Promoting the
QUALITY OF MEDICINES Plus

Guidance Document for Developing and Implementing a Risk-based PMS for Maternal, Neonatal, and Child Health Products

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About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a five-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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Acronyms

GMP	good manufacturing practice
MedRS	Medicines Risk Surveillance Tool
MNCH	maternal, neonatal, and child health
NMRA	National Medicine Regulatory Authority
PMS	post-marketing surveillance
PQM+	Promoting the Quality of Medicines Plus program
QA	Quality Assurance
RB-PMS	Risk-based Post-marketing Surveillance
TWG	Technical working group
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

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Use of This Guidance Document

National Medicine Regulatory Authorities (NMRAs) are supposed to conduct post-marketing surveillance (PMS) of medicines circulating in their country as their routine activity. The current approach to conduct PMS is a risk-based approach, which minimizes the use of resources and helps countries to have a sustainable PMS system in the country. This guidance document lists maternal, neonatal, and child health (MNCH) medicines based on their risk category or rank, and hence, countries will use this listing to conduct their routine Risk-based PMS (RB-PMS) adapted to the availability of resources. Countries are advised to use this document and approach to select MNCH medicines based on their risk level. Some risk criteria are specific to countries, like good manufacturing practice (GMP) compliance, and hence there might be slight changes in the risk scoring when evaluated by country level. Otherwise, the other risk factors are generic and will have a similar value in respect of the country.

Background

Health products and technologies are essential components of healthcare service delivery. Sustainable Development Goal 3.8 specifically mentions the importance of access to safe, effective, quality, and affordable essential medicines and vaccines for all as a central component of Universal Health Coverage, and Sustainable Development Goal 3.b emphasizes the need to develop medicines to address persistent treatment gaps. Access to good quality health products and technologies increases public confidence in healthcare systems.

Good quality medicines are essential for efficient disease management. Substandard and falsified medicines can cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to the development of drug resistance. Vulnerable populations and patients with comorbidities are at particular risk of being harmed from receiving substandard or falsified medicines. Poor-quality medicines also increase healthcare costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health.

MNCH is the health service provided to mothers (women in their childbearing age) and children. Maternal health refers to the health of women during pregnancy, childbirth, and the postpartum period. MNCH is one of the priority health programs. Coverage of health services for most MNCH areas, including immunization, integrated management of new-born and childhood illnesses, antenatal care, and family planning, has consistently increased over the years.

Improving maternal and child health is a global priority. The goal is to make affordable and effective medicines and health supplies available to the women and children who need them most. Worldwide, 358,000 women currently die during pregnancy and childbirth every year. Every year an estimated 7.6 million children die before their fifth birthday because of preventable and treatable conditions. "Many of these deaths could be prevented – if those mothers and children could only access a basic set of medicines and health supplies. Almost 358,000 women – most of them in low-income countries – died from complications of pregnancy and childbirth" [1].

According to the United Nations Commission on Life-Saving Commodities for Women and Children, many of these deaths are due to conditions such as infections, hemorrhage, pneumonia, and Malaria, which can be prevented or treated by affordable medicines [2].

The U.S. Agency for International Development (USAID) requested the Promoting the Quality of Medicines Plus program (PQM+) to provide technical assistance in evaluating MNCH

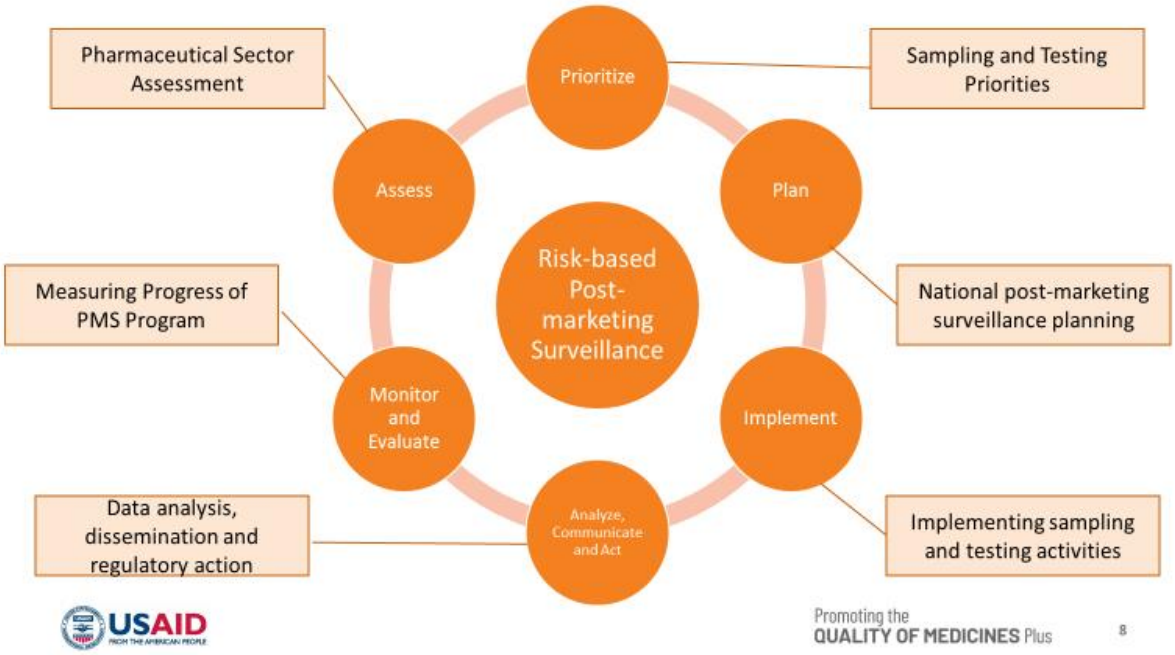
medicines by risk scoring and categorize them by risk level so that relevant PQM+ supported countries backed through MNCH funding will use this guidance document to conduct their own routine PMS. To this end, PQM+ assessed USAID priority MNCH medicines using its Medicines Risk Surveillance (MedRS) tool and ranked them by their risk level. The assessment largely focused on the MNCH medicines that are given priority by the USAID.

Methodology

To carry out this assessment, PQM+ used the PQM's MedRS tool, which categorizes medicines by their risk level using criteria set for this purpose.

Moving from sporadic medicines quality monitoring activities toward robust RB-PMS programs is critical to ensure the quality of medicines. Effective RB-PMS programs can also optimize the use of resources and create sustainable PMS programs that are integrated and implemented as a core regulatory function. Figure 1 depicts the key aspects of developing and implementing an RB-PMS program.

Figure 1. Framework for developing and implementing post-marketing surveillance programs adopted from Guideline for Implementing Risk-Based Post-Marketing Quality Surveillance in Low-and Middle-Income Countries. 2017. USP/PQM. Rockville, Maryland.



PQM+ has developed the **MedRS Tool** to assist countries in effectively developing proper sampling plans and protocols that support the implementation of an RB-PMS. The MedRS tool automates the science and practice of RB-PMS into a single platform. The tool evaluates three dimensions of risk—medicines, geographic locations, and supply chains—to assist countries in identifying the most susceptible medicines and determining the number of samples required to be collected and prioritizing sampling to the most vulnerable locations. Specifically, the tool will indicate the following: 1) **what** medicines to sample, 2) **how many** samples to collect, and 3) **where** to sample. The facilities and medicines indicated for sampling will be high risk and statistically relevant. In this assessment, the tool is used to evaluate the risk level of USAID priority MNCH medicines and rank them based on their risk level.

The tool uses different risk criteria for risk level prioritization/categorization of medicines, geographical areas, cities, and actual medicine facilities.

The assessment was conducted on the following USAID priority MNCH medicines:

Table 1. Priority MNCH medicines included in the risk characterization

No.	Service Category	Item/Drug Selected
1	Active management of third-stage labor/postpartum hemorrhage	Oxytocin 10IU,1ml
		Ergometrin maleate 0.2mg, 1ml
		Misoprostol, 200mg
		Ampicillin powder for injection, 500mg, vial
		Diazepam, injection, 5mg/ml, 2ml, ampule
		Pethidine, 50mg/ml, 2ml, ampule
		Sodium chloride, intravenous solution, 0.9%, 1000ml
		Sodium lactate solution (Ringer's),1000ml
		Lidocaine Inj 1% without epinephrine 20 ml vial
2	Pre-eclampsia	Magnesium sulphate, injection, 500mg/ml, 20ml
		Hydralazine, powder for injection, 20mg ampule
		Methyl dopa, 250mg, tab
		Calcium gluconate,10% solution for injection of 10 ml IV
		Lidocaine inj 1% without epinephrine 20 ml vial
		Water for injection, 10ml, ampule
		Dextrose in Sodium chloride (DNS), intravenous solution, 0.9%, 1000ml with giving/and infusion set
		Ceftriaxone powder for injection, 1gm vial
		Metronidazole injection, 500mg in 100ml vial

No.	Service Category	Item/Drug Selected
3	Postpartum Sepsis	Metronidazole injection, 500mg in 100ml vial
		Gentamycin of 40mg/ml, 2ml
		Ceftriaxone powder for injection, 1gm vial
		Amoxicillin, 500mg, capsule
		Metronidazole, 250mg tab
4	Post-abortion Care	Pethidine, 50mg/ml, 2ml, ampule
		Diclofenac, 50mg
		Doxycyclline,100mg
		Metronidazole, 250mg
		DMPA (Depo)
5	Emergency/Life-saving Drugs	Adrenaline, 1:1000, 1 ml
		40% dextrose of 20ml
		Atropine sulphate injection,1mg in 1 ml.
		Hydrocortisone, powder for injection, 100mg/ml, 2ml
		Promethasone, 25mg/ml, 2ml
		Dextrose in Sodium chloride (DNS), intravenous solution, 0.9%, 1000ml with giving/and infusion set
		Aminophyline, 25mg/ml,10ml
6	Newborn and Child Health	Cotrimoxazole 120 mg dispersible tablets
		Zinc 20 mg dispersible tablets
		Gentamycin 20mg/2 ml or 80 mg/2 ml

Findings

Steps for Characterization of Medicines Based on Risk Factor Scoring

Countries are advised to have a robust PMS system in place and the following are steps that countries should follow in the characterization of medicines based on risk analysis:

1. **Formation of a country technical working group (TWG**)

   TWG is a group formed from relevant country stack holders on quality assurance (QA) of medicines and will be responsible for the management of the RB-PMS with identified scope of work.

2. **Characterization of medicines based on risk level**

The TWG will analyze the potential medicines for their risk level and be able to rank them accordingly. The team can use scientifically valid tools like the MedRS tool for the risk factor scoring exercise.

3. **Updating of the PMS protocol**

   The identified medicines will be listed in the PMS protocol and then collected and analyzed for their quality.

4. **Communication**

   One of the main stems in QA of medicines through the RB-PMS is the communication of the findings to relevant stakeholders and taking relevant regulatory measures based on the findings of the survey. Countries should therefore properly communicate the findings to the relevant stakeholders and take relevant regulatory/administrative measures.

Risk-based Assessment of the Medicines

The assessment has helped to categorize the medicines based on their risk level. The MedRS tool categorizes medicines on seven risk levels, which are made using scoring of each medicine against the risk criteria for medicines:

1. Very high risk
2. High risk
3. Highly moderate risk
4. Moderate risk
5. Low risk
6. Very low risk and
7. Extremely low risk

Technical expert knowledge was used to score the medicines for each risk criterion and the tool sums of the scores to place the medicines at one of the risk levels and the following screenshots illustrate the risk assessment conducted on each of the medicines using the MedRS tool**.**

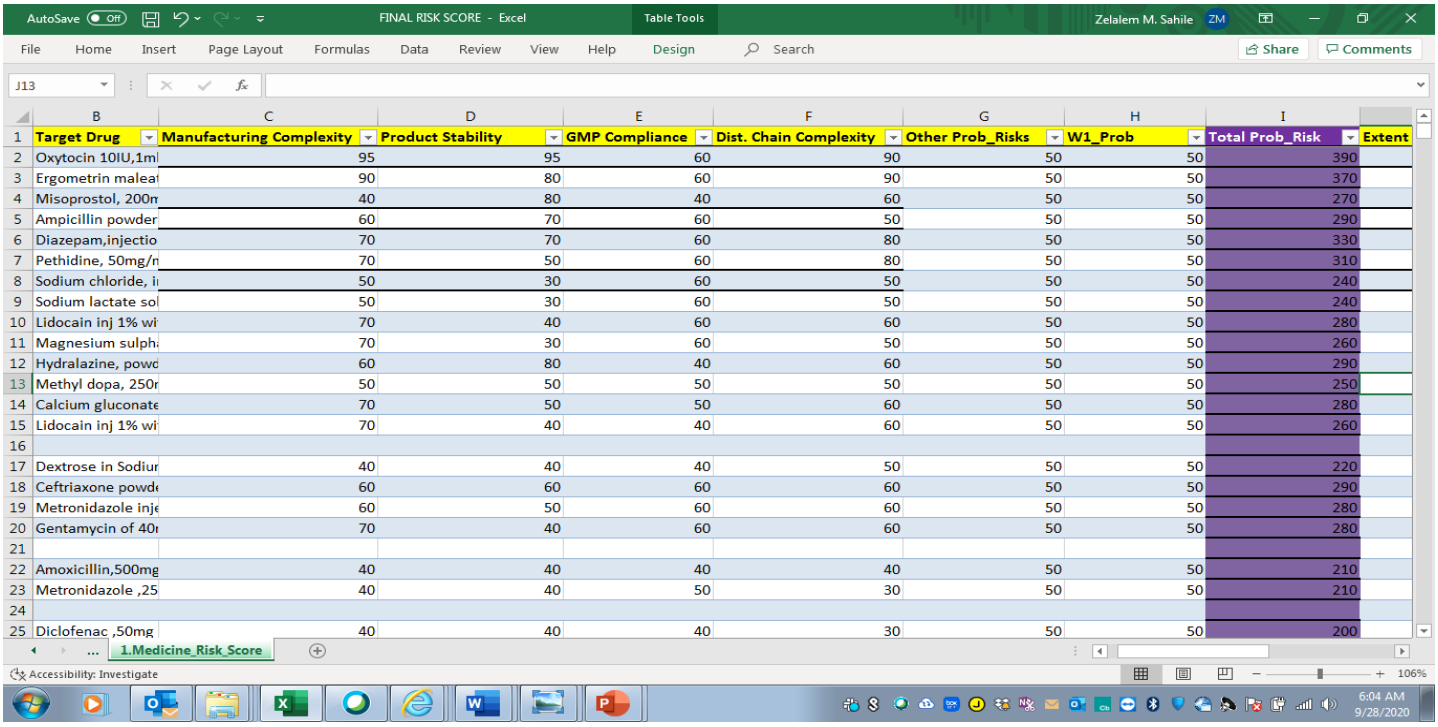
The MedRS tool has specifically designed risk criteria for the evaluation of assessment of medicines, geographical areas, cities, and facilities. In this assessment the following criteria were used to assess the risk level of the **MNCH medicines:**

- Manufacturing complexity
- Medicine/product stability
- Manufacturer’s GMP compliance
- Distribution chain complexity
- Extent of population exposure
- Patient vulnerability
- Dosage form complexity
- Therapeutic risk

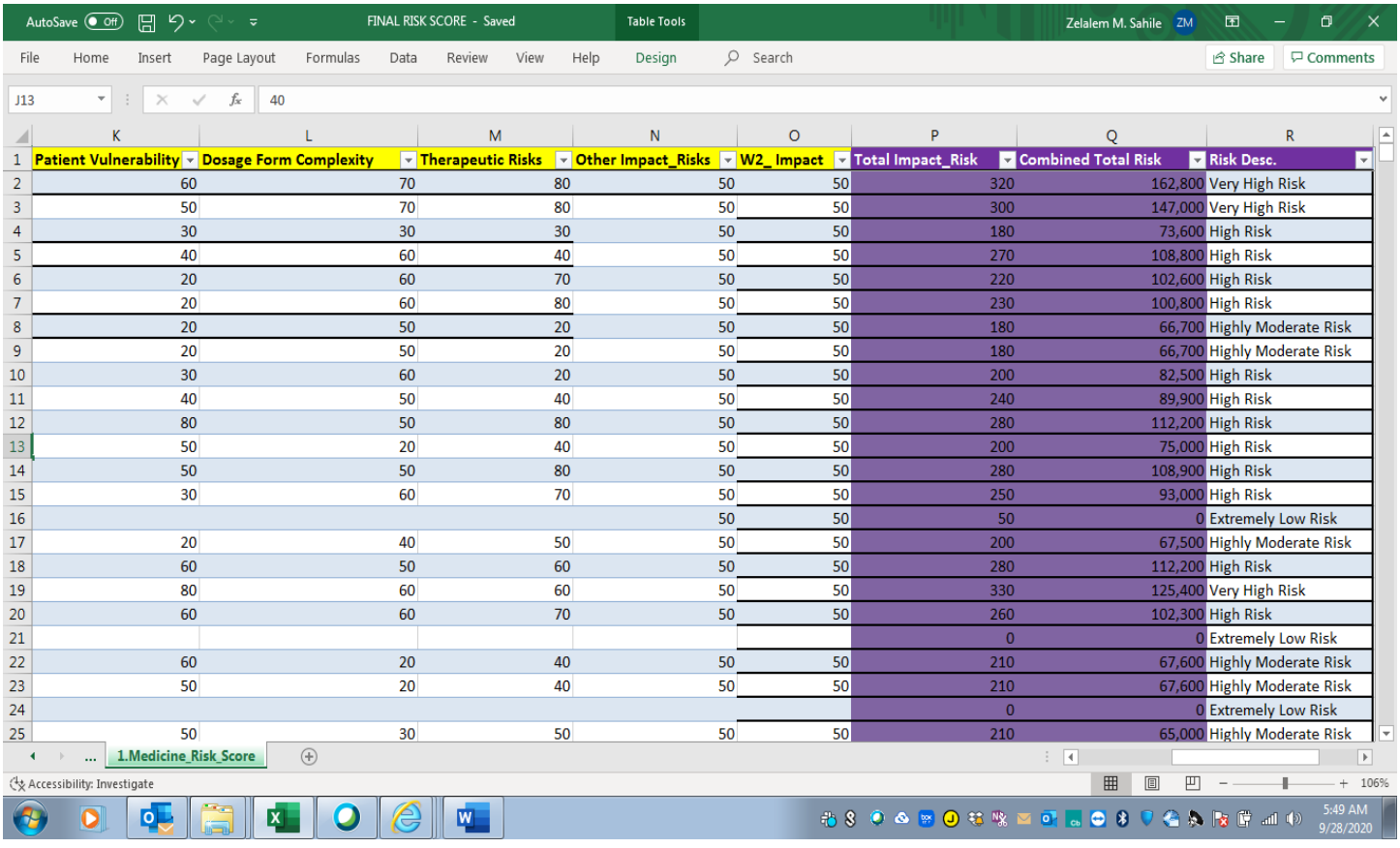
Assessment of the risk level of the candidate medicine is made by evaluating each of the medicine against the above risk criteria. Each will be ranked on a 100-point scale. Risk scores range from extremely low (1) to very high (100). Deep knowledge and experience in the local setting is required for the evaluation/assessment. The tool will then sum up the individual scores for each medicine and categorize them under one of the seven risk categories depending on the cumulative risk score of each medicine.

Note: The above criteria and approaches were used to conduct an assessment of the USAID priority MNCH medicines and categorize them based on their risk levels/ranks.

Figure 2. MedRS risk assessment result of MNCH medicines



	B	C	D	E	F	G	H	I	
1	Target Drug	Manufacturing Complexity	Product Stability	GMP Compliance	Dist. Chain Complexity	Other Prob_Risks	W1_Prob	Total Prob_Risk	Extent
2	Oxytocin 10IU,1ml	95	95	60	90	50	50	390	
3	Ergometrin maleat	90	80	60	90	50	50	370	
4	Misoprostol, 200m	40	80	40	60	50	50	270	
5	Ampicillin powder	60	70	60	50	50	50	290	
6	Diazepam,injectio	70	70	60	80	50	50	330	
7	Pethidine, 50mg/n	70	50	60	80	50	50	310	
8	Sodium chloride, i	50	30	60	50	50	50	240	
9	Sodium lactate sol	50	30	60	50	50	50	240	
10	Lidocain inj 1% wi	70	40	60	60	50	50	280	
11	Magnesium sulpha	70	30	60	50	50	50	260	
12	Hydralazine, powd	60	80	40	60	50	50	290	
13	Methyl dopa, 250r	50	50	50	50	50	50	250	
14	Calcium gluconate	70	50	50	60	50	50	280	
15	Lidocain inj 1% wi	70	40	40	60	50	50	260	
16									
17	Dextrose in Sodiur	40	40	40	50	50	50	220	
18	Ceftriaxone powde	60	60	60	60	50	50	290	
19	Metronidazole inje	60	50	60	60	50	50	280	
20	Gentamycin of 40r	70	40	60	60	50	50	280	
21									
22	Amoxicillin,500mg	40	40	40	40	50	50	210	
23	Metronidazole ,25	40	40	50	30	50	50	210	
24									
25	Diclofenac ,50mg	40	40	40	30	50	50	200	



	K	L	M	N	O	P	Q	R
1	Patient Vulnerability	Dosage Form Complexity	Therapeutic Risks	Other Impact_Risks	W2_ Impact	Total Impact_Risk	Combined Total Risk	Risk Desc.
2	60	70	80	50	50	320	162,800	Very High Risk
3	50	70	80	50	50	300	147,000	Very High Risk
4	30	30	30	50	50	180	73,600	High Risk
5	40	60	40	50	50	270	108,800	High Risk
6	20	60	70	50	50	220	102,600	High Risk
7	20	60	80	50	50	230	100,800	High Risk
8	20	50	20	50	50	180	66,700	Highly Moderate Risk
9	20	50	20	50	50	180	66,700	Highly Moderate Risk
10	30	60	20	50	50	200	82,500	High Risk
11	40	50	40	50	50	240	89,900	High Risk
12	80	50	80	50	50	280	112,200	High Risk
13	50	20	40	50	50	200	75,000	High Risk
14	50	50	80	50	50	280	108,900	High Risk
15	30	60	70	50	50	250	93,000	High Risk
16					50	50	0	Extremely Low Risk
17	20	40	50	50	50	200	67,500	Highly Moderate Risk
18	60	50	60	50	50	280	112,200	High Risk
19	80	60	60	50	50	330	125,400	Very High Risk
20	60	60	70	50	50	260	102,300	High Risk
21						0	0	Extremely Low Risk
22	60	20	40	50	50	210	67,600	Highly Moderate Risk
23	50	20	40	50	50	210	67,600	Highly Moderate Risk
24						0	0	Extremely Low Risk
25	50	30	50	50	50	210	65,000	Highly Moderate Risk

The risk criteria used for the evaluation of the medicines are defined below.

Table 2. Risk criteria for evaluation of the medicines

Term	Definition
Manufacturing Complexity	The degree of complexity associated with the manufacturing processes for a medicine. The more complex a manufacturing process is, the more the likelihood for risk. Knowledge of how a particular medicine is manufactured will help in assessing this risk.
Product Stability	The capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective, and informational specifications. Knowledge of how stable a medicine remains under varying supply chain conditions, including handling and storage from manufacture down to the patient, will help in assessing this risk.
GMP Compliance	The extent to which the product is manufactured in a GMP-compliant environment. Knowledge of GMP conditions in a medicines manufacturer's facility (prior compliance records or inspection reports) will help in assessing this risk factor.
Distribution Chain Complexity	Inter-connectedness and inter-dependencies across a network where a change in one element can affect other elements. How complex is the distribution chain for the medicine being assessed? What is the likelihood of risk within the distribution chain for this medicine? Assessed based on knowledge of the medicine distribution chain. Consult with government procurement agencies, donor procurement, or others, such as local manufacturers or importers.
Other Probabilities Risk Score	Allows users to introduce other probability risk factors. Should be used only if there is a user-specific unique risk factor to be considered. Note: this factor must apply to all medicines being assessed for effective comparison.
Weighing Factor	Expert opinion that allows NMRA to place more emphasis on either the probability or impact risks and remain neutral. The sum of these factors should be 100.
Extent of Population Exposure	Considers impact risk based on the size of the population exposed when the medicine quality is poor: How widely is this medicine used? The more the population that uses this medicine, the higher the risk.
Patient Vulnerability	How vulnerable are the patients when exposed to this poor-quality medicine? Risk is higher when poor-quality

	medicine leaves patients more vulnerable to negative consequences.
Dosage Form Complexity	Considers impact risk to patients due to dosage form concerns. Nasal sprays vs solids, vs liquids, vs injectables. Risk is higher when the dosage form is more complex. For example, poor-quality intravenous injectables are likely to have a higher negative impact on patients than solid dosage forms of the same medicine. (Is this correct? Check with Souly/Teferi.)
Therapeutic Risk	What is the impact risk associated with treatments? For example, medicines with a narrow therapeutic window have more therapeutic risk than those with a broad therapeutic window
Other Impact	User-defined impacts to be considered by the TWG in case there is an additional risk factor related to the impact.

Based on the MedRS risk assessment, the following table gives a detailed risk analysis result of the MNCH medicines.

Table 3. Risk categorization of MNCH medicines

SN	Name of Medicine	Risk Category
1	Oxytocin 10IU, 1ml	Very high risk
2	Ergometrin maleate 0.2mg, 1ml	Very high risk
3	Misoprostol, 200mg	High risk
4	Ampicillin powder for injection, 500mg, vial	High risk
5	Diazepam, injection, 5mg/ml, 2ml, ampule	High risk
6	Pethidine, 50mg/ml, 2ml, ampule	High risk
7	Sodium chloride, intravenous solution, 0.9%, 1000ml	Highly moderate risk
8	Sodium lactate solution (Ringer's), 1000ml	Highly moderate risk
9	Lidocaine inj 1% without epinephrine, 20 ml vial	High risk
10	Magnesium sulphate, injection, 500mg/ml, 20ml	High risk
11	Hydralazine, powder for injection, 20mg ampule	High risk
12	Methyl dopa, 250mg, tab	High risk
13	Calcium gluconate,10% solution for injection of 10 ml IV	High risk
14	Lidocaine Inj 1% without epinephrine, 20 ml vial	High risk
15	Dextrose in Sodium chloride (DNS), intravenous solution, 0.9%	Highly moderate risk
16	Ceftriaxone powder for injection, 1gm vial	High risk
17	Metronidazole injection, 500mg in 100ml vial	Very high risk
18	Gentamycin of 40mg/ml, 2ml	High risk

SN	Name of Medicine	Risk Category
19	Amoxicillin, 500mg, capsule	Highly moderate risk
20	Metronidazole, 250mg tab	Highly moderate risk
21	Diclofenac, 50mg	Highly moderate risk
22	Doxycyclline,100mg	Highly moderate risk
23	DMPA (Depo)	High risk
24	Adrenaline, 1:1000, 1 ml	High risk
25	40% dextrose of 20ml	Highly moderate risk
26	Atropine sulphate injection,1mg in 1 ml.	High risk
27	Hydrocortisone, powder for injection, 100mg/ml, 2ml	High risk
28	Promethasone, 25mg/ml, 2ml	High risk
29	aminophyline, 25mg/ml,10ml	High risk
30	Cotrimoxazole 120 mg dispersible tablets	Highly moderate risk

Conclusion and Recommendations

As can be seen from Table 3, the MNCH medicines are categorized as “very high risk,” “high risk,” and “highly moderate risk” levels, and none of these medicines was found to be under “moderate risk,” “low risk,” “very low risk,” or “extremely low risk” based on this analysis. Hence, much emphasis should be given to the “very high risk” products first, followed by the “high risk,” and then the “highly moderate risk” for inclusion in the RB-PMS. MRAs can use this guide in prioritization of the MNCH medicines for PMS based on their limited availability of resources.

Countries are advised to follow this guidance document to conduct their routine PMS using the RB-PMS approach.

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Resources

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