# The Product Problem: Pathways for Making Misoprostol Available for Postpartum Hemorrhage Meeting Report

March 24-25, 2011

Gynuity HEALTH PROJECTS

# List of Abbreviations

## Organizations

GHP: Gynuity Health Projects
MSI: Marie Stopes International
PAI: Population Action International
PSI: Population Services International
UNFPA: United Nations Population Fund
UNHCR: United Nations High Commissioner for Refugees
UNICEF: United Nations Children's Fund
USAID: United States Agency for International Development
USFDA: United States Food and Drug Administration
VSI: Venture Strategies for Innovations
WHO: World Health Organization

## Terms

AE: Adverse Event
ANC: Antenatal Care
API: Active Pharmaceutical Ingredient
CGMP: Current Good Manufacturing Practices
CHW: Community Health Workers
CTD: Common Technical Dossier
EC: Emergency Contraception
ECP: Emergency Contraceptive Pill
EML: Essential Medicines List
GCP: Good Clinical Practice
GMP: Good Manufacturing Practices
ICH: International Conference on Harmonization
IM: Intramuscular
MA: Marketing Authorization
NGO: Non-governmental Organization
PPH: Postpartum Hemorrhage
PQ: Prequalification
PSB: Procurement Services Branch
QA: Quality Assurance
QC: Quality Control
QMS: Quality Management Systems
SAE: Serious Adverse Event
SRA: Stringent Regulatory Agency

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## Background:

Gynuity Health Projects (GHP) is working to address operational and service delivery issues related to widely introducing misoprostol into health systems, particularly at the community and district levels. GHP also aims to influence international policies, technical guidance, and clinical practice to ensure that they reflect new evidence. An important aspect of this work involves gathering stakeholders to discuss issues related to product availability.

To this end, Gynuity Health Projects convened a meeting to clarify pathways for moving forward in accordance with scientific evidence to foster availability of misoprostol and its use for postpartum hemorrhage indications. This included discussion of what registration means, how it can be optimally pursued, where registration fits in the context of making misoprostol available to meet women's and health systems needs, and how and when it might make sense to proceed without product registration.

More than 50 participants from around the world gathered in New York City on March 24-25, 2011 to discuss "The Product Problem: Pathways for Making Misoprostol Available for Post-Partum Hemorrhage". Each day included a number of speakers as well as moderated discussions.

## Overview:

Given the diverse audience representing a variety of fields, Session 1 focused on providing all participants with background information and establishing a harmonized vocabulary for discussion. By hearing careful explanations of product registration processes, Good Manufacturing Practices, Good Clinical Practices, World Health Organization prequalification, and the World Health Organization's Model Essential Medicines List, participants gained a broad understanding of the various components of product regulation.

Session 2 began with a presentation on the quality of misoprostol products, acknowledging that a conversation about access must include a recognition that the quality of the products made accessible is of utmost concern. Then, participants learned about the post-marketing activities that should be undertaken after product registration and by using the examples of two different misoprostol products, learned about continual efforts needed to expand access and ensure that products are safe and of high-quality.

Session 3 drew upon the experiences of other drugs to illustrate what might unfold regarding misoprostol in the future. The session began with a frank discussion of the systems necessary for ensuring product availability. Then the group looked at the examples of oxytocin and dedicated emergency contraception products as models of drugs in which labeling and usage have not always been aligned.

Session 4 looked at different strategies for making misoprostol available globally. By examining the UNFPA and USAID procurement processes, participants gained clarity on some of the possible routes for obtaining misoprostol and several organizations provided explanations of the strategies they have used and challenges they have faced in their efforts to obtain registration for misoprostol in various settings.

Session 5 consisted of a moderated discussion on next steps for the PPH community and offered participants a chance to synthesize the previous discussions and determine how we might move forward towards achieving wider access to quality misoprostol products globally.

# Session 1: Product Regulation

## Welcome and Meeting Goals – Beverly Winikoff, Gynuity Health Projects

Dr. Winikoff's presentation framed the major issues to be discussed including regulation and pharmaceutical issues, how to ensure the quality of misoprostol products, lessons learned from other drugs, methods for making products available in the field, and how to create programs to provide these products. Major challenges to achieving product availability and use include: no approvals exist for misoprostol in many parts of world, existing approvals are mostly based on the original registration for gastro-intestinal indications, availability and use are not guaranteed even if there is approval, some advocates are confused about the best tools for making misoprostol available for PPH, and people are not always on the same page with the glossary of terms used relating to product registration and distribution.

Definitions of the following terms related to product registration were given to help clarify our discussion:

**"Approval"** of a drug can mean many things; authorization to market the drug, the addition of the drug to an essential medicines list, permission to use the drug in a study or program, the inclusion of the drug on a hospital's pharmacy list, or permission to use the drug in a particular facility or health system. Importantly, "approval" does not mean that the drug is widely available.

**"Registration"** is the authorization by a government for a particular company to market (sell) a particular formulation of a drug for a particular purpose. This is a commercial transaction meant to create a regulated, quality-controlled market, not to endorse use of a drug for particular indications.

Each registered drug has a **"registered indication."** In the case of misoprostol, this indication is often the original one: to prevent gastric ulcer during chronic use of NSAIDs. To add prevention or treatment of postpartum hemorrhage as a new indication, the existing regulatory file must be amended by the authorized marketer or an entire new regulatory file must be produced by another entity (which can be a daunting process). While companies cannot market a drug for an unregistered indication, there is no restriction on governments and/or providers using drugs for unregistered indications. Regulatory agencies, such as the United States Food and Drug Administration (USFDA), have regulatory power with respect to pharmaceutical companies, not individual providers. Importantly "not registered" is not equivalent to "inappropriate," "dangerous," or "ineffective." It simply means that the company has not been authorized to market the drug for that purpose.

In fact, **"off-label use,"** that which differs in indication, dose, route, or frequency from the label, is common and sanctioned by some regulatory agencies like the USFDA. Such use is common in situations where science has outpaced the willingness of pharmaceutical companies to invest money to re-label old drugs. The advantage of a labeled indication is that explicit instructions appear on packaging and allow companies to advertise and market the product for that indication. Clear labeling is also useful for drugs that will be self-administered. On the other hand, off-label use can more rapidly follow science, avoiding the excess costs of pharmaceutical company involvement that may raise the price of the drug. Furthermore, civil society institutions can provide education and advocacy for its appropriate off-label use.

Dr. Winikoff explained that understanding the limits of the label will help us resist the temptation to put service delivery ideas into the label or laws. She pointed out that "best practices" are best left to guidelines and norms rather than legal documents (such as labels), because information changes quickly and laws change slowly.

Manufacturers are required to report serious adverse events (SAEs) even if they occur during off-label use. In the U.S., practitioners are responsible for their own prescribing, however off-label use is considered good medicine if it follows community standards and/or peer-reviewed literature.

**Main Points:**

- Registration is a commercial agreement between a government and a company to market a product.
- Registration for a new indication is neither necessary nor sufficient to ensure access to misoprostol for postpartum hemorrhage.
- "Not registered" is not equivalent to "inappropriate," "dangerous," or "ineffective."
- Off-label use is common and sanctioned by some regulatory agencies. It is an effective way to allow providers to follow evidence-based practices without the significant costs and long timelines involved in label changes.

## Good Manufacturing Practice (GMP) Applied to Misoprostol Tablets – Humberto Zardo, Concept Foundation

Dr. Humberto Zardo drew on his background as a pharmacist and his experience monitoring manufacturers internationally to explain the principles of Good Manufacturing Practice. He began with an explanation of relevant vocabulary.

**"Quality Control"** (QC) refers to comparing a sample with a standard product and then accepting it or rejecting it as the same. **"Quality Management Systems"** (QMS) refer to managerial information collected from quality control efforts. This information is collected in order to identify trends, existing support and infrastructure, and to find out what happens when product goes to the field. **"Quality Assurance"** (QA) refers to the continuous status of compliance and qualification. Dr. Zardo emphasized that quality assurance is related to the intended use meaning that it might differ by indication for the drug. **"Good Manufacturing Practices"** (GMP) are part of quality assurance. GMP ensure that pharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use and as required by the marketing authorization given to each particular product.

Dr. Zardo pointed out that consistency is essential and that the same products made by different companies should be interchangeable. He also provided a brief history of GMP and how the standards have become more rigorous over time as our understanding of pharmaceuticals and science has expanded. He explained that it is not sufficient for a company to comply with any version of GMP, but rather to demonstrate compliance with Current Good Manufacturing Practices (CGMP).

With regard to misoprostol, CGMP relates to elements both inside and outside the product's packaging or box. Inside the box considerations include the tablet itself, the type of container, the batch or lot number, and the manufacturing and expiration dates. Outside the box elements include the product design/concept, list of active pharmaceutical ingredients and excipients (inert materials), certificate of analysis, processes, risks, premises and installations, equipment, systems (air, water, etc.), methods and controls, and trainings.

To supply a product of assured quality, it is important to contain, control, minimize, or mitigate risk. He suggested that while WHO Pre-qualification can be helpful, harmonized procurement and quality assurance strategy with a common set of approaches for assessing manufacturers and their products would also be helpful.

**Main Points:**

- Good Manufacturing Practices (GMP) have become increasingly rigorous in recent years. Facilities should make all efforts to comply with Current Good Manufacturing Practices (CGMP) for the most comprehensive coverage.
- Quality cannot be assessed, tested, or inspected only in finished products; it has to be built in from the initial stages of production following Current Good Manufacturing Practices (CGMP).

## Good Clinical Practice (GCP) - Heidi Jones, Biostatistics & Epidemiology Program, CUNY School of Public Health at Hunter College

Dr. Jones began by sharing the International Conference on Harmonization (ICH) definition of **Good Clinical Practices** (GCP) as: "an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects." The basis for these practices is drawn from various ethical documents including the Belmont report which emphasizes respect for autonomy, beneficence, and justice and the Declaration of Helsinki which states that "it is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects".

GCP is operationalized through a series of ethical safeguards which include obtaining approval from all relevant ethical bodies prior to screening and enrollment, obtaining informed consent from all participants, maintaining participant confidentiality, forming an external data safety and monitoring board, conducting adequate participant follow up, declaring conflicts of interest and importantly, documenting how ethical principals were maintained. Dr. Jones pointed out the tension between focusing on documentation (and subsequent liability) and truly informed choice (not overwhelming the participant with an overly long informed consent form, for example).

Another important aspect of GCP is assuring scientific integrity, or credible data. This is achieved through using an appropriate study design, collecting data with pre-tested instruments that are properly translated and used by qualified staff, ensuring sufficient sample size, implementing a clear process for altering any documentation, documenting drug compliance, and maintaining blinding. These elements create confidence in the integrity of the data.

Dr. Jones noted that the **investigator's brochure** is a key document for maintaining GCP when working with drugs not approved by governmental regulatory bodies for the purpose they are

being studied. The brochure contains a summary of the physical, chemical, and pharmaceutical properties and formulations, nonclinical studies, and effects in humans of the drug. It should be written by qualified staff and updated at least annually. Another essential document for maintaining GCP is a set of **Standard Operating Procedures** which should include sections on shipping and receiving the drug, drug storage, staff access, drug accountability, and dispensing products to participants.

Recalling Dr. Humberto's presentation, Dr. Jones stressed that GCP requires good GMP. Part of GCP is ensuring that the drugs being dispensed have been manufactured following GMP. In conclusion, Dr. Jones reflected that GCP is largely common sense with the addition of a healthy respect for participants as human beings and a commitment to standardization and documentation.

**Main Points:**

- Good Clinical Practice is common sense plus respect for participants as human beings and commitment to standardization and documentation.
- GCP requires GMP.

### Product registration and regulatory strategies: The case of Gymiso® – Nadine Vincent, HRA Pharma/Linepharma

Dr. Vincent began by explaining that in order for drugs to be commercialized, a Marketing Authorization (MA) must be received from a regulatory agency (RA). The most well known and recognized stringent regulatory agencies (SRAs) are in the US, the EU, Canada, Australia, and Japan. These agencies evaluate applications and grant MA based on risk/benefit; inspect all aspects of the drug dossier; approve and release the summary of product characteristics, product information, patient leaflets, and packaging information; and monitor drug use during commercialization.

The marketing authorization application dossier has content governed by the International Conference on Harmonization (ICH) so it is common and harmonized around the world. The specific content of a marketing application dossier depends on the drug, the indication, existing guidelines, and local specifications but the Common Technical Dossier (CTD) always follows the same format. Module 1 consists of the Administrative and Prescribing Information; Module 2 contains the CTD summaries; Module 3 contains information on the quality of manufacturing and testing of both the drug substance and the drug product; Module 4 is the presentation of all preclinical information; Module 5 is the presentation of all clinical information.

Overall, obtaining a marketing authorization (MA) is a time-consuming and expensive process. When a MA is granted, it must be maintained by post-approval activities (such as pharmacovigilence reporting). Also depending on changes in the benefit/risk evaluation, the MA can be modified, amended, suspended or removed at any time. Lastly, continuous changes in regulations necessitate frequent amendments to the MA.

**Main Points:**

- The regulatory dossier contains many types of documentation, including high-quality clinical data.
- The process of gaining registration is long, expensive, and daunting.

## The WHO Prequalification of Medicines Programme – Peter Hall, Concept Foundation

Mr. Peter Hall described the World Health Organization's "**Prequalification**" (PQ) process, which is not the same as a marketing authorization but is a guarantor of the quality of the product.

Mr. Hall began by explaining why high quality pharmaceutical products are important for both consumers and purchasers. He explained that poor quality products can contain extraneous impurities or degraded active pharmaceutical ingredients, which can lead to an increase in known side-effects; adverse events; and in extreme circumstances, serious adverse events, such as anaphylactic shock or death. One method of assuring quality is to procure products that have been prequalified by the WHO, and increasingly major procurement agencies are looking to this option.

Obtaining WHO prequalification has several benefits to manufacturers. It allows them to participate in tender procedures organized by international donors, it provides recognition as a WHO listed company, it can facilitate registration and reduce inspection in some countries, and it provides the possibility of assistance from expert consultants and technical support to improve the company's chances of succeeding with submissions to stringent regulatory authorities.

Prequalification is usually limited to priority essential medicines as published on the WHO PQ website. These eligible medicines are determined by the WHO technical departments and most are on the WHO Model List of Essential Medicines, although some may be proposed by other UN agencies, such as UNFPA. The PQ program for pharmaceuticals undertakes an evaluation of quality, safety, and efficacy of the product and inspections of manufacturers. It also prequalifies

Contract Research Organizations and quality control laboratories; monitors products after prequalification; and works to build the capacity of regulators. WHO publishes a list of prequalified drugs and prequalified laboratories.

Each dossier involves screening for completeness; in-house and external assessment by experts who review documentation on quality and on safety and efficacy of the product; and communication of results for corrective action or acceptability. If the assessment is successful, it is followed by a site inspection.

To support the WHO prequalification process, the Concept Foundation has completed a set of frequently asked questions and a primer on the program for manufacturers. This information is available on www.conceptfoundation.org.

In response to participant questions about when/why a company would choose to pursue WHO Prequalification (PQ) versus Market Authorization (MA) from a Stringent Regulator Authority (SRA), Mr. Hall explained that PQ can be useful for companies that do not wish to supply the drug in countries with SRAs that charge large fees. Further, PQ allows a product to get on tender lists without the enormous costs associated with SRAs. For now, PQ is the easiest way for a generic product to obtain approval status in a developing country. However, Mr. Hall stressed that the documentation burden for PQ and SRA approval are largely the same and that new indications or new drugs still need MA from a stringent regulatory agency for the reference drug. PQ was originally intended to approve a product for procurement within the UN system but has since become a guide for some individual countries; however, in most cases, countries still require local registration and market authorization. In sum, PQ is not a supranational registration process but it can facilitate registration in many limited-resource countries.

**Main Points:**

- The WHO prequalification of medicines programme offers a process for assuring the quality of pharmaceutical products.
- While no misoprostol products are currently under review, it is anticipated that several manufacturers will apply over the next two years and that this could be a route for increasing access to misoprostol in the future.

## WHO Essential Medicines List – Jennifer Blum, Gynuity Health Projects

In her presentation, Ms. Blum explained the history, purpose, meaning, and limitations of the WHO Model EML. She highlighted that an **Essential Medicines List** is "an inventory of medicines that treat pressing health concerns and that should be available to the population". In 1977, when WHO launched their Model Essential Medicines List, only 12 countries had their own lists. However the concept has gained traction, and currently about 80% of countries have adopted national lists.

The WHO Model EML is used by countries to develop their own national lists as the basis for procurement and supply of medicines in the public and private sectors, medical reimbursements, medicine donations and to guide local medicine production. The WHO Model EML is also used by UNICEF, UNHCR, UNFPA, various non-governmental organizations and international non-profit supply agencies as a basis for their medicine supply system. The WHO Model List has also been used to develop international lists for special conditions, e.g.: The Interagency Emergency Health Kit and Essential Medicines for Reproductive Health.

Medicines included on the WHO EML must satisfy the priority health care needs of a population and are selected based on disease prevalence, evidence of safety and efficacy, and comparative cost-effectiveness. To be selected, medicines must be available through health systems, in suitable amounts and dosage forms. Applications for inclusion, changes or deletions to the Model List are submitted to the Secretary of the Expert Committee for the Selection and Use of Essential Medicines for review and this committee also identifies knowledge gaps and makes recommendations for future research that may be needed. Every two years, the Expert Committee reviews new applications for the EML. More information on the WHO EML can be found at: http://www.who.int/mediacentre/factsheets/fs325/en/index.html

Ms. Blum updated the group on the status of misoprostol and the WHO EML. Gynuity Health Projects and Venture Strategies for Innovations prepared an application supporting listing a 600 mcg oral regimen for the prevention of postpartum hemorrhage. The application was initially submitted in 2009 but was not approved. The application was subsequently revised and resubmitted for committee review including new data from a community based trial in Pakistan that had been reported in the interim. (After this meeting, we learned that this new application was approved by the Expert Committee and misoprostol is now listed on the EML for its prevention indication. Furthermore, misoprostol was moved from the complimentary to the core list of medicines.)

Gynuity Health Projects also submitted a separate application for treatment of PPH (with an 800 mcg sublingual regimen) for the 2011 EML meeting. The PPH treatment application was not accepted and the committee referred to a lack of evidence supporting the safety of using misoprostol for PPH treatment among women who also received a prophylactic dose. Gynuity is currently undertaking research on this topic and is planning to revise and resubmit this application for reconsideration at the Expert Committee's 2013 meeting.

Ms. Blum explained that when misoprostol is added to the WHO Model list for PPH indications, it means that the WHO acknowledges that the drug is safe and effective for use in certain circumstances. This in turn can facilitate the listing of misoprostol for PPH indications on country EMLs and ease commodity acquisition from some international and UN agencies. However, Ms. Blum pointed out that inclusion on the WHO list is not essential for these last two things to occur and, in fact, some countries have included misoprostol for PPH on their EMLs in advance of its inclusion on the WHO model list. Furthermore, the inclusion of misoprostol on the WHO EML does not guarantee its inclusion on country EMLs, as this is a separate process both from the prequalification process discussed by Dr. Hall and the registration process discussed by Ms. Vincent. Importantly, inclusion on the EML does not guarantee availability. She also noted that the WHO EML does not provide any clinical guidance for providers on how the product should be used. However, should misoprostol be listed for its specific PPH indications, it could help to normalize misoprostol use for these indications.

**Main Points:**

- An essential medicines list is a cornerstone of many national medicine policies & pharmaceutical systems.
- While the WHO EML provides guidance for countries adopting national EMLs, inclusion of a particular drug on the WHO EML is neither necessary nor sufficient for national EML adoption or availability in a particular setting.

## Session 2: The Importance of High Quality Products

### What do we know about misoprostol products – Peter Hall, Concept Foundation

Mr. Hall discussed a Concept Foundation study that was supported by Gynuity Health Projects to collect available misoprostol products, assess their quality, and address the potential of manufacturers to meet international quality, safety, and efficacy requirements.

Concept Foundation analyzed the content of 74 convenience samples of misoprostol collected from eleven countries. Due to insufficient numbers of samples of some products, only 58 were analyzed for impurities. Mr. Hall clarified that due to the non-systematic nature of the study, no statistical analyses could be undertaken nor was it appropriate to identify the specific samples analyzed.

In his presentation of the study's findings, Mr. Hall concluded that there were significant problems with many misoprostol finished products. Industry standards require that between 90 and 110% of the labelled content be present in the drug. He found that 34 out of 74 samples tested had less than 90% of the misoprostol content on the label and 8 had less than 20%. Further, two products had zero misoprostol content and were likely counterfeits. After one year, 18 out of 20 samples tested for longevity had content less than 90% of labelled content; 7 had less than 20%.

This study also examined impurities that emanate from the active ingredient and focused on key impurities, 8-, 11-, and 12-epi misoprostol. Of 58 samples tested, 31 had impurities greater than the allowable limits for the US and EU, and 18 of the samples had impurities that were more than double the limits, indicating the presence of low-quality active agents. However, he noted, quality concerns may arise at later stages as well. Both the manufacture of the finished product and the product's packaging may also have quality implications. In the samples studied, misoprostol was contained in two different types of packaging: aluminum-plastic blister packs and aluminum-aluminum blister packs. Concept's analysis showed more degradation over time with aluminum-plastic blister packs as opposed to aluminum-aluminum blister packs. Importantly, the effect of heat and humidity at all stages (manufacture, before and after packaging, during transport, and at pharmacies or user homes) may affect the long-term quality of a product.

During the discussion period, participants raised the concern that as misoprostol is more widely promoted there will be more incentives to create counterfeit drugs, and low-resource countries may not be equipped to test drug quality. A participant also raised the point that while it may be virtually impossible for providers to know the quality of the Active Pharmaceutical Ingredient (API) in a drug, packaging is something they can examine to assess the likelihood of humidity seeping in and out. Several participants suggested stressing to providers the

importance of aluminum-aluminum packaging. However, it was also noted that if a poor API is used, the packaging will not matter.

Participants were interested in how drug deterioration affects efficacy, and Mr. Hall explained that to date, no one has looked at misoprostol content purity versus efficacy. Stories abound about different preparations being efficacious or not, underlining the importance of WHO Prequalification, so providers can know with certainty if a product is good or not. They expressed that it is important to determine if the drug has any 'forgiveness', or extra product beyond what is minimally necessary to cause the intended effect, built in when analyzing the API process values.

**Main Points:**

- There are significant problems with many misoprostol finished products relating to drug content and purity.
- The key issues that impact product quality are: quality and stability of the API; manufacturing of the finished product; and packaging of the tablets.

### Phase 4 Issues: Regulatory monitoring and adverse event reporting of misoprostol for this indication. Is it needed? How can it be done? – Marion Ulmann, Linepharma

Ms. Ulmann explained that the life-cycle of a drug does not end at market authorization and in fact includes various types of post-marketing studies. Pharmacovigilence studies provide knowledge on drug safety. Phase 4 (post-marketing) studies increase knowledge of the drug (i.e. effects in populations not previously studied, drug interactions, best practices for use), and non-interventional studies examine the impact of the drug on medical practice and public health.

Ms. Ulmann explained that pharmacovigilence costs about $300,000 per year. This entails following rules established by the International Conference on Harmonization, including provisions that all adverse effects be reported to regulatory agencies, that literature be reviewed to search for published safety information, and that risk management plans be implemented for new products or new indications. Furthermore, pharmacovigilence departments must include standard operating procedures, run under the supervision of a qualified safety officer, and work with a validated pharmacovigilence software package.

In the hypothetical situation in which Gymiso (Linepharma's misoprostol product) were to be approved for the treatment of postpartum hemorrhage in a European country, pharmacovigilence would include collecting serious adverse effects and reporting them within 15 days from the time they are known to the company. Additionally, periodic safety update reports would be generated and submitted to every country where the drug is approved every six months for three years and on an abbreviated schedule thereafter. Lastly, the regulatory agency would likely request that the company develop a risk management plan. Possible Phase 4 activities related to Gymiso might include studies on safety and efficacy in women under 18, multiparous versus nulliparous women, and women in different ethnic groups. Possible non-interventional studies might include PPH related mortality or blood unit consumption as a function of Gymiso availability or the cost-effectiveness of Gymiso versus oxytocin.

Ms. Ulmann also stressed the point that in order to move forward with a registration of misoprostol for PPH, Linepharma would need to partner with a dedicated organization holding the market authorization in each country on behalf of Linepharma. This dedicated organization would be responsible for managing adverse event reporting and liaising with local regulatory agencies and commercial organizations. To do this, Linepharma would likely team with NGOs.

Discussions from participants included a clarification that the importer is responsible for pharmacovigilence despite the impression that this burden gets passed on to manufacturers and a clarification that distributors are responsible for reporting AEs and SAEs. Some organizations expressed interest in contributing to passive surveillance should a coordinated effort be undertaken.

**Main Points:**

- Obtaining a market authorization of Gymiso for PPH indications is the first step in a long process.
- All the required activities are expensive, and companies can fund them only if there is a possible return on investment. Otherwise, alternative sources of funding (e.g. from NGOs) should be considered.

### Phase IV: Monitoring of Prostokos misoprostol and registering a PPH indication – Filipe Guerra, Hebron Pharmaceuticals

Mr. Guerra discussed Prostokos, the Brazilian misoprostol product. Misoprostol was available in Brazil for gastric ulcers but sales were prohibited in pharmacies due to its known off-label use for abortion. Prostokos is the only legal product available on the Brazilian market and one of the first misoprostol products to be registered for ob-gyn indications. It is also registered in Chile, Peru, and Mozambique, and registration is underway in eight additional countries.

A 25 mcg vaginal tablet was registered for induction of labor in 2001. Since that time, 100 and 200 mcg tablets were registered for intrauterine fetal death, missed abortion, and induced abortion. Most recently, in 2011, a 600 mcg sublingual tab was registered for PPH prevention. Hebron may also register their product for PPH treatment in the future.

Currently sales in Brazil are exclusively to hospitals, and Prostokos is available in about 20% of hospitals throughout the country. An important marketing challenge is to combat the negative images of the drug among doctors due to the association with abortion. Efforts are underway to increase availability of misoprostol in hospitals, share scientific literature and create education materials including a dosage pocket card.

Discussions following this presentation focused on why misoprostol is used in hospital settings where oxytocin is readily available. Participants expressed hope that future efforts would expand availability of misoprostol to other levels of the health care system where the drug is especially needed.

**Main Points:**

- Hebron's product is registered for ob-gyn indications in Brazil and a number of other Latin American countries.
- Prostokos is available in several dosages and formulations.

## Session 3: Learning from Other Drugs

### Beyond registration, what is needed for product availability: Off-label use, marketing, distribution, procurement, etc. – Grace Adeya, Management Sciences for Health Strengthening Pharmaceuticals Program

Grace Adeya's presentation described how misoprostol fits within healthcare systems and the pharmaceutical supply system. Ms. Adeya showed how pharmaceutical management cycles can affect whether or not a product is available. She noted that the key to ensuring availability of products is an understanding of pharmaceutical supply systems from the manufacturer all the way down to the end-users. She emphasized that public and private sectors are interlinked and interdependent, and, in most developing countries, public sector demand drives private sector availability. This demand is crucial in generating a market for a product. The background and knowledge of key health facility personnel involved in product procurement are also important. Using the examples of several countries in Sub-Saharan Africa, Ms. Adeya illustrated that those managing medicines at a facility level are often untrained procurers, very few of whom are pharmacists. Furthermore, these personnel have varying knowledge of their country EMLs and price-setting policies. As a result, to strengthen the supply system we need to tailor messages to non-trained procurers and to give them good reasons to order misoprostol and also encourage the adoption of standard operating procedures for procurement, dispensing and use of uterotonics.

Ms. Adeya recommends that the selection of uterotonics be conducted by a committee of experts composed of experienced clinicians who consider the following key criteria: level of health system, type of medicine (e.g. first-line), cost, safety and efficacy, quality and stability, availability for procurement, and whether the product is registered. These selected uterotonics should then be included in country EMLs and standard treatment guidelines so that they can be budgeted for using national funds.

When planning for procurement, the quantity needed is an essential decision. Incorrect predictions lead to stock-outs and wastage. In assessing the costs of the product to procure, Ms. Adeya reminded us of hidden costs such as early expiration or disintegration of drugs, air freight for late delivery, and losses due to poor packaging. Lastly, distribution issues also need to be considered, especially transportation challenges.

On the whole, Ms. Adeya elaborated several levels of considerations to ensure availability of misoprostol from the supply system, to the people making procurement decisions, to the information available on which those decisions will be based.

During the discussion participants raised the issue of working with private sector distributors to promote availability but noted that a profit incentive is needed to make such partnerships possible. They also noted that availability of misoprostol means it is available for all indications,

including those for which it is not registered. They discussed the potential danger of providing information limited to one indication, knowing that it might be used for others. Furthermore, these multiple indications have pricing implications because in countries where abortion is restricted, the market for misoprostol as an abortifacient will correspond to a higher willingness to pay.

**Main Points:**

- Product availability is affected by the structure of pharmaceutical supply systems, the people making procurement and use decisions, the accuracy of demand data, and supporting policies like EMLs and standard treatment guidelines.
- Promoting product availability requires identifying the barriers in the system and tailoring messages and advocacy efforts.

### The Case of oxytocin: A Drug that is not always registered for PPH but widely used for this indication – Steve Brooke, PATH

Mr. Brooke began his presentation by giving a brief history of the development of oxytocin, beginning in 1909 when it was first recognized in the pharmacopeia, continuing to the 1960's-70's when synthetic oxytocin became available, through its listing on the EML and mention in the 1989 WHO Prevention and Management of Postpartum Hemorrhage Technical Working Group Report.

The WHO listing specifically mentions intramuscular prophylactic use of oxytocin. However, Mr. Brooke provided examples of how the listed route and indications vary greatly by country. In the countries he surveyed he consistently found the PPH treatment indication; however PPH prevention was not always listed. Similarly, he consistently found intravenous but not intramuscular administration listed.

Mr. Brooke concluded that while IM administration of oxytocin for prevention of PPH is on-label in many countries, it is off-label for that same indication in other countries. Such variability probably exists as a result of pharmaceutical companies spending fewer resources on older products and failing to update the registered indications. However, the WHO Model List of Essential Drugs provides strong backing for off-label PPH use in countries where product registrations have not kept up with global guidelines.

Subsequent to this meeting, the Expert Committee on Essential Medicines deleted the word "ampoule" from the listing for oxytocin to allow consideration of alternative oxytocin presentations, such as delivery through Uniject™.

**Main Points:**

- Oxytocin is a widely available, off patent, generic product, and the WHO's drug of choice for PPH prevention.
- While oxytocin is registered for the PPH treatment indication in many countries, the PPH prevention indication is not always specifically listed. As a result, oxytocin for PPH prevention is technically off-label in some countries.
- Pharmaceutical companies fail to update registered indications of their oxytocin products for various reasons; however, the WHO Model Essential Medicines List provides support for use of oxytocin for PPH prevention.

### The case of emergency contraception: A concept kept alive by off-label use – Tara Shochet, Consultant, Gynuity Health Projects

Dr. Shochet provided another example of off-label use of a drug for reproductive health issues. Emergency contraception (EC) has been used off-label for over 20 years. EC is prime example of how science can be far ahead of registration and regulation, and how many providers are quick to adopt evidence-based, off-label protocols.

There was no registered or marketed emergency contraceptive pill until 1999, however spreading the word about EC off-label use began before there was a dedicated product. During the 1980s and 1990s there were advocacy and educational programs, and materials like instructional pamphlets that were made available to non-profits working worldwide. Social marketing organizations took on EC as a key issue, and the Emergency Contraception Website and Hotline emerged in the US and Canada providing instructions for use and a list of providers. Organizations focusing on service provision helped to make EC pills available ahead of need and addressed provider barriers, such as logistics and provider attitudes. A registered product was not needed to share information about EC.

EC was successful off-label for a variety of reasons. Advocacy was conducted by non-pharmaceutical, non-profit organizations, which lead to EC's promotion as a true need with a simple solution. Furthermore, regular oral contraceptives were relatively easy to access and

available, thus clinicians and/or women were easily able to cut up contraceptive pill packs to use as EC.

The use of EC off-label lead to the development of a dedicated product and provided the preconditions that demonstrated both the need and use worldwide. It showed the pharmaceutical industry that it was worthwhile to produce and market. Most of the marketing today is still done by non-pharmaceutical agencies.

During the discussion participants mentioned that while information about and access to EC was possible without a labeled product, use increased significantly after there was a dedicated product.

**Main Points:**

- The case of EC demonstrates that a registered product is not needed to share information on evidence-based, off-label drug use.
- Advocacy and education programs on EC were undertaken by non-pharmaceutical organizations that provided instructions for use and provision of services long before there was a dedicated product on the market.

## Session 4: Getting Products into the Field

### UNFPA's procurement of commodities – Sukanta Sarker, UNFPA Commodity Security Branch

Dr. Sarkar explained that there are three resources for UNFPA procurement: 1) country program budgets 2) extra budgetary resources, or 3) emergency resources. He emphasized that misoprostol could be purchased using country program budgets or extra budgetary resources but not using emergency resources.

Dr. Sarkar highlighted that the best scenario would be if the drug is registered, on the WHO Model EML, and on the country's EML. If it is not on the country EML then the country must provide sufficient rationale to UNFPA as to why it should be procured. He went on to emphasize that even if misoprostol is not on the WHO Model EML it can still be bought, but the request must go through a committee in the technical division for review. If misoprostol is registered in a country, procurement through a country program budget would present no problem.

To procure misoprostol through extra budgetary resources, a request must be submitted, validated, and sent to UNFPA's Procurement Services Branch (PSB) in Copenhagen, which handles the bulk of UNFPA procurement. Currently reproductive health kits do include some life-saving drugs, but misoprostol is not included. While it would possible to buy misoprostol under "essential life-saving maternal drugs", there have been very few country-level requests to date.

Looking to the future, Dr. Sarkar mentioned Access RH which began in 2010. Access RH is a mechanism by which countries can buy commodities through the internet at the UNFPA negotiated price. So far it has been used to procure male condoms but it may be possible in the future to use this modality for buying misoprostol.

**Main Points:**

- There are several mechanisms by which UNFPA could procure misoprostol.
- To date UNFPA has received very few country-level requests.

### USAID procurement of drugs for use in programs – Deborah Armbruster, USAID

Ms. Armbruster explained that while there is no official USAID policy that prevents procurement of maternal health medicines, pharmaceuticals are considered restricted commodities in USAID contracts and cooperative agreements. They cannot be procured in USAID projects without approval. The process of gaining approval can be cumbersome and involves making a request, developing specifications, and identifying an approved manufacturer.

Specifically regarding misoprostol, Ms. Armbruster noted that USAID has supported activities using misoprostol for PPH prevention but it does not procure misoprostol. For example, for a USAID supported pilot project in Senegal, VSI procured the drug and provided it to the local project implementing agency. Importantly, Ms. Armbruster pointed out that if USAID were to procure pharmaceuticals, those drugs would need to be approved or registered for use in the country where they would be used.

Ms. Armbruster drew attention to the results of a Population Action International (PAI) study which does not recommend that donors fund procurement of maternal health medicines and instead recommends that government systems should maintain this responsibility. This report suggests that donors support efforts to ensure that drugs are purchased and distributed appropriately, including monitoring government budgets to ensure proper use of funds.

**Main Points:**

- USAID does not procure misoprostol.
- USAID can and has supported projects that use misoprostol that is procured through partner agencies or other groups.

### Registering misoprostol for PPH in developing countries: The process, successes, and challenges – Ndola Prata, Venture Strategies for Innovations/UC Berkeley

Dr. Prata began by listing countries where VSI has facilitated the registration of misoprostol for postpartum hemorrhage including: Bangladesh, Ethiopia, Ghana, Kenya, Malawi, Mozambique, Nepal, Nigeria, Pakistan, Sierra Leone, Somaliland, Sudan, Tanzania/Zanzibar, Uganda, and Zambia. She explained that for each country there is a specific manufacturer and distributor pair that VSI has identified, vetted, selected, and with whom they have negotiated prices and established a formal agreement. VSI does not hold registrations; rather they facilitate putting together the manufacturer and distributor. The process of registration involves compiling a

dossier, managing submission, and following up with the drug authority which can take two to three years. Drug authority requirements, registration requirements, staffing, Ministry of Health commitment and capacity, the position of international agencies in country, and the status of misoprostol on country EMLs can all affect registration. Dr. Prata stressed the need for in-country champions to overcome the hurdles.

Importantly, Dr. Prata noted that registration of a product does not guarantee a program. To illustrate this, she spoke of Malawi where misoprostol was registered in 2010 with private sector availability. However, the public sector still does not have access due to a Ministry of Health request for operations research, workforce training, country-level EML inclusion, and importation systems setup. Dr. Prata also drew attention to Ghana where misoprostol was registered for PPH in 2008 and the country-level EML was updated, and standard treatment guidelines were adopted. However, registration was conditional on successful community-level operations research before the drug could be released to pharmacies.

In moving "from product to program" Dr. Prata stresses that it is important to consider steps like conducting operations research, adopting clinical guidelines, and identifying local implementing agencies. In the case of Tanzania, registration was achieved in 2007 but it wasn't until 2011 that the Ministry of Health approved it for distribution to communities. Similarly, in Nigeria misoprostol was registered in 2006 but it wasn't until 2011 that a policy was approved for community health worker distribution.

In reflecting on where we are now with misoprostol registration, Dr. Prata stressed that registration is a critical first step but not sufficient to increase access to the drug. She stressed that products can move faster when there is a program in which to use them, and she called for greater coordination among stakeholders to ensure that registration leads to a program. Dr. Prata closed with the reminder to consider who will lead the scale-up once registration and initial programmatic "success" has been achieved.

**Main Points:**

- Registration does not guarantee a program.
- In moving from product to program, one must consider political sensitivities, programmatic hurdles, and institutionalization.
- Once registration is achieved and a program is in place, scale-up must be undertaken.

## Session 5: From Products to Programs

### Moving misoprostol in Afghanistan – Jeff Smith, Jhpiego

Dr. Smith discussed the use of misoprostol for postpartum hemorrhage prevention in Afghanistan. He explained that action around misoprostol was galvanized in the Ministry of Public Health after a regional PPH meeting and was supported by the fact that other regional colleagues were using it already.

In 2004, instead of registration, the Afghan Ministry of Public Health opted to provide authorization for limited use of the drug. The Ministry set up a technical advisory group and issued limited permission only to Jhpiego for controlled implementation of a misoprostol program and a phased approach. The current model for distribution uses community health workers (CHW) who provide misoprostol late in pregnancy so that women can self-administer their misoprostol after delivery. Drugs are repackaged in small, single-dose packages with illustrations and instructions, and there are stringent drug tracking controls that include the collection of all unused drugs.

Registration was obtained in 2008, but misoprostol is not on the country-level essential drug list but rather on a "special drug list." Also, procurement remains a challenge because, to date, no regular procurement mechanism has been put in place.

Dr. Smith was optimistic about the future of misoprostol in Afghanistan. He noted that the Ministry seems eager to expand use of misoprostol for PPH prevention nationally. Misoprostol is currently in the CHW curriculum and efforts are underway to include it in CHW kits. There are also efforts to add it to the national EML. Dr. Smith described the attitude of the Afghanistan Ministry of Public Health as "convinced yet cautious".

**Main Points:**

- Dissemination meetings and programs in neighboring countries influenced the decision of the Ministry of Health in Afghanistan to pursue misoprostol for PPH.
- Misoprostol was initially made available through an "authorization for limited use" as opposed to through registration.

### Integrated marketing of branded misoprostol through multiple delivery channels – Soumitro Ghosh, Marie Stopes International

Dr. Ghosh explained integrated marketing of branded misoprostol using multiple delivery channels for maximizing access as well as correct use of high quality and affordable misoprostol. He began by discussing MSI's Power of 10 strategy which seeks to expand and scale up operations. PPH is one of the major focus areas for this initiative. Dr. Ghosh explained that the product, misoprostol, is the starting point and the most important bottleneck. In some markets there are too many products and quality issues, in others there are availability issues, and in others there are price problems.

To conduct scaling-up there are five requirements: 1) following the MSI recommended regimen for PPH, 2) procuring high quality products, 3) registering misoprostol for PPH, 4) promoting the MSI branded misoprostol product, and 5) using multi-channel distribution.

The MSI branded misoprostol product is Misoclear, and this branding is intended to indicate a product of consistent quality and value and to differentiate the product from fake drugs. MSI distributes Misoclear through its clinics, outreach camps, trained social franchisees (BlueStar providers), as well as pharmacies. MSI also conducts a wide range of operations research to track customer profiles, product use, efficacy, and side effects in collaboration with partner agencies.

**Main Points:**

- MSI uses a branded product of misoprostol called Misoclear.
- MSI distributes its product through multiple delivery channels to maximize access.

### PSI's Misoprostol Products and Programs: To Market and Beyond – Krishna Jafa, Population Services International

Dr. Jafa provided an overview of Population Services International (PSI), the world's largest social marketing and social franchising agency, working in 65 countries. She explained that PSI's misoprostol for PPH activities include distribution, provider training, medical detailing, monitoring and evaluation, community-based distribution pilots, ANC distribution pilots, and landscape analyses. This work has demonstrated to PSI that engaging with the government early on is the best long-term strategy. Generally governments prefer registration as part of the process of developing a program.

Dr. Jafa reviewed the steps necessary to bring a product to market. PSI begins by conducting a situational analysis by speaking with key stakeholders and then conducts market, product, and consumer research. This process allows them to determine the "4Ps" of social marketing: product, price, place, and promotion.

Dr. Jafa explained that often locally available products are not registered, expensive, of unknown quality, and associated primarily with abortion. PSI registers an over-branded generic product, Misosafe, which is of assured quality and contains instructions for use in prevention of postpartum hemorrhage. PSI focuses its efforts on home births and lower-level clinics where oxytocin may not be available. This strategy necessitates challenging the perception that providing misoprostol at home discourages facility births. In addition, PSI targets providers with information on country guidelines and consumers with behavior change campaigns.

Dr. Jafa used the case study of Somaliland to illustrate this process. In Somaliliand, most births occur at home, and the use of misoprostol for PPH is not well known. Together with its partners, PSI worked with in-country champions and achieved Ministry of Health permission for importation and distribution of misoprostol for PPH. However, there was significant fear about use for abortion, including newspaper articles. PSI conducted a pilot study demonstrating tight monitoring of the drug and eventually the Ministry of Health allowed them to roll out distribution to clinics and health posts.

**Main Points:**

- To bring misoprostol to the market, PSI conducts extensive research to address the Four P's: Product, Price, Place, and Promotion.
- Experiences in Tanzania and Somaliland demonstrate that through understanding the local barriers and working closely with partners, success with misoprostol can be achieved.

# Session 6: Moving Forward- How Do We Plan Next Steps as the PPH Community?

### Moving Forward- How Do We Plan Next Steps as the PPH Community?—Discussion moderator: Paul Blumenthal, Stanford University/SPIRES, PSI

Participants discussed whether operations research was a good use of resources and whether it was sustainable to continually conduct such studies in every country prior to implementation of misoprostol programs. Uterine physiology is similar everywhere and systematic reviews exist. One participant suggested working with regional organizations to get policy changed across governments instead of generating more evidence for research questions that have previously been answered. A database of operations research that has been conducted could be created for use as a reference in countries new to misoprostol for PPH. In response to this line of discussion, other participants were quick to point out that even if the efficacy question is satisfactorily answered, there are country-specific considerations when implementing misoprostol in different contexts (such as distribution mechanisms) that could benefit from research. Also, any research builds confidence among providers using the method which is of value.

Dr. Blumenthal posed the question of "how formal a community we want to be." The group came up with some concrete ideas for what they would like to see such a community accomplish. One participant suggested that as a community this group could work together to discourage non-evidence-based regimens for treating PPH. Another participant thought the group should develop specifications desired in a misoprostol product, beginning with a double-aluminum package. The idea was raised to have a research template so that studies in different countries could be comparable and more widely applicable. One participant urged the community to ensure that PPH prevention programs include a provision for PPH treatment and another felt that a taskforce on procurement was necessary. A call was made to move together as a community to advocate for misoprostol to be added to country essential medicines lists. The final point raised was how to find a stable donor base for moving forward as a community.

# The Product Problem: Pathways for Making Misoprostol Available for Postpartum Hemorrhage


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Gynuity HEALTH PROJECTS

# The Product Problem: Pathways for Making Misoprostol Available for Post-Partum Hemorrhage

The Carlton Hotel, 88 Madison Ave, New York, NY

| Thursday, March 24 | |
|---|---|
| **8:45-9:15** | ***Registration and continental breakfast*** |
| 9:15-9:30 | Welcome and meeting goals<br>➢ *Beverly Winikoff, Gynuity Health Projects* |
| **Session 1: Product Regulation**<br>***Moderator: Beverly Winikoff, Gynuity Health Projects*** | |
| 9:30-9:50 | Good Manufacturing Practice (GMP)<br>➢ *Humberto Zardo, Concept Foundation* |
| 9:50-10:10 | Good Clinical Practice (GCP)<br>➢ *Heidi Jones, Biostatistics & Epidemiology Program, CUNY School of Public Health at Hunter College* |
| 10:10-10:30 | Product registration and regulatory strategies: The case of Gymiso®<br>➢ *Nadine Vincent, HRA Pharma/Linepharma* |
| **10:30-10:45** | ***Coffee break*** |
| 10:45-11:15 | WHO Prequalification and Essential Medicines List: What are these and what do they mean?<br>➢ *Peter Hall, Concept Foundation and Jennifer Blum, Gynuity Health Projects* |
| 11:15-12:00 | Moderated discussion for Session 1 |
| **12:00-1:00** | ***Lunch*** |
| **Session 2: The Importance of Quality Products**<br>***Moderator: Jennifer Blum, Gynuity Health Projects*** | |
| 1:00-1:20 | What do we know about misoprostol products?<br>➢ *Peter Hall, Concept Foundation* |
| 1:20-1:40 | Phase 4 Issues: Regulatory monitoring and adverse event reporting of misoprostol for this indication. Is it needed? How can it be done?<br>➢ *Marion Ulmann, Linepharma* |
| 1:40 – 2:00 | Phase IV: Monitoring of Prostokos® misoprostol and registering a PPH Indication<br>➢ *Filipe Guerra, Hebron Pharmaceuticals* |
| 2:00-3:00 | Q&A for Session 2 panel |
| **3:00-3:15** | ***Coffee break*** |
| **Session 3: Learning From Other Drugs**<br>***Moderator: Melanie Peña, Gynuity Health Projects*** | |
| 3:15-3:30 | Beyond registration, what is needed for product availability: Off-label use, marketing, distribution, procurement, etc.<br>➢ *Grace Adeya, Management Sciences for Health Strengthening Pharmaceuticals Program* |
| 3:30-3:45 | The case of oxytocin: A drug that is not always registered for PPH but widely used for this indication<br>➢ *Steve Brooke, PATH* |
| 3:45-4:00 | The case of emergency contraception: A concept kept alive by off-label use<br>➢ *Tara Shochet, Consultant* |
| 4:00-4:45 | Moderated discussion: How can we apply these lessons to misoprostol for PPH? |

Gynuity HEALTH PROJECTS

# The Product Problem: Pathways for Making Misoprostol Available for Post-Partum Hemorrhage

The Carlton Hotel, 88 Madison Ave, New York, NY

| Friday, March 25 | |
|---|---|
| **8:30-9:00** | ***Continental breakfast*** |
| **Session 4: Getting Products into the Field**<br>***Moderator: Sheila Raghavan, Gynuity Health Projects*** | |
| 9:00-9:15 | UNFPA's procurement of commodities<br>➢ *Sukanta Sarker, UNFPA Commodity Security Branch* |
| 9:15-9:30 | USAID procurement of drugs for use in programs<br>➢ *Deborah Armbruster, USAID* |
| 9:30-9:45 | Registering misoprostol for PPH in developing countries: The process, successes, and challenges<br>➢ *Ndola Prata, Venture Strategies for Innovations/ UC Berkeley* |
| 9:45 – 10:30 | Moderated discussion: Questions and answers for presenters |
| **10:30- 10:45** | ***Coffee break*** |
| **Session 5: From Products to Programs**<br>***Moderator: Rasha Dabash, Gynuity Health Projects*** | |
| 10:45-11:00 | Moving misoprostol in Afghanistan<br>➢ *Jeff Smith, JHPIEGO* |
| 11:00-11:15 | Integrated marketing of branded misoprostol through multiple delivery channels<br>➢ *Soumitro Ghosh, Marie Stopes International* |
| 11:15-11:30 | PSI's Misoprostol Products and Programs: To Market and Beyond<br>➢ *Krishna Jafa, Population Services International* |
| 11:30-12:15 | Moderated discussion: Questions and answers for presenters |
| **12:15-1:15** | ***Lunch*** |
| **Session 5: Moving Forward- How Do We Plan Next Steps as the PPH Community?**<br>***Moderator: Paul Blumenthal, Stanford University/SPIRES, PSI*** | |
| 1:15-2:15 | Moderated discussion:<br>- Strategic decision making - Where should we spend our resources?<br>- Registration vs. labeling vs. use<br>- Country-specific strategies – How to move forward with or without formal registration?<br>- Needs/barriers to implementing PPH programs |
| 2:15- | Meeting wrap-up<br>➢ *Beverly Winikoff, Gynuity Health Projects* |