# *Translational Research in Endometriosis*

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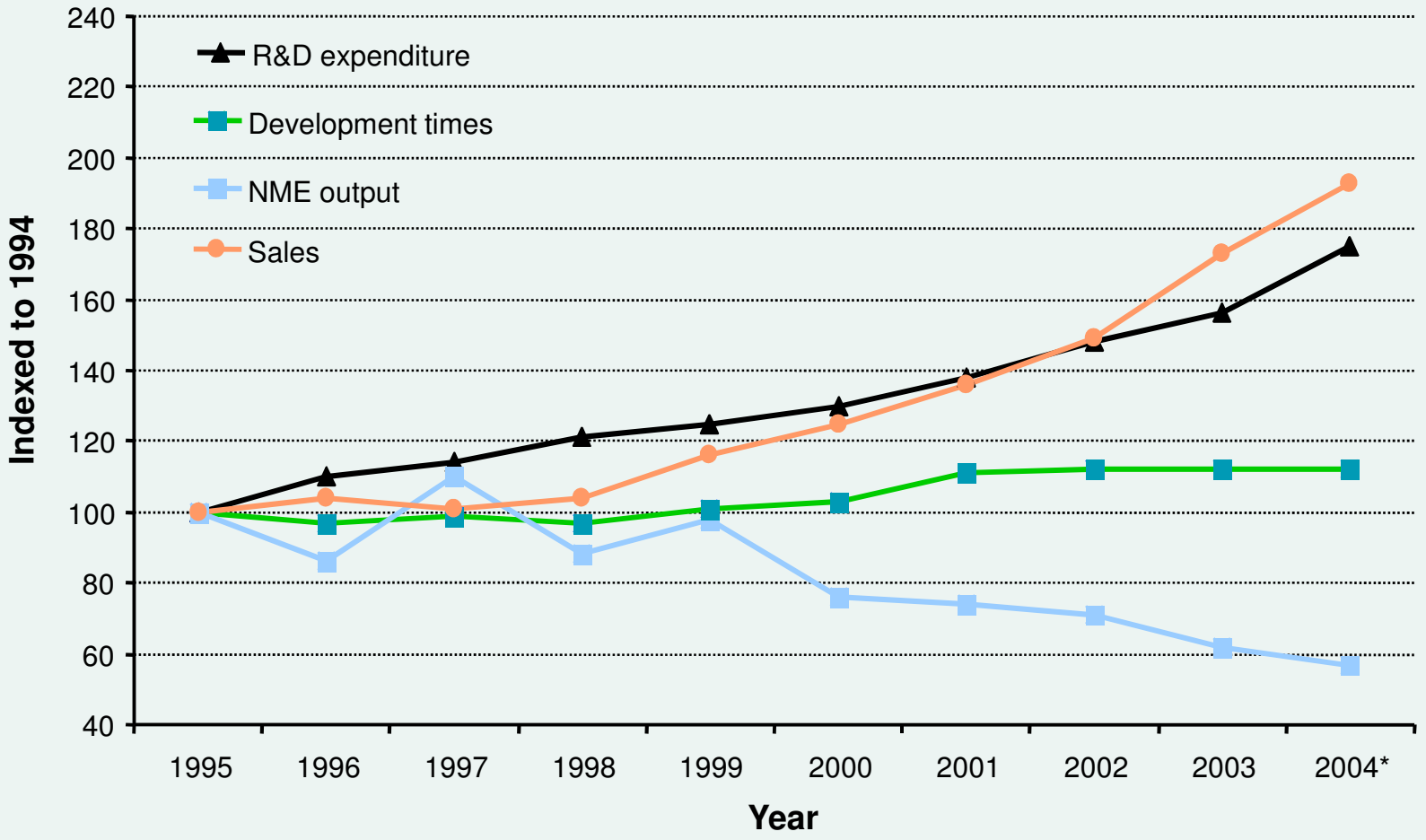
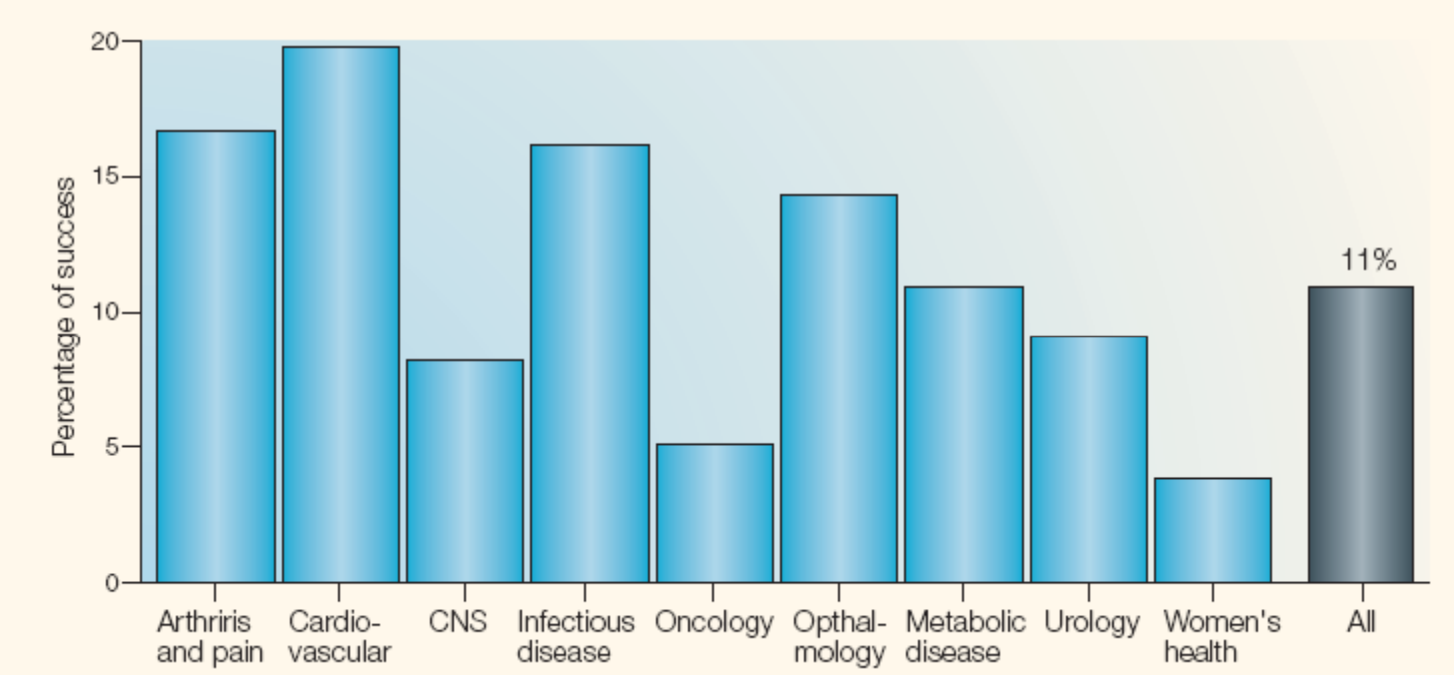
Schering-Plough

*ESHRE Campus Course, Leuven 2009*

# *Key global R&D facts, 1995-2004*

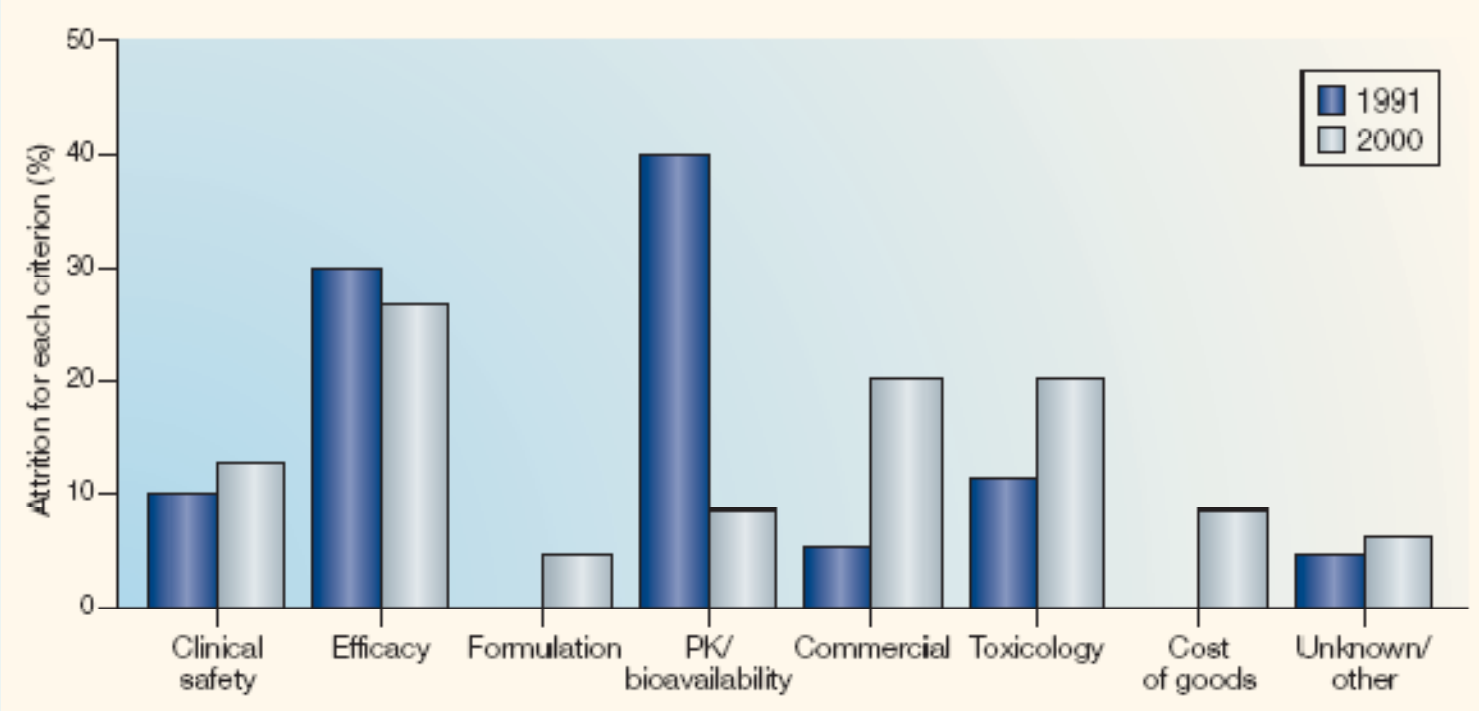


# *Success rates from first-in-man to registration*




*(Kola I., 2004 Nat Rev Drug Discovery)*

# *Reasons for attrition in the clinic*




*(Kola I., 2004 Nat Rev Drug Discovery)*

# *What is slowing down drug development in endometriosis*

- No validated, predictive therapeutic models
- No therapeutic models for endometriosis-related pain
- No diagnostic tools
- Clinical studies complicated: no biomarkers for patient stratification or early proof-of-concept
- No biomarkers/surrogate endpoints to monitor therapeutic efficacy endpoint, pain
- Lack of novel, innovative targets

# *Endometriosis pipeline late development*

**Overview of the endometriosis pipeline, 2007**

| Brand/ Research code | Generic | Formulation | MoA | Originator | Licensee | Status | Country |
|---|---|---|---|---|---|---|---|
| Visanne | dienogest | Oral | Progesterone agonist | Jenapharm GmbH & Co KG | Mochida, Bayer/ Schering | Pre-registration (Japan), Phase III3 (W.EU) | Japan, W.EU |
| Libra | deslorelin, estradiol, testosterone | nasal spray | GnRH agonist; estradiol agonist; Androgen receptor agonist | Balance Pharma | n/a | Phase III | US |
| FP-1096 | n/k | vaginal/ intrauterine | possible androgen | FemmePharma | KV Pharma | Phase III | US |
| Proellex/ Progenta (CDB-4124) | n/k | oral capsule | Selective progesterone modulator | National Institutes of Health | Repros Therapeutics | Phase II | EU & US |
| Femathina (MPI-674) | n/k | n/k | aromatase inhibitor | Meditrina Pharma Pfizer[1] | | Phase II | US |
| ERB-041, WAY-202041 | prinaberel | oral tablet | estrogen receptor beta agonist | Wyeth Research | n/a | Phase II | US |
| NBI-56418 | n/k | Oral | GnRH antagonist | Neurocrine Biosciences | n/a | Phase II | US |
| | terbutaline | vaginal gel | beta 2 adrenoreceptor | Columbia Laboratories and | n/a | Phase II | US |

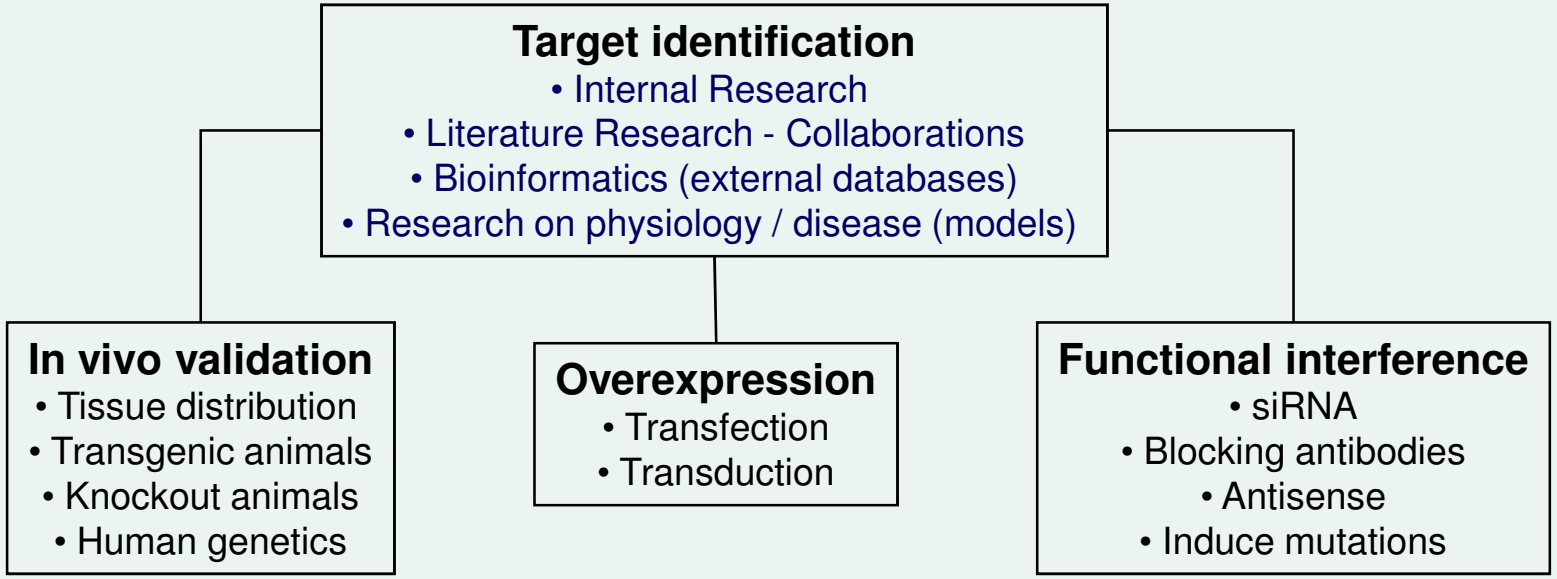
**Overview of the endometriosis pipeline, 2007**

| Brand/ Research code | Generic | Formulation | MoA | Originator | Licensee | Status | Country |
|---|---|---|---|---|---|---|---|
| | | | agonist; | Ardana | | | |
| A-ENDO | n/k | Oral | Androgen modulator; estrogen & progesterone receptor agonist | Dantarhei Bioscience | n/a | Phase II | Netherlands |
| SH-T-04268-H | n/k | Oral | Chemokine receptor antagonist | Bayer Schering Pharma AG | n/a | Phase II | EU |
| Antarelix (EP-24332, TZTX-00a) | teverelix extended release | sub cutaneous injection | GnRH antagonist | Zentaris GmbH | Ardana | Phase I | UK |
| PGL2001 | n/k | n/k | steroid sulfatase inhibitor | PregLem | n/a | Phase I | |
| PSD-509 (M-5004) | n/k | vaginal/ intrauterine | sodium channel inhibitor | Metris Therapeutics | Plethora Solutions | Preclinical | UK |
| Nestorone (ST-1435) | synthetic progestin | subdermal implant | Progesterone receptor agonist | Population Council | n/a | Preclinical | US |

1. Contract manufacturing and supply agreement with Pfizer
GnRH – gonadotrophin, MoA – mechanism of action, n/a – not applicable, n/k – not known

Source: MedTRACK, October 2007, Copyright Datamonitor Plc; IDdB, October 2007, Copyright Thomson Scientific

# *Target discovery*



# ***Research focusses of academia and industry:***

*an understandable mismatch*

| University (Medical Center) | Pharma |
| --- | --- |
| Hypothesis driven<br>Funding guided<br>Publication oriented | Target/compound driven<br>Patent/market oriented |

***How to create synergy***

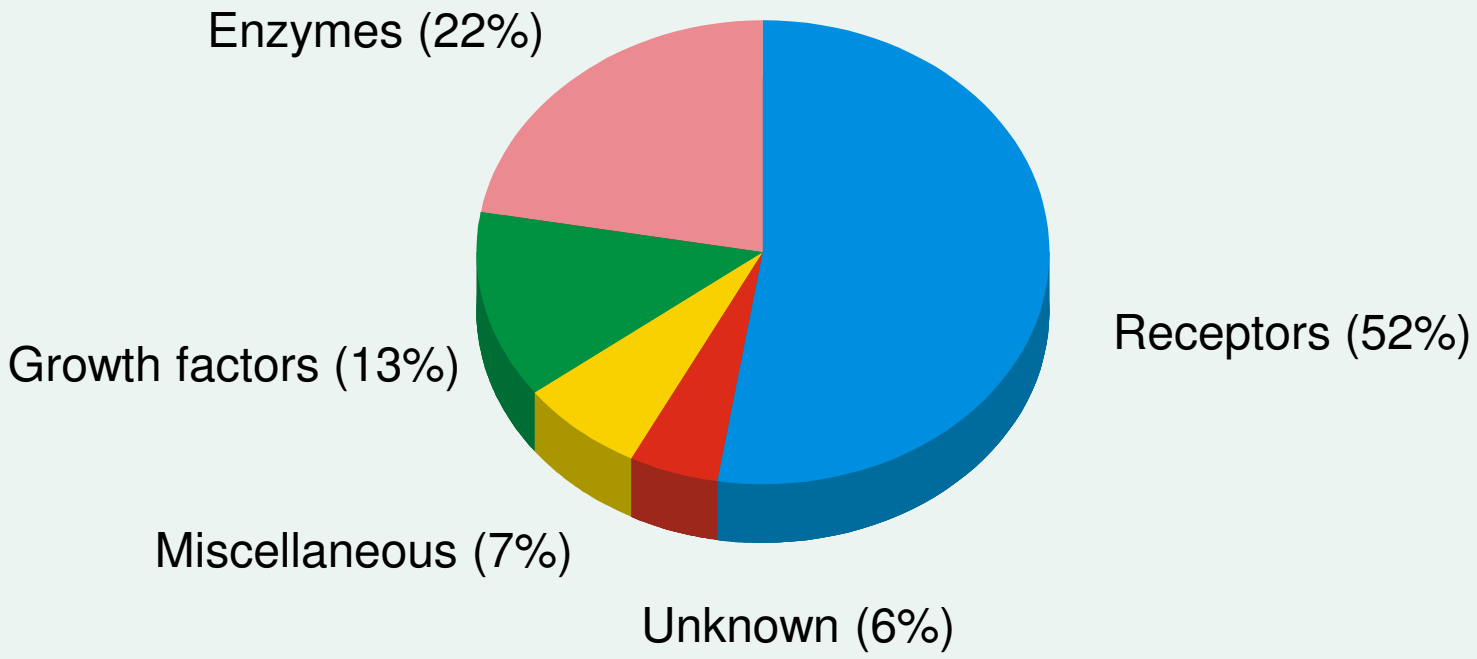
Understand biology
Improve diagnosis/therapy

Identification of NCEs
Proof-of-mechanism
Structure-activity relation
Develop novel, better, safer drugs

## *What makes a target*

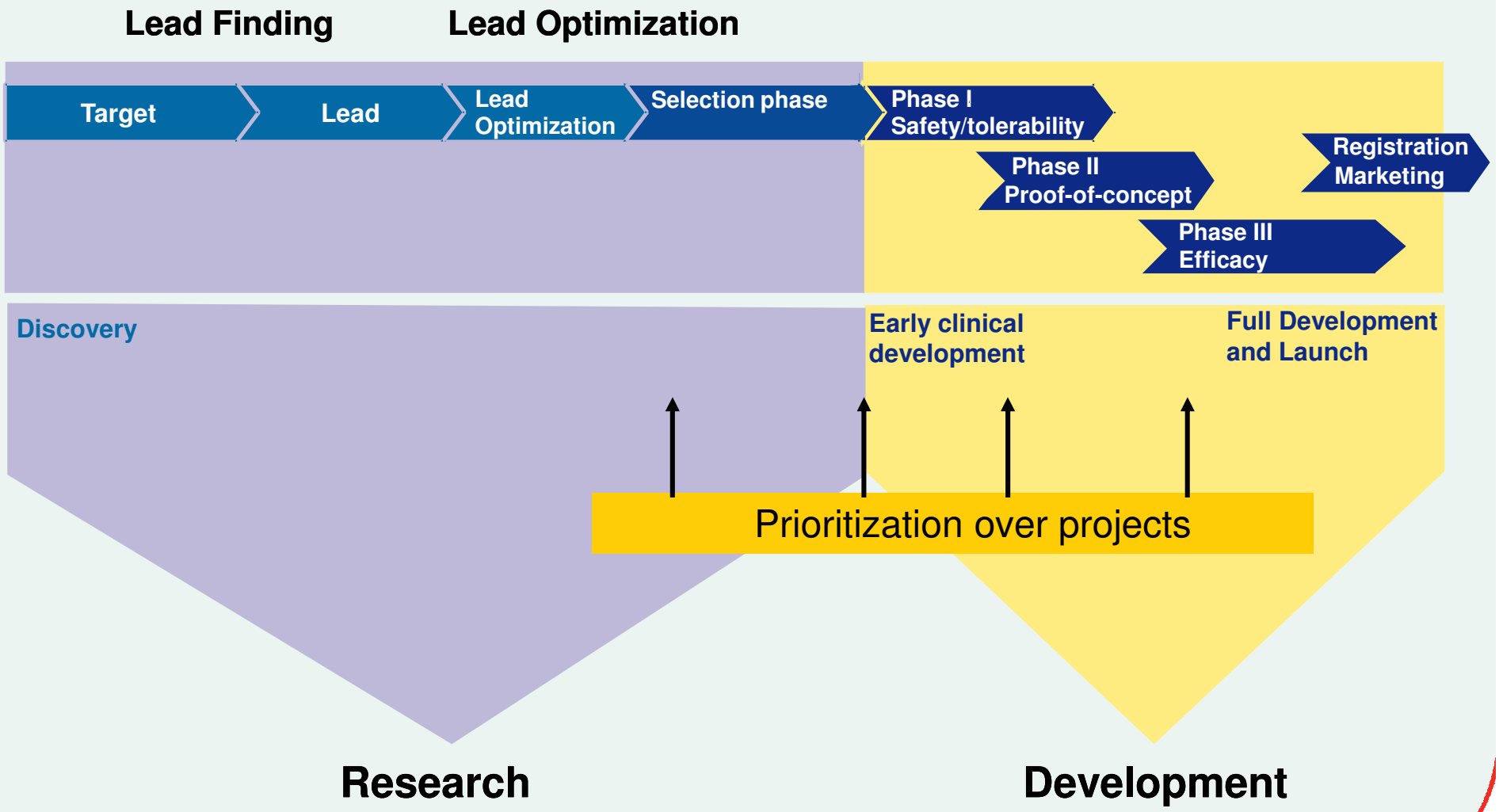
- A biological entity that is linked to a disease
- Inhibition (or activation) of this biological entity should reverse the development or inhibit progression of the disease
- Must be assayable in order to develop HTS assays
- Must be drugable

# Currently Identified Drug Targets: ~500

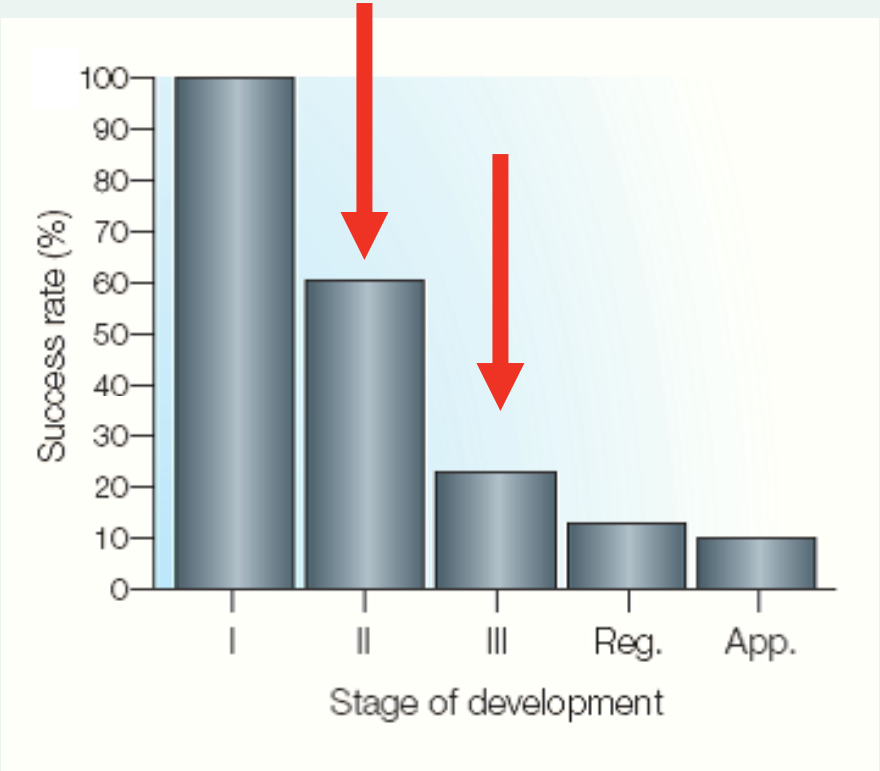



*Source: J. Drews, Hoffman - La Roche, Nature Biotechnology, November 1996*

# General R&D process

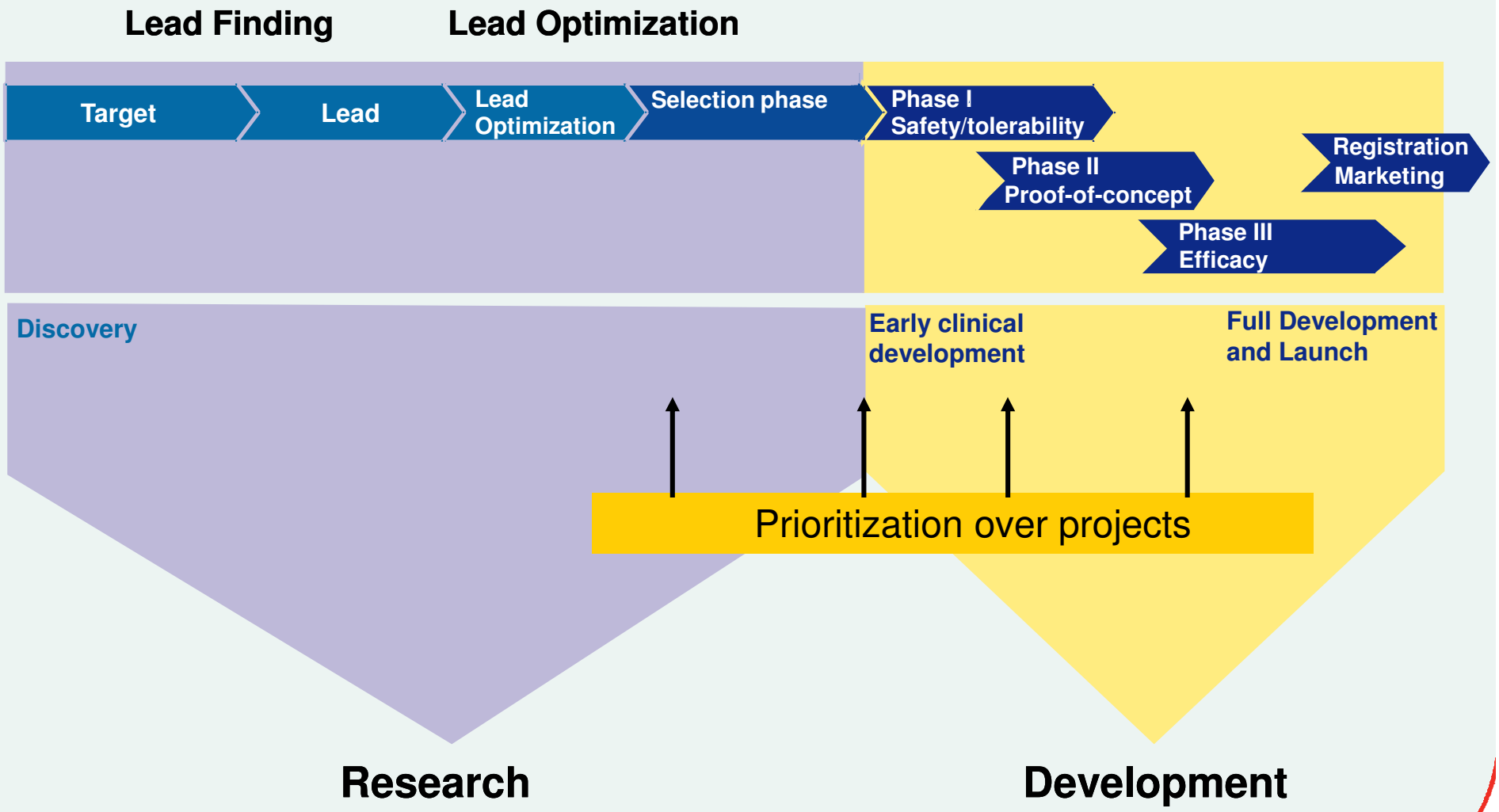


# *Success rates by phase of development*




Failure rate of Proof-of-concept (Phase II) and efficacy studies (Phase III) is 80 %

# General R&D process



# *Translational Research/Medicine*

*Translational medicine is the integrated application of:*

- *innovative pharmacology tools*
- *biomarkers*
- *clinical methods and technologies*
- *study designs to improve confidence in drug targets*
- *increase confidence in drug candidates*
- *understand the therapeutic index in humans*
- *enhance cost effective decision making*

*in exploratory development and increase phase II success leading to a sustainable pipeline of new products*

*Bruce H. Littman MD*
*VP translational medicine Pfizer, quote 2006*

# *Implementation*

- Predictive therapeutic models
- ID and validate biomarkers prior to FIH
- Develop clinical assays/technolgies, i.e. MRI, serum/urine-based assays biomarkers/surrogate endpoints
- PK/PD
- Ask the right questions to get the right answers, to make the right decisions
- Early feedback from clinical studies

*Ask the right questions to get the right answers,to make the right decisions*

- Compound selection

- Traditionally we only ask: does the drug work and is it safe?

- We need to ask other questions as well: why does it (not) work and why is it (not) safe?

# Question based approach

- Does the compound get to the site of action?
- Does the compound modulate the target?
- Does the compound cause its intended pharmacological/functional effects?
- Does the compound have beneficial effects on disease or clinical pathophysiology?
- Does the compound modulate non-registration endpoints the predict efficacy
- What are the key toxicity issues related to the therapeutic target/compound that determines the efficacy/safety ratio
- What is the therapeutic window (how safe is the drug)?
- How do sources of variability in drug response in target population affect efficacy and safety?

BIOMARKERS

# *PK-PD models transform biomarkers into a quantitative decision making tool*

- In many cases, biomarkers are the PD in PK-PD
- Optimal use of a biomarker requires that we relate the biomarker response to the PK data in order to understand the determinants of the response
- Mechanistic PK-PD models describing exposure-response and time course of response of biomarkers can:
  - increase our confidence in the mechanism of action
  - help predict the anticipated human dose and assess therapeutic window

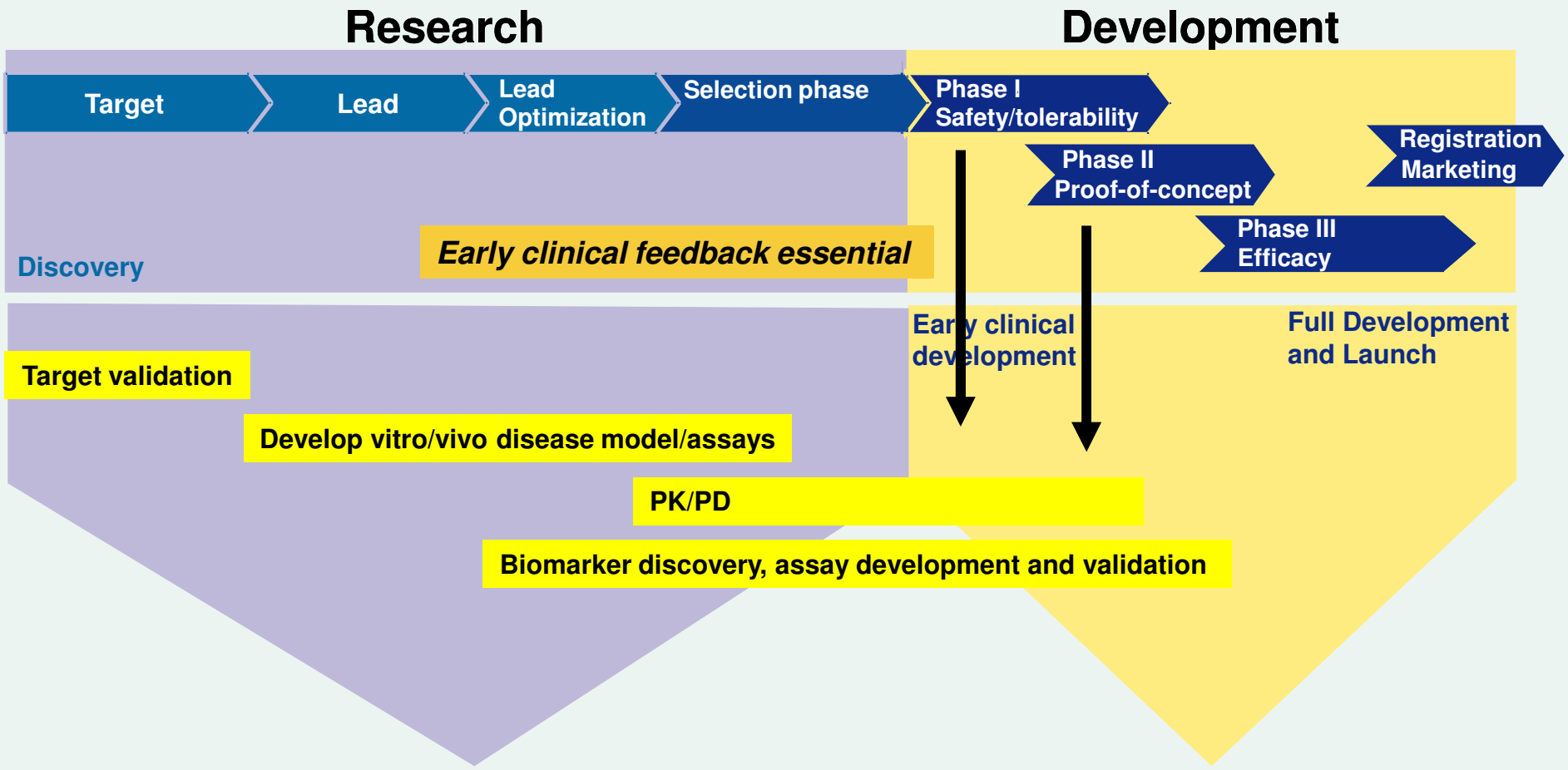
# *Important assets of PK-PD M&S in relation to biomarker data*

- PK-PD models can do more than describing concentration response relationships:
  - Can describe **time dependencies** in response to treatment
  - Can range from **empirical** to **mechanistic**
  - Allow **pooling of data** from different trials and different sources (e.g. literature)
  - **Translate** biomarker data across species
  - Models enable **predictions** of drug effects in situations that have not yet been tested

# *Preclinical vitro/vivo disease models*

- Cultures (immortalised) cells from endometrium/endometriotic tissue
- Tissue recombination under renal capsule immortalized human endometriotic cell lines
- Mouse primary xenografts (human endometrium/endometriosis tissue from patients)
- Non-human primate models for endometriosis (Rhesus maqaque, baboon)

# General R&D process



# *Translational research in endometriosis*

- Rigorous validation of targets and disease models is needed in order to confidently select the best compounds as early as possible

- Biomarkers/surrogate endpoints (and validated assays to measure them, are essential to be able to receive clinical feedback in a much earlier stage in order to realise earlier deselection/selection of clinically active compounds