



Misoprostol Registration for PPH: One Pharmaceutical Company's Perspective

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- **Pharmaceutical regulatory framework**
- **For PPH, what role might a registered product serve?**
- **Feasibility analysis and conclusions**

WHY HRA PHARMA?

MISSION STATEMENT

HRA Pharma is an emerging privately-held pharma company that engineers drugs, devices and services in reproductive health and endocrinology and makes them available worldwide.

By targeting niche market segments and designing custom-made solutions, our objective is to fill therapeutic gaps. With headquarters in Paris, Europe is our home market and our mindset is international.

HRA Pharma makes the difference by combining its health mission with a socially conscious approach to ensure that its products are accessible everywhere.

WHY HRA PHARMA?

- **GyMiso[®] (misoprostol 200 µg tablets, 2-tablet packs) registered and marketed in France since 2004**
 - labelled for Ob/Gyn use (medical TOP, cervical priming)
 - supplied to various research groups for studies in other clinical Ob/Gyn indications (incomplete abortion, PPH)
 - registration has not been sought broadly for commercial reasons (high manufacturing costs in a low-price market), but internal discussions are ongoing

WHY HRA PHARMA?

- **NorLevo® (levonorgestrel emergency contraception) registered and marketed in over 50 countries**
 - regulatory experience and expertise: host of approvals in developing-world countries
 - creative distribution mechanisms: classical pharma distribution channels combined with social marketing programs



REGULATORY FRAMEWORK

- **Mandate of our regulatory authorities: protect the public health**



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FDA's Mission Statement

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

- **Safety and efficacy: favorable assessment of benefit/risk**
- **Security: manufacturing according to quality standards**
- **Approval process**

REGULATORY FRAMEWORK



U.S. Food and Drug Administration



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- **Favorable therapeutic benefit/risk assessment**
 - Clear (statistical) evidence of clinical safety and effectiveness
 - Focus on population “protected” under the jurisdiction of the reviewing agency as well as therapeutic alternatives / current standard of care

REGULATORY FRAMEWORK



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- **Manufacturing**
 - In line with international quality standards (GMP)
 - Robust reproducible manufacturing process
 - Well-characterized product with specific criteria for batch release
 - Pure, stable, packaged, distributed and stored appropriately

REGULATORY FRAMEWORK



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- **Approval process differs from country-to-country**
 - Local and national regulations and procedures vary but all carry significant costs
 - Certain countries have the infrastructure and expertise to evaluate product registration files whereas others do not – these latter ones may therefore require proof of “first-world” approval

REGULATORY FRAMEWORK

- **Product registration provides rights...**
 - Right to distribute (sell) and promote the product
 - within the labeled indication
 - according to the approved prescribing information
 - according to conditions of approval and dispensation status (restricted distribution, Rx or OTC status, ...)
 - via all regular pharmaceutical distribution channels (pharmacies, hospitals, public health agencies)
 - and to seek (public) pricing and reimbursement

REGULATORY FRAMEWORK

- **... but also carries obligations**
 - Obligation to monitor product safety on a continual basis
 - development and implementation of a risk management plan
 - post-marketing surveillance / pharmacovigilance system to regularly re-evaluate benefit/risk assessment
 - Obligation to implement a quality assurance system to ensure ongoing product security
 - capacity to detect and analyze defects / quality concerns
 - infrastructure to perform batch recalls
 - ongoing manufacturing audits and agency inspections
 - compliance with other local/national requirements (qualified personnel, standard operating procedures, ...)

FOR PPH, WHAT ROLE MIGHT REGISTRATION SERVE?

- **Access**
 - Misoprostol is not available everywhere; in some countries distribution is banned/limited due to risk of off-label use +++
- **Programmatic questions**
 - Facilitates program implementation and service delivery because the product label is self-explanatory ++
 - Ability to provide drug through classical pharma distribution channels depends on regulatory approval +
 - Registration may be required for certain public health agencies to issue tender offers... but not necessarily ~
 - Makes reimbursement possible ~
 - Existing packaging may not be suited for PPH use ~

FEASIBILITY OF REGISTRATION OF MISOPROSTOL FOR PPH

- **“First-world” registration (FDA, EMEA/EU, Health Canada, TGA) would appear challenging**
 - Evidence of safety and effectiveness versus current standard of care in developed-world clinical context
 - Label would likely be highly restricted (no oxytocin available)
- **Local (developing-country) registration necessitates further research and analysis**
 - Assumes existence of stand-alone local infrastructure willing to grant approval without prior review by FDA/EMA/other agency
 - Risk of appearance of double-standard in health care provision

FEASIBILITY OF REGISTRATION OF MISOPROSTOL FOR PPH

- **Finding an industrial partner to sponsor and fund the project (alone) would be a challenge**
 - High barriers to entry (data requirements, costs)
 - Very low prices
 - Limited market potential
 - Therefore tough economic conditions for a business that has an obligation to provide returns to its shareholders
- **Is registration the only way to make the product available?**
 - For a manufacturer, yes
 - For a government or a public health agency, not necessarily...

ELEVATE THE CONCERN TO EPIDEMIC PROPORTIONS

- **The case of Tamiflu®**
 - Registered for the treatment of uncomplicated illness due to influenza as well as for the prophylaxis of influenza, launched in the US in 1999 and throughout Europe by 2003
 - Upon the emergence of the H5N1 avian influenza strain in 2006, Tamiflu® was identified as the most promising medicinal product for prophylaxis and treatment based on pharmacological and animal data
 - Dramatic measures were taken to increase manufacturing capacity, and millions of doses were produced in record time in response to requests from public health agencies in some 75 countries
 - Confirmatory clinical trials are still ongoing