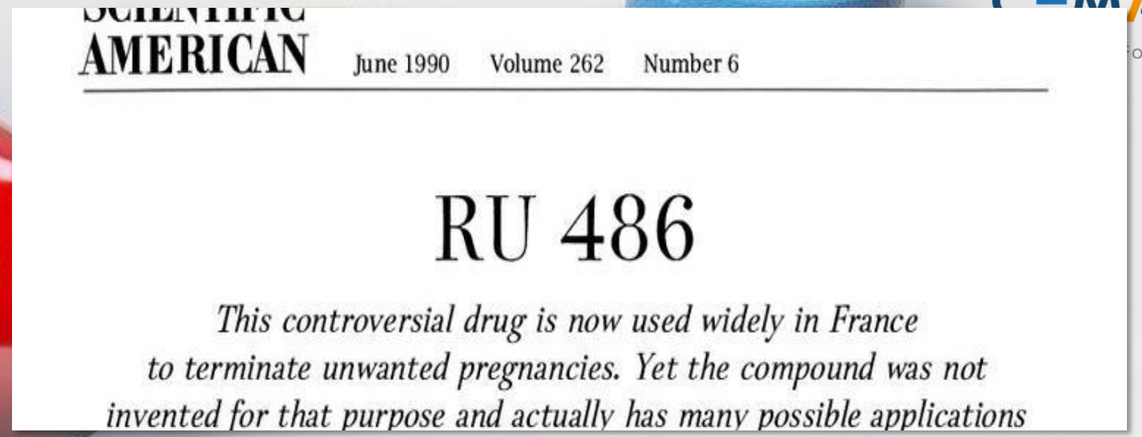
THE DEVELOPMENT OF MIFEPRISTONE (RU486), 1980 TO 2023

André Ulmann, MD, PhD


The Development of Mifepristone:
A Pharmaceutical Drama in Three Acts

ANDRÉ ULMANN, MD, PHD

Roussel's capital was split between


SCIENTIFIC AMERICAN June 1990 Volume 262 Number 6

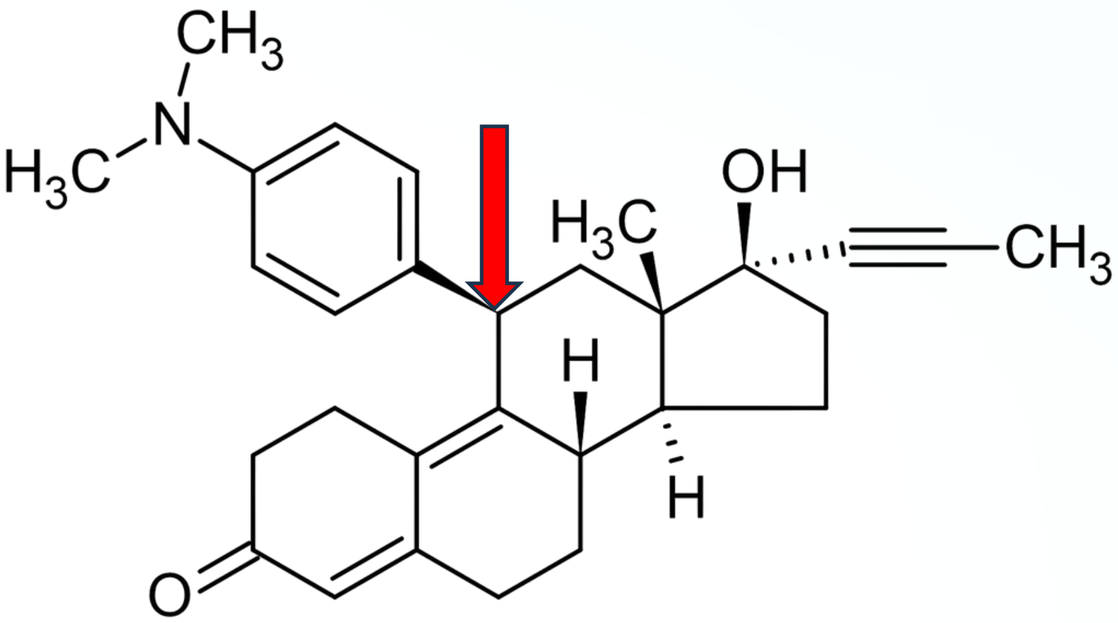
RU 486

This controversial drug is now used widely in France to terminate unwanted pregnancies. Yet the compound was not invented for that purpose and actually has many possible applications

01

About.

Mifepristone (RU486 - MF) has a unique and complex history, marked by numerous technical, ethical, political, social, and personal challenges that have impacted its development and global accessibility.



The initial discovery.

- Discovered by Roussel-Uclaf (RU) in France
  - Initial patent filed in 1980
  - RU staff as inventors
  - Prof. Etienne Emile Baulieu: RU adviser, “godfather”
- First human administration in 1982 for termination of pregnancy (ToP) by Prof. Walter Hermann in Geneva.
- RU handled market authorization development (Catherine Dubois, Louise Silvestre, Meng Ung)
- Parallel studies by WHO, Population Council, NIH, ICMR using RU-supplied tablets.

03

Pharma & preclinical development conducted by RU (1980 - 1990).

Pharmaceutical development

- Initially, 50-mg tablets were used but were soon replaced by 200-mg tablets

Preclinical development

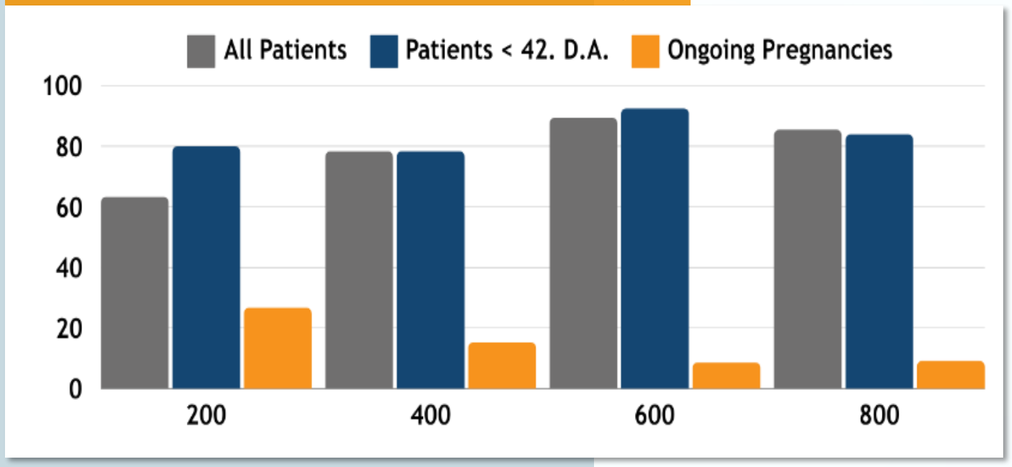
- Standard preclinical package including genotoxicity and peri/postnatal studies
- Long-term (6 months) toxicity studies conducted on rats and monkeys
- Extensive pharmacological studies across various indications

Clinical development conducted by RU (1).

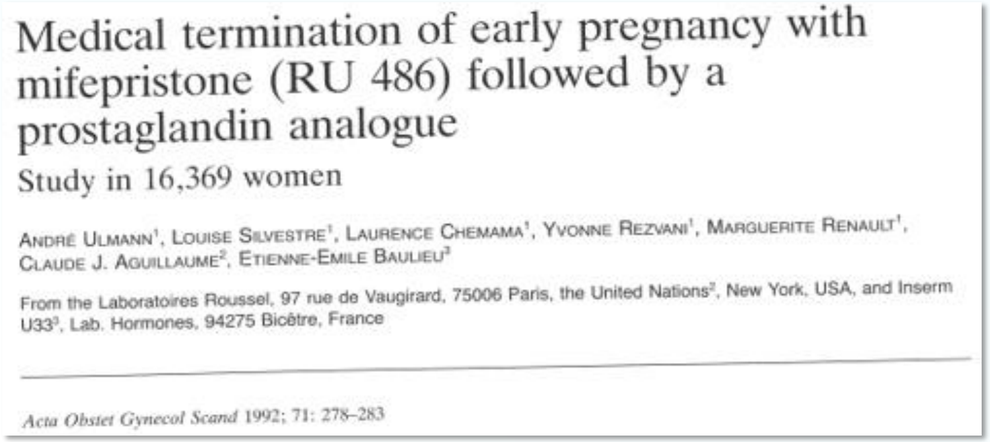
Initial development:

- ToP, product alone, 50mg tid for 3 days
- Shifted to single doses, starting with 450mg
- Phase 2 showed 600mg alone had higher efficacy than 200 or 400mg
- Overall efficacy rate of approximately 80%, which is lower compared to instrumental ToP

Phase 2 clinical studies (MF alone), results obtained by RU



Internal report by RU



Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue

Study in 16,369 women

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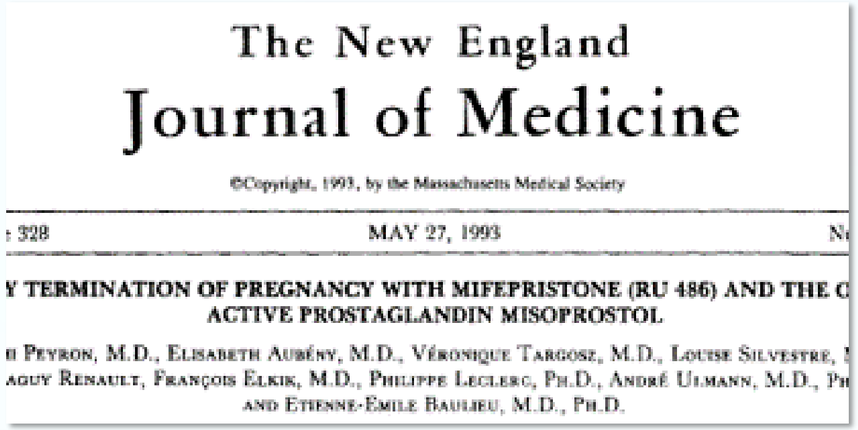
Acta Obstet Gynecol Scand 1992; 71: 278–283



The New England Journal of Medicine

: 328 MAY 27, 1993 N

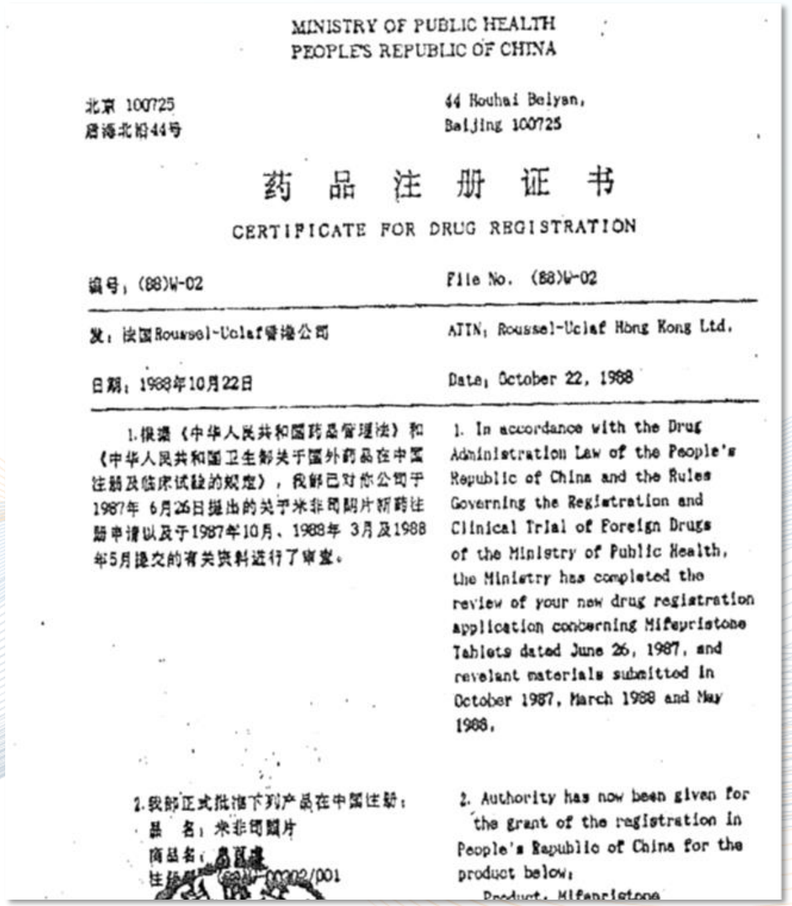
Y TERMINATION OF PREGNANCY WITH MIFEPRISTONE (RU 486) AND THE C ACTIVE PROSTAGLANDIN MISOPROSTOL

E Peyron, M.D., Elisabeth Aubény, M.D., Véronique Targosz, M.D., Louise Silvestre, M aguy Renault, François Elkik, M.D., Philippe Leclerc, Ph.D., André Ulmann, M.D., Ph and Etienne-Emile Baulieu, M.D., Ph.D.

Clinical development conducted by RU (2).

Swedish studies indicated mifepristone followed by a prostaglandin analogue (PG) achieved efficacy >90%

- Optimal interval between MF and PG: 36 – 48 hrs
- PG analogues initially used:
  - Gemeprost (PGE1): 1mg pessary
  - Sulprostone (PGE2): 0.5 mg im injection, discontinued after MF due to cardiovascular adverse effects in smoking women
- Later, it was demonstrated that oral misoprostol is equally effective, although its use was off-label



MINISTRY OF PUBLIC HEALTH
PEOPLE'S REPUBLIC OF CHINA

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磨海北粉44号

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Beijing 100725

药 品 注 册 证 书

CERTIFICATE FOR DRUG REGISTRATION

编号：(88)W-02

File No. (88)W-02

发：法国Roussel-Uclaf香港公司

ATTN: Roussel-Uclaf Hong Kong Ltd.

日期：1988年10月22日

Date: October 22, 1988

1.根据《中华人民共和国药品管理法》和《中华人民共和国卫生部关于国外药品在中国注册及临床试验的规定》，我部已对你公司于1987年 6月26日提出的关于米非司酮片新药注册申请以及于1987年10月、1988年 3月及1988年5月提交的有关资料进行了审查。

1. In accordance with the Drug Administration Law of the People's Republic of China and the Rules Governing the Registration and Clinical Trial of Foreign Drugs of the Ministry of Public Health, the Ministry has completed the review of your new drug registration application concerning Mifepristone Tablets dated June 26, 1987, and revelant materials submitted in October 1987, March 1988 and May 1988.

2.我部正式批准下列产品在中国注册：
品 名：米非司酮片
商品名：
注册号：(88)W-00002/001

2. Authority has now been given for the grant of the registration in People's Republic of China for the product below:
Product: Mifepristone

Market Authorizations (MA) obtained by RU.

Extensive efficacy and safety data at submission (>20,000 subjects)

- Failed attempts by Hoechst Roussel to remove the files in 1988 - 1989
- First Market Authorizations (MAs): France and China in 1988
- MAs followed in the UK (1991) and Sweden (1992)
- No additional MAs pursued by RU post-1992

New MAs obtained by other companies post-1992.

- 1997: MAs in 12 EU countries (Exelgyn)
- 2000: USA (Danco)
- 2012 Mexico (Linepharma)
- 2013 Australia (Linepharma)
- 2015 Canada (Linepharma)
- 2023 Japan (Linepharma/ Nordic)

07 The story of RU rights.

RU was the discoverer and initial owner of RU486 (initial patents filed in 1980)
Nevertheless…

- In 1993, US rights were granted to the Population Council
  - RU has transferred manufacture know-how and has never provided product for US market
  - Rights licensed by Pop. Council to Danco
- RoW: at the time of Aventis creation (1997) global rights granted to former RU CEO (Edouard Sakiz) who founded Exelgyn
  - Single product company, no further development, no dedicated misoprostol
  - No development in Australia / Canada
  - Exelgyn was sold to Nordic Pharma in 2007

- In China, Hoechst, the main RU shareholder, opposed MF.
  - RU obtained Market Authorization (MA) in 1988, but lack of sales led to local copies.

Since 2007, RU486 has been free of rights with no patent coverage.

Further regimen improvements.

Based on studies funded by non-profit organizations (WHO, Gynuity)

- MF dose can be decreased to 200 mg
- Misoprostol route & dose redefined: buccal route, 800µg
- Current consensus on the optimal regimen / indication
  - MF 200mg (oral)
  - Miso 800µg (buccal), home use approved in certain countries, Approved in Australia, Canada and recently in the US
  - Gestational age up to 63 DA (70 DA in the US)
- Combipack MF / Miso
- Home use

The main threats are primarily associated with product mishandling and political issues, particularly in the USA…

- Unregulated use of MF / Miso of unknown origin, with non validated regimen, improperly trained healthcare professionals, …
- Use of MF in non-approved indications leading to adverse events
- In an ideal world, an independent body should
  - Maintain safety records and optimize safety recommendations
  - Set standards for product quality
  - Issue guidelines for optimal use

The availability of Mifepristone has resulted in significant positive outcomes.

Significant benefits for women

- Providing additional fertility control
- Hundred of thousands have used mifepristone since 1984

Availability of this class of molecules (e.g. ulipristal acetate) in other indications

- Emergency contraception
- Benign gynecological diseases (fibroids)
- Cushing's syndrome (Corlux®, USA)

Despite these benefits, many women still lack access to mifepristone….

THANK YOU ...

André Ulmann, MD, PhD, 2024

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