as part of the paediatric plans (usually initiated by companies).

5. Conclusions and next steps
Dr Alysha Croker, PRN Co-Chair, briefly summarized the two days of meeting, which had demonstrated the strong engagement for collaboration from the international paediatric regulators community. Discussion highlighted the need for prioritization in the global paediatric arena to focus efforts and for the different stakeholders to work towards the same goals. The different speakers and presentations demonstrated the importance of work-sharing and reliance approaches for paediatric medicines. The role of the PRN will be to leverage the existing networks and harmonization initiatives to facilitate access to quality paediatric medicines globally. The WHO prequalification and CRP are essential tools and should be capitalized for paediatric medicines. Regarding the next steps, the PRN Chairs and Secretariat
will review suggestions and recommendations received during the meeting to inform the work of the PRN and topics for discussion for future meetings. The PRN Chairs and Secretariat thanked all participants for their participation. After the customary exchange of courtesies, Dr Croker declared the meeting closed.
References


## Annex 1. Agenda
All times CEST

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speakers</th>
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<tbody>
<tr>
<td>13:00–13:15</td>
<td>Welcoming remarks</td>
<td>Dr Mariângela Simão, WHO</td>
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<tr>
<td>13:15–13:30</td>
<td>Agenda and objectives of the Meeting</td>
<td>Professor Moji Christianah Adeyeye, PRN [Paediatric Regulatory Network] Chair</td>
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<tr>
<td>13:30–14:30</td>
<td>Introductions – Tour de Table</td>
<td>Dr Lynne Yao, FDA</td>
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<td></td>
<td>• Updates from FDA [United States Food and Drug Administration] on the implementation of FDA Reauthorization Act (FDARA) – 10 minutes.</td>
<td>Dr Ralph Bax, EMA [European Medicines Agency]</td>
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<td></td>
<td>• Updates from EMA on ongoing paediatric work in the European Union – 10 minutes.</td>
<td>Dr Alysha Croker, Health Canada</td>
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<td>• Access Consortium – 10 minutes</td>
<td>Dr Samvel Azatyan, WHO</td>
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<td>• WHO Good Regulatory Practices and Good Reliance Practices – 15 minutes.</td>
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<tr>
<td>14:30–14:45</td>
<td>Short break – Please stay connected</td>
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<tr>
<td>14:45–15:15</td>
<td>Results of the PRN survey and where can the PRN help?</td>
<td>Professor Moji Christianah Adeyeye, Dr Alysha Croker, Marie Valentin</td>
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<tr>
<td>15:15–15:45</td>
<td>Discussion</td>
<td>Moderated by Professor Moji Christianah Adeyeye, PRN Chair</td>
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<tr>
<td>15:45–16:00</td>
<td>Wrap-up and end of Day 1</td>
<td>Professor Moji Christianah Adeyeye, PRN Chair</td>
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<tr>
<td>13:00–13:15</td>
<td>Welcome and agenda</td>
<td>Dr Alysha Croker, PRN Co-chair</td>
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<tr>
<td>13:15–13:45</td>
<td>How to best optimize reliance and work-sharing for paediatric medicines</td>
<td>Dr Cornelia Bigler, Swissmedic Dr Angelo de Claro, FDA Ms. Sybil Ossei Agyeman Yeboah, Medicine West Africa Regulatory Harmonization</td>
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<tr>
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<td>Reliance for Paediatric Plan – Swissmedic example – 10 minutes</td>
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<td>Project Orbis – FDA – 10 minutes</td>
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<td>African Medicines Regulatory Harmonization work-sharing activities – 10 minutes</td>
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<tr>
<td>13:45–14:00</td>
<td>Experience of WHO Prequalification with paediatric medicines</td>
<td>Dr Ray Corrin, WHO</td>
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<tr>
<td>14:00–14:15</td>
<td>The WHO Collaborative Registration procedure: a useful tool for paediatric medicines</td>
<td>Dr Luther Gwaza, WHO</td>
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<td>14:15–14:45</td>
<td>Discussion</td>
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<tr>
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<td>Joining efforts and working towards the same goals: examples the Vatican initiatives and GAP-f</td>
<td>Dr Martina Penazzato, WHO</td>
</tr>
<tr>
<td>15:15–15:45</td>
<td>COVID-19 no child left behind</td>
<td>Dr John Alexander, FDA and Dr Laura Fregonese, EMA</td>
</tr>
<tr>
<td>15:45–16:00</td>
<td>Wrap-up and end of the meeting</td>
<td>Dr Alysha Croker, PRN Co-chair</td>
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- Day 2: Dr Alysha Croker, Co-Chair of the PRN Manager, Office of Paediatrics and Patient Involvement Centre for Regulatory Excellence, Statistics and Trials, Health Canada
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