# The Risk Management Initiatives and Drug Development

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# Definitions. Pharmacovigilance Plan (PVP)

- All products launched with PVP
  - Data from pre-clinical development
  - Data from clinical development
  - Class or “family” safety “issues”
  - Data from population intended to receive the agent
  - Steps needed to gain further knowledge
- PVP (ICH) = PV Specification + Action Plan

# Risk Minimization Action Plan (formerly Risk Management Plan)

- RMP. Similar to PVP +
  - Risk assessment/measurement
  - Risk confrontation
  - Risk intervention (minimization or tools)
  - Risk management evaluation
  - Risk communication
- RM (FDA) = Risk assessment + risk minimization

# Risk Management

# Where we are

- FDA PDUFA III.
  - Pre NDA meeting packages should include safety information and proposal for Risk Management Plans (RMP)
  - NDA Review. RMP must be submitted no later than one month prior to official action date
  - Guidance Papers. 2nd draft released on May 5th and is open for comments
- Implementation expected in 2004

# Where we are (cont.)

- EMEA. EU Heads of Agencies developed a “EU Risk Management Strategy” in January 2003
  - Guidance on Risk Management can be obtained during “scientific advice”
  - By the time of approval all products are expected to have a RMP or a statement that no specific “safety measure” is needed

# Where we are (cont.)

- ICH Guideline (E2E) has been adopted by FDA
- FDA will issue its guidelines in 2004

# Where we are (cont.)

- RM concept has shifted
- RMP were originally designed to manage KNOWN risks (terfenadine, mebefranil, astemizole, bromfenac)

# Where we are (cont.)

- RM concept now involves pre-marketing risk assessment during which, by definition, post-marketing risks are not known

# Why is RM here? Perception vs. Reality

- General perception of an “increased regulatory pressure”:
  - There are less regulatory approvals
  - More drugs are withdrawn
  - Agencies are more cautious in granting approvals

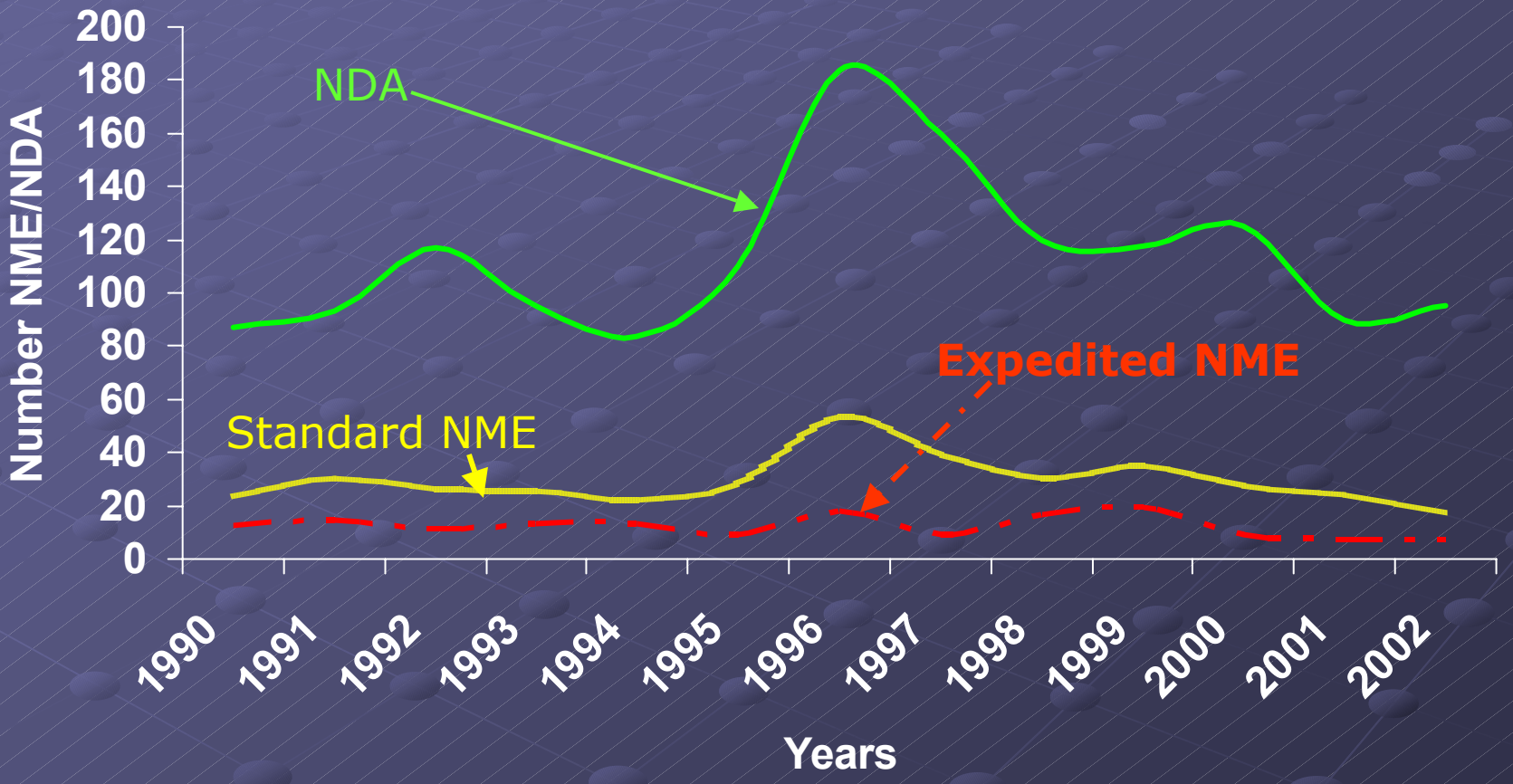
# Average Number of Drugs Approved per Year. FDA 1939-2000

| Decade | No. Drugs |
|---|---|
| 1940s | 3 |
| 1950s | 10 |
| 1960s | 11 |
| 1970s | 17 |
| 1980s | 28 |
| 1990s | 41 |

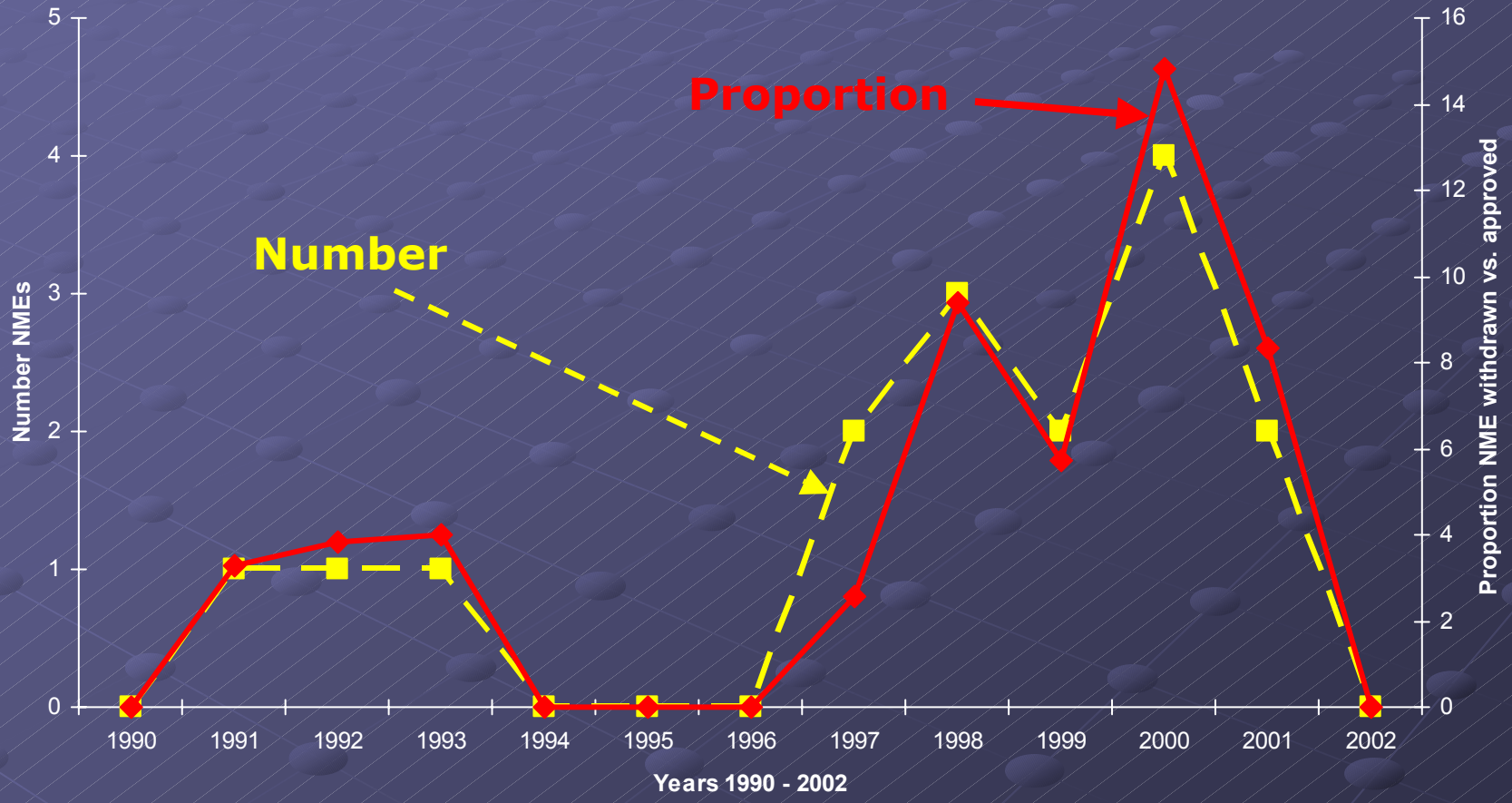
# Last 5 years of the 20th Century (FDA)

- Almost a drug per week!!!

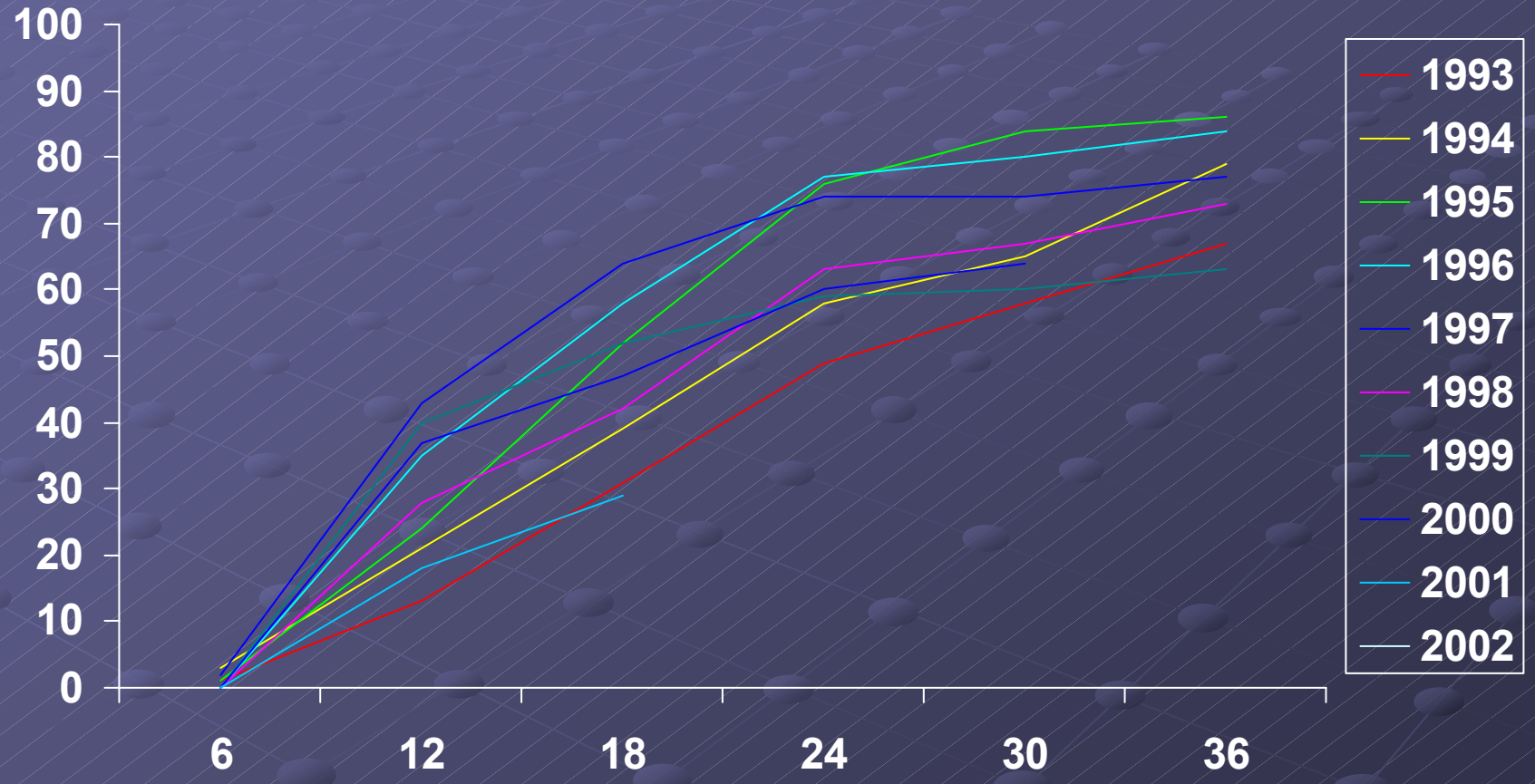
# Number of NME/NDA Approved per Calendar Year 1990-2002



# Number of NMEs Withdrawn as a Percentage of NME Approved 1990-2002



# Proportion of Standard NDA Approved 1993-2002



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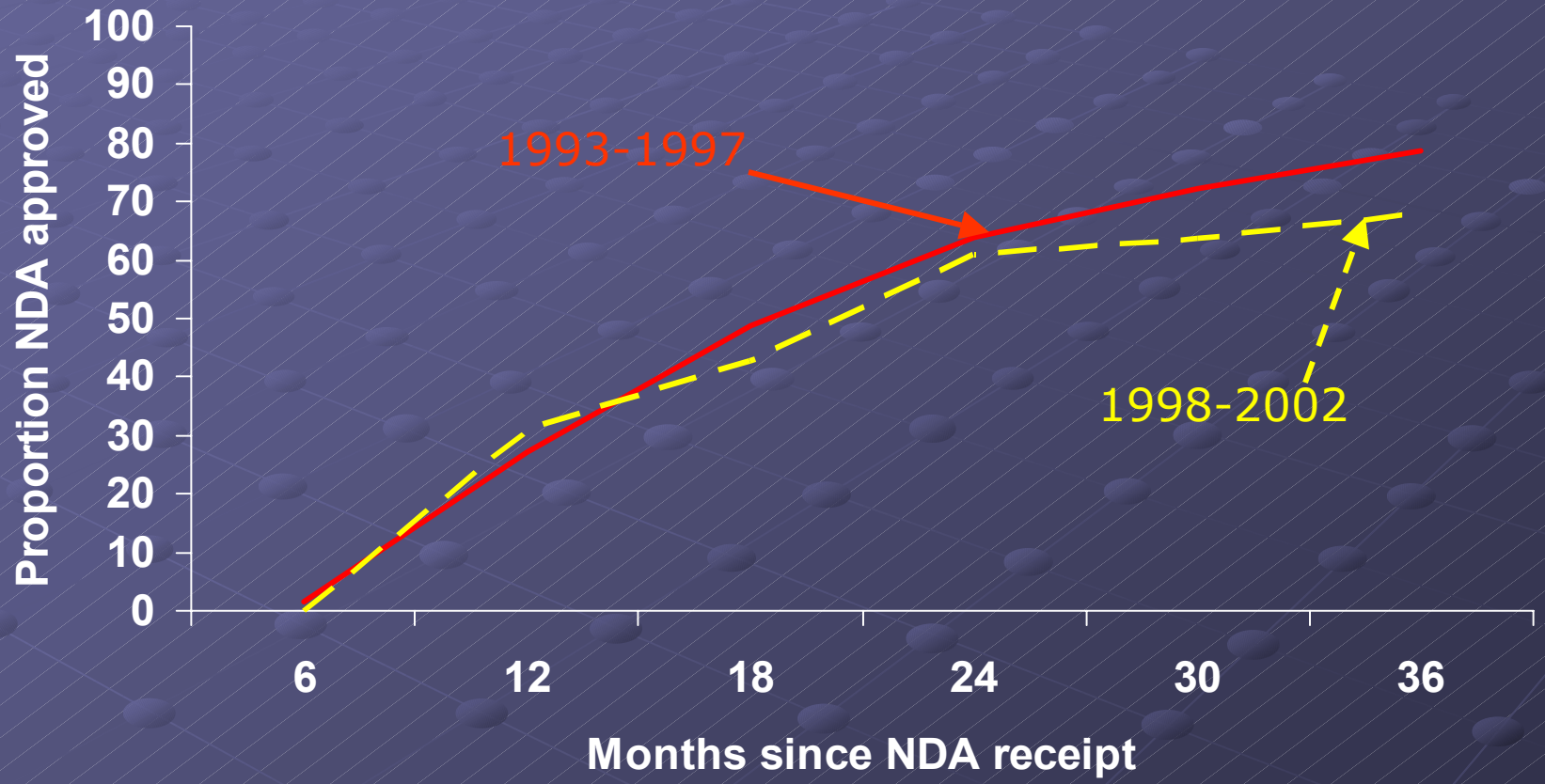


# Number of Drug Safety Alerts (1996-2001)

- clinical alert of SAEs, black box warnings, voluntary recalls, counterfeits and market withdrawals
- CAGR 18%

# Number of Safety – Related Label Changes (1997-2001)

- CAGR 21%
- Flat after 1997 – 1998
- Skepticism over effectiveness of label changes as RM tool

# Why is RM here? Perception vs. Reality

- General Perception of an increased regulatory pressure:
  - There are less regulatory approvals +/-
  - More drugs are withdrawn +
  - Agencies are more cautious in granting approvals +
  - Overall increase in regulatory pressure over label changes ++

# Why do companies need RM?

- It is the right thing to do
- It is here, whether you like it or not
- R & D reasons:
  - Leaner Pipelines
  - Less “unmet medical needs”
  - Narrower indications
  - Higher R & D Costs

# Why do companies need RM? (cont)

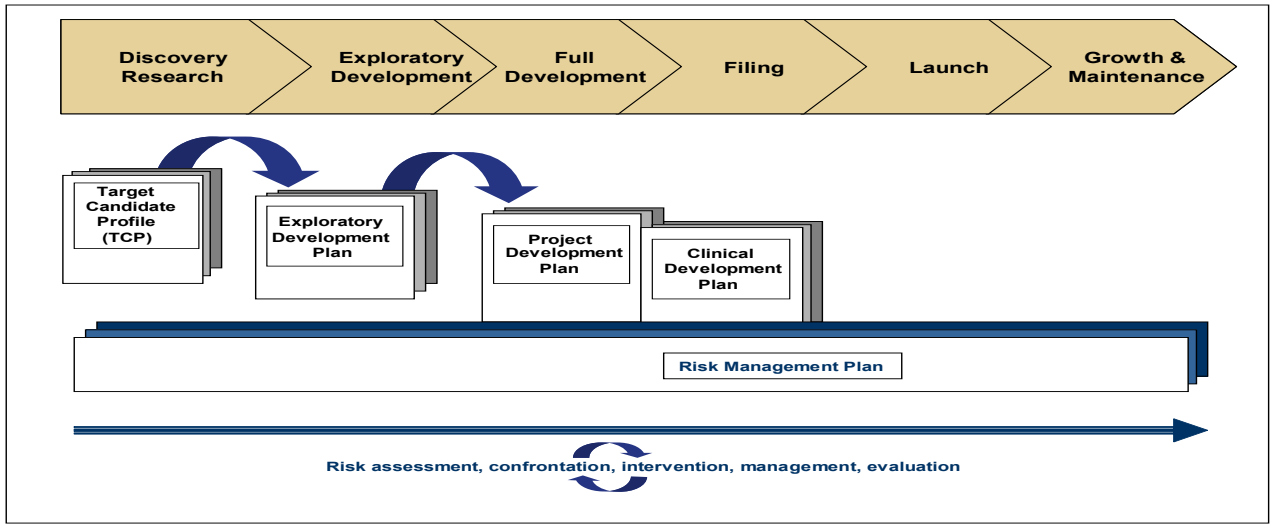
- Regulatory Reasons
  - Agencies (and society) are becoming increasingly risk-averse
  - Smaller benefits; make benefit: risk analysis challenging
  - “Err on caution” translates in restrictions, delays, withdrawals (or all the above) = lower revenues
- Opportunity is to translate challenge to advantage

# What to Expect

- Compliance must be a given
- Focus on life cycle management
  - Peri-launch and post-marketing periods are simply part of a continuum
- Sponsors cannot be expected to predict completely the safety profile…
  - But they will be expected to follow up on the identified ones, and…
  - Actively look for new ones

# PVP/RMP in Development

- Pharmacovigilance Plans (PVP) starting in exploratory development and being followed through development

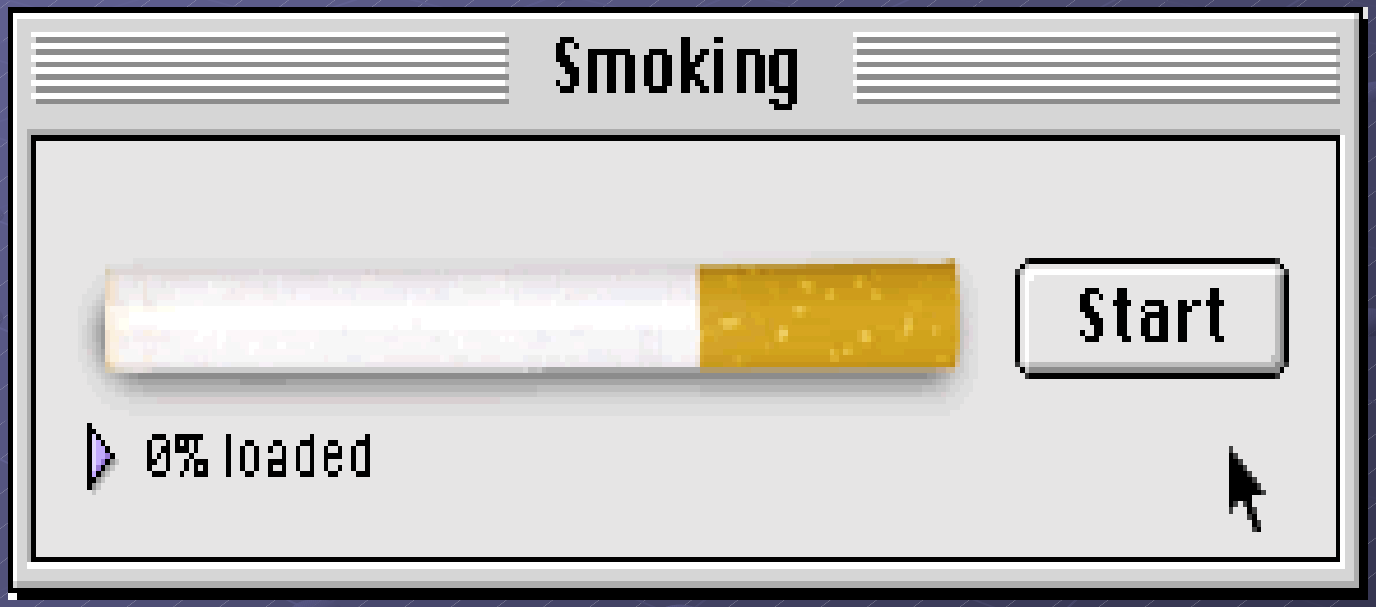


# Risk Communication

- Of all the components of the RMP this is the most complex, multidisciplinary and challenging
- Balance between adequate, and exaggerated
- Communication of risk falls on underlying perceptions of the receiver


Welcome to Marlboro Country.

# Risk Communication



# Issues

- Monumental task impossible to tackle pleasing everyone
- Categorization of drugs was removed from new version
- Risk minimization, not avoidance. Risk reduction better
- Endorses RM as part of life-cycle
- Endorsees and guides on RM in pre and post-marketing

# Issues. Cons

- Lack of precision regarding when to prepare PVP and RMAP as well as “routine PV”
- Confusion around whether RM will narrow exposure to drugs
- Older drug issue not tackled
- Avoiding need for PVP
- Contradiction with ICH E2E (endorsed by FDA)
- Label as risk communication tool and cornerstone

- Exclusion of industry from certain forums

# Issues

- Will companies take RM seriously without clear guidelines?
  - Precedents are not reassuring
- Traditionally, pharmacovigilance is considered an expense, not an investment

# Issues

- Distribution of burden among society members
- Including patients, and its “informed” consent

# Issues (cont)

- Implementation of RM concept cannot be harmonized
- Information overload
- Not a panacea. E.g. toxicity in elderly due to misadministration

# THANK YOU

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