

PDP Regulatory Discussion Paper
Regulatory challenges in ensuring equitable access to new health products in
low income countries

Julie Milstein¹ October 2010

Abstract

In order to develop more effective strategic pathways for introducing products for global diseases via Product Development Partnerships (PDPs), a number of discussion papers were commissioned to document the strategies currently being used by PDPs. This document, focused on regulatory strategies, is based on telephone interviews with 10 PDPs, five dealing with medicines (including microbicides), three with vaccines, and one each with diagnostics and pesticides. Telephone and email communications with stakeholders and experts in WHO prequalification were also undertaken. The regulatory strategies in use by the PDPs vary, but for the most part depend on the use of Stringent Regulatory Authorities (SRAs) and/or the WHO prequalification program and recommendations for global use. Alternative approaches that may involve endemic country regulators were viewed with skepticism by a few PDPs, although endorsed by the vaccine PDPs contacted and by at least one medicines PDP. A PDP “wish list” included requests for improvements in the following areas: the comparative quality of regulatory pathways, prequalification, understanding differences among products and their impact on regulation, and capacity building. Stakeholders, including developing country regulatory authorities and donor agencies, identified specific activities for PDPs in the area of capacity building. Finally a list of PDP proposals to maximize regulatory impact was assembled. It included (1) proposals for more efficient sharing of personnel resources and information regarding regulatory requirements, sharing lessons learned in key countries; (2) activities to improve the quality of the regulatory process, such as PDP commitment to certain standards of quality and on-going harmonization efforts; and (3) a shared commitment to capacity building, including support for initiatives that can expedite registration while building capacity.

Introduction – context of the study

Non-profit product development partnerships (PDPs) have been increasingly used to enhance the development, manufacture, regulation, and distribution to target countries of products for public health use, especially in lower income countries. These products encompass vaccines, chemical medicines, diagnostics, microbicides, pesticides and other interventions that contribute to lessening the impact of global diseases such as tuberculosis, malaria, HIV/AIDS, dengue and others that particularly affect emerging and developing nations. For these products, according to Saul Walker, of DFID, “All the elements – availability, acceptability, accessibility, and affordability – are needed to reach an eventual health impact.” [1] The effectiveness of a PDP’s regulatory strategy for approving clinical trial protocols, assessing the characteristics of a product and obtaining a license or marketing authorization can directly impact all of the critical elements that lead to enhanced public health.

¹ Julie Milstein (consultant) on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept, DNDi, FIND, IAVI, iOWH, IPM, IVAC, IVCC, MMV, MVI, PDVI, and TB Alliance

Because of the importance of regulatory strategies to global access, a discussion paper has been commissioned by the PDP Access Steering Committee to explore and document PDP experiences with regard to regulatory challenges, particularly in low income countries, with an emphasis on what strategies have been successful and the accompanying rationales. This document is intended to act as a reference for future PDP efforts, but it cannot be prescriptive, given that strategic choices differ by modality (vaccines, chemical medicines, diagnostics, insecticides), disease, product and intervention characteristics, among other factors. Instead, it will outline the range of strategies devised by different PDPs and the reasons for their use.

The terms of reference for this paper are provided in Annex 1. The list of organizational representatives interviewed is in Annex 2. Ten PDPs were interviewed, covering five working on medicines (one of which is dealing with the preventive pharmaceutical approach, microbicides), three on vaccines, one on diagnostic products and one on pesticides. In addition, different stakeholders were interviewed to understand the impacts and implications of current PDP practices. Where relevant, documents both formally published in the literature and those of WHO and other agencies (meeting reports, white papers, websites, etc) are referenced.

In addition to developing different products, which have different regulatory modalities, at any specific time a PDP may emphasize work only at specific stages of the product lifecycle. This is summarized in Table 1 for a number of PDPs at the time of this report. This has implications for the type of regulatory activities performed by particular PDPs. For example, PDPs concentrating on product development and early phase clinical trials (1 and 2) will be focusing primarily on trial approval and oversight processes and the assurance of Good Clinical Practices and appropriate ethics review. Those who are moving products through late stage clinical trials (phase 2B, 3) and initial registration will have knowledge of these areas and, in addition, will be assuring manufacture under Good Manufacturing Practice (GMP) conditions at appropriate capacity. They will look to assure registration that will be acceptable to the target population and will be considering WHO prequalification or WHO Pesticide Evaluation Scheme (WHOPES) recommendation. Lastly, those with final product approval will be concerned with post-marketing surveillance, including monitoring of adverse events and other phase 4 studies, efficacy, variances, continuing GMP compliance, and for vaccines, lot release, as well as coordination of registration in endemic countries, with or without WHO prequalification or WHOPES recommendation. In summary, while it is important that all PDPs have a clear regulatory strategy for each stage of product advancement even from the earliest stage of product development, their experiences and expectations will vary depending on where their activities are focused.

Table 1. PDPs are currently at different stages of product development and regulatory review.
(Note that font size corresponds to relative degree of focus at each stage for each PDP.)*

Product Development Stage	Medicines	Vaccines	Diagnostics	Pesticides
R&D, early clinical trials	DNDi IPM MMV TB Alliance	Aeras MVI MVP	Find	IVCC

Late clinical, registration	Concept DNDi IPM MMV TB Alliance	Aeras MVI MVP	FIND	IVCC
Wider registration, access	Concept DNDi IPM MMV TB Alliance	MVI MVP	FIND	IVCC

* Complete names for PDPs are provided in Annex 2

A brief outline of possible regulatory pathways

To date products for global diseases have most often been first developed and produced in industrialized countries. This can challenge the normal regulatory pathways of stringent regulatory authorities (SRAs), because the products are targeted towards diseases of generally lower income countries which may be limited or nonexistent in developed countries,. On the other hand, if other regulatory strategies are used where products are not registered by SRAs [2, 3] the product might not be considered to be of acceptable quality by the endemic countries. The following regulatory strategies have been implemented by the ten PDPs studied to address the challenge of choosing the most efficient regulatory pathway.

- a. Stringent regulatory authority. The description below covers both the standard pathways used by stringent regulatory authorities, which include for this discussion the US Food and Drug Administration (FDA), the European Medicines Authority (EMA), Health Canada, Swiss Medic, and the Australian Therapeutic Goods Administration, and the variations implicit in such approaches as Article 58 (EMA) and the FDA Global Disease Approach (vaccines only). This approach has the advantage that SRA decisions are readily recognized the world over and are in fact considered a “gold standard” by many regulatory agencies. In the case of medicines, registration by one of these agencies expedite WHO prequalification status. These agencies have the funding, staff and advisor expertise, and experience to deal with innovative products. There are two major disadvantages to an approach through SRAs: (1) the inability of a regulatory authority to register or grant marketing authorization for a product that will not be actually marketed or distributed in the geographic area, and (2) the possible lack of expertise of these SRAs with diseases for which these products are proposed, and perhaps a lack of clinical data amassed in the endemic countries.

There are now in place various approaches that can overcome some of these deficits. Article 58 refers to a process enacted by EMA [4] to deliver a scientific opinion on products with sponsors located within Europe which will not be marketed in Europe. The scientific opinion is developed in a manner as rigorous as usual marketing authorization decisions taken by the EMA, but cannot by definition lead to a marketing

authorization. The process is initiated by application to WHO from the sponsor to request that EMEA proceed with the process. To date three pharmaceutical products and one vaccine have been considered under Article 58 [5], but more are in the pipeline. To overcome the potential problem of lack of expertise, the Article 58 process specifically includes the proposal that experts in endemic country epidemiology and practice will be included in the group that delivers the scientific opinion.

The second approach is the FDA Global Disease Approach, defined by guidelines issued by the FDA's Center for Biologics Evaluation and Review [6] and explained in detail by Brennan [7]. To date this process is defined only for vaccines, and has not been tested for products targeted at endemic countries. It specifically provides for the use of foreign data to be considered for an FDA decision. It is not yet known whether relevant endemic country experts will be included in the process, nor whether the process will be extended to other products under FDA oversight.

- b. WHO prequalification or recommendation. WHO prequalification is not just one activity, but a series of activities performed by several groups within WHO for medicines, vaccines, and diagnostics. Pesticides undergo a different process with similar intent which is recommendation by the WHO Pesticide Evaluation Scheme - WHOPEP. These groups work within the context of the products for which they are assessing, and should not be considered as a single unit. They have been working for different lengths of time; however, their primary purpose is to narrow the scope of an international tender by limiting bidders to those proposed products that already meet the tender specifications, including relevant quality standards. The purchasers using this list include UN agencies and other large volume procurers (e.g. the Global Drugs Facility), as well as individual country groups. Annex 3 provides a detailed summary of the similarities and differences among the processes for different products.

WHO prequalification may be granted (except for vaccines) in the absence of registration of a product. It is often used as a basis for registration in endemic countries, and may be obligatory for purchase of a product by large procurement agencies. In the case of vaccines, the prequalification process cannot be initiated without reference to the prior registration of the product by a regulatory authority considered by WHO to be functional [8].²

A major disadvantage of using the WHO process is the time it takes for the review, which can average two years [9], although efforts and approaches are in place to reduce this time. A second disadvantage is the limited product list: for medicines, to date only medicines for treatment of HIV/AIDS, malaria, tuberculosis, some human reproduction products, plus influenza treatment and zinc sulfate are included. Also, the prioritization process applied to a decision to consider a particular product for prequalification may not be applicable to needed products. However, depending on the product, the WHO prequalification process can be highly relevant. For vaccines, for example, consideration is given not only to the epidemiology of the target countries but also to the utility of the particular presentation and labeling aspects.

² Another part of the team in WHO dealing with vaccine quality provides RA assessments and capacity building activities.

- c. Joint or twinned review. This is a regulatory review process which might be initiated in an endemic country or countries for which one or more SRAs works with the local RA(s) to provide a comprehensive review process that takes into account both innovative product characteristics as well as the epidemiologic characteristics and medical practices in endemic countries. Such a process has been described in a recent paper commissioned by DNDi [10], and has been used in groups of regulators representing developing countries, such as in meetings of WHO's Developing Country Vaccine Regulator's Network [11], where it has been used to consider regulatory decisions on rotavirus vaccines, for example, or the African Vaccine Regulatory Forum (AVAREF) [12], which has considered the clinical trial process for a meningitis A conjugate vaccine for the African meningitis belt. This approach is strong in capacity building. In fact, the process for registration of the meningitis A conjugate vaccine developed through MVP has been an example of a twinned approach, not only because of joint review of the clinical trial documents through AVAREF, but also because Health Canada participated in file review with the competent regulatory authority, the Drugs Controller General (India), for the registration process. The advantages of this approach are overall acceptability and relevance of the decision-making process, as well as capacity building. The disadvantages are that it is not yet formalized, it may not shorten regulatory review times at least in the pilot programs, and it depends on the will and capacity of the SRAs as well as the endemic country RAs to participate.
- d. Licensure by a competent RA in the country of production. The competent RA is the authority in the country of production who certifies the product, with no indication as to its ability to carry out a thorough and rigorous regulatory assessment. In the case of vaccines, this designation may be further restricted by specifying that the RA be also functional as defined above [8]. An example of this approach, the case of the fixed dose regimen of ASAQ drugs for malaria, is further described in Annex 4, for which DNDi coordinated further registration of the product after it was initially registered by Sanofi-Aventis in Morocco, the country of production. A disadvantage of this approach is that there may be disagreements on the acceptability of the decision of the original RA if that RA is not considered stringent or functional. A second example, registration of GSK's rotavirus vaccines first in Mexico, may be relevant, since Mexico's RA did not meet WHO's definition of "functional," creating problems for national RAs to accept their recommendations.

Another issue is the time taken for even the initial approval process. Annex 5 illustrates this problem for authorizing vaccine clinical trials in different countries, as well as demonstrating the lack of harmonization in approaches, which is a third problem.

Table 2 estimates the characteristics of the approaches that have been discussed.

Table 2. How do the various registration approaches meet PDP requirements?

Approach*	Acceptable	Timely	Capacity Building	Relevant
SRA	√√	√	-	-
Article 58	√√	±	√	√√
WHO PreQual	√√	-	√	√ (√√)
Joint/Twinned	√√	-	√√	√√
Local RA	√	±	√	√√

- SRA = Stringent Regulatory Authority (eg. FDA, EMEA); PreQualification = approved by the relevant WHO prequalification program or WHOPES; RA = Regulatory Authority

For products for global diseases, it has been considered that the most useful regulatory approach would be one that (1) was acceptable to the target population, (2) contributed to building capacity for regulation in the endemic countries, (3) was relevant to the epidemiological situation and clinical practice in the endemic countries and (4) was timely, that is, proceeding as quickly as possible without compromising the safety and effectiveness analyses of the product.

Experience of PDPs with regulatory pathways

- a. **Pathways that are being used and why.** As part of the interview process, PDPs were asked which pathways they had used for their products and why (see Table 3).
 - *DNDi* is considering a twinned or Article 58 process for a New Chemical Entity (NCE), in order to have the expertise of an SRA but to still to involve the local RAs, who may have a better knowledge of the epidemiological situation and clinical practice in the target countries. In addition, the twinned approach may be a powerful tool for exposing RAs to the types of evaluation processes used by SRAs. For new combinations of already registered products *DNDi* has used registration by the local RA as mentioned above (see Annex 4).
 - *IPM* has proceeded with Article 58 for a dapivirine-based microbicide in a vaginal ring format, as it would be the first use for a new Active Pharmaceutical Ingredient (API), a new vehicle, and a new dosing form, and thus would need SRA expertise. They are thus also looking into registration through FDA, which might be needed for the President's Emergency Plan for AIDS Relief (PEPFAR) procurement. *IPM* believes that WHO prequalification, which is at this time not applicable to microbicides, is less well suited to new APIs and the complex issues involved in evaluation of microbicides,
 - *MMV* usually partners with a pharmaceutical manufacturer, and selects SRA review and possibly WHO prequalification to assure both stringent review and acceptability of the decision. It counts on WHO to do the capacity building.

- The philosophy of the *TB Alliance* registration of novel tuberculosis treatments is global registration – in high burden countries but also in industrialized countries. Stringent RAs, primarily FDA and EMEA, are often key to getting registration in high burden countries. The other approach being considered is WHO prequalification.
- *Concept's* goal is documents compliant with the formats promulgated by the International Conference on Harmonization (ICH) of a product originally registered in the country of manufacture and produced under GMP conditions, and all product dossiers must meet international regulatory standards. These are then submitted to the relevant local RAs. They are also submitting dossiers for WHO prequalification, mostly to facilitate procurement.
- *Aeras* has several products in clinical development and the approaches differ slightly. *Aeras* prefers to have phase 1 trials and initial registration performed by an SRA, with registration next in an endemic country with a functional RA. Joint review is part of their strategy, as is WHO prequalification, which is necessary for procurement and use in the target countries.
- *MVI* has several products in clinical development and the details of the regulatory strategies are being worked out. WHO prequalification is a given, as is ensuring that the strategy will be optimal for the target population, infants and children in endemic countries. *MVI* has also had good experience with the joint review process as performed by AVAREF.
- The *MVP* product, meningitis A conjugate vaccine, has a marketing authorization in India and is now in the process of fast track WHO prequalification. The pivotal trials were done in endemic countries after the initial phase 1 trial, which had to be in India. These trials underwent joint review and inspection by the endemic countries involved. The registration process was twinned, with Health Canada participating in file review with the Indian RA.
- *FIND* development partners are commercial companies certified by the International Organization for Standardization (ISO) with regulatory departments. The commercial partner is fully responsible for regulatory compliance in the country of origin, and the manufacturing partner is regularly inspected by national RAs to ensure ISO compliance and GMP. Prequalification does not seem to be a major part of the strategy, perhaps because it may not be applicable to all their products.
- *IVCC* has two types of approaches: (1) reformulation, for which the regulatory process is fairly straightforward as the Active Ingredients (AIs) already have approval in industrialized countries for agricultural use and maybe even for vector control use; (2) new ingredient research, which is still just starting because no one has yet registered a product for first use for vector control. For already registered AIs, they get WHOPEs recommendation, because a lot of African country regulatory processes have this as a criterion, and all major purchasers require it. For the new ingredients the process has not yet been worked out.

Comment [B1]: How?

Table 3. Regulatory approaches used by PDPs studied

PDP*	Type of products	Approaches used/considered**
DNDi	Medicines for neglected tropical diseases	Twinned, Article 58 for NCEs, local RA for combos of already registered products

IMP	Microbicides	Article 58 for new API/delivery system, FDA to facilitate PEPFAR procurement
MMV	Medicines for malaria	SRA with or without WHO prequalification
TB Alliance	Medicines for TB	SRAs with or without WHO prequalification
Concept	Medicines for human reproduction	ICH-compliant dossiers to local RAs and WHO prequalification
Aeras	TB vaccines	Initial Phase 1 trial in SRA, joint review, WHO prequalification
MVI	Malaria vaccines	Article 58, joint review by AVAREF, WHO prequalification
MVP	Meningitis A conjugate vaccine	Local RA, twinned review, joint review, WHO prequalification
FIND	Diagnostics	Local RA to ensure ISO compliance
IVCC	Pesticides	For reformulated AI, WHOPEs; for new AIs, still considering

* see Annex 2 for complete names of PDPs

** *NCE = New chemical entities; API = Active pharmaceutical ingredient; PEPFAR = President's Emergency Plan for AIDS Relief; ICH = International Conference on Harmonization; AVAREF = African Vaccine Regulators Forum; ISO = International Organization for Standardization; AI = Active ingredient*

b. **Selected regulatory issues.** During the interview process PDPs were asked for details on how they were handling some specific regulatory issues. These included the handling of safety/adverse event monitoring, whether in clinical trials or post-registration; whether or not they would consider prequalification and/or registration by an SRA; and how they proposed to handle registration in their priority target countries.

- *Handling of monitoring and reporting of adverse events and safety issues.* Virtually all the PDPs said that during clinical trials and also post-registration, if there were a pharmaceutical partner, whether the manufacturer or the distributor, that partner would be responsible for all safety issues. Only in the event that the product was not developed and manufactured by a major pharma partner would the PDP then undertake to take responsibility for reporting of safety issues, either using their own staff, or through a Contract Research Organization (CRO). However, for two of the vaccine PDPs with products in clinical development, the regulatory departments were more experienced, and they reported taking charge of assuring all clinical trial safety issues, through Data Safety Monitoring Boards and working with the clinical trial sites in endemic countries to ensure prompt and thorough reporting and compliance.
- *The need for a regulatory pathway that includes review by an SRA and/or WHO prequalification.* Except in the case of the one diagnostics PDP interviewed, WHO prequalification seems to be an important step because of its role in public sector procurement. Virtually all PDPs would have gone through with one or the other, and sometimes both of these pathways. In the case of vaccines, the fact that prequalification requires as a prerequisite the intervention of a functional RA was cited as a constraint by some; however, the assessment of functionality of these RAs was also an asset. For innovative products, using joint or twinned review as a means

of getting SRA input as well as capacity building, or using a process like Article 58, were mentioned as ways to deal with their registration. Use of the new FDA policy on licensing vaccines for global diseases needs to be better understood. It was also acknowledged that the WHO vaccines policy of expedited review for prequalified products [13] would be useful for PDPs, as well as the possibility of receiving “fast-track” prequalification review [14]. In the case of pesticides, WHOPES recommendation was stated to be the unquestioned approach, even though there had been complaints about the length of time, the cost, and the transparency of the process [15].

- *Strategies for registration in priority target countries.* Most PDPs said that they had a list of priority countries for each of the products they were developing to help them coordinate regulatory strategies that would assure acceptability and access to the final product. Concept’s strategy is in fact dedicated almost totally to the aspect of promoting registration in target countries, and for this they have developed an extensive working knowledge of practices and constraints in the countries where they are working, which they could offer to share with other PDP members. DNDi, which is developing products for neglected tropical diseases that are not eligible for WHO prequalification, and because of their mission to develop regulatory capacity in endemic countries, has determined that joint or twinned review will be the most useful for them to meet their goals [10].
- c. **PDP “wish list”**. PDPs were asked what they would like to see in terms of regulatory pathways that could increase their ability to meet their objectives. What follows is a list of suggestions that PDPs would like to see put in place (note not all PDPs supported all suggestions).

Improving the quality of regulatory pathways

- Ensure a fast track regulatory pathway that assures the same standard of quality for the industrialized and the developing world.
- Ensure a central registration process that is acceptable to all.
- Shorten delays without compromising quality, for example, by parallel review.
- Formalize the twinned/joint review process.
- Harmonize regulatory policy across countries through a supranational decision making body.

Prequalification

- Extend the prequalification process to tools targeted against neglected tropical diseases.
- Assure that the WHO prequalification/recommendation processes are as efficient and free from bias as possible.
- To the extent possible, harmonize the prequalification processes for medicines, vaccines and diagnostics, while recognizing that the special characteristics of vaccines may require a slightly different approach.
- Work to decrease time delays in the prequalification processes.

Understanding product differences

- Promote a better understanding of the difference between products and what that implies in terms of their respective regulatory pathways.

Capacity building

- Promote mutual recognition within geographical groupings.
- Involve regulators of endemic countries in regulatory assessment of new products.
- Develop regional centers of regulatory excellence.

Key messages from external stakeholders

The stakeholder groups interviewed included donor agencies and endemic country RAs (see Annex 2).

- a. What is the perception of the regulatory processes being used? There is a general perception on the part of donors that the processes and strategies used will result in high quality products. However, there was some concern that the WHO prequalification process for medicines could be improved by accelerating the time frame and increasing the rigor for evaluation of NCEs, as there have been questions raised as to the quality of some approvals. It was noted that the WHO prequalification procedures must be free from conflicts of interest even from within their own organization. Regarding other regulatory pathways, it was not clear to donors that PDPs understand the different SRA options, that is, the advantages and disadvantages of using FDA or EMEA. One suggestion was for PDPs to make use of parallel regulatory approval pathways in order to accelerate the regulatory process.

The endemic country RAs consulted felt that the acceptability of products in terms of meeting relevant quality standards was sufficient, but that in some cases WHO-prequalification of vaccines may not comply with local expectations. Two specific issues were raised related to the requirement for prior registration, which may cause problems, specifically the first Rotarix® registration in Mexico as mentioned above, and prequalified vaccines being labeled “for export only,” raising concerns that they were not receiving proper regulatory oversight.

- b. Are PDPs facilitating access ? Donors are primarily interested in rapid access to the relevant products of assured high quality, and thus want the regulatory process to enhance access, not to impede it. However, they generally do not get involved in access details.

Endemic country RAs have little knowledge of PDP activities in this area.

- c. Are PDPs building capacity ? Donors are supporting some efforts to improve regulatory capacity, such as the African Medicines Registration Harmonization Initiative under the leadership of NEPAD, in collaboration with the African Union Commission, WHO, Pan African Parliament, Bill and Melinda Gates Foundation, DFID, and the Clinton Foundation. They note that few PDPs choose to go outside the FDA-EMEA-WHO prequalification route, thus limiting opportunities to build capacity.

The endemic country RAs felt that twinned review and joint review under AVAREF have provided a good platform for regulatory capacity building in developing countries, but that the processes are not synchronized or harmonized enough to provide a sustainable capacity building approach.

How can PDPs maximize their impact on regulatory issues:

The suggestions below are synthesized from the interviews.

Information sharing

- Maintain and share a database of requirements and processes in countries of common interest
- Share lessons learned from trial hurdles, types of documentation needed, approaches that have succeeded without confidentiality worries
- Establish local offices for knowledge sharing, and develop close relationships with these target countries
- Share effective regulatory resource personnel across projects where appropriate
- Establish a consolidated organization that could be available for all products that are of PDP focus, specialized in not-for-profit pharmaceutical regulatory development

Improving the quality of the regulatory process

- Promote PDP agreement and commitment to a consistent standard of quality
- Use standard ICH-compliant formats for registration files
- Formalize the WHOPEs process to reduce its time and increase its transparency
- Support ongoing medicines regulatory harmonization initiatives

Capacity building

- Commit to a shared vision of capacity building
- Identify pools of experts and regulatory centers of excellence in regions, and promote their use
- Identify regulatory approaches that promote retention of a measure of control by endemic RAs despite SRA approval and/or WHO prequalification
- Integrate PDP regulatory pathways into existing regulatory structures, such as the AVAREF joint review process
- Systematize capacity building initiatives, such as joint review, training programs

References

1. Saul Walker. A Bilateral Funder's Strategy and Bilateral Work in Metrics of PDP Success." PDPs and Access: What Works; What Doesn't. Geneva, September 17-18, 2008.
2. Stringent Drug Regulatory Authority (SRA) means a regulatory authority (in case of the European Union both EMEA and national competent authorities are included) which is (a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH (as specified on its website:); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as

represented by SwissMedic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time) [3].

3. WHO, Guideline on Submission of Documentation for Prequalification of Multisource (generic) Finished Pharmaceutical Products (FPPs) approved by Stringent Regulatory Authorities (SRAs), PQP09001 Version 1, June 2009
4. Committee on Medicinal Products for Human Use (CHMP). Guideline on Procedural Aspects Regarding a CHMP Scientific Opinion in the Context of Cooperation with the World Health Organisation (WHO) for the Evaluation of Medicinal Products Intended Exclusive for Markets Outside the Community. EMEA/CHMP/5579/04. London, 23 May 2005, at http://www.who.int/immunization_standards/vaccine_regulation/article_58_guidelines_0505.pdf, accessed 16 March 2010.
5. These were all products of multinational pharmaceutical companies. The vaccine application was withdrawn, and the remaining three, all label extensions or new formulations of existing HIV drugs, received a positive scientific opinion, reference 10, p 12.
6. Food and Drug Administration (2008) Guidance for industry: General principles for the development of vaccines to protect against global infectious diseases. At <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074762.htm>, accessed 16 March 2010.
7. Michael Brennan. The US Food and Drug Administration Provides a Pathway for Licensing Vaccines for Global Diseases. PLOS Medicine, July 2009. Volume 6 (Issue 7) e1000095.
8. Defined at WHO, Strengthening National Regulatory Authorities, at http://www.who.int/immunization_standards/national_regulatory_authorities%20strengthening/en/index.html/, accessed 16 March, 2010.
9. Information provided in interviews
10. Dr Mary Moran, Dr Javier Guzman, Alina McDonald, Lindsey Wu, Dr Brenda Omune, Health Policy Division, George Institute for International Health. Registering New Drugs: the African Context. New Tools for New Times. Sydney: January 2010.
11. Developing Countries' Vaccine Regulators Network Establishment, at http://www.who.int/immunization_standards/vaccine_regulation/dcvrn/en/index.html/, accessed 16 March 2010.
12. African Vaccine Regulatory Forum (AVAREF), at http://www.who.int/immunization_standards/vaccine_regulation/africa_network/en/, accessed 16 March 2010; Maïga D, Akanmori BD, Chocarro L. Joint reviews and

inspections: strategic forms of collaboration for strengthening the regulatory oversight of vaccine clinical trials in Africa.

Vaccine. 2009 Dec 11;28(2):571-5; Maïga D, Akanmori BD, Chocarro L. Regulatory oversight of clinical trials in Africa: progress over the past 5 years. Vaccine. 2009 Dec 9;27(52):7249-52. Epub 2009 Sep 11.

13. Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes, at http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.08_eng.pdf, accessed 16 March 2010.
14. Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies, p.12, at <http://www.who.int/vaccines-documents/DocsPDF06/812.pdf>, accessed 16 March 2010.
15. CropLife Vector Control Group. White paper. Improving the development time and speed to market of new and innovative Vector Control Products. 15 May 2009
16. See meeting report of the 4th Consultative Stakeholder Meeting for WHO Prequalification of Diagnostics, Medicines, and Vaccines, and presentations therein, at http://www.who.int/diagnostics_laboratory/stakeholder09/en/, accessed 16 March 2010.
17. The Global Training Network on Vaccine Quality, at http://www.who.int/immunization_standards/vaccine_quality/gtn_index/en/index.html, accessed 16 March 2010
18. The WHO Prequalification Project (for medicines), at <http://www.who.int/mediacentre/factsheets/fs278/en/>; WHO Prequalification of Diagnostics Programme, at http://www.who.int/diagnostics_laboratory/evaluations/en/; A system for the prequalification of vaccines for UN supply, at http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/; WHO Pesticides Evaluation Scheme – “WHOPES”, at <http://www.who.int/whopes/en/>, all accessed 16 March 2010
19. Robert Hecht, Julie Milstien, Sarah Post. Regulatory and Ethical Approval for AIDS Vaccine Clinical Trials – Experience from Five Developing Countries. Presented at International AIDS Meeting in Toronto, 2006.

Annex 1. Terms of Reference, Regulatory Strategies paper*

Because of the importance of regulatory strategies and other subjects to access, the PDP Access Steering Committee has commissioned a series of short papers. The purpose of the discussion papers is to explore and document PDP experiences and challenges with regard to access, with an emphasis on documenting the different strategies taken by various PDPs and the accompanying rationales. The output documents are intended to act as a reference for PDPs' own, future efforts – as a kind of “how to” manual. They cannot, however, be prescriptive, given that strategic choices differ by modality (vaccines, drugs, diagnostics, insecticides), disease, product and competitor product/intervention characteristics, and other factors. Instead, they will outline the range of strategies devised by different PDPs and the reasons why individual PDPs believed (at the time) that these strategies were the most effective (a) in general or (b) for their particular situation.

The regulatory discussion paper is expected to address at minimum the following questions:

- 1) Who is responsible for post-marketing surveillance / pharmacovigilance? What are the practicalities of strengthening or establishing pharmacovigilance in low income settings? What actions by (a) pharma partners and (b) PDPs would most improve the current situation?
- 2) Should USFDA and/or EMEA always be the first regulatory approval? If not, why not, and what is the better alternative?
- 3) What are the relative benefits and challenges of WHO prequalification for (a) vaccines (b) drugs (c) diagnostics (d) insecticides? Why?
- 4) Is it useful to include a list of countries where a product “must” be registered?
- 5) What entity is best placed to coordinate the registration of an individual product in low income countries: (a) big pharma partner; (b) the PDP; (c) a CRO? What are the relative advantages and disadvantages of each approach?
- 6) How can PDPs encourage/incentivize timely registration in non-lucrative markets (assuming registration is being done by pharma partners)?

* These “Terms of Reference” summarize the original intent of the discussion papers and suggested interview questions as determined by the PDP Access Steering Committee.

Annex 2. List of organizational representatives interviewed

PDPs

Aeras – Aeras Global TB Vaccine Foundation: Mike Brennan and Dale Wierenga

Concept Foundation: Peter Hall

DNDi – Drugs for Neglected Diseases Institute: Pascale Boulet

FIND – Foundation for Innovative New Diagnostics (by email): Nora Champouillon, Baerbel Porstmann, Evan Lee, David Bell (now with WHO)

IPM – International Partnership for Pesticides: Thomas Mertenskoetter, Ron Nardi

IVCC – International Vector Control Consortium: Robert Sloss

MMV – Medicines for Malaria Venture: Ambrose Talisuna

MVI – PATH Malaria Vaccine Initiative: Alan Brooks, Carla Botting, Florence Kaltovich, Julia Nunes

MVP – Meningitis Vaccine Project (Joint project of PATH and WHO): Marc LaForce

TB Alliance – Global Alliance for TB Drug Development: Ann Ginsberg, Elizabeth Gardiner

Stakeholders and International Organizations

WHO – World Health Organization (by email)

Pharmaceuticals Prequalification: Tony Gould

Vaccines Prequalification: Nora Dellepiane, Liliana Chocarro, Lahouari Belgharbi, Drew Meek

Diagnostics Prequalification: Gabrielle Vercauteren

WHOPES – WHO Pesticide Evaluation Scheme: contacted but no response

Bill and Melinda Gates Foundation

Vincent Ahonkhai

DFID – Department for International Development

Saul Walker

USAID- United States Agency for International Development (by email)

Carter Diggs

Susan McKinney

MCC – Medicines Control Council, South Africa (by email)

James Southern, expert

National Regulatory Authority, Tanzania

Margareth Ndomondo-Sigonda

Annex 3. Description of WHO Prequalification/Recommendation Processes for Different Products

Experts in the WHO prequalification/WHOPES recommendation teams and their websites were consulted to develop this summary.

Prequalification is an activity performed by several independent departments within WHO to assess the quality of medicines, vaccines, and diagnostics. Pesticides do not undergo a prequalification process as such, but rather a different process with similar intent, *recommendation* by the WHO Pesticide Evaluation Scheme - WHOPES. These groups have different histories and have been in existence for various lengths of time; however, their primary purpose is to give guidance to purchasers on the quality of products available for procurement. Purchasers of these products may include UN agencies and other large volume procurers (e.g. the Global Drugs Facility), as well as individual country groups.

All the prequalification processes have in common a file review, laboratory testing of proposed products (except in the case of medicines, where instead the specifications and methods for testing are reviewed during dossier assessment and manufacturer inspections), and review of safety. For medicines, vaccines and diagnostics, there is an inspection process to ensure the compliance of the manufacturer with the principles of Good Manufacturing Practice. For medicines and vaccines the process includes a review of data generated on administration of the product to human subjects, while for pesticides, the emphasis is more on how the products perform under field conditions. The laboratory testing of diagnostics products is actually an assessment of performance, in that it uses large panels to assess the sensitivity and specificity of the products to correctly identify the analyte in question.

A major difference for vaccines is that to start the process the product must be under the oversight of a regulatory authority considered by WHO to be functional, and this oversight must continue as long as the product is prequalified. This is important, first because of the biological nature of vaccines, which demands more ongoing oversight and lot by lot release, but also because it has provided an opportunity to expand the capacity of some key regulatory agencies. For the other groups, prequalification (or recommendation in the case of WHOPES) can take place if the product is not registered, and countries may use prequalification status as a basis for their own in-country registration process, even for vaccines [13]. In the case of medicines, registration by a stringent regulatory authority [2,3] is recognized and an abridged process is followed to prequalify such a product. For diagnostics, depending on the stringency of the regulatory approval process applied for a particular product by the RA, the prequalification process may be fast-tracked.

WHO websites for each of the prequalification processes [16] state that capacity building is an intrinsic part of their process, although the details of how this is carried out differ. All three include representatives of the local regulatory authority as part of the team on inspection visits. In addition the medicines group encourages rotations within WHO in Geneva, includes assessors from developing countries at assessment meetings, and organizes regional level meetings and workshops on different topics relevant to regulation of medicines. For vaccines and diagnostics a more formalized training program has been established; because of the pivotal role of a functional regulatory authority in vaccine prequalification, a large program of assessments,

development of training plans, and provision of training through the Global Training Network on Vaccine Quality [17].

All groups have a prioritization process which helps the programs meet their responsibilities with limited resources. For medicines, the process is currently limited to treatments for HIV/AIDS, malaria, tuberculosis, and a few products related to human reproduction, influenza, and zinc sulfate. This means that prevention products such as microbicides and many medicines for neglected tropical diseases are not yet eligible for the prequalification process. Vaccines include all those bought by major UN purchasing agencies for national immunization programs as well as others for epidemic or pandemic use, but some are considered higher priority than others. Diagnostic products handled in the prequalification program include currently commercially available test kits and technologies for HIV, malaria, hepatitis B, hepatitis C, HIV nucleic acid test and CD4 cell enumeration. The WHOPES program is for pesticides intended for public health use. The details of the prioritization process for each product are given on their respective websites [18].

Specifications of the product to be prequalified will include such characteristics as performance under various conditions, presentation or dosage form, and packaging. For medicines, vaccines, and diagnostics, the basis of the specifications they use are those of the relevant Expert Committees and the International Pharmacopeia, which then dictate the international tender. In some cases, the international tender also includes specific presentation and labeling details that are also taken into account. WHOPES uses the International Code of Conduct on Distribution and Use of Pesticides, FAO, 1990 as a framework, but as part of the recommendation process, specifications are established for the technical product.

Some of the characteristics of the prequalification/recommendation process for different classes of products are summarized in the table below.

Comparison of WHO Prequalification/Recommendation Processes

Function	Medicines	Vaccines	Diagnostics	Pesticides (WHOPES recommendation)
Prior licensing	-	+	-	-
File review	+	+	+	+
Lab testing	Review of data	+	+	+
GMP inspections	+	+	+	-
Evaluation in humans	+	+	Assessment of specificity and sensitivity using human samples	Field evaluation
Adverse events/safety	+	+	+	+

Annex 4. A Case study for the registration process
[The case of ASAQ [reference 10; Annex 5]

ASAQ is a fixed dose combination (FDC) of artesunate and amodiaquine for malaria, and its development has been managed by DNDi in partnership with Sanofi-aventis. Because of widespread drug resistance and limited access to artemisinin-based FDCs, the need to make it available was considered urgent. Both active ingredients were already widely established and available in co-blister packs.

The registration strategy devised by the partnership was to seek registration first in Morocco, the country of production, and in endemic countries, and to apply for WHO prequalification. Co-blisters were already registered in Morocco. The ASAQ dossier was submitted in November 2006 and marketing approval was granted on 1 February 2007.

A full quality-review file in ICH format was submitted to the WHO prequalification team, which included a complete clinical package. The file was assessed by WHO expert assessors from Canada, Germany, the Netherlands, South Africa, Spain, Switzerland, and Uganda. Prequalification status was granted 1 October 2008.

In order to promote capacity building among endemic country RAs, DNDi made available the ASAQ file as a case study for WHO regulatory training in Africa in 2008, which included regulatory experts from Africa, EMEA, and WHO. The file was then discussed and received “virtual approval” from the participating African regulatory experts. Once registration was complete in Morocco, the priority focus for registration was in malaria-endemic countries, and ASAQ is now registered and available in 24 countries.

Annex 5 Case studies – regulatory oversight of clinical trials

Sources: Information from Aeras, reference 19

Country	Scientific Review	Ethics Committee Review	Regulatory Review	GMO Review	Import Permission Issuer	Total time	Comments
Brazil	RA	National and local	RA	Yes	RA	1-9 months	Defined system
India	Local scientific committee	National and local	RA	Yes	RA	??	Recently revised – new timeframes not known
Kenya	Local scientific committee	US and national	-	-	Pharmaceutical Dept	4-6 months	
Mozambique	Investigator's institution	National	MOH*	-	Pharmaceutics Dept,	6-7 months	*RA approved but not yet functional
South Africa	RA	National	RA	Yes	RA	4-6 months	Need to enter trial onto data-Base
Uganda	Local scientific committee	US and national	RA	-	Local scientific committee	4-5 months	Ethics and regulatory review can be concurrent

Authors Biography

Julie Milstein

Julie B. Milstien, Ph.D, is an independent consultant in vaccine supply and regulatory issues. She is also an Adjunct Professor, University of Maryland School of Medicine in Baltimore, MD USA Department of Geographic Medicine, where part of her work relates to regulatory issues in vaccine development, including work with the Dengue. Vaccine Initiative. She is retired from the World Health Organization where her responsibilities included planning and co-coordinating activities related to supply, financing and quality of vaccines and immunization-related technologies in global immunization programmes. Before joining the World Health Organization in 1988, she worked for the Food and Drug Administration of the United States of America for 14 years, where her area of responsibility included vaccine research, review of vaccine licensing applications, and evaluation of adverse reactions for biological and some pharmaceutical products.

Contact details: Julie Milstien : jmilstien@gmail.com