What can be done to increase the affordability of a quality assured combi-packs? Analysis of the cost components and dynamics behind the pricing of combi-packs.
MEDICAL ABORTION

• There are multiple challenges to be overcome in order to improve access to medical abortion (MA) – from creating an enabling environment to effect legal and policy change, increasing market demand, procurement & distribution through to regulatory barriers.

• These products need to accessible and affordable in LMIC settings.

• In addition, there are ongoing manufacturing challenges that impact the availability of combi-packs – linked to the challenges above:
  • There are multiple manufacturers of combi-packs and stand-alone mifepristone, misoprostol products, but a limited number which are quality-assured (QA).
  • The manufacturing processes are challenging.
  • Registration requirements/pathway to registration modalities are complex and can be costly
  • There is limited access to affordable mifepristone & misoprostol active pharmaceutical ingredients (API), which, for LMIC, need to be both AFFORDABLE + DOCUMENTED QUALITY ASSURED.

• Concept Foundation engaged directly with selected industry in order to understand these barriers from a manufacturers perspective and identify possible solutions.

• The outcome was the recently published “Cost of goods sold analysis and recommendations to reduce costs of co-packaged mifepristone–misoprostol for medical abortion”.

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QUALITY ASSURED (QA) MIFEPRISTONE MANUFACTURERS

How could we identify QA assured API manufacturers?

- Manufacturers with WHO-PQ, CEP or SRA approval
- Manufacturers included as part of the finished drug product application that are already WHO-PQ or SRA approved.

  Some examples: PCAS (France), Expansia (France), VLG CHEM (France), Crystal Pharma (Spain), Qinhuangdao Zizhu Pharmaceutical Co Ltd (China)

- Other manufacturers of mifepristone API should provide evidence for GMP compliance and API quality documentation as per the WHO guidelines.
QUALITY ASSURED MISOPROSTOL MANUFACTURERS

How could we identify QA assured API manufacturers?

• Manufacturers with WHO-PQ, CEP or SRA approval
• Manufacturers included as part of the finished drug product application that are already WHO-PQ or SRA approved.

Some examples: Piramal Healthcare (UK), Chinoin Pharmaceutical and Chemical Works Private Co., Ltd (Hungary)
• Other manufacturers of misoprostol API should provide evidence for GMP compliance and API quality documentation as per the WHO guidelines.
LIMITED SOURCE OF QA MIFE/MISO API SUPPLIER

• Geographical location: suppliers are mainly located in Europe or US leading to highly costly APIs.

• Marketing strategy: QA suppliers located in other areas are mainly focused on supplying SRAs markets

VERY LIMITED NBR OF SRA/WHO PQ COMBI-PACK

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product names (availability)</th>
<th>SRA</th>
<th>WHO PQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linepharma (Europe)</td>
<td>Mifegymiso (Canada)</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td></td>
<td>MS 2-Step (Australia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun Pharmaceuticals (India)</td>
<td>Medabon (20+ countries)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>China Resources Zizhu Pharmaceutical</td>
<td>Mifepristone + Misoprostol (China)</td>
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</tbody>
</table>
BUILDING A COGS MODEL

The COGs report is the outcome of a collaboration between various services: Safe abortion dept., Technical dept. and Market Access Team dept.

Understanding the current public health context

Defining the components of the COGs with data that can be collected ACROSS countries/manufacturers

Identify the technical and commercial assumptions that should be considered (ponderation requ.)

Building a COGs Model

Collecting the data:
- Manufacturers
- Suppliers
- Publicly available documentation

Providing policy recommendation

Analyzing the COGs

Each manufacturer has its own COGs model reflecting its company’s specific costs settings
Cost of Goods Model sold:

The sum of the direct costs attributable to the production of the goods sold by a company. It includes the cost:

- Admin cost
- Operating Expenses
- Direct Labour cost
- Material cost

Admin cost were included to better understand the drug benchmark price.

The COGS ≠ Final cost

Commercial cost factors may vary drastically from one manufacturer to another and involve different considerations such as:

- manufacturer’s pricing strategy,
- Cash flow and return on Investment timeline,
- etc…
ASSUMPTIONS BEHIND THE MODEL

TECHNICAL ASSUMPTIONS:

1. Formulation. The combi-pack is the combination of two drugs: misoprostol (4 tablets) and mifepristone (1 tablet) in the strength 0.2 mg and 200 mg respectively, packaged and ideally blistered in Alu/Alu.

2. Corrections to apply formulation. Assay, anhydrous basis + the manufacturer’s experience in producing the product.

3. The batch size is set at 100,000 units for each product; which in terms of combi-pack is equivalent to:
   • 100,000 units of mifepristone;
   • 400,000 units of misoprostol.

4. Etc..

COMMERCIAL ASSUMPTIONS:

1. Production location and structural costs. Manufactures are located in LMICs countries with an existing pharmaceutical industry:
   ▪ India, Bangladesh

2. Existing combi-pack manufacturer. manufacturers are already producing the combi-pack with the following implications:
   discount on raw material applied (15%)

3. Material. The raw material, API are outsourced

4. Depreciation. The depreciation on equipment is set at 15%/year

5. Optimal market situation (i.e. all manufactured units are consumed)

6. etc...
**FINDINGS**

The COGS modelling exercise showed that the combi-pack direct production cost ranges from **US$1.08 to US$3.05** (Total COGS), which means that with a 30% administrative fee applied to those prices, a combi-pack could be made available at a cost of between **US$1.40 and US$3.97** depending on location, type of material.

Scenario where the combi-pack is the cheapest: Bangladesh with Non QA API source

- Cost of Combi-pack $1.40
  - $0.48 (4 miso) + $0.2513 (mife) + $0.346 (pack) + $0.32 (Admin 30%)

Scenario where the combi-pack is the most expansive: India with QA API source

- Cost of the Combi-pack $3.97
  - $1,0477 (4xmis)+$1,695 (mife) +$0,346 (pack.) + $0.92 (Admin 30%)
Analysis of Misoprostol (QA):

✓ Operating expenses is the primary cost component of misoprostol. It accounts for 72% of the production cost (excl. packaging)

Analysis of Mifepristone (QA):

✓ API is the primary cost component of mifepristone and accounts for 87% of the production cost (excl. packaging)
Analysis

- Mifepristone is the most expansive component of the combi-pack.

- QA material is more expansive than non-QA. The gap in pricing is very important for mifepristone production.

- The manufacturing cost are higher in India than in Bangladesh. However, this is driven by the OPERATING EXPENSES COST and not by the labour cost.
WHY A QUALITY ASSURED API IS MORE EXPENSIVE?

• Manufacturers usually need to invest on facilities and equipment to ensure the compliance with SRAs requirements:
  • containment (environmental and workers protection) and cross contamination risks mitigation.
• Keeping a quality management system is costly.
• The product documentation (APIMF) is more detailed and complex to prepare and keep it updated.
• Any post submission variation requires regulatory screening.
• Additional controls during manufacturing and API release are needed.
• Stability data needs to be provided to support the expire date or retest date.
• Cost of production in higher in HICs.
WHY A QUALITY ASSURED API IS MORE EXPENSIVE?

Some examples:

- To reach lower impurities level:
  - Additional purification steps are usually required – increases the cost and decreases the yield.
  - Less toxic and high purity solvents are required. Recycling solvents cannot be incorporated in final steps.
  - Synthetic route evaluation to control/mitigate risks related to mutagenic substances and nitrosamines.

- Additional costing on validation
  - All manufacturing steps need to be validated (since starting material introduction).
  - Analytical methods, including the ones used to test intermediates, needs to be validated
MIFEPRISTONE API ADDITIONAL CHALLENGES

• Mifepristone is an established active substance however not described in the US, European, or International Pharmacopoeia.

• An in-house specification should be established according to ICH's Q6A guideline, with additional controls on polymorphism and particle size distribution (PSD).
  • Polymorphism: Mifepristone may exist in two types of polymorphic forms. The polymorphic Form I is used by the innovator product.
  • PSD: the PSD can have an effect on the in vitro and/or in vivo behaviour of the drug product and its control is important to ensure consistency with the material in the batch used in the bioequivalence study.

Why polymorphism is so important?

• Different polymorphic forms of the same chemical compound may possess different chemical and physical properties, which can impact the product manufacturability and product quality and performance, including stability, dissolution and bioavailability.

• The specification of mifepristone API should include a test and acceptance criteria for a preferred polymorphic form to ensure polymorphic equivalence to that used in the innovator product.
MISOPROSTOL API ADDITIONAL CHALLENGES

• Misoprostol API is viscous oil, which must be stored below -20°C. It is extremely susceptible to degradation.

• A dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC) is more stable than the pure misoprostol oil and is commonly used as the API for misoprostol tablets manufacturing.

• The specification of misoprostol API should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP or USP).

• Misoprostol dispersion (1:100 in HPMC) should be in line with a pharmacopoeial monograph (Ph.Int. or USP).

Note: the dispersion water content control is important to avoid the Misoprostol degradation to A-type misoprostol.
IS IT POSSIBLE TO SEE QA COMBI-PACK AT A MORE AFFORDABLE PRICE IN THE FUTURE?

The cost of the Combi-pack could be lowered as a result of:

- Additional QA API source of mifepristone and misoprostol in order to reduce the price
- Delocalisation of manufacturing site in countries where operational costs are more competitive.

Cheaper commodity doesn’t automatically mean healthier market

- The production of the good must remain sustainable and thus profitable to the manufacturers, otherwise they may leave the market.
- The Covid pandemic has highlighted the danger of overreliance on a single source/geography location.
IMPACT ON THE COGS OF AN AFFORBALE QA API FOR MIFEPRISTONE

The modelling undertaken and shown above is based upon a price of US$8,278/kg with a discount of 15% making the material available at US$7,036/kg. If mifepristone API was made available to manufacturers at US$5,000/kg, a price which we believe is both feasible and viable for the producers, the reduction by itself, would be sufficient to reduce the cost of the combi-pack to $3.42 in India and $2.74 in Bangladesh.
CONCEPT FOUNDATION - SUPPORTING SAFE MEDICAL ABORTION 2021

• Is currently supporting selected manufacturers with the objective of having one misoprostol API and one mifepristone API prequalified by WHO.

• Is currently supporting two manufacturers towards the prequalification of their combi-packs.

• Is supporting the government of Argentina on the introduction of MA drugs following the recent change of law.

• Is collaborating with IPPF on the quality assessment of MA drugs in 10 markets.

• Is supporting combi-pack registration in two countries.

• Is developing a business case for manufactures to support their investments in MA drugs.
THANK YOU