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Results of the EUFEMED Survey as compared with the Club Phase I Survey

EUFEMED First Forum
KU Leuven

presented by H. Sourgens and Y. Donazzolo

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Context of the French survey

- The BIA 10-2474 case occurred in France in January 2016
- March 2016 : new French regulation ; a study in healthy volunteer should be put on-hold in case of the occurrence of any serious adverse effect

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Context of the French survey

- November 2016 : start of public consultation of the Revised EMA Guideline for FIH and early clinical trials
  - Pre-clinical requirements
  - Stopping rules for HV trials including a serious adverse reaction in one subject and severe non-serious adverse reactions in 2 subjects in the same cohort
  - Definition of starting dose, dose escalation steps, top dose
  - Notion of maximum clinical exposure
  - Sentinel approach
  - Transition from SAD to MAD
  - PK/PD results…

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Context of the French survey

- March 2017 : new revised version
- July 2017 : adoption by CHMP
- February 2018 : date of coming into effect

- CPI organized in November 2017 a workshop “how to implement the recently released EMA guideline on FIH trials”
- CPI board decided to start a survey before this workshop
- EUFEMED board decided to extend this survey to all members

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Results of the French survey

- Population:
  - N = 39 (European Survey N = 100)
  - Big-pharma and mid-pharma, small biotechs, CROs, academics, consultants
  - Clinical pharmacologists, clinicians, pre-clinicians, PK/PD specialists, statisticians, …

- Fall 2017 (European Survey Spring 2018)

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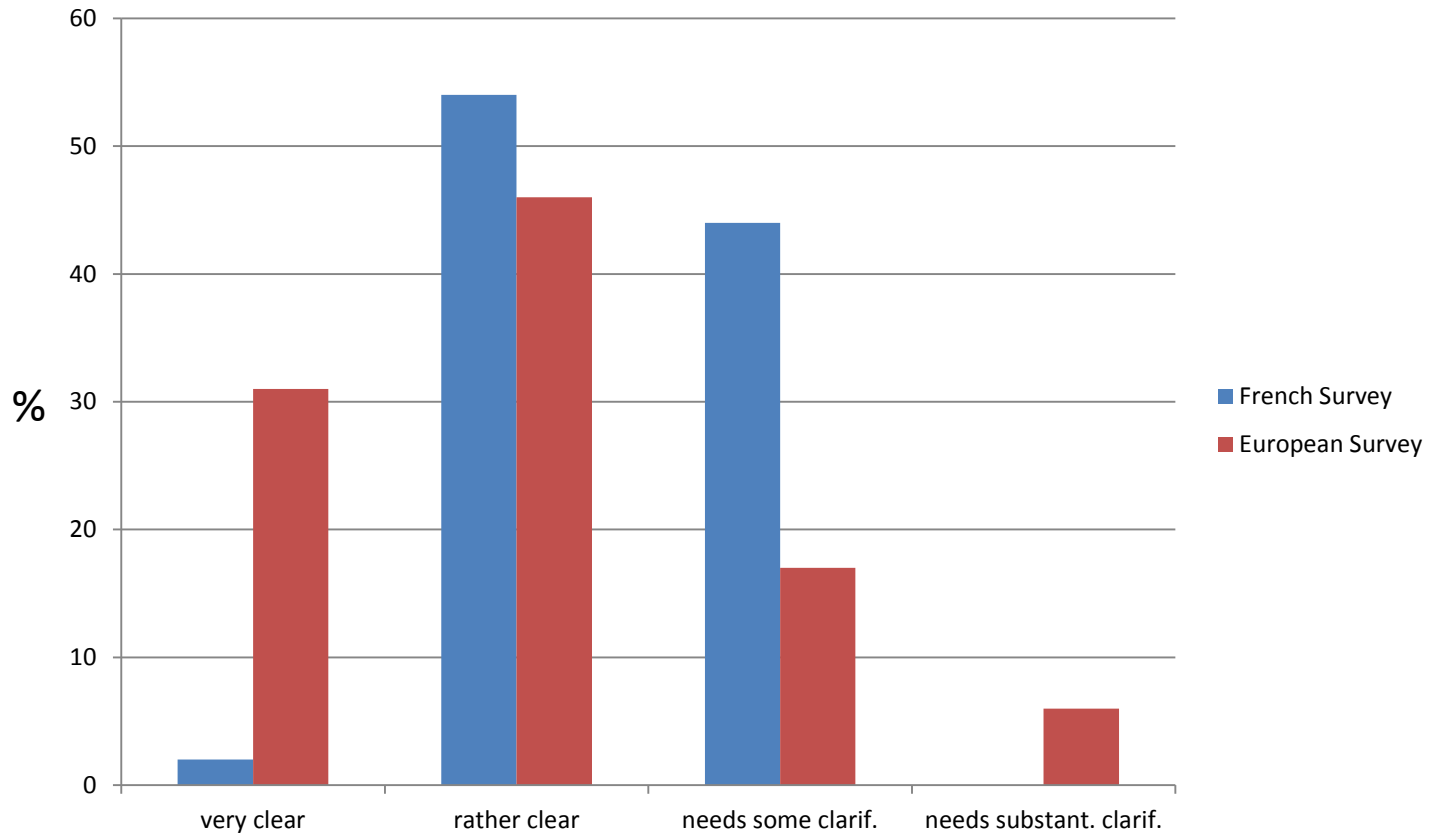
Overall, how clear is your understanding of the requirements of the new EMA guideline?



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Wording differences

- French Survey : Do you think that the application of the recently revised EMA FIM directive will be a point of concern for you regarding xxx

  Answers :
  - *Not at all*
  - *A few concerns*
  - *Lots of concerns*
  - *Major concerns*

- European Survey : What effect will the implementation of the definition of xxx have on your current practices?

  Answers :
  - *No changes*
  - *Minor changes*
  - *Some changes*
  - *Major changes*

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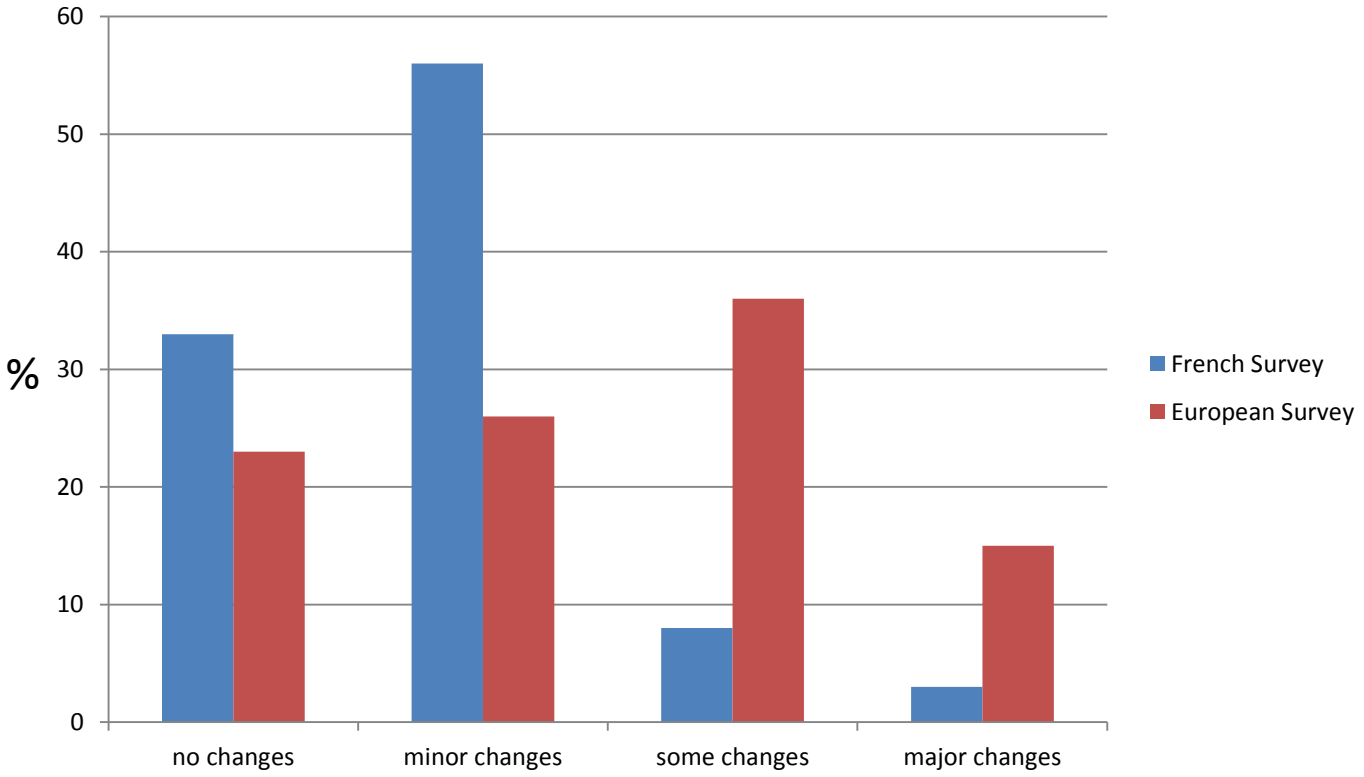
Definition of the starting dose



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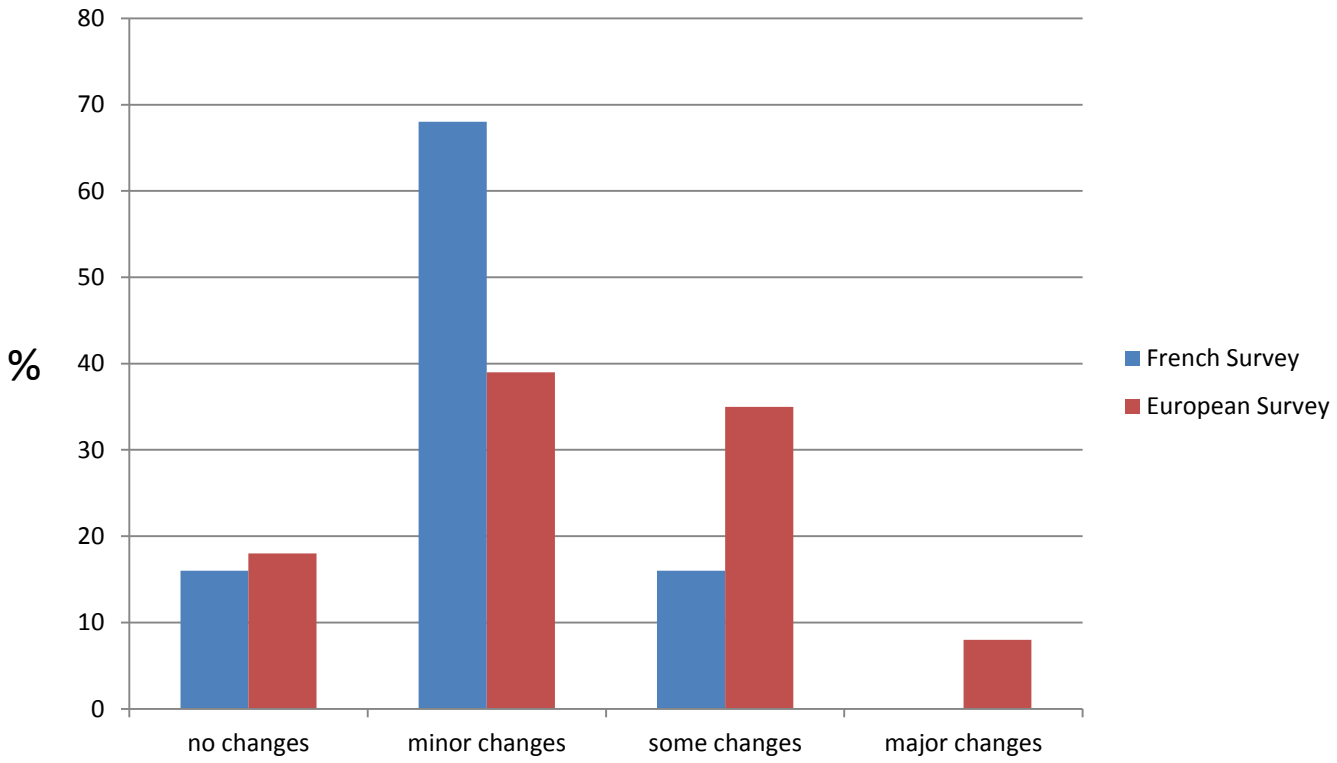
Definition of dose escalation steps



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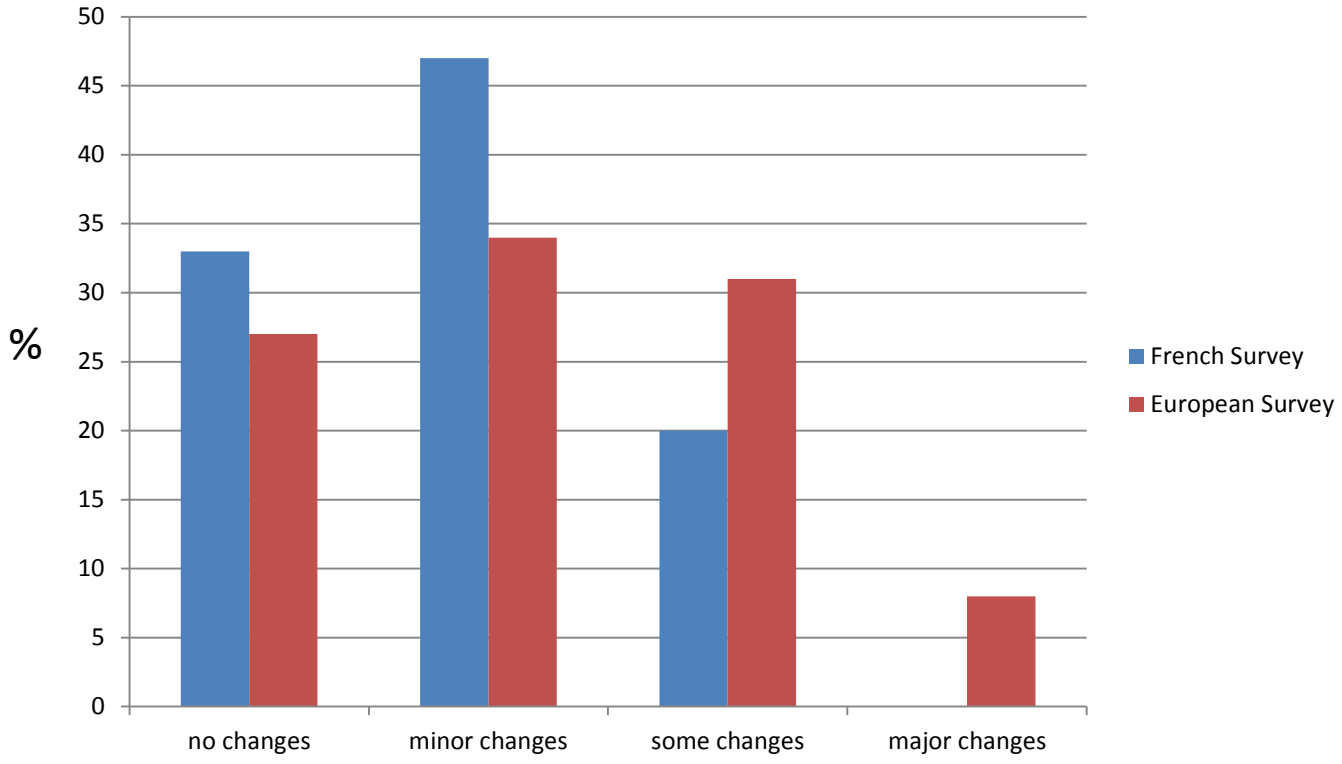
Transition between SAD and MAD



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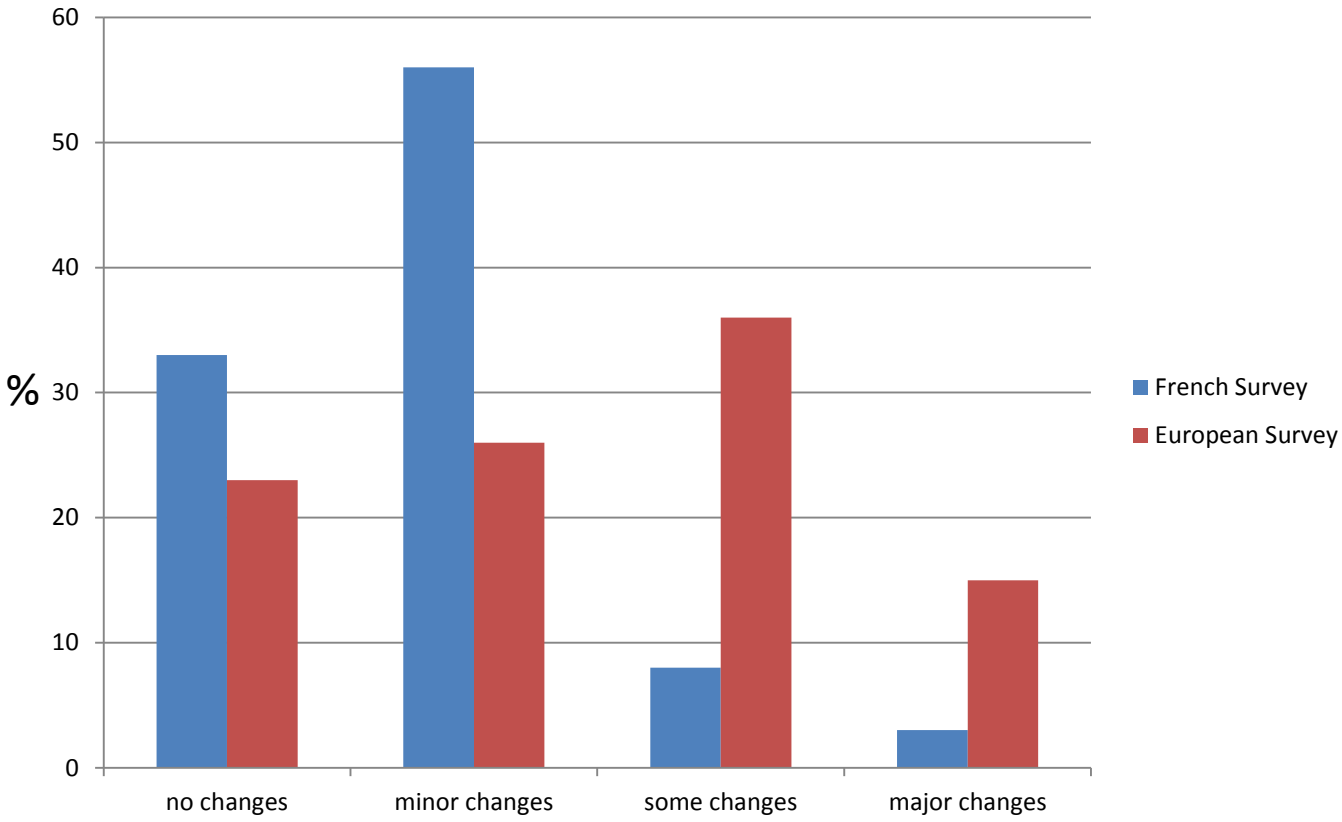
Sentinel approach



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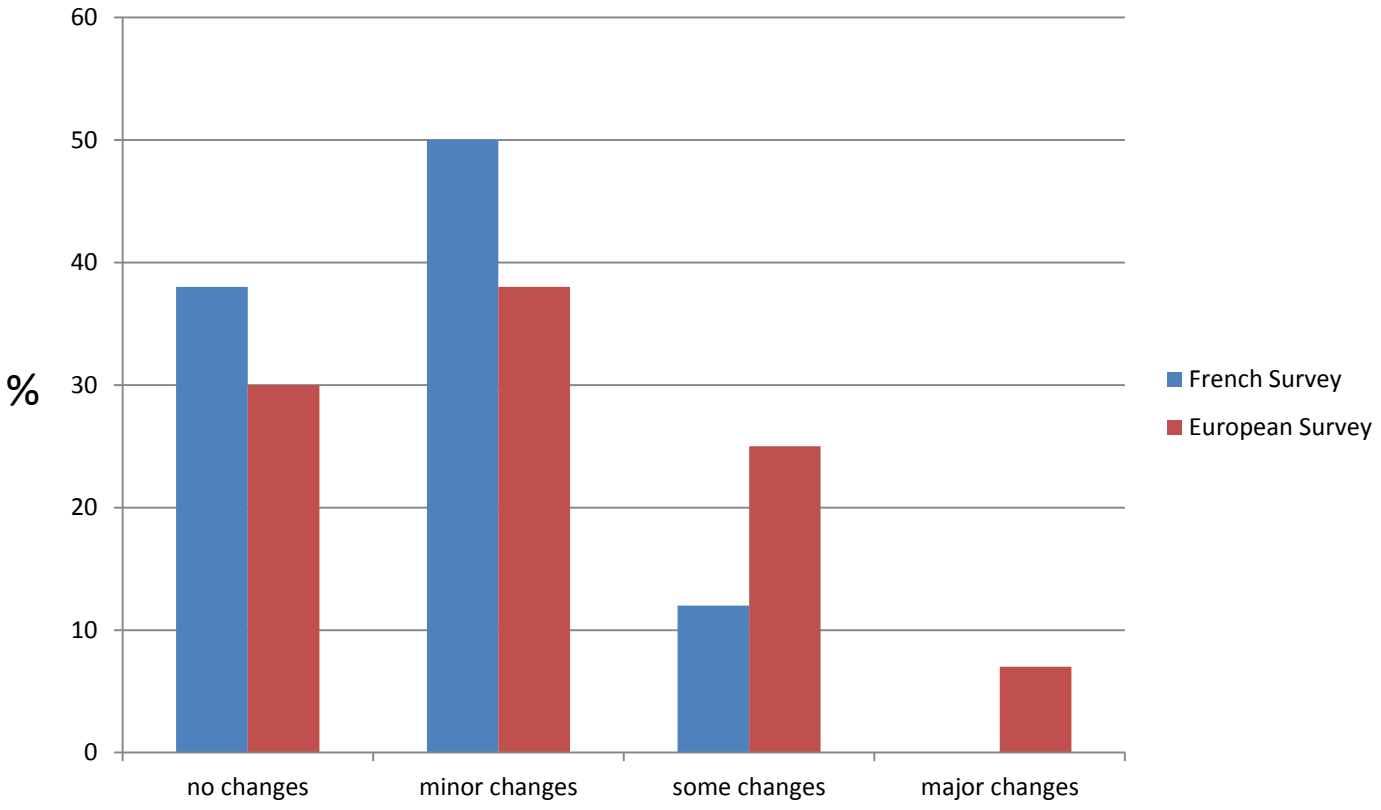
Definition of the stopping rules



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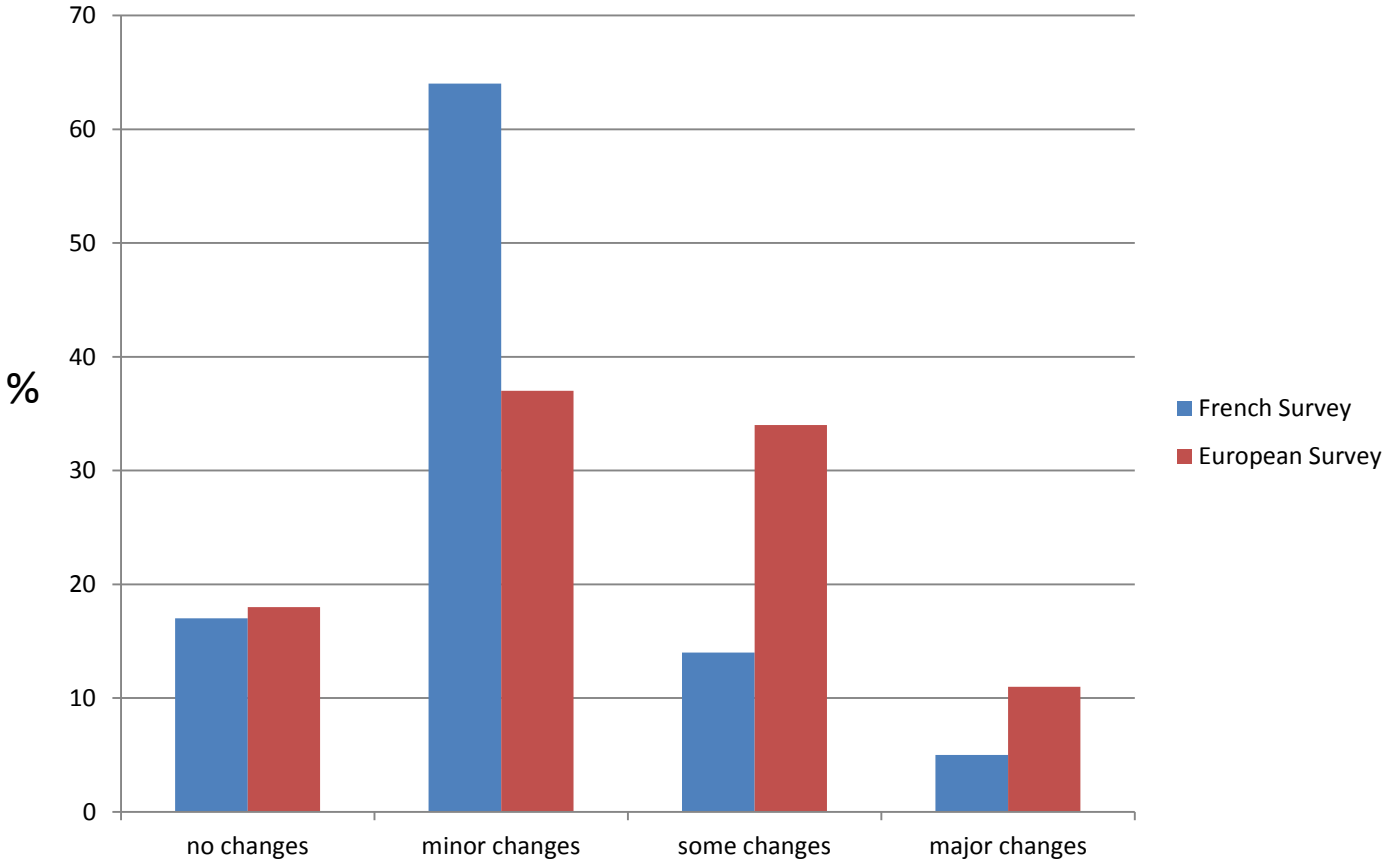
Availability of PK/PD data



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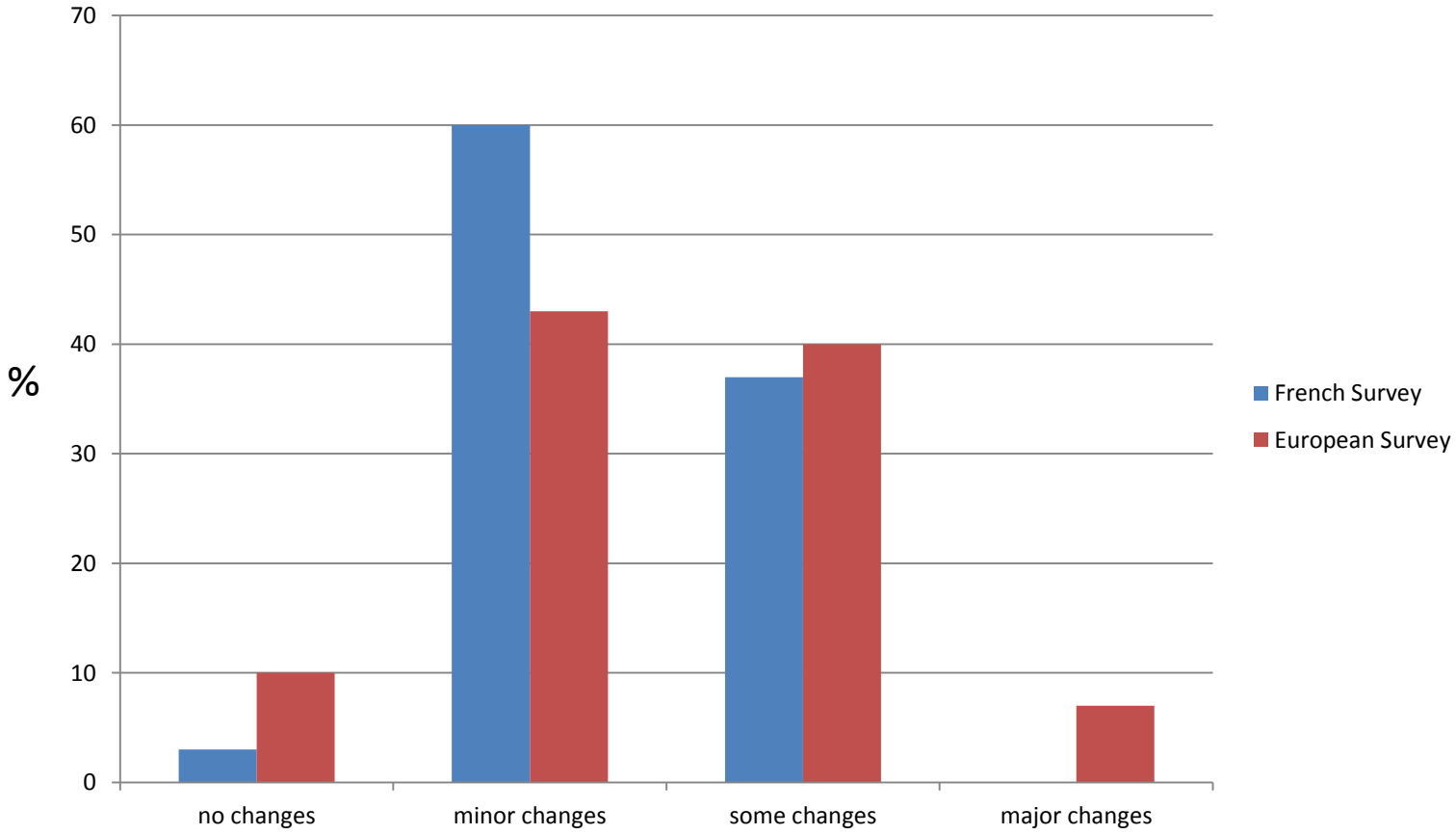
Level of changes in current practices



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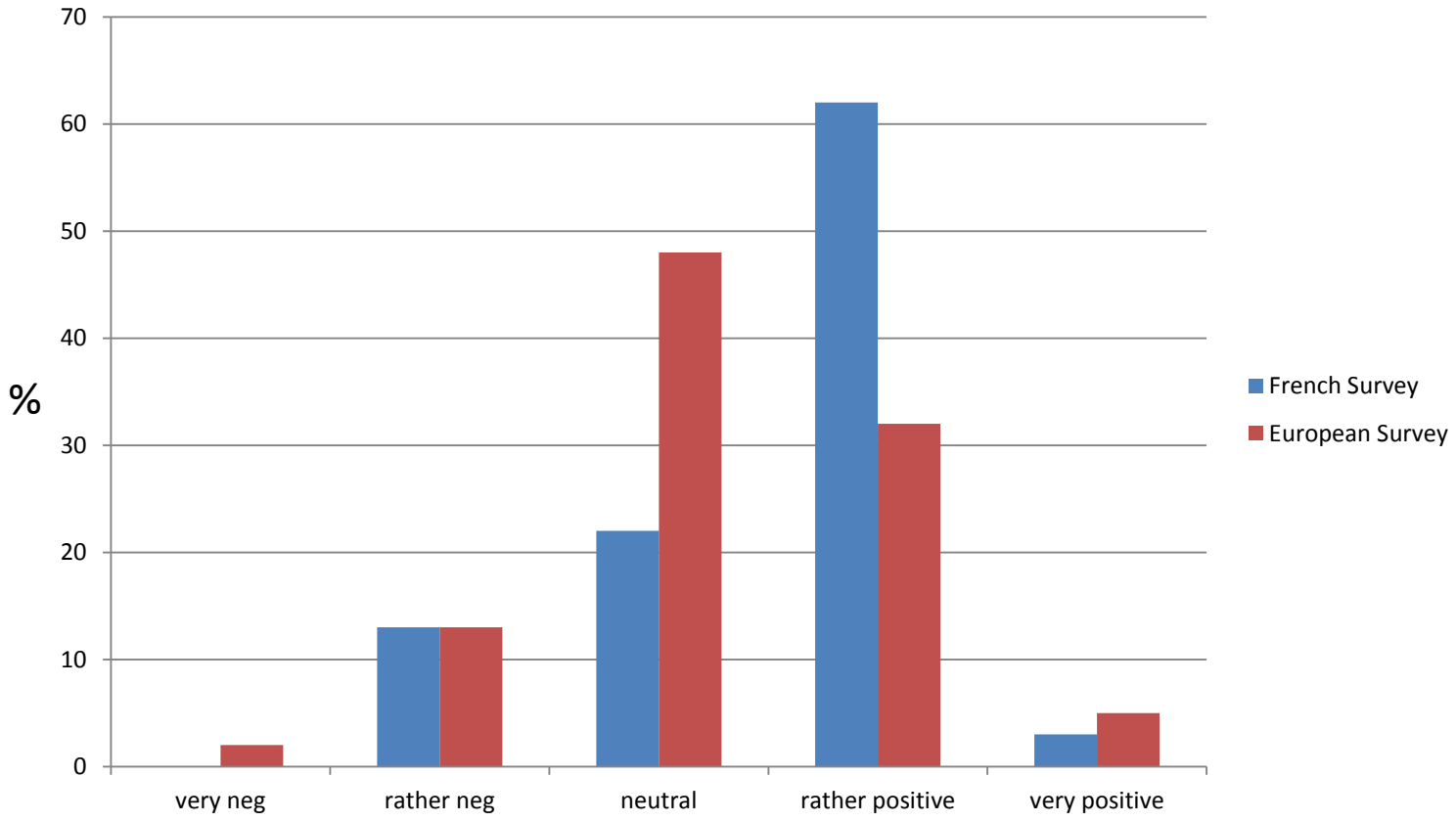
Impact of the revised guideline for EU



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Major concerns :

- Animal species to be relevant for pharmacology AND toxicity AND metabolism
- To clarify investigations needed regarding metabolites in toxicology and safety pharmacology studies
- Top dose : evaluation of a supra-therapeutic dose ?
- More difficult to increase doses beyond animal NOAEL ?
- Define meaningful target PD changes in healthy subjects
- Limitation of dose to pharmacologically active dose in healthy subjects
- To clarify on which data are based the top dose; only on pharmacological or PK data?
- Number of amendments ?
- Difference of interpretation between countries ?