Pharmaco-Epidemiological Studies

A French experience

CVZ, Diemen, December 1st, 2006

Hubert MECHIN, MD

CEO MAPI-NAXIS – Lyon, France

Vocabulary

- Pharmaco epidemiological studies
- Observational studies
- Post-authorization studies
- Post-approval studies
- Post-listing studies

Use of drug in real life

(as opposed to RCTs)

A new paradigm

- Drugs are more and more focused and difficult to prescribe (restrictive authorizations)
- Adverse Events are becoming rare and less present in RCTs
- Patients in RCTs are different from patients in real life
- Drugs represents at present 20% of Healthcare costs and the payer (Health Insurance) needs to be confident with the benefit / risk balance of new drugs

Medicinal Products Assessments in France

MAPI – NAXIS
La CRO late phase

Ag. Française de sécurité sanitaire des produits de santé

CHMP / Afssaps benefit/risk asssessment

Europ. Commission /Afssaps : Marketing Authorisation

Haute Autorité de santé

Transparency Committee (TC) : **medical benefit, added value, importance for public health, target population**

Ministre de la santé et de la SS

Healthcare Products Economic Committee : agreement / price -volumes

Public Price

Minister: inscription

Nat. Health Insurance Level of co-payment

Product Launch

Advertising Control

-Pharmacovigilance, Risk Management Plans
- Observational Studies

Periodic Reassessment

Access to Reimbursement in France

- « Positive lists » of products covered by the National Health Insurance System
  - One list for Hospital Products
  - One list for Community Pharmacies
- Who decides ?
  - The Ministries of Health and Social Security

    Based on the opinion of an independent appraisal committee

    HAS HAUTE AUTORITÉ DE SANTÉ « TRANSPARENCY COMMITTEE »
  - Price: regulated and negotiated between the company and the

    « ECONOMIC COMMITTEE FOR HEALTH PRODUCTS »

Criteria for Drug Appraisal

HAS performs medicinal products appraisal according to criteria defined in French regulations

- Cost-effectiveness assessment not part of the « legal » criteria
- SERVICE MEDICAL RENDU (SMR) = Drug Intrinsic Value
  - «Medical value»
    - severity of the disease
    - clinical effectiveness
  - «Importance for Public Health»:
    - Impact on Health Status of the global population,
      Impact on Healthcare organisation and/or Use of Healthcare resources...
- AMELIORATION DU SMR (ASMR) Drug Added Value
  - Comparison to other existing therapies
  - 4-level scale: from MAJOR improvement (ASMR I)
    to minor improvement (ASMR IV)
  - No improvement over existing therapies: (ASMR V)

Drug Listing: Decision

- Decision
  - Ministers in charge of Health and Social Security
- Based on SMR appraisal
  - SERVICE MEDICAL RENDU (SMR) = Drug Intrinsic Value
    « Medical value » + « Importance for Public Health »
    - Insufficient to justify reimbursement: no listing
    - Sufficient to justify reimbursement: listing possible
      Weak or Moderate: reimbursement rate = 35 %
      Important: reimbursement rate = 65 %
- Indication - specific
  - Possible restrictions of licensed indication
- Product listed if:
  - TC's opinion is positive and
  - Agreement is reached between company and Economic Committee for Health Products

Pricing

- Economic Committee for Health Products
  - Drug price negociated within 3 year master agreement set up between industry in general and the above Committee
- Price negociations depend on the score provided by TC
  - if no added value (ASMR V): Price must be lower than competing drugs
  - if added value (ASMR I to IV): Price can be higher than competing
- Price/volumes agreement:
  - Target population, as assessed by TC, is taken into account

Transparency Committee Activity

- Rapid, single technology assessments
  - Every new drug, assessment mandatory before reimbursement
  - 180 days = maximum for TC assessment + price negotiation (90 Days for TC + 90 Days for Economic Committee)
  - Every 5 year : renewal of inscription after re-assessment of the drug
- 600 to >800 opinions issued every year
- First appraisal:
  - Assumptions have to be made on how « experimental » data from clinical trials will translate in « real-life » setting:
    - from surrogate endpoints to clinical data
    - from selected population to « real life » population
  - To improve knowledge on the use and effects of drugs after their initial listing is necessary

Transparency Committee Opinions

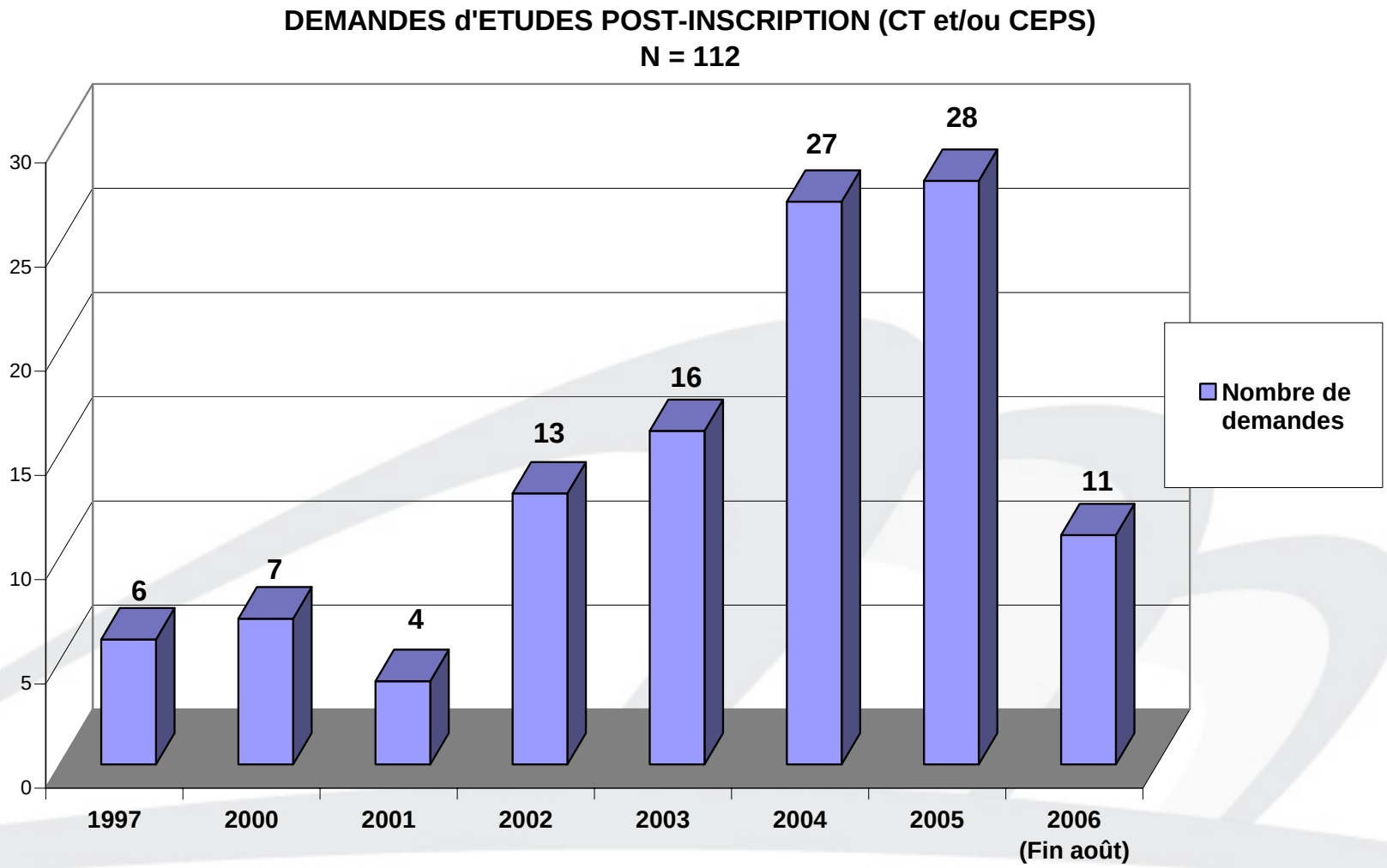
- Positive or negative opinion:
  - SERVICE MEDICAL RENDU (SMR) = Drug Intrinsic Value
    « Medical value » + « Importance for Public Health »
    - Insufficient to justify reimbursement: no listing
    - Sufficient to justify reimbursement: listing possible
- ASMR = Drug Added Value
- Target population
- Guidance for rational use of the product
- Need for additional data
  - Questions to be documented by «post-listing» studies
  - Protocols to be submitted to the HAS, Transparency Committee and its Working Group (Impact on Public Health)

TC Working Group on Public Health

- Methodologists, epidemiologists
- Chairperson:
  - Prof. Jacques Massol, Vice Chairperson of Transparency Committee
- Mission
  - Guidance on the assessment of the importance for Public Health of medicinal products
  - Assessment of the impact of new drugs on public health and healthcare organisation
  - «Post-listing» studies
    - Questions to be addressed
    - Review of protocols of observational studies submitted by companies:

      Are the protocols adequate to answer TC questions ?

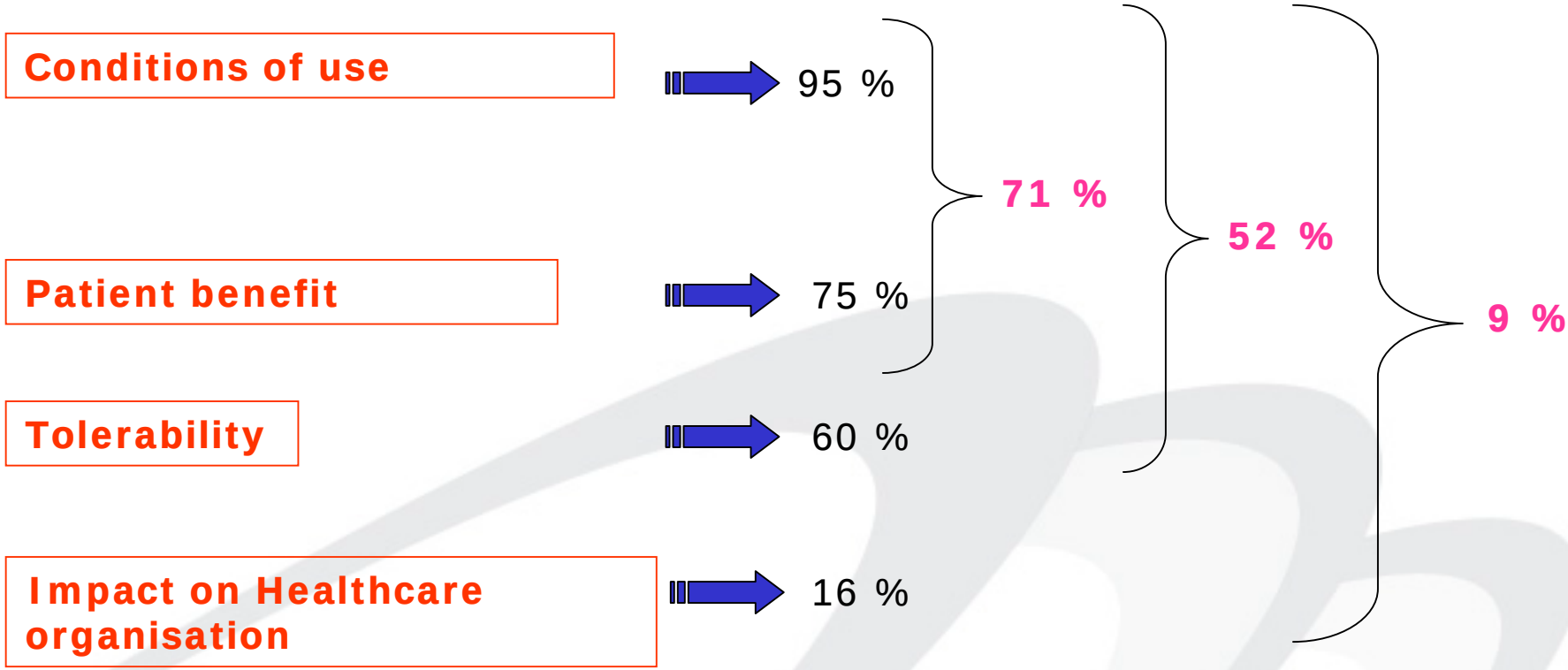
Number of studies required



Types of questions

- Conditions of use
  - Prescribers characteristics, dosage and duration of treatment, co-prescriptions, prescriptions according to guidance ?
  - Observance, reasons for treatment withdrawal, …
- Patient benefit
  - Effectiveness vs. efficacy : comparison of results in a real-life setting with what was expected when extrapolating data from clinical trials
  - Mortality, morbidity, response rate, QoL, other clinical criteria
- Safety – Tolerability
  - Adverse Effects in real life setting… long term AEs
- Impact on Healthcare Organisation
  - Changes in medical practice, use of health care resources…

Type of questions



Types of questions to be addressed by «post-listing» studies

Post-listing studies Inventory

From 1997 to the end of August 2006

112 requests for study

99 different specialities

41 laboratories concerned

What are the results ?

- First studies to be finished and published are arriving ... at the end of 2006 ...
- Pharmaceutical companies are still waiting for the first decisions (depend on results)
  - Price reduction ? (if no effectiveness / no respect of indication)
  - Reimbursement reduction ? (if no effectiveness / no respect of indication)
  - Risk Management Plan mandatory ? (if new AEs)
  - Training for physicians ? (if incorrect use)
  - ...

Issues (1)

- Access to data in real life
- Lack of existing data base
- In 80 % of the case = need for an ad hoc observational study

Lot of bias

Bias Management Plan

Issues (2)

- The main issue is:
  - Provide medical information about the patient

    (access to physicians)

    BUT

    Without the feeling that the physician is « observed » by health Authorities (he will choose the best patients)

  - Provide real life information about the patient

    (access to patients)

    BUT

    Without the feeling that condition of drug use (compliance) is modified by the study itself

Issues (3)

All the different actors are inventing new processes...

One way is to use pharmacists who deliver drugs, with access to physician via the patient

We estimate than 25 % of these studies can be conducted with pharmacists

MAPI – NAXIS

La CRO late phase

Post-listing studies

2 examples

CARDENSIEL® *(bisoprolol)*

- Beta blocker / Heart failure

- Indication = stable heart failure, mild to severe, with a reduction of systolic ventricular fonction (Ejection Fraction ≤ 35 % / echo), already treated with ACE inhibitors
- «A prescription observational study is required with : the original pathology, dosage and duration, associate drugs, to be sure that this drug is correctly used in the indication where it has obtained its ASMR»

Issues

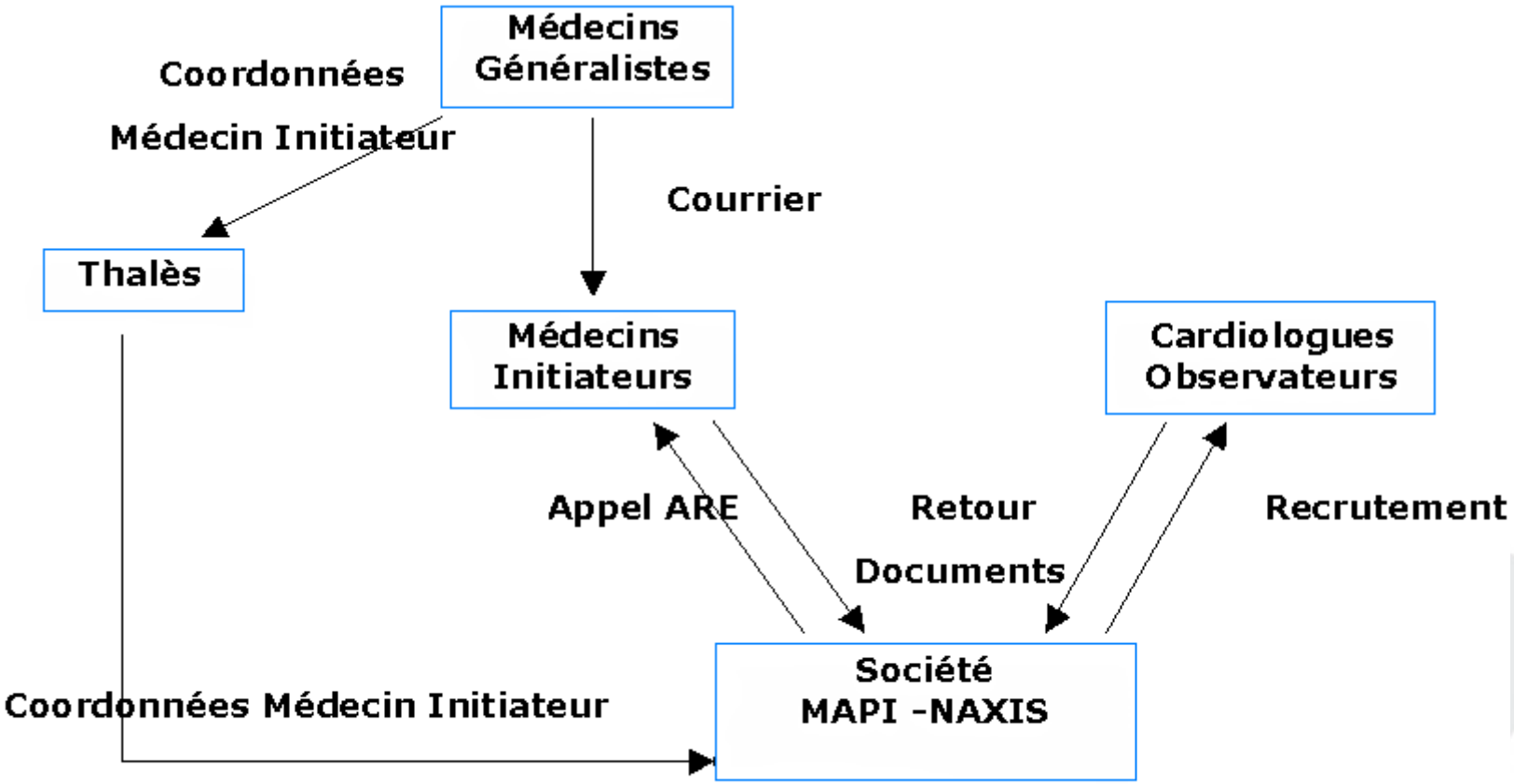
- Cardiologists must initiate but GP can prescribe secondary
- More than 60 % of prescriptions are with GP
- How can we get the information about the initial prescription without a selection bias ?
- How can we get the informations about the initial prescriber (a cardiologist) with GP's patients ?

Our solutions

- THALES® data base with 1.200 computerized GP's

- Search for all CARDENSIEL® patients and, if available, transmission of information about the cardiologist, (to be contacted directly by the monitor, just after a letter from the GP)

Logistic


Médecins Généralistes
Coordonnées Médecin Initiateur
Courrier
Thalès
Médecins Initiateurs
Cardiologues Observateurs
Appel ARE
Retour Documents
Recrutement
Coordonnées Médecin Initiateur
Société MAPI -NAXIS

OPTRUMA® / EVISTA® (raloxifène)

- Indication = treatment and prevention of osteoporosis
- Reimbursement = osteoporosis with at least 1 fracture
- 02/2002 = requirement for an observational study about condition of use regarding use on reimbursement or not
- PIERRE FABRE & LILLY have implementing a unic study (they are co-promotor) with a representative sample of pharmacists

Method

- Pharmacist include the patient when he deliver the drug (either OPTRUMA® or EVISTA®)

- Pharmacist gives to the patient a questionnaire to be completed by his physician (either a rhumatologist, a GP or a gynecologist)

Data collected

Nature de la donnée*	Source de la donnée		
	Patiente	Pharmacien	Médecin Prescripteur
Socio-démographie	X	X	
Modalités de prescription et de traitement	X	X	
Co-prescriptions	X	X	X
Profil du prescripteur	X	X	X
Diagnostic	X		X
Antécédents de fracture et médicaux	X		X
Informations concernant les contre-indications et les mises en garde			X
Examens complémentaires (e.g. ostéodensimétrie)			X
Cause(s) d'arrêt du traitement	X		X
Observance et tolérance	X		X

* Pour une même catégorie de données, les informations fournies peuvent être complémentaires (ex : le pharmacien précise la zone géographique de la pharmacie, la patiente indique sa catégorie socio-professionnelle) ou similaires (afin de valider ou compléter les informations recueillies).