UN COMMISSION ON LIFE-SAVING COMMODITIES FOR WOMEN AND CHILDREN

Draft Summary Report Supporting Documents

Compilation of Recommendation Reports Submitted by Work Streams

May 17, 2012

EVERY WOMAN
EVERY CHILD

Regulatory Environment

Submitted by Work Stream Lead: Hans Hogerzeil

Content:

Background

The regulatory environment

Regulation of medicines and devices is a valuable and necessary investment of society to ensure the efficacy, safety and quality of medicines and devices in the market, and to protect the health of women and children. Regulatory assessment and market control are *not* an unnecessary bureaucratic evil that needs to be evaded, reduced or removed.

Essential components of regulation are: legislation and regulation; licensing of importers, wholesalers, pharmacies and other drug outlets; clinical trial authorization; assessment and market approval of medical products; post-marketing surveillance and pharmacovigilance (safety reporting, side effects); inspection and market control; quality control; information exchange with other regulatory agencies, health professionals and the general public.

Continued focus on up-dating regulation is important, both at regional and country level. In recent years we more often see use of a substance for many difference purposes – as medicines, as a combination of a medicine and a device, as food product, as a cosmetic product. Products can no longer be defined solely by their form but increasingly by their use. As products are evolving, the same substance can be regulated in different ways. Sometimes an important product (eg. zinc tablets) cannot be registered in the country of origin because it is not classified as a medicine, creating a barrier for registration as a medicine required in some destination countries. In addition, medical devices are becoming both more important and more complicated while their regulation is still weak in most countries.

The Problem

Examples of practical problems noted by the technical working group:

1) The right dosage forms are not always available: sometimes the pack-size or concentration is not standardized (e.g. magnesium sulfate), not appropriate for use in children, or oral tablets are used vaginally

2) Evidence on efficacy and safety of the life-saving medicines has usually been well-documented (with some exceptions). However, the real problem is not the regulatory review, but the general lack of good quality products, and the documented evidence (e.g. relevant stability and bioequivalence studies) in the quality part of the dossier. For example, none of six injectable contraceptives in the market has proper bioequivalence data, while these would cost $0.3-1.0 million per study. Similarly, the stability data for some products are missing or not relevant to humid

tropical climates. For some products the storage guidelines (cool, refrigerated, room temperature) are divergent or not clear (e.g. oxytocin injection). In a recent study from Ghana, none of sampled oxytocin products were registered in the country; one third of those with pending registration and all of those without any registration were out of specifications for active ingredient.

3) When new products are used in many low- and middle income countries, safety reporting mechanisms are often missing. These would be essential, especially when new formulations are to be used by non-medical staff (para-medical staff, community workers).

4) Registration of co-packed items poses a problem (for example, zinc and ORS) if they are from two different manufacturers; the co-pack is considered a new product. In addition, co-packaging may prevent the necessary flexibility of use (in particular of ORS).

In general terms, regulatory challenges may occur in five distinct areas (Table 1):

1) Clinical evidence on efficacy, safety, bioequivalence, presentation and dosage as documented in the WHO Model List of Essential Medicines (11x);
2) National registration and regulation of existing products (9x)
3) Registration of new doses, formulations and combinations of existing products (13x)
4) Full registration of a new product (3x)
5) Proposed change in level of use, or need for medical prescription (e.g. promoting use by community health workers) (12x).

Further examples of practical problems:

Misoprostol: innovator has only registered for gastric treatment and gives a black-box warning not to use the product in pregnancy. Manufacturers are not willing to invest in registration fort two small orders per year.

The problem with the three injectable antibiotics for neonates is that the quantities are really small; in fact, the requirement for special injections has further split the market (off the paediatric market) making it even less attractive for manufacturers. Here, as with amoxicillin, prescribing behaviour change and training are needed first.

Amoxicillin dispersible tablets: there is now more interest from generic manufacturers. Demand needs to be increased as many countries do not or rarely use amoxicillin yet.

Zinc tablet: They are more complicated than people think; but some serious applications are now in the PQ pipeline. An example of a problem is the fact that some countries (eg. Ethiopia) do not register a product that is not registered in the country of origin, which excludes the French-made product (now also being produced in India).

This recommendation needs to be combined/checked with the market shaping group.

The move towards standard quality policies among agencies is slowly taking place in the Reproductive Health community; but the market for paediatric and neonatal medicines is much more divided (and smaller). The tendency to split the market further between neonates and children, and asking for special labelling, market authorization number and barcode on the label does not help to create market volume. There is scope for streamlining that between countries.

National procurement agencies will continue to buy the cheapest products, independent of good quality, as long as national regulators allow them to get away with it. This is another argument to continue and even step up efforts to strengthen national regulatory agencies.

Table 1: Overview of different types of regulatory challenges for life-saving commodities

	WHO Model List	Regulate existing product	Register new dose, formulation, combination	Register new medicine or device	Change level of use
Contraceptive implants	X	X	X		X
Emergency contraceptives	X	X	X		X
Female condom	X	X		X	
Oxytocin - injection	X	X	X	X	X
Misoprostol - tablet	X	X	X		X
Magnesium sulfate - injection	X		X		X
Calcium gluconate - injection			X		X
Antenatal corticosteroids - injection	X	X			X
Neonatal resuscitation devices	X	X			
Chlorhexidine - solution, gel	X	X	X		
Procain benzyl penicillin - injection			X		X
Gentamycin - injection			X	X	X
Ceftriaxone - injection			X		X
Zinc - tablet, separately or with ORS			X		X
Amoxicillin - dispersible tablet	X		X		X
ARI respiratory timer	X	X		X	

The Solution

Three arguments to recommend investments in the regulatory environment in order to promote access to life-saving commodities for maternal and child health:

1) There are real quality problems with many of the life-saving commodities: e.g. many misoprostol and oxytocin products are substandard, certain generic oral contraceptives are of uncertain quality, and storage requirements for oxytocin are inconsistent leading to unstable and ineffective products; many national regulatory agencies in inadequately resource to stop the influx of unregistered products of unknown (often substandard) quality.

2) National medical products regulators are there and should be there: Most countries have national medicine regulatory authorities (although these are not functional in about one-third of countries, and weak in many others) that cannot and should not be ignored. Mechanisms for market approval and market control are getting stricter in many developing countries; legal free importation of medicines is rarely possible any longer without national registration (even for UN agencies such as UNICEF, UNFPA and WHO that used to be automatically exempt but no longer are). However, competences may be limited in some areas and joint assessments could bring complementary expertise.

3) There is long-term development goal: There is a strong argument to support the development of cost-effective national medicine regulatory agencies and use the life-saving commodities for maternal and child health as a mechanism to do so. This positions support to better regulation of these life-saving commodities within an established long-term developmental objective

Key regulatory challenges identified, with recommended solutions:

PROBLEM 1

For several of the life-saving commodities, there is no international agreement and/or WHO endorsement of the recommended presentation or dosage. This is sometimes due to a lack of clinical evidence of efficacy and safety.

What is being done already: For misoprostol and oxytocin, many clinical data and stability data are being collected which can be used for the registration file. For chlorhexidine, studies are on-going to get the necessary clinical data for the right concentration; a community case management guideline is in preparation. The WHO Model List of Essential Medicines, updated every two years since 1977, is a well-established global mechanism to document evidence on efficacy, safety and comparative cost-effectiveness of essential medicines.

Recommended solution: Where needed, WHO should collect further clinical evidence on safety and efficacy under circumstances of intended use and make this information available to national regulators. Depending on the situation of the product this can be achieved in different ways. If no originator product is available or no stringent review has taken place for the intended indications which can serve as a model, an ad-hoc mechanism should be used to collect and review the necessary evidence by a group of senior regulators from stringent authorities and target countries. This may especially be needed for misoprostol and antenatal corticosteroids.

PROBLEM 2

The most important problem with the life-saving commodities is the lack of good quality products in the market, partly due to inexperience from manufacturers and a lack of strict regulation in many countries. However, the relative risk profile of the various life-saving commodities is not known (some products carry more quality or safety risks than others). This should be studied as a matter of urgency in order to decide where regulatory attention should be focused and where international procurement agencies and national medicine regulators may need guidance most.

What is being done already: The Expert Review Panel (ERP) process was established by WHO to advise on procurement of medicines for which there is a lack of prequalified products (e.g. second line TB medicines). It is a rapid joint assessment of product dossiers by a global group of national regulators convened by WHO and managed by very strict procedures. For the RH items, the ERP process has also been started between WHO and UNFPA, covering all life-saving medicines for maternal health. A good overview of the world market and the problems and needs of the manufacturers is now being developed. At the same time, the quality policies of the large RH procurement agencies are slowly converging which concentrates the markets and creates the necessary financial incentive for manufacturers of good quality products. These manufacturers are supported with advice on the selection of active ingredients and protocols for bioequivalence studies. The assessment of female condoms is done as with the male condoms, between UNFPA and WHO/RH; global standards are being developed and a prequalification programme has been set up. The ERP has not started for children's medicines, as there is little advance market commitment.

Recommended solution: The UN agencies should use the existing Expert Review Panel (ERP) process to identify the most common safety and quality risks of key products for child health, such as zinc tablets and amoxicillin dispersible tablets. The outcome of this review should help focus the attention of national regulators to priority problems, identify good quality products and focus technical support to committed manufacturers.

PROBLEM 3

For many medicines, new essential formulations or dosages have not yet been manufactured and registered in many countries. The reasons are two-fold: (1) All countries maintain their autonomous national regulatory assessment process; but there is little justification for each national regulator to separately assess the same new products and a different model is needed; and (2) manufacturers do not want to make expensive investments in different registration dossiers for different countries because of low economic interest (prices are low and fragmented market volumes are small)

What is being done already: If a product is prequalified by WHO or reviewed by the ERP process, fast-tracked registration is often possible. On one occasions, the joint assessment of a first-line HIV antiretroviral product managed by WHO has led to rapid regulatory approval in the five countries of the East African Community (proof of concept). The Common Technical Document developed by OECD countries is already promoted and used for regional harmonization, e.g. in the EAC and EUMOA. Technical support is already given to >20 manufacturers of life-saving commodities for maternal health.

Recommended solution (1): National regulatory agencies should standardize their registration requirements following the (abridged) format of the internationally agreed Common Technical Document. This format should also be used as the standard for regional harmonization programmes. NMRAs should not request for additional clinical studies done in their own country as a condition of registration.

Recommended solution (2): WHO should support global or regional joint reviews of new priority products, involving national regulators following the model of the WHO/UN Prequalification Programme and the EAC, in order to facilitate a predictable fast-track approval in target countries. Examples are: misoprostol, new micro-needle technology (needle patch) for gentamycin, new chlorhexidine gel products, amoxicillin dispersible tablets, devices for children's health. This should be used as the main vehicle of training and strengthening NMRAs.

Recommendation (3): Donors and global technical agencies should support committed manufacturers in low- and middle income countries in developing good quality products and preparing acceptable standardized regulatory dossiers; with focus on good manufacturing practices, quality, region-relevant stability data and bioequivalence studies.

Recommendation (4): Donors, stringent regulatory Agencies and WHO should support NMRAs in target countries in streamlining their assessment procedures, and in making maximum use of existing information from UN agencies and other NMRAs. This should include on-going work to strengthen regional harmonization, e.g. in African regional blocks and would be especially relevant for joint assessments of new essential products (see above).

PROBLEM 4

For many commodities (e.g. antibiotics for children) a change in level of use is proposed towards prescription by paramedical workers or full Over-The-Counter (OTC) status, in order to facilitate universal access in rural areas. However, this is a major regulatory decision because medicines for OTC use must be completely safe when used without medical supervision. As these are mostly off-patent products, most generic manufacturers are neither able nor willing to perform the necessary clinical studies to prove efficacy and safety under the intended level of use. If a product is promoted for OTC use, it implies the need for investing in (1) public education in its proper use and (2) a better safety-reporting system.

What is being done: No global activity exists to facilitate re-scheduling of commodities to OTC

Recommended solution: The WHO should collect the necessary clinical evidence on efficacy and safety (including potential for misuse and antimicrobial resistance) of the life-saving commodities when used by lower-level health workers or as OTC product in the community. This evidence should be presented and discussed with a group of senior regulators from stringent authorities and target countries, to assist the latter in deciding whether full OTC status of the product can be justified. This is especially relevant for essential medicines for maternal health such as injectable contraceptives, misoprostol and oxytocin; injectable (or needle patches) antibiotics for neonatal sepsis, dispersible tablets of amoxicillin for community treatment of pneumonia, and zinc tablets for acute diarrhoea

PROBLEM 5

Manufacturers will not invest in quality product development and regulatory approval unless there is a guaranteed market volume by large national and international procurement agencies with a strong quality policy (such as the Global Fund, UNICEF and UNFPA), especially as they can sell substandard products anyway through other international channels and national procurement agencies

What is being done already: Prequalification of condoms and IUDs is performed by WHO and UNFPA, based on large volumes procured by the agency. Prequalification and Expert Review Panel (ERP) review of oral and injectable contraceptives purchased by UNFPA are performed by WHO and UNFPA, but there is little interest from manufacturers as they can sell their products anyway.

Recommended solution (to be combined with market shaping group)
National governments and the international community should, at least for a number of years, fund and/or procure a number of these life-saving commodities following a strict quality assurance policy. From a regulatory point of view, those commodities with the highest quality or safety risks (e.g. misoprostol, oxytocin) would constitute the first priority. Large international and national procurement agencies should stop procuring products of un-assured quality, even if these are cheaper, and should only procure commodities approved through either the WHO/UN Prequalification Programme or the WHO ERP process, or stringent regulatory authorities.

Next Steps

Accountability

In order to maximize the impact of the Commission, it is good to describe success with the regulatory uptake/ERP/PQ of the 15 medicines (few milestones or indicators) and link that to a process of accountability, eg by linking this to the Commission on Accountability; or to ask for reporting at the WHA in 2015. This can be done as a next step after the formulation and costing of the exact Plan of Action, which should list exactly what is to be done with each of the 15 commodities.

It may also be interesting to make a study of which national EMLs have now included low-osmolarity ORS, zinc and amoxicillin dispersible tablets on their national EML and national clinical guidelines (e.g. national IMCI guidelines); and how countries many are actually buying these medicines for the public sector.
Another idea was to add this life-saving medicine accountability (national registration, national EML, public sector procurement) in the existing national scorecard.

How to use the Commission

The opportunity of the Commission can be used to draw attention to some important but unknown issues, using very visible "stories" of lack of quality (oxytocin, misoprostol), cost of BE studies and need to support manufacturers (injectable contraceptives), pipeline of new promising products (photograph of dispersible tablets versus syrups, gentamycin needle patches, chlorhexidine gel) and regulatory challenges (OTC use, zinc in Ethiopia) and need for advance procurement commitments to create an industry incentive for quality.

The commission could perhaps also be used to get commitment from certain industries to invest in a product of public health importance, for example by publicly writing to them.

Annex 1
Regulatory issues with Life-saving Commodities for Maternal and Child Health

	Add or review on WHO Model List of Essential Medicines	Regulation of existing products	Regulation of new combinations or formulations	Regulation of new medicines or devices	Change in level of prescriber or use
Contraceptive implants Indication: Long-term (3-5 year) female contraception	One-rod product not listed	Both one and two-rod innovator products prequalified by WHO, one generic submitted	Currently new combinations of existing medicines and new formulations are registered as new products.		Insertion and removal not always allowed by paramedical workers; no register of licensed workers Midwives can train community health nurses to improve access (Ghana)
Emergency contraception Indication: Emergency contraception ("morning after pill")		>60 products. Innovator (2x750µg) prequalified by WHO. Several products close to submission. Possible patent issue with 1x1.5mg presentation.			Pharmacists and drug-sellers not trained in advocacy and prescription
Female condom Indication: Women-initiated barrier method, for contraception and prevention of STIs and HIV/AIDS	Not specifically included in WHO Model List (Model List does not specify "male" or "female")	Only one manufacturer prequalified by WHO			
Oxytocin injection 10 IU, 40 IU Indications: induction of labour, prevention of post-partum haemorrhage (PPH), treatment of PPH		Many products are unstable under tropical conditions; variations in storage requirements; needs good product information to prevent potential misuse for induction of labour; No products prequalified by WHO. Two submitted (one in ampoules and one in Uniject).	Many formulations not in line with WHO (no economic interest in small-dose formulations); oxytocin in Uniject not registered in many countries	In some countries, Uniject may need to be registered as a new device	Use by midwives not allowed in BOL, GUA, HON
Misoprostol tablets 25, 100, 200 microgram; preferably in pack of 3x200microgram (only for prevention of PPH); Indication: prevention of post-partum haemorrhage (PPH), treatment of PPH where oxytocin is not available	Listed for several obstetric and gynaecological indications, including prevention but not treatment of PPH	Approved for stomach pain but not for PPH in many countries (e.g. AFG, ANG, DRC, GUA, GUI, INO, KEN, LIB, MAD, MLI, MOZ, NIC, SEN, SSU); Lack of evidence of clinical superiority over oxytocin in treatment of PPH; Serious quality problems (rapid degradation) in 34/76 samples from 12 countries (ARG, BAN, CAM, EGY, KEN, IND, MEX, NIA, PAK, PER, VNM; Some products use alu/plastic blisters which can lead to degradation. ; No products prequalified by WHO. Expect up to 4 to be submitted in 6-12 months	Many packs are 3, 4, 10, 20, 30, 60 or 120 tablets; re-packing of large packs requires re-registration. Different pack sizes should not require registration if strength and dosage form are the same Other strengths and dosage forms require registration		No WHO support yet for community use Lack of evidence of clinical superiority over oxytocin in treatment of PPH

Magnesium sulfate, injection 50% Indication: prevention/treatment of eclampsia		No products prequalified by WHO	Many formulations not in line with WHO (e.g. 15, 20%); needs package in right dose with needle, syringe and calcium gluconate		Use by midwives not allowed in BOL, DRC, ETH, GUA, ZIM (1) Need for product improvement to better suit the emergency use of the product
Calcium gluconate Indication: antidote to magnesium sulfate			See above under magnesium sulfate		
Antenatal corticosteroids Dexamethasone 5mg injection Betamethasone 5 mg injection	Dexamethasone is on WHO list (cheap and widely available); but not listed for fetal lung maturation	Indication for fetal lung maturation not registered, except in ARG, AUS and NZL			Use of dexamethasone by midwives not allowed
Neonatal resuscitation devices (mask, bag, suction)	Must be added to WHO or Interagency Essential Devices List	Most developing countries do not have any regulation or market control of devices			
Chlorhexidine solution 5% (digluconate); 20% (digluconate) (needs to be diluted prior to use for cord care). Indication: neonatal umbilical cord care, prevents tetanus and neonatal sepsis	Needs to be re-listed as: chlorhexidine 7.1% as digluconate, delivering 4% chlorhexidine; in three single-use packages. (NB: This will only be listed as such by WHO if sufficient products are marketed)	Chlorhexidine is not registered as a medicine in many countries; clinical evidence from Africa is lacking; evidence on quality, shelf-life and GMP will need to be submitted (PATH study suggests stability for 24m at room temperature in all climatic zones is not a problem)	Widely available in different dosages, but not in the preferred concentration or three single-unit pack size. Preferred product: 7.1% in aqueous solution (TAN, ZAM) or gel (BAN, NEP, IND) Preferred container liquid: white plastic bottle with nozzle Preferred container gel: aluminum tube New gel and bundle/packing in Clean Delivery Kits may need new regulatory approval		
Procain benzyl penicillin powder for injection: 1g (=1 million IU); 3 gr (=3 million IU) in vial Indication: neonatal sepsis (first line) 50mg/kg IM every 6-8 hours			Formulations in appropriate dosage may not be available		Task-shifting to lower level facilities recommended; most clinical studies outdated; lack of studies on safety and efficacy in neonates and/or used by community health workers; but relatively favorable efficacy and safety profile
Gentamycin injection: 10mg; 40mg (as sulfate)/ml in 2ml vial Indication: neonatal sepsis (first line) 7.5mg/kg per day, in 2 doses			Formulations in appropriate dosage may not be available (e.g. only 80mg/ml); Special small syringe needed for neonates; Gentamycin (10mg and 13.5mg) in Uniject being tested in Nepal;	In some countries, Uniject may need to be registered as a new device. There is also the issue of a potentially new device: the needle patch for gentamycin which would prevent overdose in neonates. If that comes, it needs to be reviewed and registered as a new product; global assessment of the file would help to get it registered in countries	Task-shifting to lower level facilities recommended; No blood monitoring possible in low-resource settings and community-based care. Use of higher doses once daily mitigates the effect

Ceftriaxone powder for injection: 250mg; 1g (as sodium salt) in vial Indication: neonatal sepsis (second line) 50mg/kg once daily (<1wk, <2kg); 75mg/kg once daily (>1wk, >2kg)			Formulations in appropriate dosage may not be available		Task-shifting to lower level facilities recommended; Excellent safety profile; especially when used once daily
Zinc		Only few products (how many?) prequalified by WHO	Zinc/ORS co-packed (as two separate products) in Diarrhea Treatment Kit. A Zinc Taskforce is working on these issues.		Change Zinc to OTC status (as done in Ghana)
Amoxicillin Powder for oral liquid: 125 mg (as trihydrate)/5 ml; 250 mg (as trihydrate)/5ml Solid oral dosage form: 250 mg; 500 mg (as trihydrate) Indication: pneumonia	Amoxicillin 250mg solid oral form is listed. This should include dispersible tablets, although it might not be clear. The policy on nomenclatures combines everything under tablet – chewable, dispersible, etc. There is a glossary in the EML that explains what is meant by respective formulations		Dispersible tablet 250mg needs to be registered more specifically, in packs of 10 or 20 tablets. This needs good package to protect against humidity, otherwise unstable; may need color code for bodyweight bands for easy dosing		Use of amoxicillin in communities and informal sector officially not allowed in most countries; training in rational use therefore illegal
ARI-timer The need for ARI-timer is not universal, but might be of value/complement other diagnostics tools in specific settings, and support improved diagnostic process etc.	Listed in WHO list of medical devices	No prequalification programme.		New variations (automated) will need regulation	Currently only used by community health workers – could benefit all primary care workers

Market Shaping

Submitted by Work Stream Co-Leads: Oliver Sabot and Kanika Bahl

Key Challenges

Access to the 13 products under the Commission's review is impacted by three key issue areas:

1. **Global market challenges:** Global "market traps" in which high prices fuel limited demand and sub-optimal volumes lead to limited supplier competition, keeping prices high *(e.g. markets for implantable contraceptives, female condoms).*
2. **Local delivery market challenges:** Local "market traps" in which limited consumer and provider demand for products delivered through private facilities and retail shops drives low supplier investment in promotion and product improvement, leading to poor availability *(e.g. markets for zinc/ORS, amoxicillin).*
3. **Non-market barriers:** Underlying 'non-market' issues which fundamentally underpin the issues above, suppressing demand and maintaining low volumes. This in turn feeds insufficient supply engagement at the global and local levels. Key issues include insufficient focus on and accountability for product access at all levels of the health system, and inconsistent availability of products at service delivery points due to weak public supply chains.

Recommendations

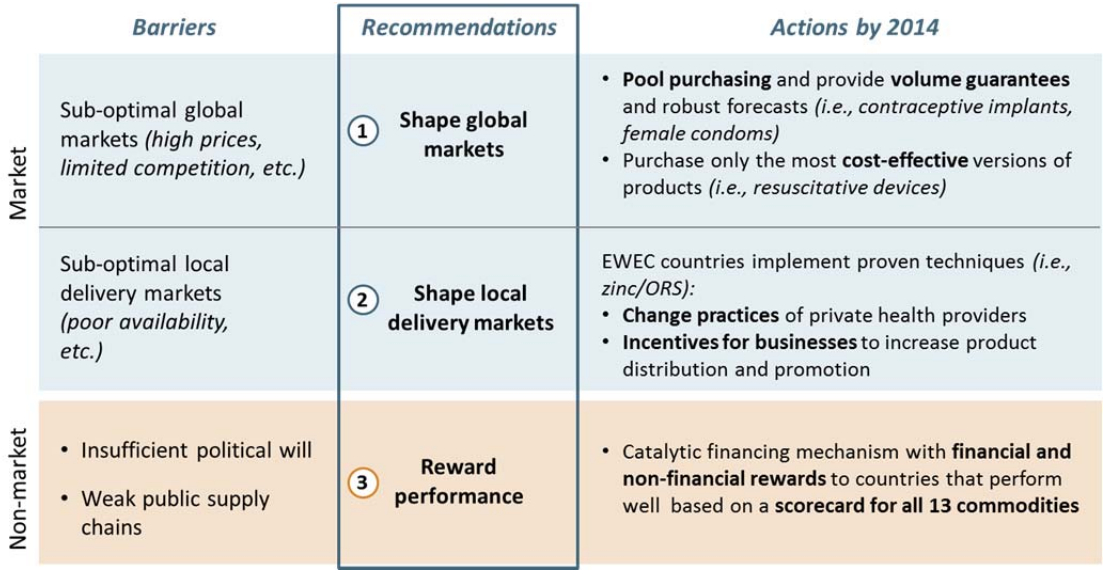
The market shaping working group supports four recommendations to address these challenges:

1. **Shape global product markets:** By 2014, relevant organizations have established effective mechanisms, including a global infomediary for MCH product markets, to promote a range of market shaping interventions including: pooled procurement; volume guarantees and robust forecasts to obtain optimal pricing and supply[1]; and, enhanced product selection procedures to support countries in only purchasing the most cost-effective commodities.[2]
2. **Shape local delivery markets:** By 2014, all Every Woman Every Child countries have increased appropriate use of products provided through in-country private delivery channels by implementing proven techniques[3] to change the practices of private health providers and incentives for businesses to increase distribution and promotion of the products.
3. **Reward performance:** By 2013, a catalytic financing mechanism will be established that will provide financial and non-financial (i.e., global recognition) rewards to countries that perform well, based on a scorecard of a limited number of key indicators directly linked to increased access to essential health commodities. The mechanism will be aligned with relevant major health financing initiatives and will provide funds that are flexible, primarily for non-commodity interventions, and that are allocated and managed through a highly efficient entity.

See summary in *Figure 1,* below.

[1] Applies to reproductive health commodities (see further detail below)
[2] Applies to resuscitative devices (see further detail below)
[3] Including social mobilization, mass media, sales force detailing and interpersonal outreach

Figure 1



Methodology and Approach

The market shaping work stream's recommendations were informed by the Commission's essential commodity case studies; consultations with 40 technical working group members and market dynamics experts; a review of major global health financiers' market-shaping strategies; and guidance from the Commissioners and Contact Group.

Recommendation Details

Two strategic interventions that will help dramatically increase access to products that face major market-related challenges are:

1. **Shape global product markets** by selecting from a range of interventions (see Annex Figure B 'Global Toolkit'), which includes:
    - Organizing demand (i.e., via pooled procurement) and diversifying the supply base (i.e., via volume guarantees), to increase the number of high-quality, affordable suppliers and secure lower prices. It is important to note that these interventions fundamentally rely on high-quality forecast data at the country level. This should begin with **implantable contraceptives and female condoms,** in parallel with efforts to expedite regulatory approval for these products, and be applied to other products, if appropriate, based on further analysis (See Annex 1 for 'Diagnostic').
    - Support procurement of the most cost-effective products by optimizing 'product selection'. This is achieved by procuring only the most affordable versions of clinically equivalent products, as determined based on normative guidance, to reduce product fragmentation and decrease overall costs. This should begin with **resuscitative devices**, where there is currently high product fragmentation, and be applied to other products, if appropriate, based on further analysis (see Annex Figure A 'Diagnostic').

To enable these interventions, the Commission should support the creation of a global clearinghouse of demand and supply data—i.e. a global "infomediary"— for these products to provide organizations with the information they need to make the best procurement and other market-related decisions.

2. **Shape local delivery markets** by selecting from a portfolio of interventions (see Annex Figure C 'Local Delivery Toolkit'), which include a) increasing demand among consumers and private health providers b) adapting products to patient preferences, and c) creating incentives for distributors, suppliers, and other retailers to actively promote products. This should begin with **zinc and oral rehydration salts** for the treatment of diarrhoea and be applied to other products, if appropriate, based on further analysis.

The Commission should also endorse a solution that can apply to cross-cutting issues for many or all of the product range:

3. **Reward performance:** develop **a catalytic financing mechanism** that provides **highly visible non-financial and financial rewards** to countries based on MCH scorecard performance. Key characteristics and principles of this solution include the following:

   - ***Performance-based catalytic financing mechanism***: Countries should receive both financial and non-financial rewards and recognition to drive political will and overcome barriers to access:
     i. **Financial rewards** – High-performing countries will receive limited amounts of *catalytic and flexible resources* to further resolve major barriers to product access. These funds will not be primarily intended for procurement of products, but rather for key enabling interventions such as training of health providers and/or policy change and dissemination. All reward funding would have to be matched by local contributions to further demonstrate the country's commitment to product access.
     ii. **Non-financial rewards** –A major event each year would provide high-level visibility to the leaders of top performing countries based on the scorecard and shine light on those that perform poorly.

     The mechanism should also allow for country-level partnership and financing mechanisms for countries such as **India** and **Nigeria** as they have current or nascent performance-based mechanisms and bear a significant share of the global burden (for example, over half a million (35%) of all deaths from diarrhoea occur in these two countries alone each year[4]). These partnerships should focus on incentivizing improved performance both at a national and sub-national (e.g. state) level.

   - ***Scorecard:*** The scorecard should be regularly published and widely publicized both globally and in high-burden countries. The definition and measurement of the **indicators** used in this scorecard will be critical to the success of this approach and will be determined by a working group established by the Commission. Key principles include that there should be no more than six critical indicators, that they can be efficiently measured, and that they are output-oriented.

   This should be harmonized with approaches under development by the Partnership for Maternal, Newborn and Child Health (PMNCH) and other partners working to expand access to reproductive health products. It should also be extremely efficient, with minimal administrative burden, and rely on a limited number of highly relevant but existing performance indicators collected within national systems (e.g., frequency of stock outs in all health facilities).

   The neonatal health product **chlorhexidine** demonstrates the potential impact of a catalytic and performance-based mechanism. This product costs less than $0.01 to manufacture, is safe and easy to use, and could help avert hundreds of thousands of neonatal deaths every year. Once the WHO makes the expected clear recommendation regarding this product, the steps needed to rapidly increase access to it will be relatively simple: **inclusion of the product on national registries, training of birth attendants, and distribution of this very low cost product.** However, experience shows that many countries may not take

[4] "Diarrhoea: Why children are still dying and what can be done." UNICEF/WHO 2009. Data source: World Health Organization, Global Burden of Disease estimates, 2004 update.

these steps for years due to lack of visibility and focus. The scorecard and reward mechanisms would help to overcome this challenge by ensuring high-level awareness of and support for progress in those key steps to scale-up access to the product. This could accelerate widespread use by years.[5]

Annexes

Figure A: Market diagnosis framework

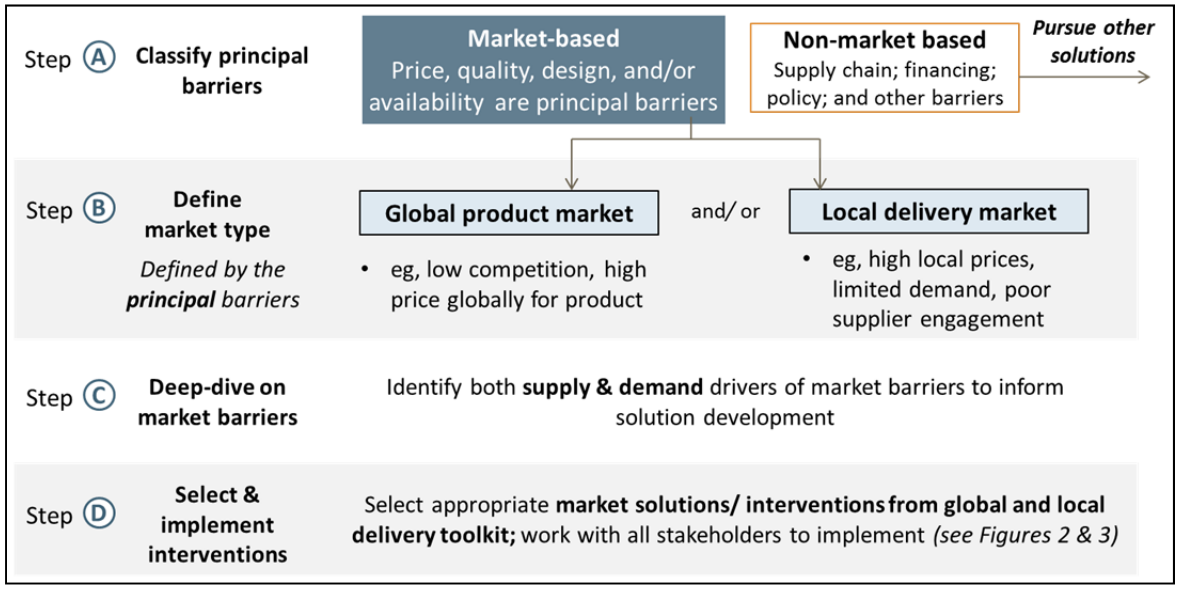


Figure B: Global market shaping toolkit

	Marketplace issue	Possible solutions / interventions
Supply and demand	**High price / low volume trap** *Low volumes keep prices high; high prices prevent demand growth*	***Catalyze demand & negotiate prices based on forward-looking volumes*** • Price negotiations on behalf of a 'consortium' of purchasers • Pooled procurement and minimum volume guarantees
Demand	**Limited demand visibility,** *which can render suppliers unable to plan capacity and respond to demand increases* **Demand fragmentation,** *which can lead to suboptimal patient outcomes, supply risks, and/or higher costs* **Unattractive market fundamentals** *– e.g. small size, low growth – which can lead to poor availability and/or supplier exit*	***Minimize market risks*** • Improve demand predictability, e.g. through provision of high-quality forecasts to suppliers or demand smoothing mechanisms • Coordinated or pooled procurement • Sole-source commodities (vs. creating a competitive market) • Long-term supply agreements • Public sector production ***Consolidate demand around most effective & affordable products*** • Normative guidance on product selection • Comparative cost-effectiveness analysis via Health Technology Assessments (HTAs)
Supply	**Limited supply base,** *which can lead to high prices, poor service or quality, and/or availability issues* **Suboptimal product design / innovation,** *due to inadequate incentives for suppliers*	***Improve incentives for new supplier entry / innovation*** • Split tender awards between 2+ suppliers • Tender-based incentives for desired product attributes • Pooled procurement and minimum volume guarantees • Reduce relevant barriers to entry – e.g. through streamlining regulatory processes, funding R&D, etc. • Advance market commitment

[5] Black RE, Cousens S, Johnson HL, Lawn JE, et al. "Global, regional and national causes of mortality in 2008: a systematic analysis." *Lancet 2010*; 375:1969-1987.

Figure C: Local delivery market shaping toolkit

	Marketplace issue	Possible solutions / interventions
Demand	**Limited consumer & caregiver demand** *Consumers seeks inappropriate treatment or no treatment* **Low caregiver awareness/training** *Caregivers not aware of product as appropriate treatment or lack skills*	***Increase patient and caregiver demand for optimal products*** • Initial government action to increase demand, e.g. mass marketing and free product trial • Funding for high-impact marketing/promotion • Umbrella logo for optimal products/ presentations • Training curriculums for resource -limited situations • Simplified products to leverage community health workers & nurses
Supply	**Limited supplier engagement** *Manufacturers deprioritize low volume, low margin products* **Low product availability** *Regulatory barriers & poor in country supply chain management limit access*	***Incentivize supplier investment*** • Incentives to manufacturers, wholesalers, and retailers for availability in remote areas • Incentives to suppliers for marketing and promotion • "De-risk" investment through common quality standards • Prioritize development of improved product presentations • Look for opportunities to engage suppliers across a multiple-product bundle ***Improve regulatory & operating environment*** • Ensure product registration & OTC status • Enhanced government attention on in-country supply chain management • Creation of PPPs to sustain broad participation

Best Practices & Innovation

Submitted by Work Stream Co-Leads: Catharine H. Taylor and Patricia Mechael

Expanded access to and utilization of essential maternal and child health care commodities will lower death rates and improve overall health for women and children. The UN Commission on Life-Saving Commodities for Women and Children has identified 13 commodities that will require interventions around market shaping, regulatory processes, and innovations in supply and demand creation at a country level to facilitate scale-up in low-resource settings.

This document describes the Best Practices and Innovation Working Group's recommendations for facilitating scale up of the 13 life-saving commodities. The recommendations focus on product innovations and optimized delivery devices, improvements in supply chain management and information systems, and demand creation among health workers and patients.

The working group adopted the following working definitions in order to frame its recommendations:

Best practice: A method or technique that has consistently shown results superior to those achieved with other means, and that is used as a benchmark.

Innovation: The creation of a better or more effective product, process, service, technology, or idea that is accepted by markets, governments, and society. The intervention should contribute to (or facilitate) rapid market growth of a commodity or rapidly increase the size of the market (or create an entirely new market).

Product innovations and optimized delivery devices

Principal challenges

To facilitate demand for maternal and child health commodities, product refinement is required. In particular, there is a need to optimize formulation, packaging, and/or delivery devices for a number of the essential commodities. Product improvements will require investment in research and development. Given the low cost of many of these products, manufacturers are often reluctant to develop better delivery devices, packaging, or formulations that will potentially increase costs.

Maternal health commodities such as oxytocin, misoprostol, and magnesium sulfate all require further research and development to improve quality, packaging, stability and/or ease of administration[6]. For instance, misoprostol degrades quickly if not packaged in aluminium; thus new manufacturing standards are required to ensure that aluminium packaging is used. Similarly, there is a need to invest in ramping up manufacturing capacity for a 4% formulation of chlorhexidine for newborn cord care. Although it is highly effective in reducing newborn sepsis, only two manufacturers—one in Bangladesh and one in Nepal—produce the 4% gel/solution required for umbilical cord application.[7] Continued refinement of newborn resuscitation, such as the development of a simplified bag and mask, is needed to enable expansion of newborn resuscitation among health workers in peripheral facilities and communities.[8] Please see Table 1 for a list of selected product innovations needed to address barriers to uptake for each commodity.

[6] PATH, United Nations Children's Fund, US Agency for International Development. Key Data and Findings: Medicines for Maternal Health. Prepared for the United Nations Commission on Commodities for Women and Children's Health. 2012.
[7] Segre J, Coffey P, Metzler M, et al. Case Study: Chlorhexidine for Umbilical Cord Care. Prepared for the United Nations Commission for Women's and Children's Health: 2012.
[8] Coffey P, Kak, L, Narayanan I, et al. Case Study: Newborn Resuscitation Devices. Prepared for the United National commission on Commodities for Women's and Children's Health: 2012.

Best practices

There are a number of best practices that can serve as models for facilitating future research and development.

- Through the United States Agency for International Development Global Development Alliance, Laerdal Global Health has developed the NeoNatalie suite of neonatal resuscitation devices and made it available to all 68 Millennium Development Goal countries at a not-for-profit cost to address the difficulty in procuring high-quality, affordable resuscitation equipment for low-resource settings.
- Public-private partnerships like GlaxoSmithKline and Fiocruz are investing in the research and development necessary to create new innovations for low- resource settings, such as collaboration on dengue fever.
- GAVI's Advance Market Commitment, in which volumes and prices are agreed upon in advance, incentivizes vaccine manufacturers to invest in the research and development necessary to bring vaccines targeted for "southern countries" to market.

Proposed recommendation

Product innovation: by 2014, interested countries, donors, NGO partners, and UN agencies have designed and developed an incentive mechanism to support regular consumer marketing research and further research and development to optimize formulation, improve packaging, and enhance delivery devices of the 13 essential commodities in line with consumer and provider preferences, safety, and ease of use.

Table 1: Potential product innovations by commodity

This table describes potential product innovations to address barriers to uptake for the 13 commodities. Commodities not listed do not require further product innovations.

Commodity	Barriers to uptake	Product innovations required
Oxytocin	• Oxytocin is temperature sensitive and loses effectiveness after three months of being stored at temperatures higher than 30 degrees Celsius. • Confusion may result when multiple formulations of the same medicine are available within a given health care facility and are not necessarily the same as national treatment guidelines. This requires providers to calculate the difference and adjust administration accordingly.	• Thermostable oxytocin formulation. • Temperature monitoring devices for oxytocin packaging. • Oxytocin in pre-loaded, single-use injection device for use by lower cadres of health workers. • Non-parenteral inhalation stroke intranasal spray-dried (dry powder)
Misoprostol	• Quality assurance mechanisms vary widely between countries. • Poor packaging results in degraded commodity	• Address issues with the manufacturing processes and packaging. • Aluminium packaging required.
Magnesium sulfate	• Dosing regimen is complicated and confusing. • Providers are afraid of toxicity and need to have a user-friendly administration method. • Continuous dosing with IV pumps relies on electricity and is expensive.	• Simplified dosing regimen and single dose packaging. • Spring-driven infuser pump or other devices.
Injectable antibiotics	• Need to improve safety, ease of delivery, and reduce training requirements and possibility of health worker error. • Difficult to develop alternative delivery mechanisms for procaine benzylpenicillin and ceftriaxone powders because they must be reconstituted with sterile water before use.	• Fixed-dose presentations for basic needles and syringes and prefilled delivery devices such as Uniject© for administering gentamicin. • Auto-disable syringes for administering gentamicin. • Micro-needle patch technology for administering gentamicin.
Antenatal Corticosteroid (ANCS)	• Ease of use.	• Prefilled delivery systems.

Chlorhexidine	• Current practice of dry cord care does not sufficiently address newborn sepsis. • Limited manufacturing capacity of 4% CHX gel/liquid.	• Increased manufacturing capacity for the 4% CHX gel or liquid formulation.
Resuscitation Equipment	• Infrequent users at peripheral health centres not using the technology correctly.	• Need for simplification of device design and parts so that infrequent users at peripheral health centres will be better able to use the technology.
Amoxicillin	• Amoxicillin instructions not given to caregivers. They need instructions to give and complete the course. • Children can't swallow pills. Amoxicillin must be in formulation that a child can take. • Need amoxicillin that is safe and won't expire.	• Child friendly packaging that clearly directs caregivers how to use it. • Dispersible tablet. • Packaging that can protect from degradation.
Oral Rehydration Salts (ORS)	• Consumer uptake of ORS has consistently lagged behind expectations. • ORS regulated as a drug in most countries, which limits product innovations.	• Improve ORS product presentation and formulation, as well as marketing and "positioning" in order to increase consumer appeal. • Investigate alternative rehydrating products in food/beverage categories.
Zinc	• Zinc not easily available while ORS is.	• Co-packaged ORS, zinc and water purification tablets.

Ensuring access to commodities

Principal challenges

Supply chain management bottlenecks exist in all areas of procurement, distribution, storage, information systems, and inventory management. There is often a lack of standard product specifications for procurement, leasing, and donations; a lack of funding to procure commodities at critical times of the year; poor commodity forecasting; poor data for supply chain decision-making including the quantification of commodities; poor distribution channels and storage which expose drugs and commodities to conditions causing product degradation; and poor stock inventory management leading to frequent stock-outs. Frequent health facility stock-outs lead to increased burden on patients and their families because health workers often advise them to purchase essential commodities from private drug sellers. As a result, their out-of-pocket expenses increase without a guarantee of product quality.

Additionally, some commodities are only available at certain levels of the health system. For example, resuscitation equipment is available in most tertiary and district level hospitals but it is often not available in sub-district health facilities. Compromised drug quality is a serious concern in low-resource settings where the largest share of counterfeit drugs exists because of weak regulation and procurement practices. In Nigeria and Pakistan, 50 percent of some medicines are substandard, meaning they do not have the correct potency and can lead to significant harm. Fake malaria and TB drugs alone have led to 700,000 deaths[9].

Best practices and innovations

- The United Nations Population Fund's Access RH assists countries by allowing them to order family planning commodities online from multiple manufacturers at once and to track the orders. The service also identifies products that are currently in stock to help users avoid ordering products that may require long manufacturing lead times. The United Nations Foundation's Pledge Guarantee for Health is an innovative financing mechanism that assists in preventing stock-outs by providing countries with bridge financing for family planning commodities when countries have cash flow difficulties. It has been used to procure bed nets in Zambia and

[9] Harris J et al. "Keeping it Real –Combating the spread of fake drugs in poor countries." International Policy Network, 2009.

could be explored for maternal and child health commodities. These two mechanisms could be explored for maternal and child health commodities.

- In 2008, Nepal launched a web-based Logistics Management Information System (LMIS) with the main objective of increasing the LMIS reporting frequency by making it monthly. The Web-based LMIS is now expanded to all 75 districts of Nepal. Resources from local government budgets now provide annual refresher training to district staff on web-based LMIS and inventory management system.
- The combination of mobile phones and cloud computing are used to provide free access to a timely drug quality verification system using simple short message service (SMS) functions. A scratch card reveals a single-use numeric code on drugs that users can text for free from their mobile phone, instantly receiving information if the drugs are genuine or counterfeit. Currently, this service is available through mPedigree and Sproxil in Africa and South Asia[10].
- The SMS for Life Initiative uses a combination of mobile phones, SMS, Internet, and electronic mapping technology to track weekly stock levels of key medicines or commodities at the health facility level in several countries.[11]
- System innovations implemented by the Tunisia Ministry of Health and project Optimize are demonstrating the benefits of a streamlined and integrated single supply chain system for all vaccines, drugs, and temperature-sensitive products by regrouping all of these products into a single cold storage and delivery chain from the national level down to regional levels. Similarly, the Senegal Ministry of Health is evaluating a new integrated supply chain model in the Saint Louis region. The project aims to ensure that vaccines and other health commodities are consistently maintained at appropriate stock levels.

Proposed recommendations

Supply and awareness: By end 2013, all EWEC countries will have in place mechanisms to regularly review, adapt and/or adopt state-of-the-art practices in mobile Health (mHealth) and electronic Logistics Management Information Systems (eLMIS), such as SMS for Life, cStock, MAMA, into their national supply chain and health information systems.

Creating demand, increasing coverage, and ensuring safe use

Principal challenges

Both health worker and patient factors inhibit increased demand for products. Barriers to increased demand among health workers include lack of training in and knowledge of the efficacy and use of a particular commodity, outdated standards of practice, and policies restricting certain levels of health workers from prescribing and administering essential commodities. Patients often lack awareness of a commodity and its ability to improve health outcomes. For instance, emergency contraception is often available through private sector pharmacies but requires patient awareness to request the commodity. Complex socio-cultural issues also limit uptake of commodities. Understanding these issues and patient perspectives is critical for developing and refining commodities that are acceptable to those who need them. In particular, there is a need for increased emphasis on assessing the acceptability of commodities in different settings and in understanding patient requirements for product design and packages featuring pictorial instructions or in local dialects.

Even though almost all of the commodities cost only pennies, this cost may still be prohibitive for poorer sections of society, who largely pay out-of-pocket for health-related expenditures. The UNFPA *State of the World's Midwifery report* (2011) found that countries were not implementing incentive schemes, conditional cash transfers, or insurance schemes to support increased access to services and commodities. Slightly less than half of the countries surveyed provided free access to institutional births and only a third had cost-recovery models in place.

[10] Zax, D. "Fighting counterfeit drugs with mobile technology." The Fast Company, 2010.
[11] Asiimw C, Gelvin D, Lee E, et al. Use of an Innovative, Affordable, and Open-Source Short Message Service–Based Tool to Monitor Malaria in Remote Areas of Uganda. Am. J. Trop. Med. Hyg., 85(1), 2011, pp. 26–33.

Best practices and innovations

- Some countries have changed policies to enable lower level workers to provide care at the community level. However, some WHO guidelines are not in agreement that community health workers have enough training to safely administer the product (e.g., antibiotics).
- The use of checklists offers the potential to ensure that health care workers are up-to-date on the latest procedures, as well as ensure that no important step is missed in a time-sensitive situation. The Innovation Working Group on Checklists has come up with a number of recommendations, including how to effectively combine checklists with mobile technology.
- Rashtriya Swasthya Bima Yojana in India is providing prepaid health *smart cards* that can be swiped at empanelled health facilities for available free medicines, hospitalization, and treatment. Plugging into such efforts harnessing information and communications technology and mobile platforms can track and increase uptake of maternal and newborn health services.
- The removal of fees at the point of care has shown increased demand and uptake of services[12].
- The Living Goods model is a social franchise aiming to increase demand by using private sector community health workers who sell child health and other health products and conduct home visits emphasizing health education.
- The Uganda program also has cash transfers for facility delivery and neonatal home health checks. It is a technology-based model in which community health workers undertake community case management for respiratory illness, including giving antibiotics.
- In India, the government launched Janani Suraksha Yojana (JSY), using conditional cash transfers to incentivize women of low socioeconomic status to give birth in health facilities. Preliminary evaluation of JSY showed an increase in the proportion of women who delivered in a health facility and a reduction in peri-natal and neonatal mortality. However, there is still a great need to reach the most disadvantaged populations[13]. The balance between demand for commodities and the quality and supply of these commodities needs to be assured, as conditional cash transfers have been shown to increase demand but it may not be matched by quality supply.
- The White Ribbon Alliance has effectively used Social Watch techniques to mobilize citizens to hold governments accountable for translating maternal and newborn health commitments and policies into improved access to services. In India, for example, hosting public hearings allowed more than 30,000 women to interface with decision makers on the issue of maternal health services, leading to increased accountability in the health sector[14].

Proposed recommendations

- Performance and accountability: By end 2013, all EWEC countries will have in place mechanisms to regularly review, adapt and/or adopt state-of-the-art practices in health provider performance and accountability mechanisms, including performance based financing and new checklist tools.
- Reaching women and children: By end 2013, all EWEC country governments are undertaking regular reviews of financial and regulatory barriers parents and children, including adolescents, face in accessing services and commodities in their country, and are actively proposing financial mechanisms (i.e. user fee waivers, cash transfers, insurance and voucher schemes) and adapted regulatory mechanisms to overcome these barriers in the next fiscal cycle.
- By end 2013, all EWEC countries have reviewed their own and other countries' examples of best practices in social and behaviour change communication interventions—such as mass media, women's support groups and social marketing—and have developed plans in conjunction with the private-for-profit sector and civil society to scale up proven approaches for creating appropriate demand and promoting safe use of commodities among all levels of society.

[12] Yeates R. "Women and children first: an appropriate first step towards universal coverage." World Health Organization, 2010.
[13] Lim S et al. "India's Janani Suraksha Yojana, a conditional cash transfer programme to increase births in health facilities: an impact evaluation." The Lancet. 2010.
[14] United States Agency for International Development Health Policy Initiative. "Promoting Accountability for Safe Motherhood: The White Ribbon Alliance's Social Watch Approach." 2010.

For more information:

Visit the UN Commission on Life-Saving Commodities for Women and Children online at: http://www.everywomaneverychild.org/resources/un-commission-on-life-saving-commodities

The Commission is part of the Every Woman Every Child movement to save the lives of 16 million women and children and improve the lives of millions more.

Visit: **www.everywomaneverychild.org**

EVERY WOMAN EVERY CHILD

May 17, 2012