

Regulatory Challenges in Ensuring Equitable Access to New Health Products in Low Income Countries

*** Prepared by Julie Milstien and Mike Brennan**

General PDP Objective:

How to choose the best regulatory pathway if product is intended for developing countries

**The best regulatory pathway =
timely response w/o compromising quality**

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 – Malaria Vaccine Initiative: Alan Brooks, Carla Botting, Florence Kaltovich, Julia Nunes
MVP – Meningococcal Vaccine Project: 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

Interview Questions for PDPs:

▪What approach is your _PDP currently taking to handle the regulatory pathway for _____ products in development?

▪How has this process worked to date?

▪What other approaches have you considered, and what are the pros and cons of each?

▪In the best of all possible worlds, what would be your ideal approach?

What are the constraints to that?

▪Who currently is handling adverse events for your studies?

Is this the same group that will continue to do so post-licensing?

Who do you think should handle adverse events? Why?

▪Do you intend to seek prequalification for your products?

What are the pros and cons of so doing?

▪Do you consider registration by FDA and/or EMEA to be necessary?

If so, why? If not, why not? Could it be a drawback?

▪Would you consider it important to have a list of countries

where your products must be licensed?

▪What entity is best placed to coordinate the registration of an individual product in low income countries?

What are the relative advantages and disadvantages of each approach?

▪How can PDPs encourage timely registration of products for use in non-lucrative markets?

Primary registration strategies used by PDPs

**(Info from 5 medicines, 3 vaccines,
1 diagnostics, 1 pesticides PDPs)**

- **Stringent regulatory authority [Fully Functional]**
- **Article 58 or FDA Global Disease Approach**
- **WHO prequalification**
- **Joint/twinned review**
- **Licensing by competent regulatory authority in country of production**

Table 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
IPM	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

Table How do the various registration approaches meet PDP requirements?

Approach*	Acceptable In target pop.	Timely	Capacity Building	Relevant to clinical practice
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

Annex 5 Case studies – regulatory oversight of clinical trials

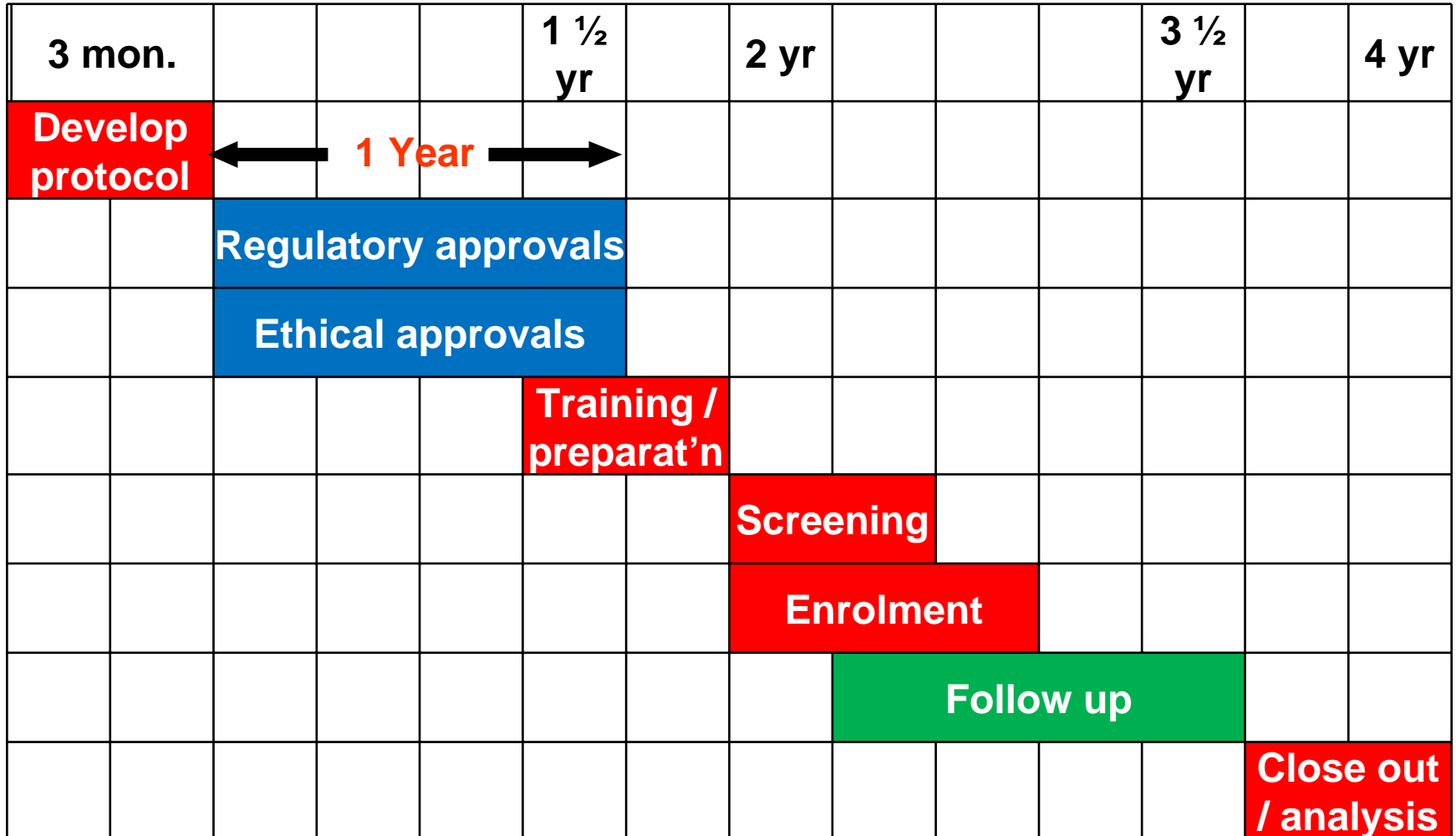
Sources: Information from Aeras, reference 19

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	31 months	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
US			FDA			30 days	

Time frame of Phase I clinical trial w **3 month Regulatory and Ethical Review**

3 months	6 months	9 months	1 year		1 ½ years
Develop protocol	3 mon				
	Regulatory approvals				
	Ethical approvals				
	Training / preparat'n				
		Screening			
		Enrolment			
		Follow up			
					Close out / analysis

Time frame of Phase I clinical trial w 1 year Regulatory and Ethical Review



Interview Questions for WHO Prequalification Staff - Medicines Programme

- How does the pharmaceuticals prequalification process differ?
- Is prequalification an option without the oversight of a competent DRA? And if so, how is “competent” defined?
- Do you think that prequalification has been/will be helpful to PDPs in increasing access to their products? If so, how? Or detrimental? And if not, how ?
- How are adverse events handled for prequalified medicines ? Who takes the primary responsibility for their collection and analysis?
- Do you have additional comments on the relative advantages or disadvantages of the process for medicines compared to vaccines?
- Any other comments on how the prequalification process might be useful or not for PDPs?

WHO Prequalification/Procurement

- Objective: to ensure products are high quality and appropriate for purchase for global communities
- Process differs somewhat for different products eg
Prequalification for drugs can be granted w/o registration by a RA BUT not for vaccines.
- Can take time, ave. ~ 2 years
- Need priority product status

Comparison of WHO Prequalification/Recommendation Processes

Function	Medicines	Vaccines	Diagnostics	Pesticides (WHOPES recs)
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	+	+	+	+

Interview Questions for Stakeholders:

Are the approaches that PDPs are using for regulatory strategies, which vary from PDP to PDP but seem to be focused on WHO prequalification, FDA or EMEA review or opinion, and joint review in developing countries:

-achieving the desired results in terms of assuring safety, quality, and efficacy of the products?

-achieving the desired results in terms of assuring eventual access for the products to their target population?

-achieving the desired results in terms of building regulatory capacity in the target countries?

How could the PDPs work together to achieve better results in the 3 areas above?

Messages from Stakeholders [Donors]

PDPs need to better understand regulatory options

A general need to improve the WHO Prequalification process

Ensure NRAs that new products have received sufficient regulatory oversight

Need to evaluate how well PDPs are doing in facilitating regulatory approval and introduction of products into endemic countries

Endemic country NRAs know little about PDPs

Need harmonized regulatory initiatives (eg **joint review) that lead to sustained regulatory capacity building in low income countries**

PDP Wish List

Improve the global regulatory pathway

- **Fast track reg pathway w one global standard of quality (eg.ICHs - CTD)**
- **Centralized registration procedures acceptable to all [harmonization]**
- **Set & Shorten timelines w/o compromising quality**
- **Formalize joint/twinned review process**
- **Establish a supra-national decision making body**

PDP Wish List

Prequalification

- **Expand priority list for global disease products**
- **Improve efficiency of WHO recommendaton and prequalification processes (reduce time delays)**
- **Harmonize Prequal. processes for medicines, vaccines, diagnostics, pesticides, etc**
- **Address potential areas of bias in Prequal program**
- **Formalize the WHOPES process**

PDP Wish List

Capacity Building

- **Establish structures for information sharing among regulators within regional settings**
- **Involve regulators from endemic countries more in assessment of new products**
- **Develop regional centers of regulatory excellence**
- **Build sustainable regulatory capacity in endemic countries (global shared vision); systematize training programs; exchange programs, etc**

PDP Wish List

Information sharing among PDPs

- **Build a PDP Database of Regulatory requirements and processes in countries of interest**
- **Structure for sharing lessons learned**
- **Share regulatory personnel**
- **Cadre of regulatory experts for PDPs**

PDP Wish List

PDP Product Differences

- **Provide a forum for understanding how regulatory pathways differ for different products**

Back to the Beginning

- **What are the best strategies for licensing a PDP product in endemic countries?**