# How is model building reported for population PK-PD ?
# A 2002 to 2004 literature survey

*C. Dartois [1], K. Brendel [2], E. Comets [2],*
*C. Laveille [3], C. Laffont [4], B. Tranchand [1,5],*
*F. Mentré [2], A. Lemenuel-Diot [4], and P. Girard [1,6].*

*(1) EA3738, Lyon; (2) INSERM, Paris; (3) Exprimo, Lumnen; (4) IRIS Servier, Courbevoie; (5) CLB, Lyon; (6) INSERM, Lyon.* (France)

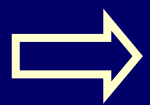
*PAGE 2006*

# Introduction

Since the 2 seminal papers [1,2], publications in this field ⇗

Few measurements, explain variability, therapeutic drug monitoring, clinical trial simulations

Statistical complexity (many models, assumptions, and estimation methods)



Should be performed carefully and precisely described

(1) Sheiner L.,1972 (2) Sheiner L., 1977

# Objectives

- Primary objective
  - Survey the different models built in PK and/or PD analyses
- Secondary objective
  - Assess whether model building were adequately described

# Method

- Article selection
- Data abstraction form building
- Data abstraction form qualification
- Data collection
- Statistical analysis

# Method

- Article selection

# Article selection in Pubmed

- Keywords

((*population* AND *model**) OR (*non* AND *linear* AND *mixed* AND *effect**) OR *bayesian* OR *hierarchical* OR *NONMEM* OR *nlme* OR *NLMIXED* OR *P-PHARM* OR *WinNonMix* OR **bugs* OR *NPLM* OR *NPEM* OR *Kinetica* OR *ADAPT* OR *ITRLS* OR *MP2*) AND (*PK-PD* OR *PKPD* OR *PBPK* OR *pharmacokinetic** OR *pharmacodynamic**)

- Limits

Title/Abstract, English, Humans, original data

Date from 2002/01/01 to 2004/12/31

# Method

- Data abstraction form building
- Data abstraction form qualification
- Data collection

# Method

- Data abstraction form building / qualification
  - 9 modelers with different backgrounds, skill levels, origins

Relevance of the questions

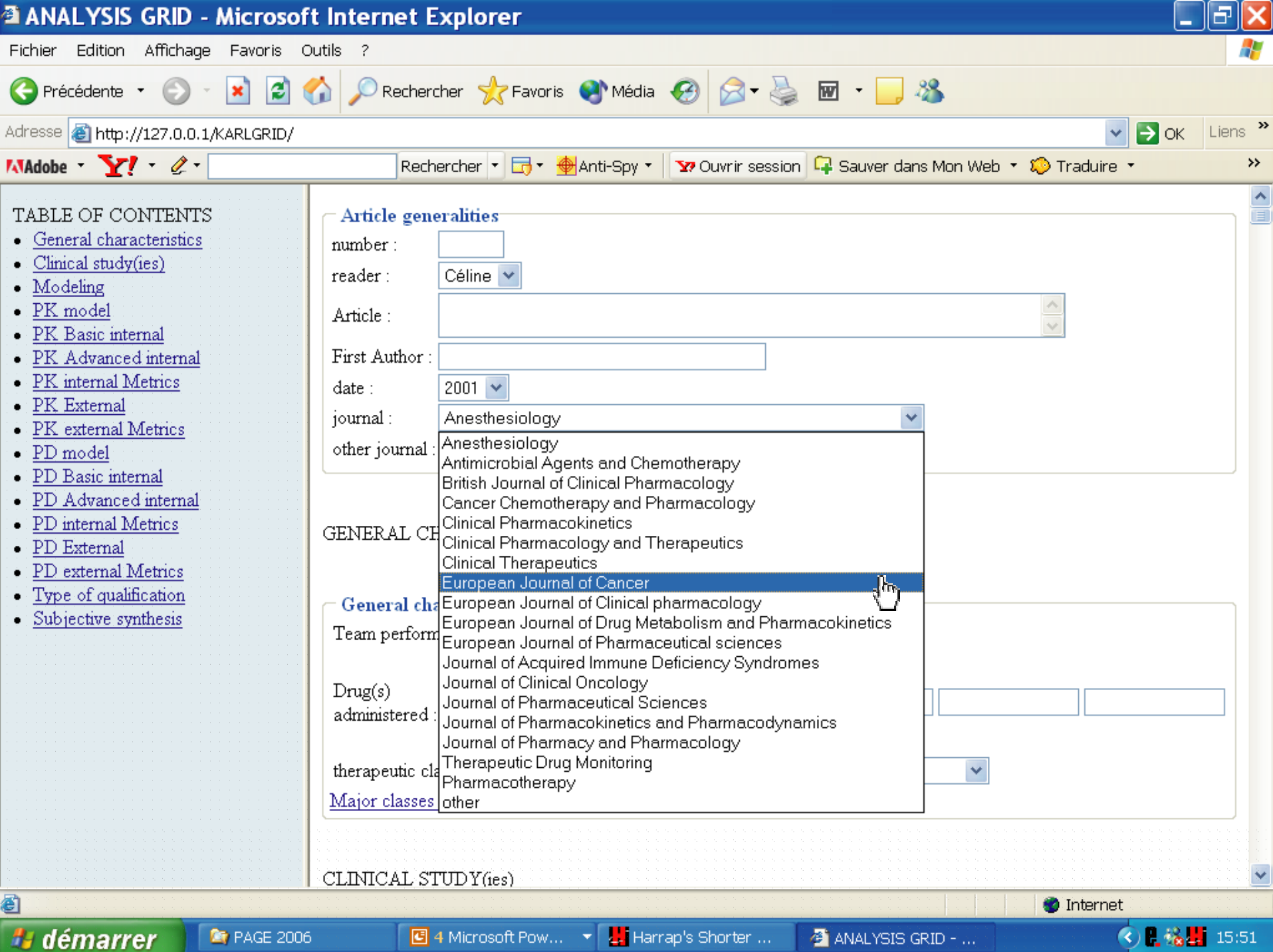
Questions simple, unambiguous, defined check lists

  - Tested on numerous articles

# Method

- Data abstraction form building

I. ARTICLE GENERALITIES (date, title, authors, journal)
II. GENERAL CHARACTERISTICS OF THE ANALYSIS (Team, drug(s) administered, therapeutic class)
III. CLINICAL STUDY(ies) (Phase(s) of clinical development, Main objective(s) of the clinical study(ies), Target population of the clinical study(ies), Administration route(s), Number of Dose, Number of center(s) involved, Duration of the clinical study(ies), Duration of the treatment(s), Experimental design.
IV. MODELING (Purpose(s) of modeling, Software, Data, Structural model, Inter Individual Variability model, Inter Occasion Variability model, Error model, Basic model selection criteria, Covariate model)
V. QUALIFICATION (Basic Internal, Advanced Internal ,External)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PK Advanced internal
PK internal Metrics
PK External
PK external Metrics
PD model
PD Basic internal
PD Advanced internal
PD internal Metrics
PD External
PD external Metrics
Type of qualification
Subjective synthesis
Article generalities
number :
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Article :
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date :
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European Journal of Clinical pharmacology
European Journal of Drug Metabolism and Pharmacokinetics
European Journal of Pharmaceutical sciences
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- Modeling
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- PK Basic internal
- PK Advanced internal
- PK internal Metrics
- PK External
- PK external Metrics
- PD model
- PD Basic internal
- PD Advanced internal
- PD internal Metrics
- PD External
- PD external Metrics
- Type of qualification
- Subjective synthesis

for the PK: none for the PD: none

☐ qualification of a PKPD model in one step

SUBJECTIVE SYNTHESIS

**SUBJECTIVE SYNTHESIS I**

| | |
|---|---|
| Is the purpose of the model well defined?: | good |
| Is the model building well described?: | poor |
| Are the different choices in the building process justified?: | excellent |
| Does the model answer to its purpose?: | poor |

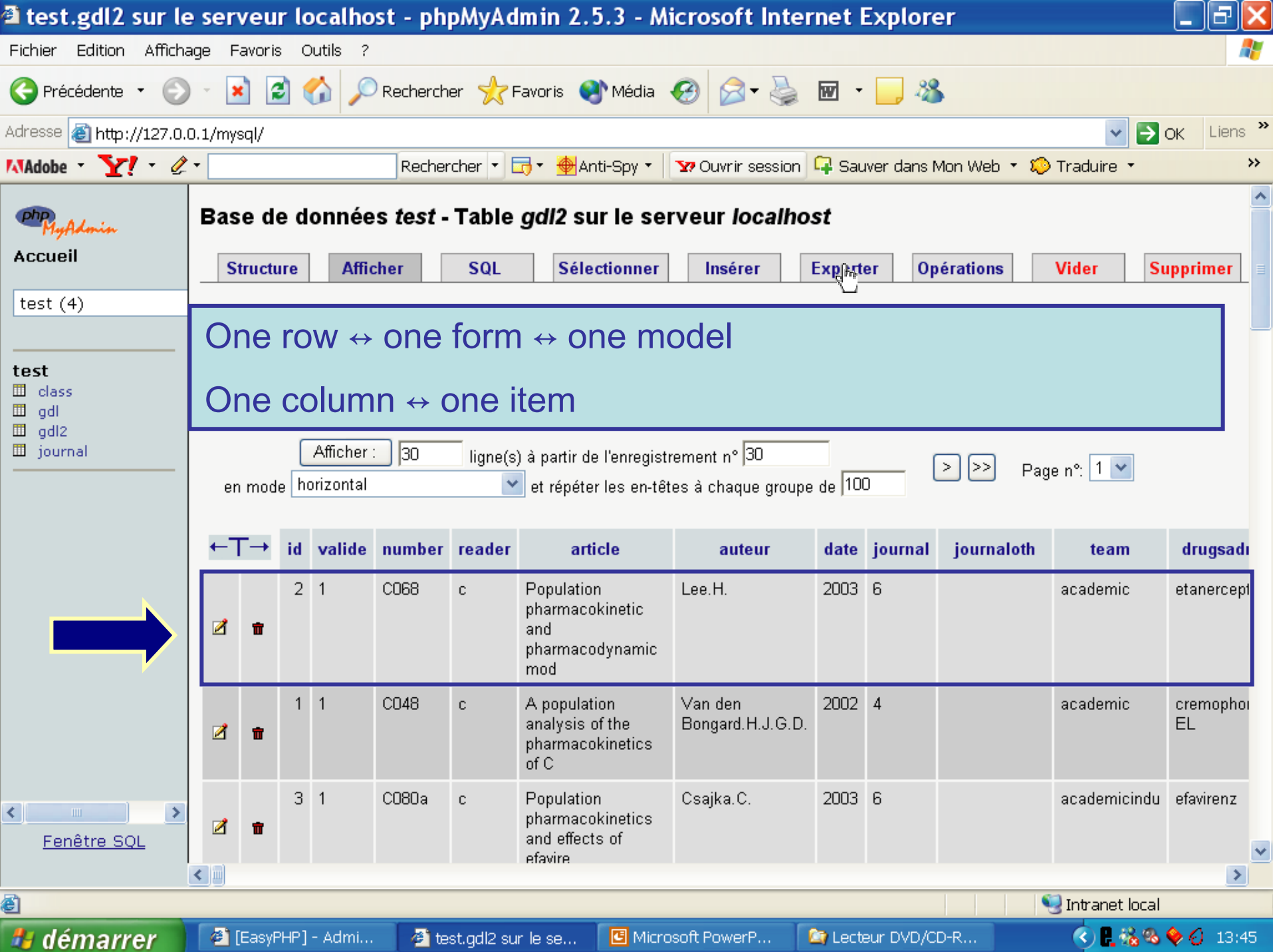
**SUBJECTIVE SYNTHESIS II**

| | |
|---|---|
| Was there an attempt to qualify the model?: | no |
| Was the type of qualification justified?: | no |
| Was the choice of the metrics appropriate?: | no |
| Was the model qualified?: | no |

Envoyer

Pour sauvegarder cet enregistrement et en créer un nouveau avec un nouvel ID cliquer sur ENVOYER puis actualiser

envoyez moi vos questions sur la grille


test.gdl2 sur le serveur localhost - phpMyAdmin 2.5.3 - Microsoft Internet Explorer
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test
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gdl
gdl2
journal
Fenêtre SQL
Base de données test - Table gdl2 sur le serveur localhost
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One column ↔ one item
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en mode horizontal et répéter les en-têtes à chaque groupe de 100
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# Method

- Statistical analysis

# Method

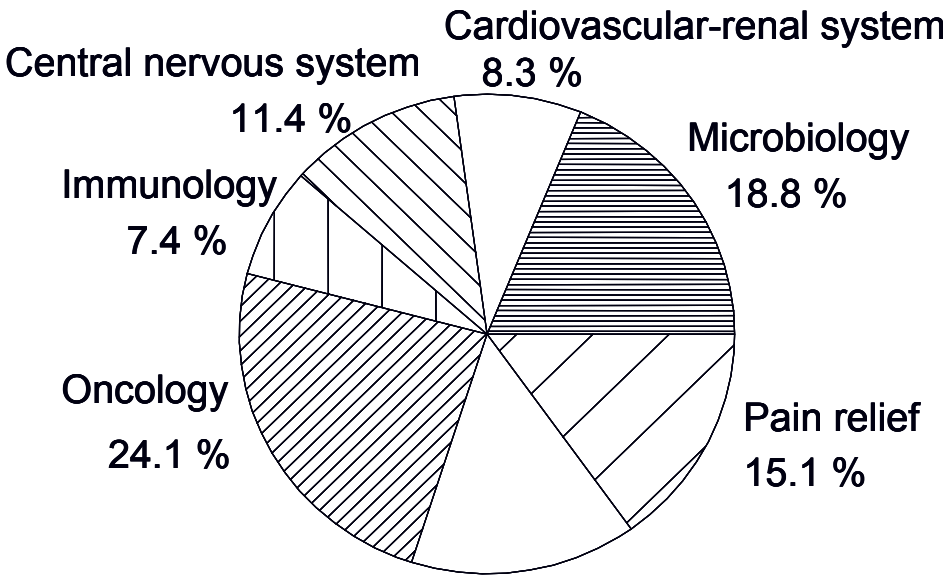
- Statistical analysis (in SAS and S-plus)
  - descriptive statistics
  - cross analyses
  - reproducibility between readers

# Results

| 2002 | 2003 | 2004 |
|---|---|---|
| 108 | 100 | 116 |

- 324 articles finally selected:

360 PK and 118 PD models (91 PKPD models)



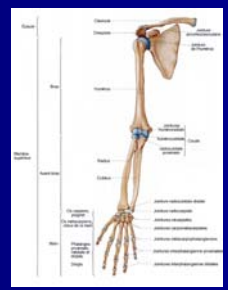
# Results

- Clinical study

In majority, we found data from a Phase I or a post marketing authorization ….

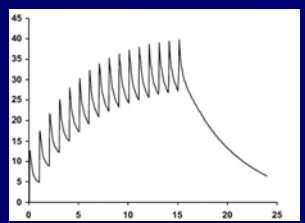
single clinical study

with single arm



performed on patients, on adults

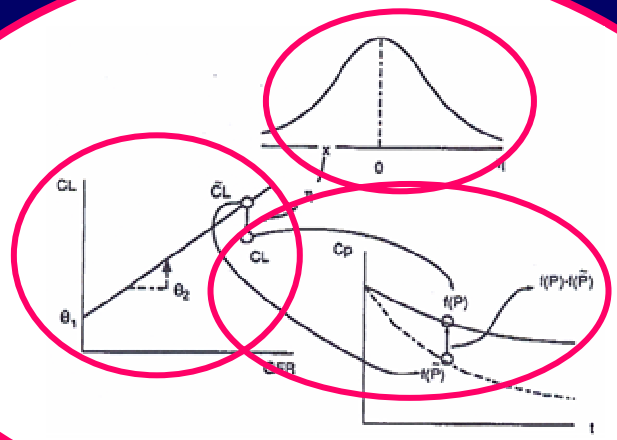
With multiple doses



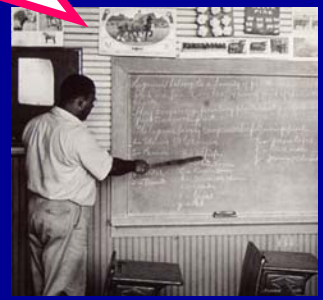

IV Infusion

or oral route

# Results

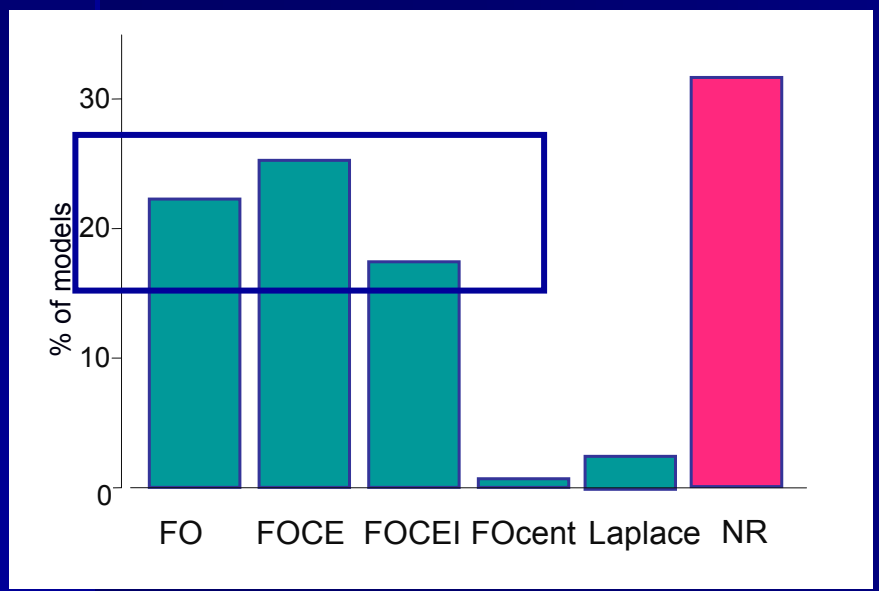


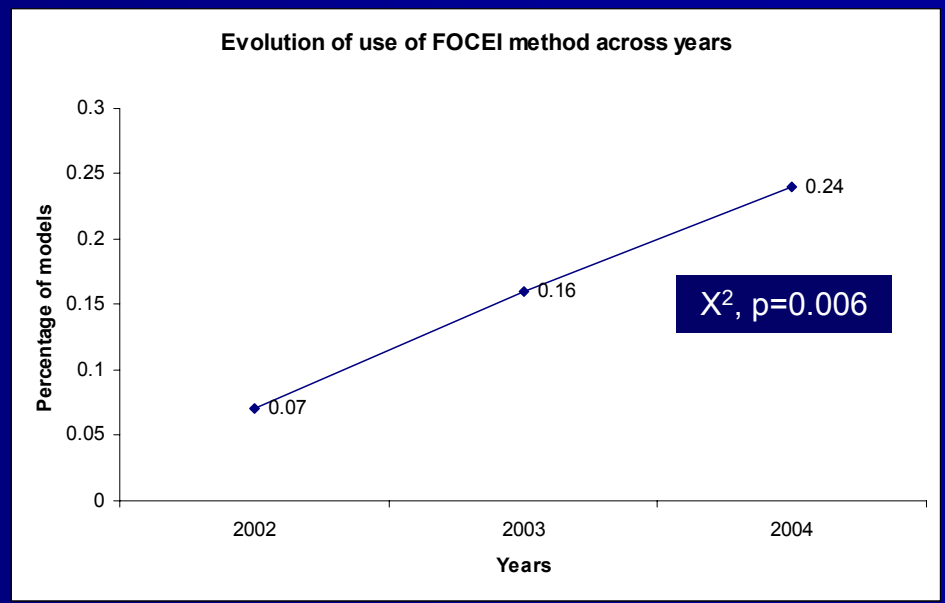

- Modeling
  - 81% of descriptive purpose
    - Estimate parameters 99%
    - Estimate variability 21%
    - Test covariates 58%
  - One compound in 89%
  - NONMEM in 69%



# Results

- NONMEM algorithms, 32% Not Reported (NR)!

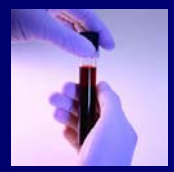


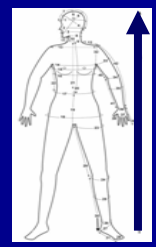
# Results

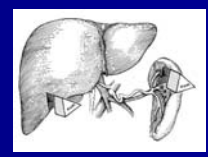
- PK models

Subjects per model: median=50



Samples per subject >3 in 75% of the subjects

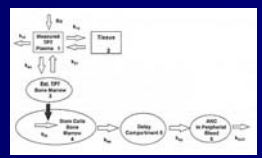




Covariates tested in 70% of the models
Covariates kept: median = 2

- PD models

Subjects per model: median=42

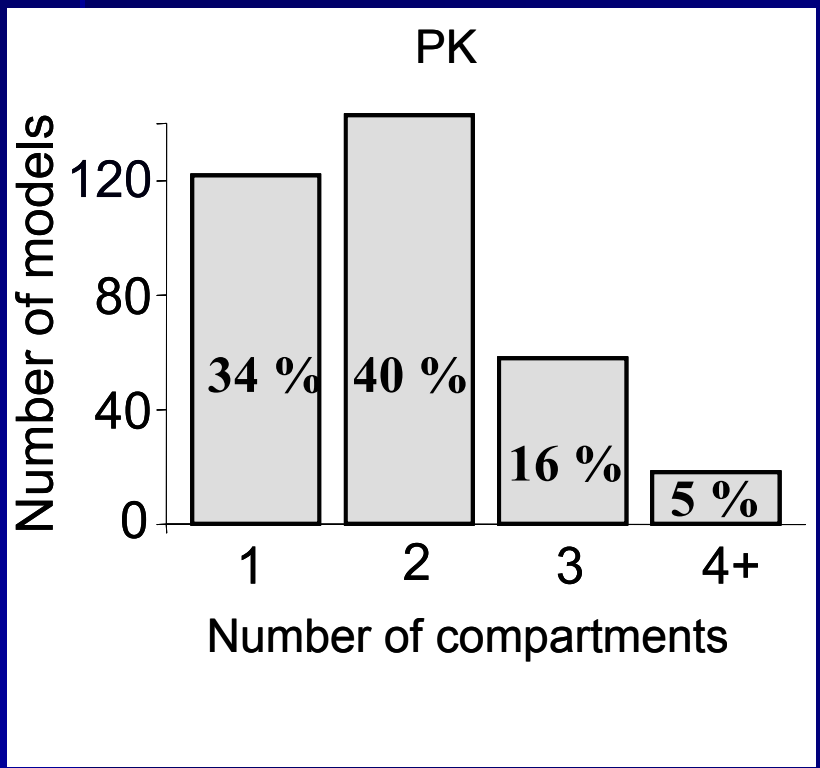


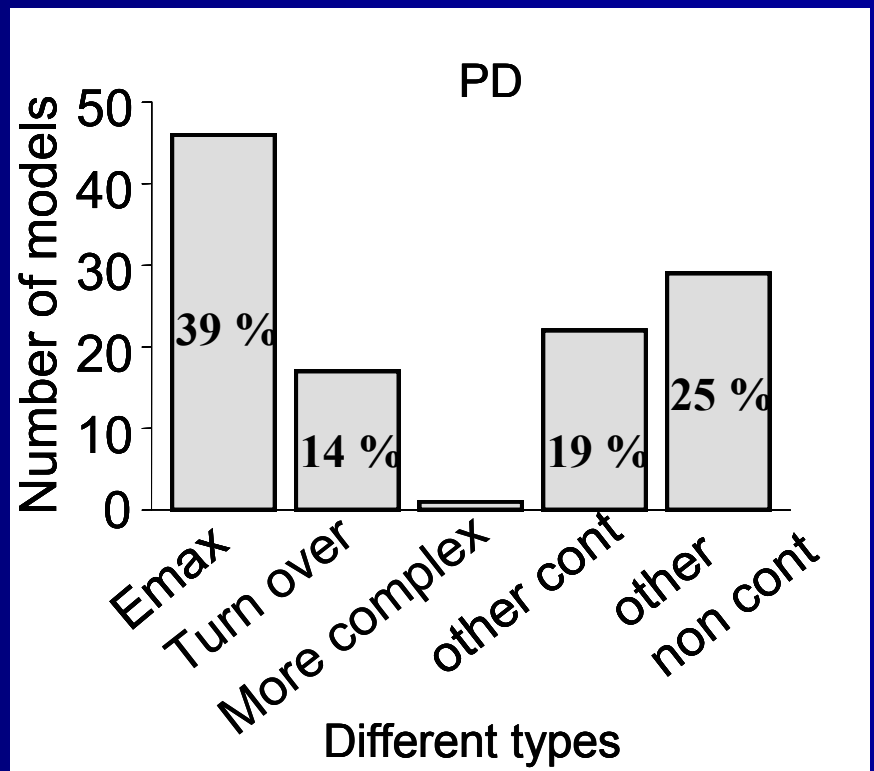
77% of simultaneous PKPD modelling

Covariates tested in 36% of the models no covariates kept for 54% of models

# Results

- Type of PK and PD structural models



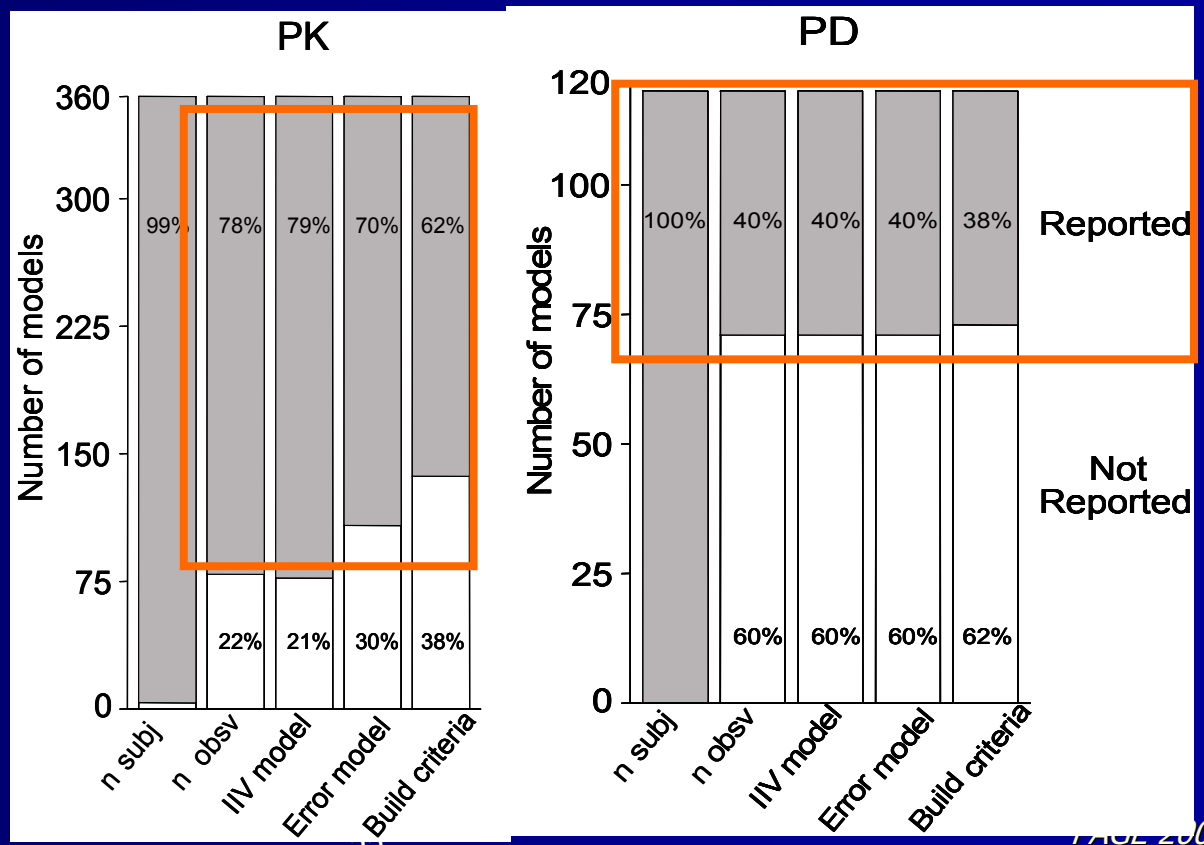



# Results

- PK models
  - IIV model: exp 53%, multp 11%
  - Error model: add 17%, comb 21%,multp 24%
- PD models
  - IIV model: exp 25%
  - Error model: add 18%

# Results

- Information reported for PK and PD models



# Conclusion (1/3)

- Less PD models than PK → difficulty in modelling and measuring drug effects
- Majority of descriptive models, simple, estimated by NONMEM
- Covariate testing in only 36% of the PD models → PK often explains PD variability

# Conclusion (2/3)

- Lack of standardized report
- Lot of missing information

Need of “standard” in publications

Define a list of items we definitively would like to see

# Conclusion (3/3)

- Items we would like to see
  - Subjects
    - Number
    - Characteristic ( healthy/ patient)
  - Treatment
    - Route of administration
    - Dosage (multiple/single)
  - Number of observations
  - Type of the structural, IIV and error model
  - Estimation method

% of models reporting this information in 2002-04 :

39% of the PK models

8.5% of the PD models


I am sure this information is available somewhere...