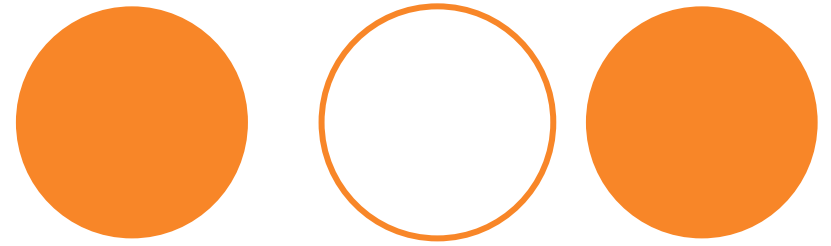
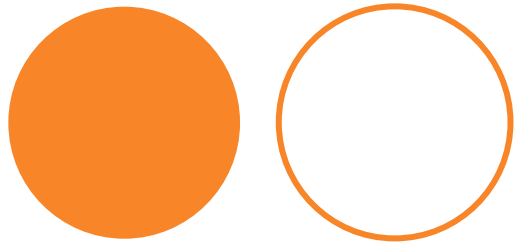


Mifepristone Medical Abortion: Off-label = better access & use

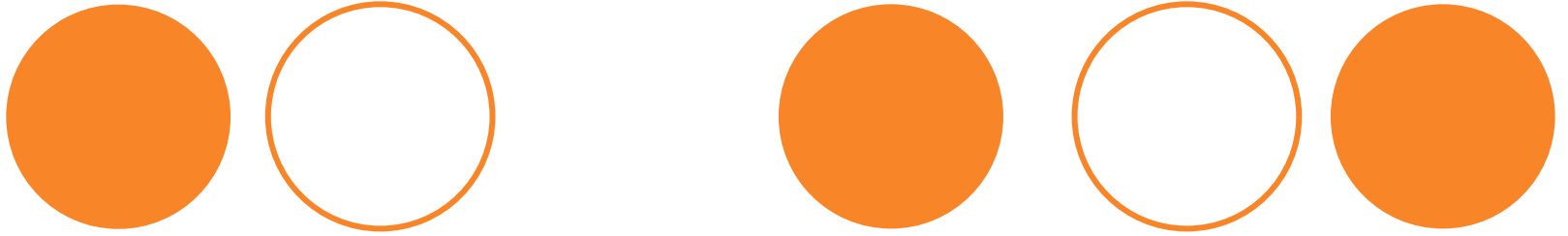


Beverly Winikoff, MD, MPH
Gynuity Health Projects

ICMA Meeting
Lisbon, Portugal
March 2, 2010

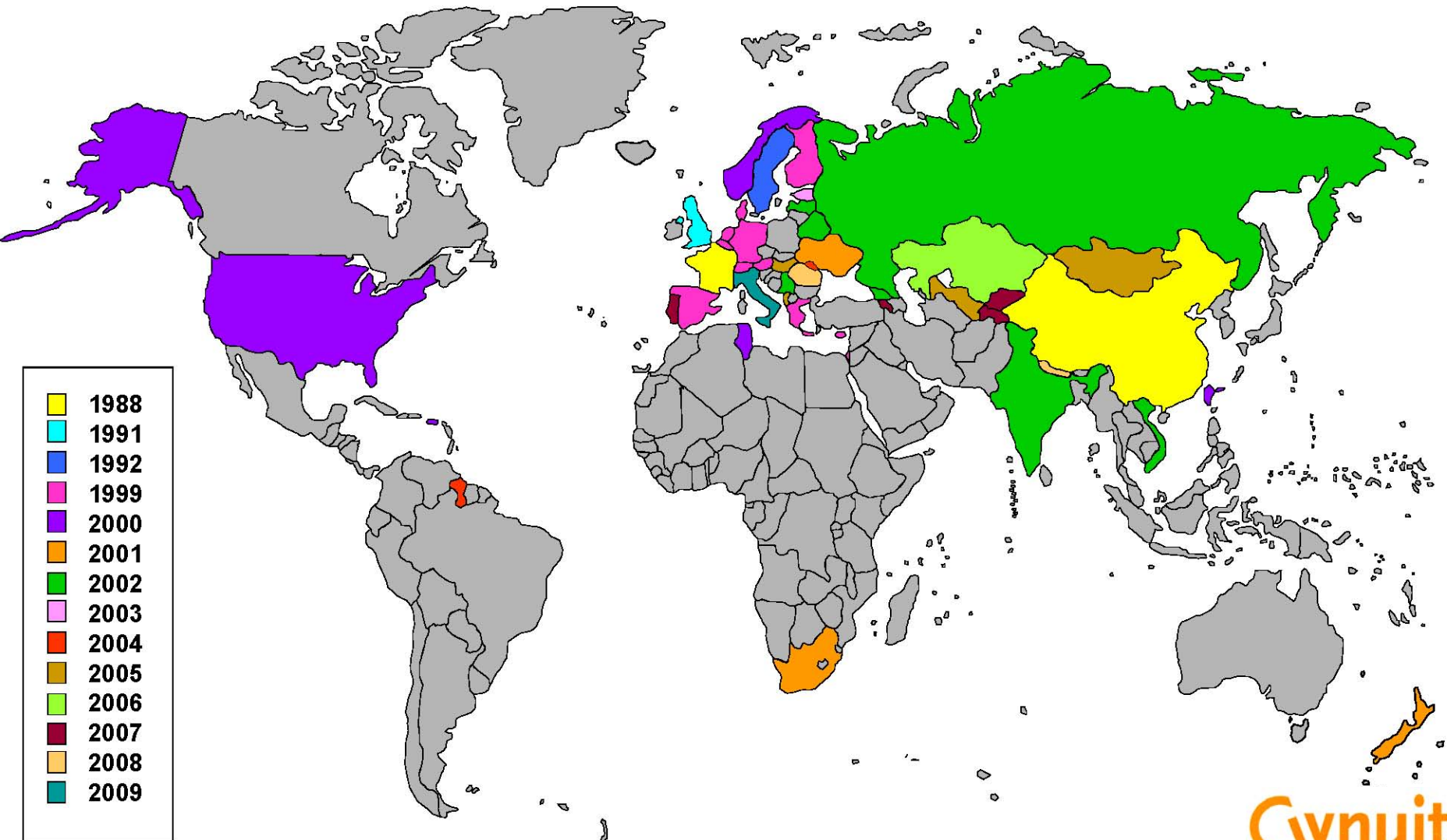


WHAT'S THE PROBLEM?



- **No approvals in many parts of world**
- **Approvals almost on based on original French registration**
- **Science is over 20 years old**
- **Label reflects attitudes about abortion services when the idea of an abortion pill was novel and scary**

Mifepristone Approved





Drug registration:

The authorization by a government for a particular company to market (sell) a particular formulation of a drug for a particular purpose.

Drug registration is a commercial transaction

Registered indication:

The purpose for which the authorized drug may be marketed. The safety and efficacy of the drug for this indication must be proven scientifically to the satisfaction of the drug regulatory agency.

An authorized marketer can add a new indication to its file if it produces scientific evidence validating the safety and efficacy of the new use to the satisfaction of the regulatory agency.



Regulatory file:

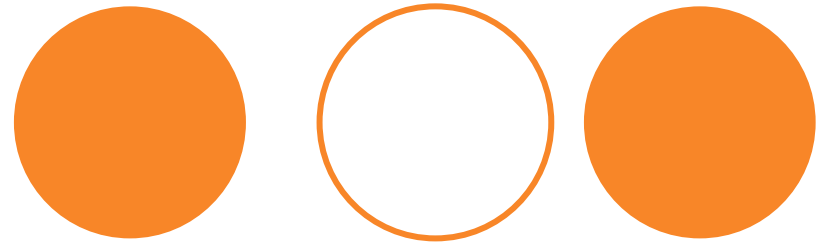
The entire dossier of information on which regulatory bodies base their market authorizations (registrations). The file contains:

- Information about the compound, including chemistry, pharmacology, animal and human toxicity
- Specifications about the manufacturing process
- Scientific data meeting regulatory standards proving the drug is safe and effective for its proposed indications
- Instructions for use of the drug

PIECES OF THE PUZZLE

- **A company cannot market a drug it owns for an indication that is not registered. This means it cannot advertise, provide brochures or educational information on unauthorized indications.**
- **Use of drugs for unregistered indications may not be reimbursable in certain insurance schemes, may not be permitted in some government run health services, and may pose risks to provide in certain environments.**

Off-label use



- **Any use of a drug different from the label: indication, dose, route, frequency**
- **In almost all medical practice, off-label drug use is extremely common**
- **Estimates of up to 80% of certain prescriptions are for “off-label” uses, depending on drug type**
- **Off label use most common for older drugs and where science has outpaced the willingness of pharma to invest more to re-label an old drug**

Initial registrations

- Termination of pregnancy to 49 d LMP
- 600 mg mife
- 400 mcg oral miso (or not specified!)
- Miso 2 days after mife
- Miso in clinic
- Follow up visit

Off-label uses: drugs

- 200 mg vs. 600 mg mifepristone
- Dose and route of misoprostol (though not specified in some European registrations)
- Home use of mife or miso
- Use after 49 days LMP
- Timing of misoprostol
- Repeat dose of misoprostol

Off-label uses: services

Depending on how label is written, “off-label” may also apply to:

- Use of ultrasound
- Number of visits
- Routine follow-up

200 vs. 600 mg of Mifepristone

- Drug provided as 200 mg tablets
- WHO study shows two doses similar:
88.1% (600 mg) vs. 89.3% (200 mg)
- Extra tablets not necessary
 - Mifepristone is expensive; using less would reduce cost a lot
 - Clinical studies and use clearly show higher dose is not needed.

Misoprostol: routes of administration

Oral	Rapid absorption (peak 30 mins) Levels fall sharply in 1-2 hours
Vaginal	Peak later (80 mins) but lower Higher levels longer in plasma
Buccal	Later, lower peak, sustained levels (similar to vaginal)
Sublingual	Rapid absorption, high peak, sustained levels
Rectal	Lower peak but higher levels longer than oral (not used in MA)

Dose and route of miso



- To 56 days LMP most miso choices (dose and route) can work equally well
- For gestations over 56 days LMP, vaginal, buccal, sublingual routes are more effective
- Off-label use permits use to later gestational ages, serving more women

Home Use of Misoprostol



- **Overwhelmingly preferred choice in U.S.**
 - **98-99% (n = 4345) Schaff, 1998, 1999, 2000**
- **Similar preference in developing countries:**
 - **Vietnam 80% (n =112) Elul, et al., 2000**
 - **Tunisia 87% (n =191) Elul, et al., 2000**
- **Home administrations increasing in Europe**

Home use of mife - - Why not?

?

Efficacy beyond 49 days

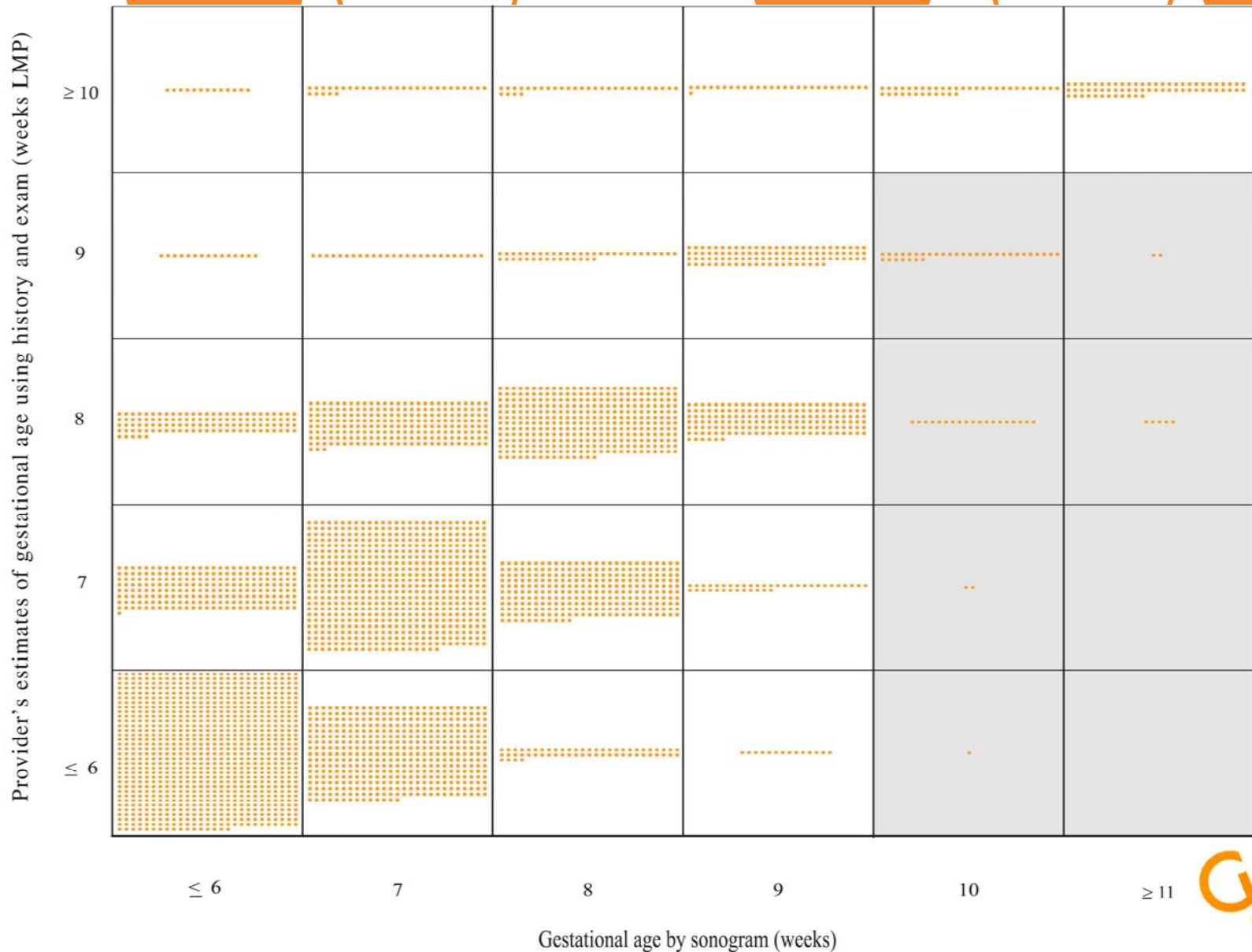
- Dozens of studies showing high efficacy to 63 days' LMP using 200 mg mife + vaginal, buccal, or sublingual miso
- General use in US, UK and Sweden – but not off-label in UK and Sweden
- Registered to 56 days in South Africa; most of world registered to 49 d
- No mechanism to use registration in one country to support change in another
- Pharma not willing to invest in changes

Effect of Timing of Misoprostol After Mife, to 56 days LMP

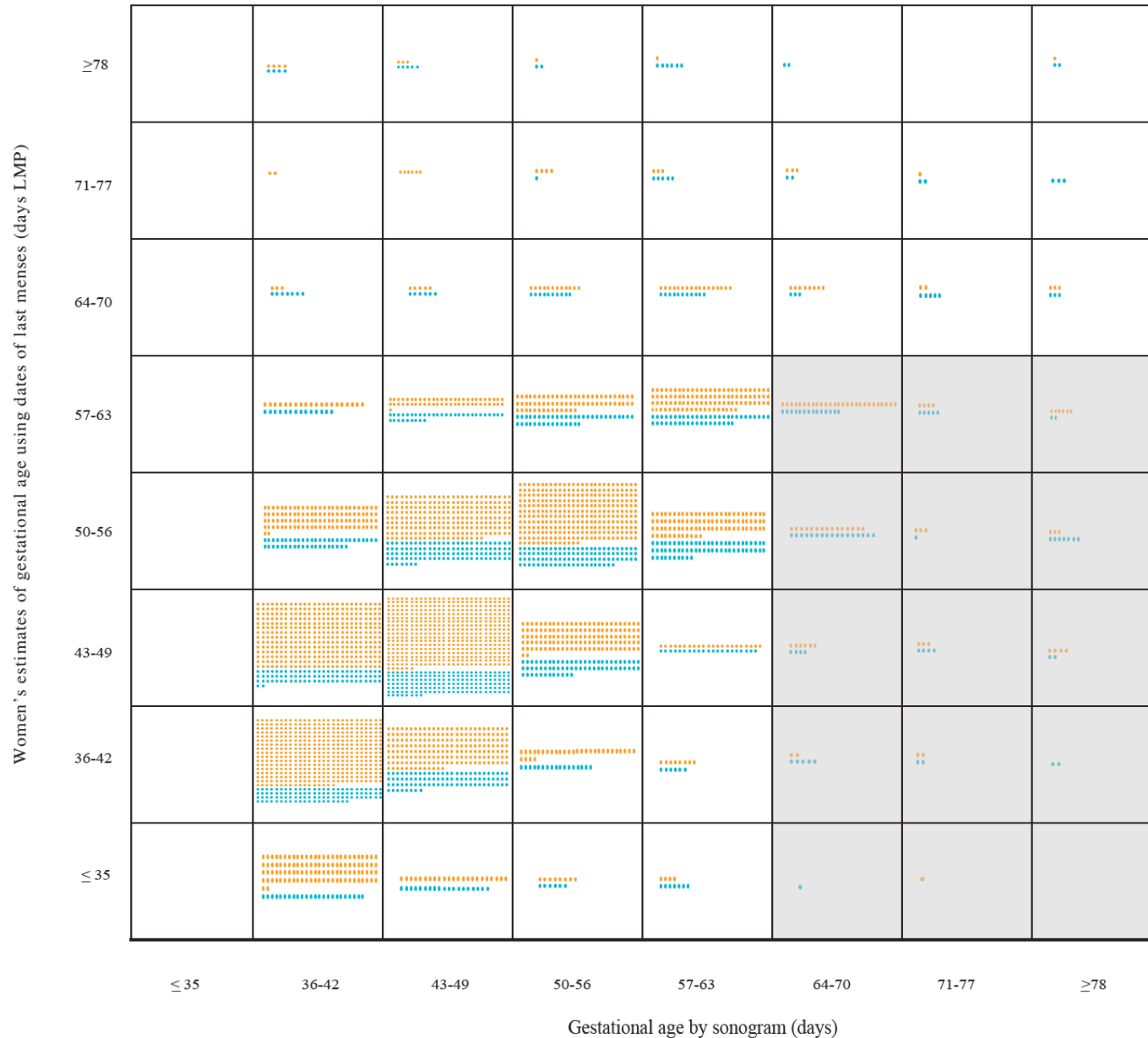
(200 mg mife, then 800 μ g miso, PV)

	<u>Study Day 2</u>	<u>Study Day 3</u>	<u>Study Day 4</u>
Took miso	704	470	654
Success (%)	98 \pm 1	98 \pm 1	96 \pm 1.5

Providers can accurately assess gestational age eligibility without ultrasound (n=4481)



Women themselves can accurately assess gestational age eligibility (n=4481)

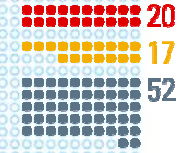


Current Standard of Care

3054

100%

NEEDS IDENTIFIED



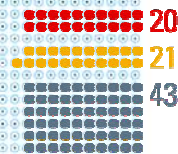
NOT IDENTIFIED



Algorithm 4

3054

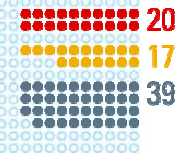
64.1%



Algorithm 5

2798*

34.3%

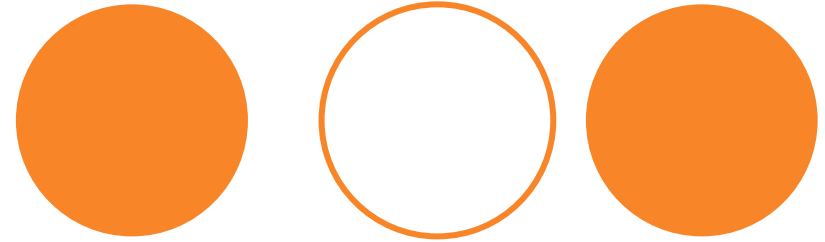


- — ultrasound
- — patient assesment without ultrasound
- — low-sensitivity pregnancy test and self- assesment questionnaire

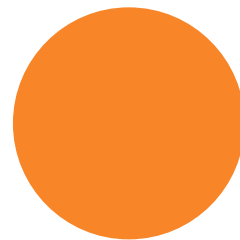
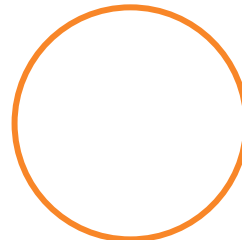
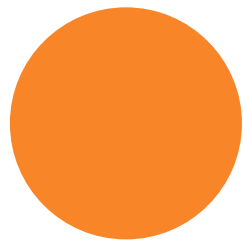
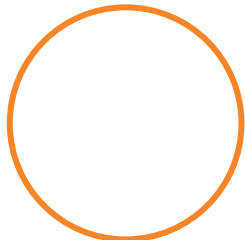
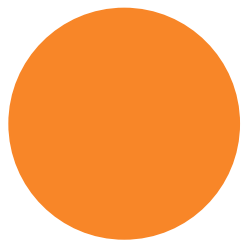
- — ongoing pregnancy
- — surgical completion or rx for infection
- — other medical care

*Data from physical exam missing 256 cases

Lessons



- **Do not fear off-label use: it is your friend**
- **Determine the exact limits of the label and the usual conditions of off-label use**
- **In advocacy and technical consultation, resist temptation to put “optimum” service delivery ideas into the label or the law**
- **“Best practices” are best left to guidelines and norms rather than documents with legal force**
- **Information changes quickly; laws change slowly**



Thank you!

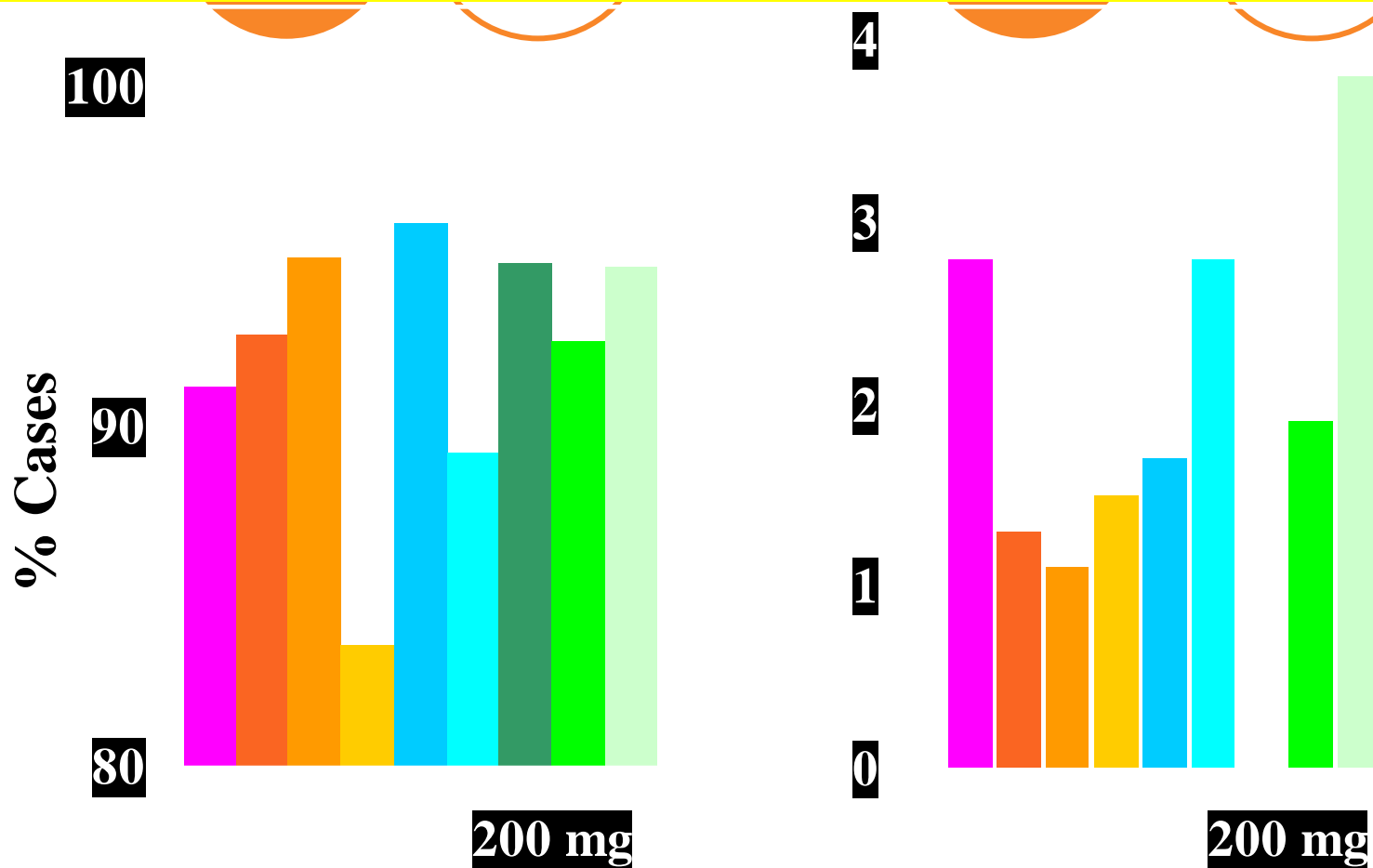
The Big Picture: Regimens

- **The original regimen and variants are very safe, effective, and acceptable**
- **A trend toward lower effectiveness with increasing gestational age**
- **Vaginal (maybe other routes?) misoprostol may increase efficacy, especially after 56 d. LMP**
- **Women generally prefer and clearly can manage misoprostol self-administration**

TERMS FOR DISCUSSION OF DRUG AVAILABILITY

- **Drug registration (or authorization or licensing)**
- **Registered (or authorized or licensed) indication**
- **Patented drug**
- **Generic drug**
- **Regulatory file**

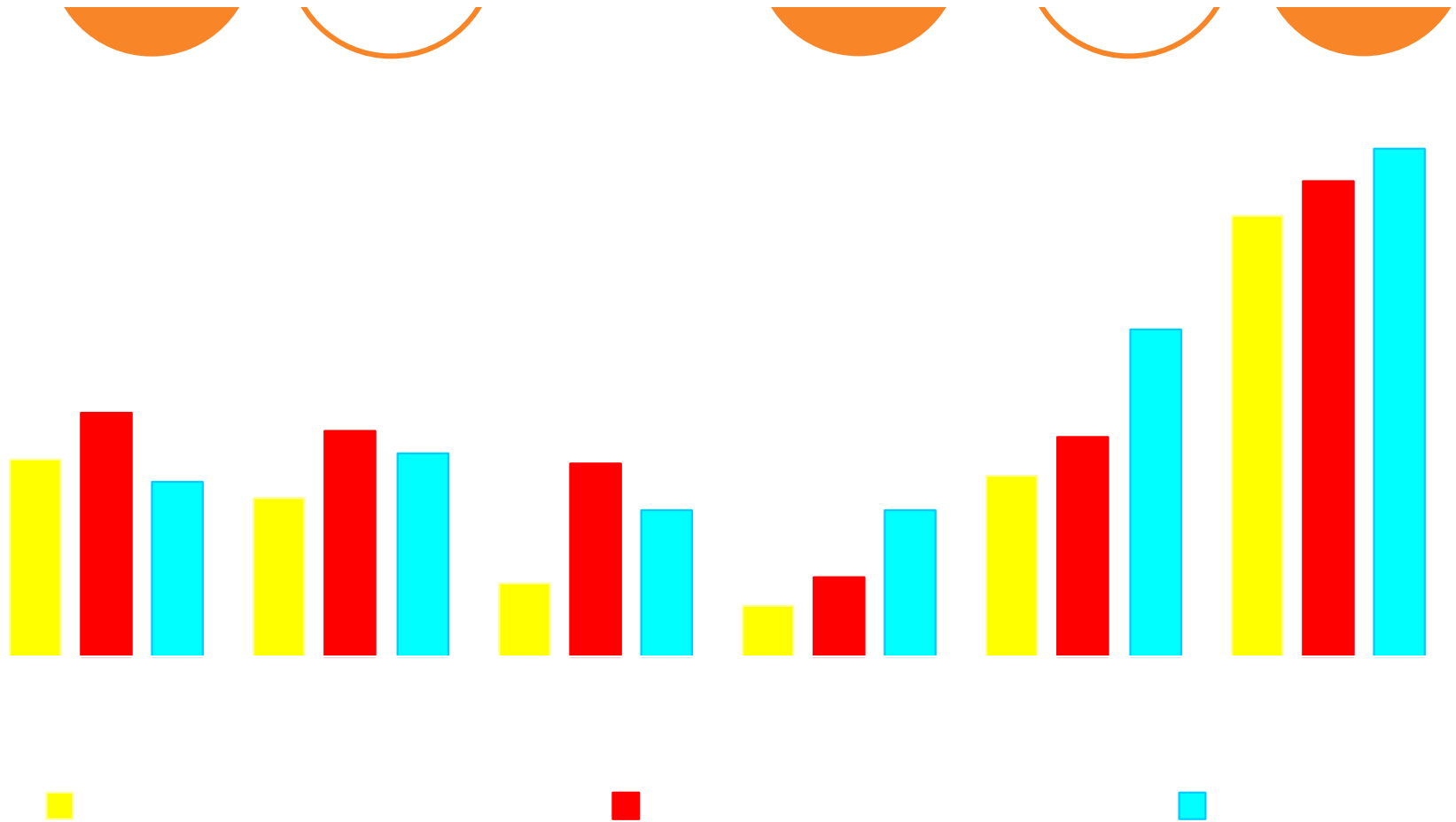
Efficacy and ongoing pregnancy: regimens of 200 mg mife and 400 µg oral misoprostol



Efficacy: 9 studies, Unadjusted mean efficacy = 92.2%, Range = [83.6% - 96.0%]

Ongoing: 9 studies, Unadjusted mean ongoing rate = 1.9%, Range = [0.0% - 3.8%]

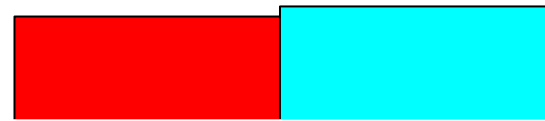
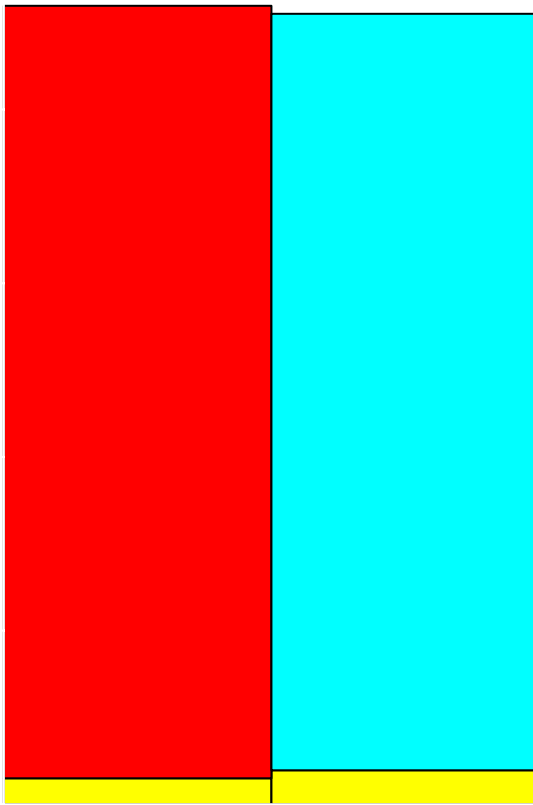
Side effects by dose of misoprostol



Regimen Innovations

- 200 mg vs. 600 mg mifepristone
- Dose and route of misoprostol
- Home use of misoprostol
- Use after 49 days LMP
- Timing of misoprostol
- Repeat dose of misoprostol

Misoprostol Administration Choice



Is Misoprostol in Clinic Needed for Safety Reasons?

- **No serious adverse events in 4 hours post-misoprostol in clinic – 1059 patients in 4 developing countries**
- **Pop Council trial in 2121 U.S. women: 4 transfusions, none during clinic waiting time**
- **Schaff study of 2295 women: no interventions required within 4 hours of misoprostol**

Regimen Innovations

- 200 mg vs. 600 mg mifepristone
- Dose and route of misoprostol
- Home use of mifepristone or misoprostol
- Use after 49 days LMP
- Timing of misoprostol
- Repeat dose of misoprostol

Regimen Innovations

- 200 mg vs. 600 mg mifepristone
- Dose and route of misoprostol
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- Repeat dose of misoprostol

Efficacy beyond 49 days

Mifepristone 200 mg

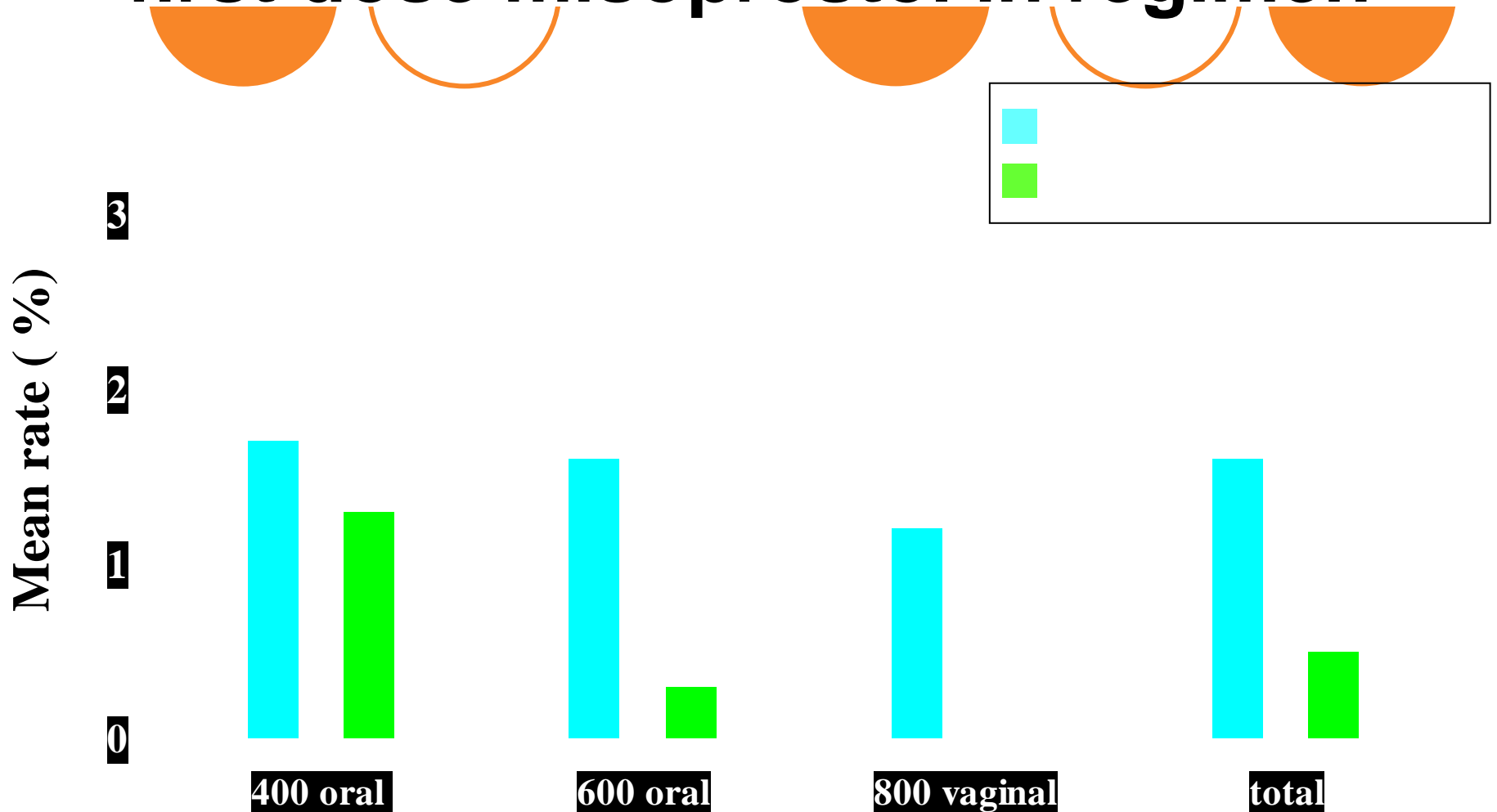
	GA studied	Efficacy(%)
Penny (1995)	50-63	93
Ashok (1998a)	<64	98
Ashok (1998b)	63-91	95
Schaff (1999)	<57	97
Elul (2000)	<57	92
Schaff (1999)	<57	97
Schaff (1999)	57-63	96

And many more in the decade since then!

Regimen Innovations

- 200 mg vs. 600 mg mifepristone
- Dose and route of misoprostol
- Home use of mifepristone or misoprostol
- Use after 49 days LMP
- Timing of misoprostol
- Repeat dose of misoprostol

Ongoing pregnancy rate by amount of first dose misoprostol in regimen



One dose: 31 studies, Mean total rate = 1.8%, Range = [0.0% - 6.7%]

Repeat dose: 13 studies, Mean total rate = 0.5%, Range = [0.0% - 3.0%]

Outcomes may be related to misoprostol management choices

- **Experienced services: failure is infrequent and ongoing pregnancy is a rare event**
- **Variations in rates of failure and ongoing pregnancies may associated with number of doses: no conclusive studies**
- **Outcomes may also be affected by:**
 - **total misoprostol dose**
 - **timing of doses**

Buccal v. Vaginal Use of Miso

800 mcg after 200 mg mife

	Buccal (n = 216)	Vaginal (n = 213)
Success rate %*	94.9	93.4
All surgical interventions %	5	6.6
<i>Reason for surgery</i>		
Ongoing pregnancy %	1	1.8
Incomplete abortion %	4	3.8
Medically necessary %	0	0.5
Patient preference %	0	0.5

Success with several miso doses/routes

A study of over 900 women in Canada:

Mifepristone 200 mg followed by miso to
57 days LMP

- ⇒ 400 µg oral miso: 94.7 [92.4-97.1]
- ⇒ 600 µg oral miso: 93.4 [91.1-95.8]
- ⇒ 800 µg vaginal miso: 94.3 [92.0-96.7]

Generic Drug:

A compound biologically equivalent to an originally patented drug and registered for the same indication and in the same dose as the original drug.

PIECES OF THE PUZZLE

- **Only a generic (same drug/same indication) does not require a complete regulatory file. A new indication can be registered by the original file holder-or an entity with a complete new file.**
- **If the original marketer does not want to add an indication, the task of registering an equivalent drug for a new indication is daunting.**