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

presented by H. Sourgens and Y. Donazzolo

Content

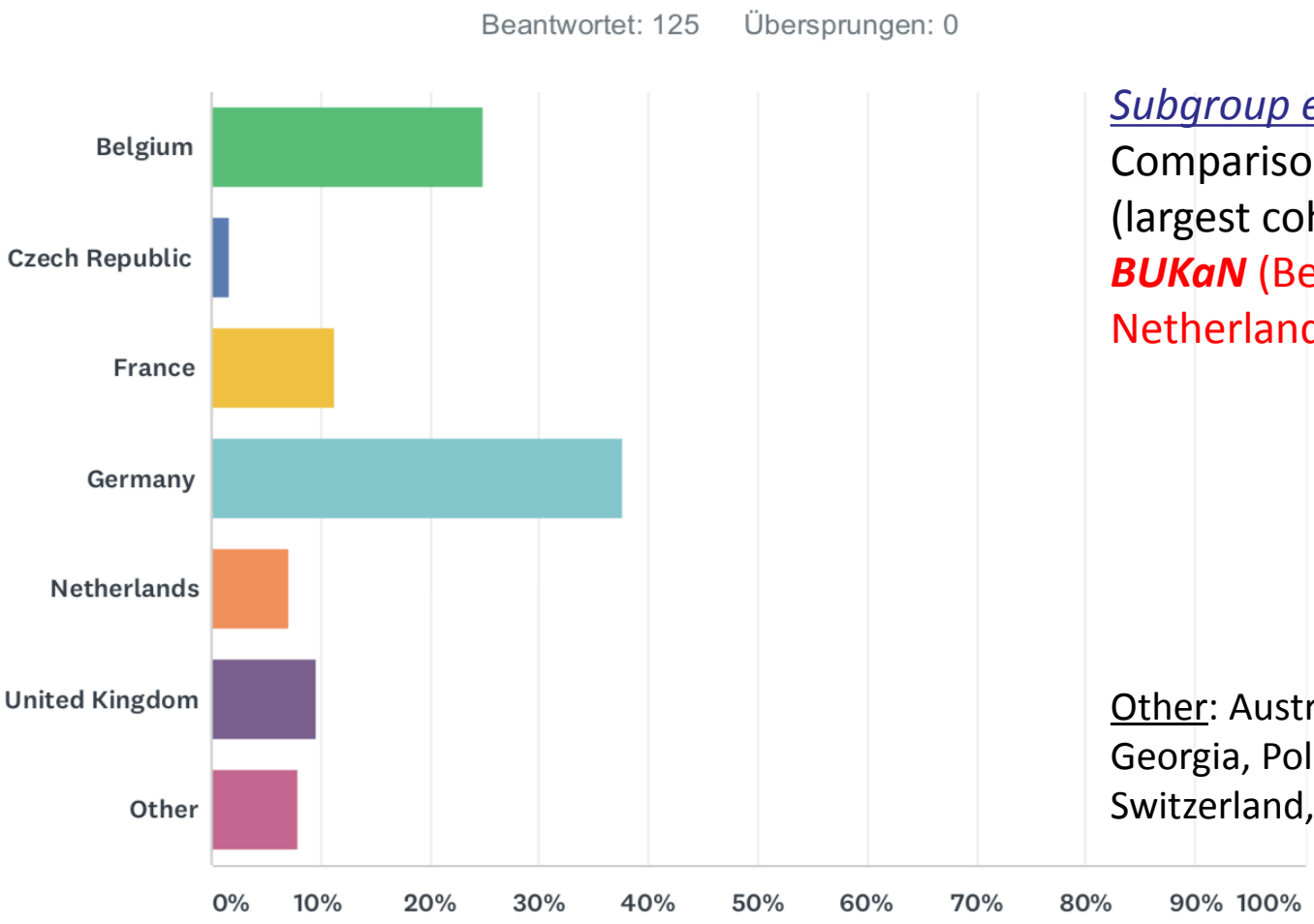
- Baseline characteristics
- Level of experience
- Specific questions to the implementation of the revised EMA FIH guidance
- Impact on European Union / Innovation
- Interpretation – Conclusions

Basis of the Survey

- Recruitment of respondents via email-newsletter by
  - the EUFEMED office
  - EUFEMED member societies /organisations
- Target group: European colleagues involved in FIH trials

- 125 respondents (≈1000 contacts)
- No representative sample - 'high motivation' spotlight

Location of Respondents

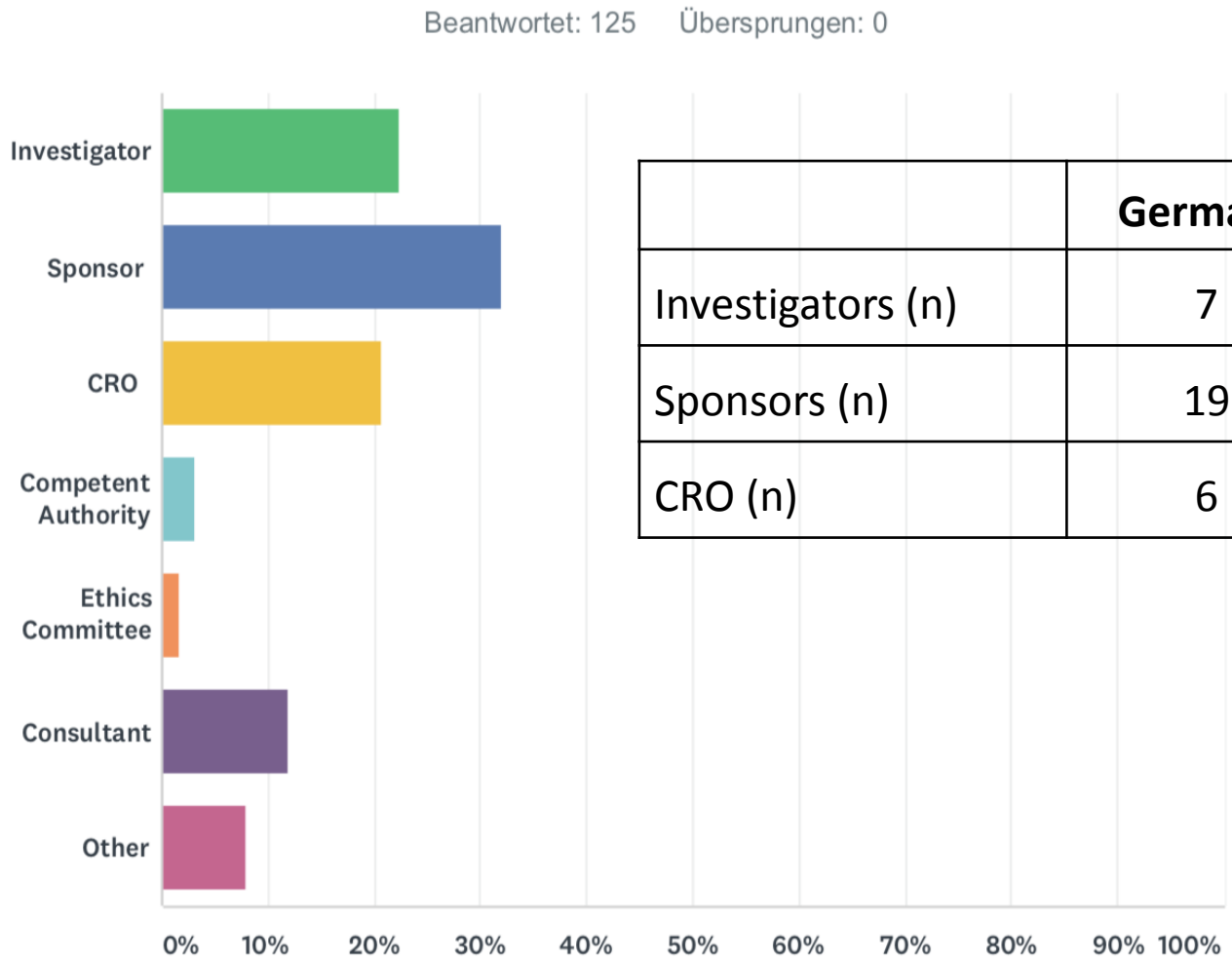


Subgroup evaluation:

Comparison between Germany (largest cohort: 37.5%) versus ***BUKaN*** (Belgium, UK, and Netherlands: 42.4%)

Other: Austria, Bulgaria, Denmark, Georgia, Poland, Russian Federation, Switzerland, USA

Characterisation of Survey Respondents



	Germany	BUKaN
Investigators (n)	7	16
Sponsors (n)	19	10
CRO (n)	6	14

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Level of experience

Have you or your organisation ever conducted FIH trials?

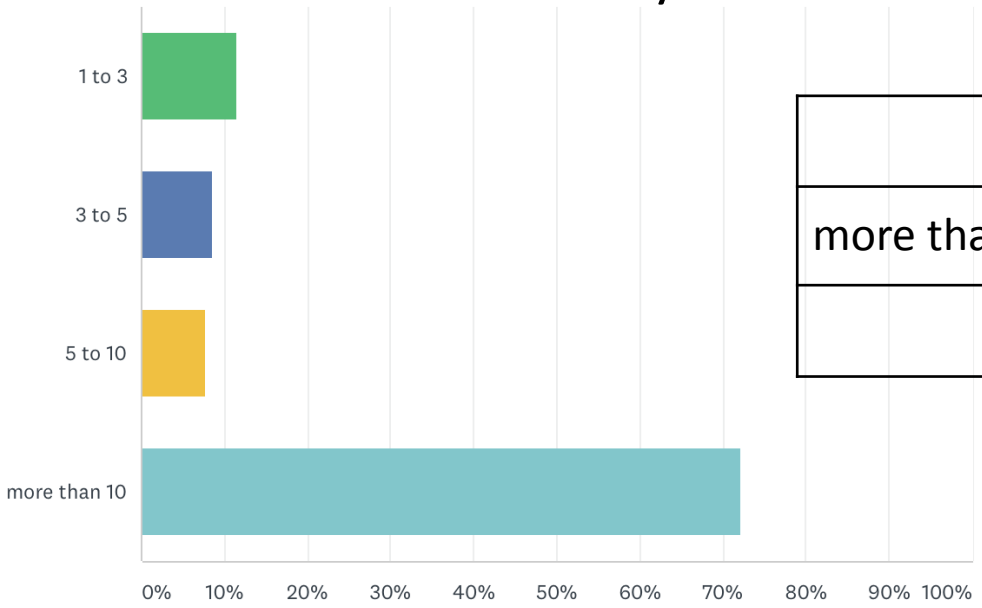
- Yes: 88% n=110
- No: 12% n=15

	Germany	BUKaN
YES	83%	96%
NO	17%	4%

Level of experience

Beantwortet: 104 Übersprungen: 21

How many FIH trials in the last 10 years?



	Germany	BUKaN
more than 10 trials	35%	65%
based on 75 = 100%		

ANTWORTOPTIONEN	BEANTWORTUNGEN	
1 to 3	11.54%	12
3 to 5	8.65%	9
5 to 10	7.69%	8
more than 10	72.12%	75

Level of experience

ANTWORTOPTIONEN	BEANTWORTUNGEN	
FIH first-in-class	84.76%	89
FIH with small molecules	86.67%	91
FIH with biologicals	76.19%	80
FIH with well-known substance classes	77.14%	81
Total Respondents: 105		

	Germany	BUKaN
First-in-class	61%	85%
Small molecular entity	55%	81%
Biologicals	**43%**	**83%**
Well-known substances	45%	77%

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Specific questions

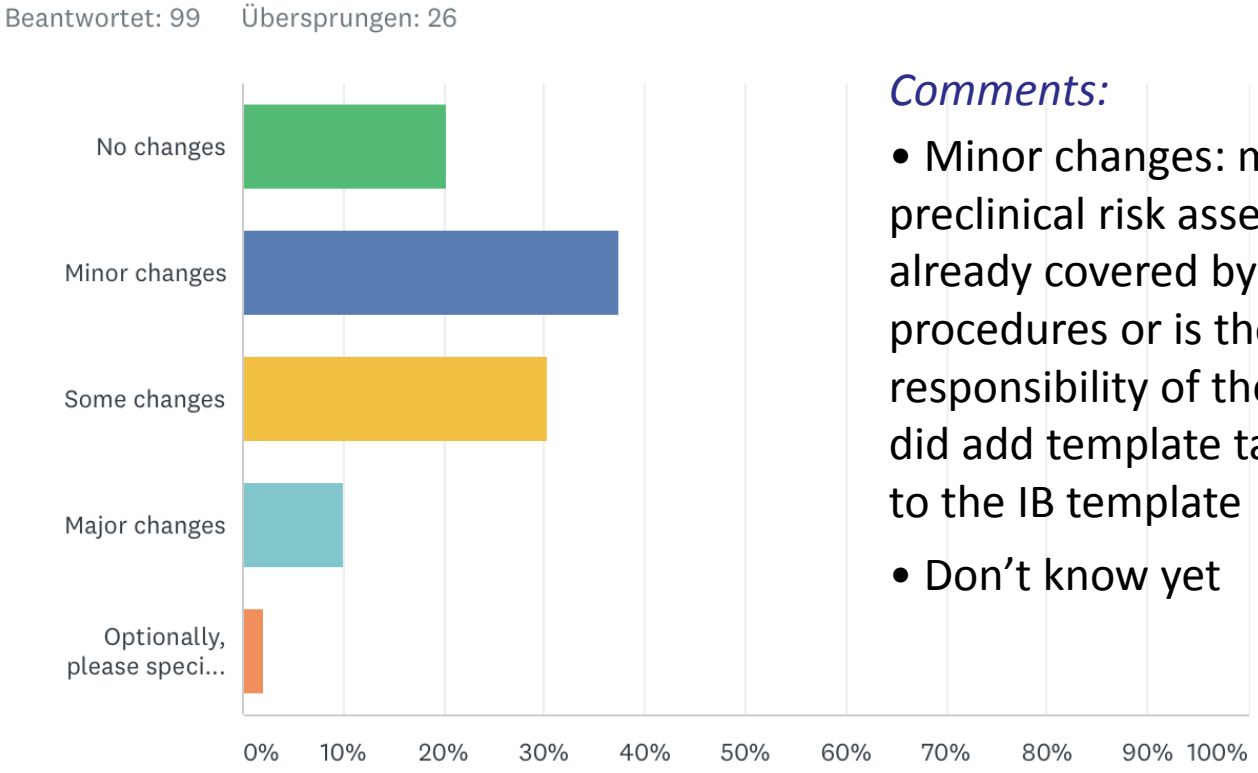
Overall, how clear is your understanding of the requirements of the new EMA guideline?

ANTWORTOPTIONEN	BEANTWORTUNGEN	
Very clear	30.69%	31
Rather clear	46.53%	47
Needs some clarification	16.83%	17
Needs substantial clarification	5.94%	6
TOTAL		101

No remarkable differences between Germany and BUKaN for ‘very clear’, ‘rather clear’

Specific questions

To what extent will the implementation of the revised nonclinical requirements impact on your current practices?



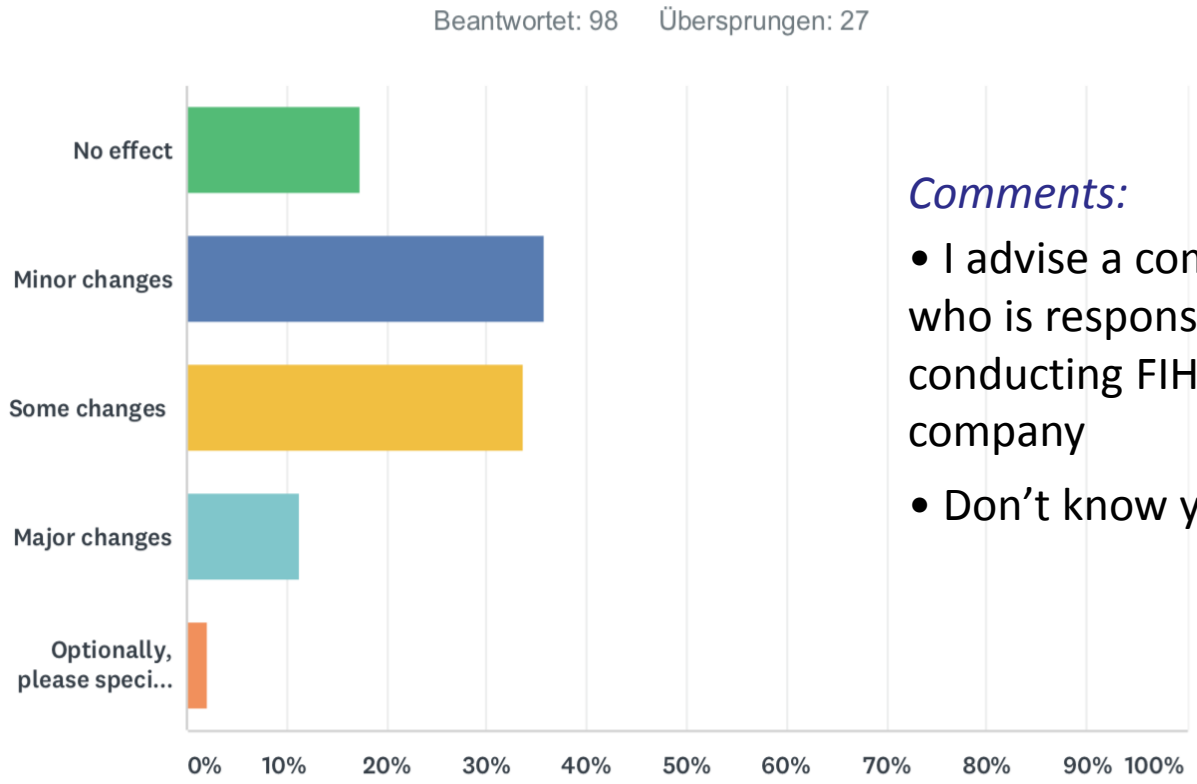
Comments:

- Minor changes: most of the preclinical risk assessment was already covered by existing procedures or is the responsibility of the sponsor. We did add template tabular formats to the IB template
- Don't know yet

No remarkable differences Germany vs. BUKaN for 'minor changes', 'some changes'

Specific questions

What effect will the guidance on the need for PK/PD data for dose escalation decisions have on your current practices?



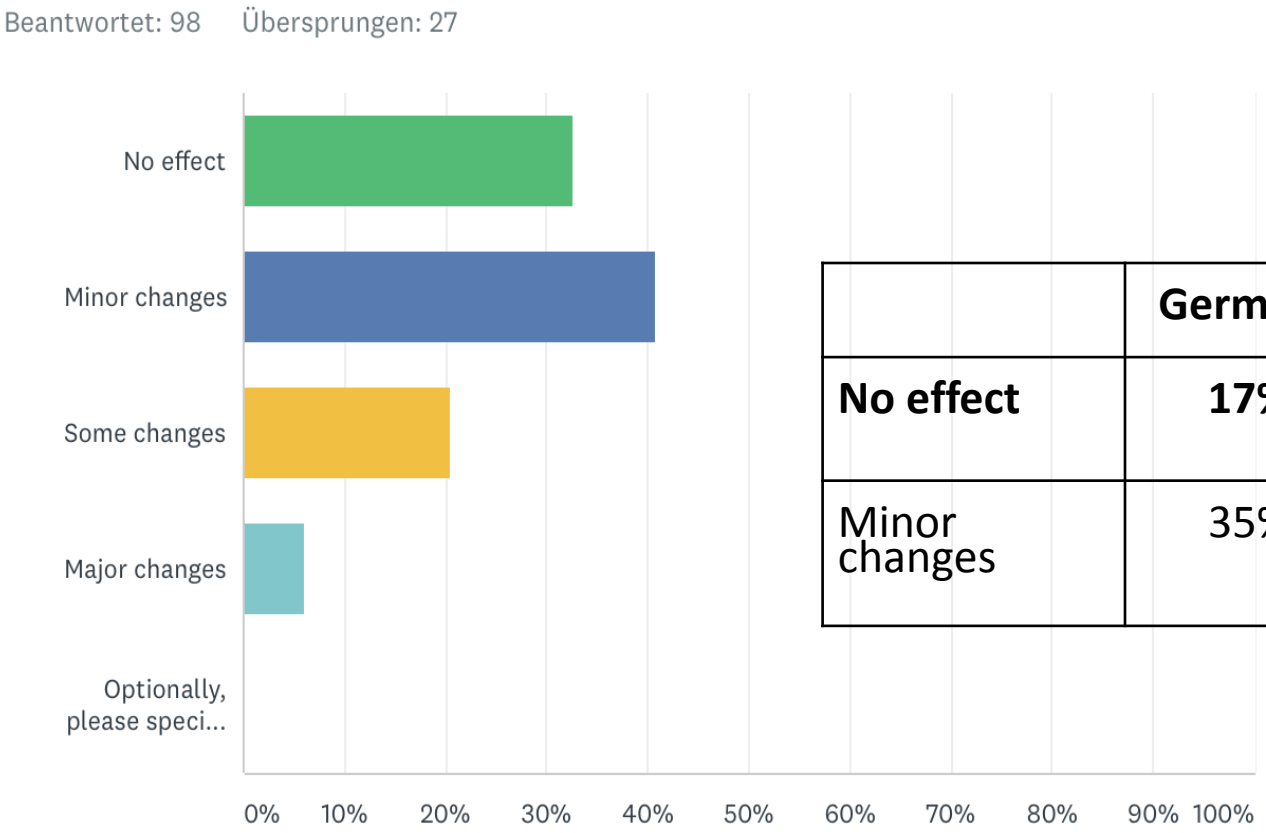
Comments:

- I advise a competent trainee who is responsible for conducting FIH studies for his company
- Don't know yet

No remarkable differences Germany vs. BUKaN for 'minor changes', 'some changes'

Specific questions

What effect will the implementation of the way starting dose is selected have on your current practices?

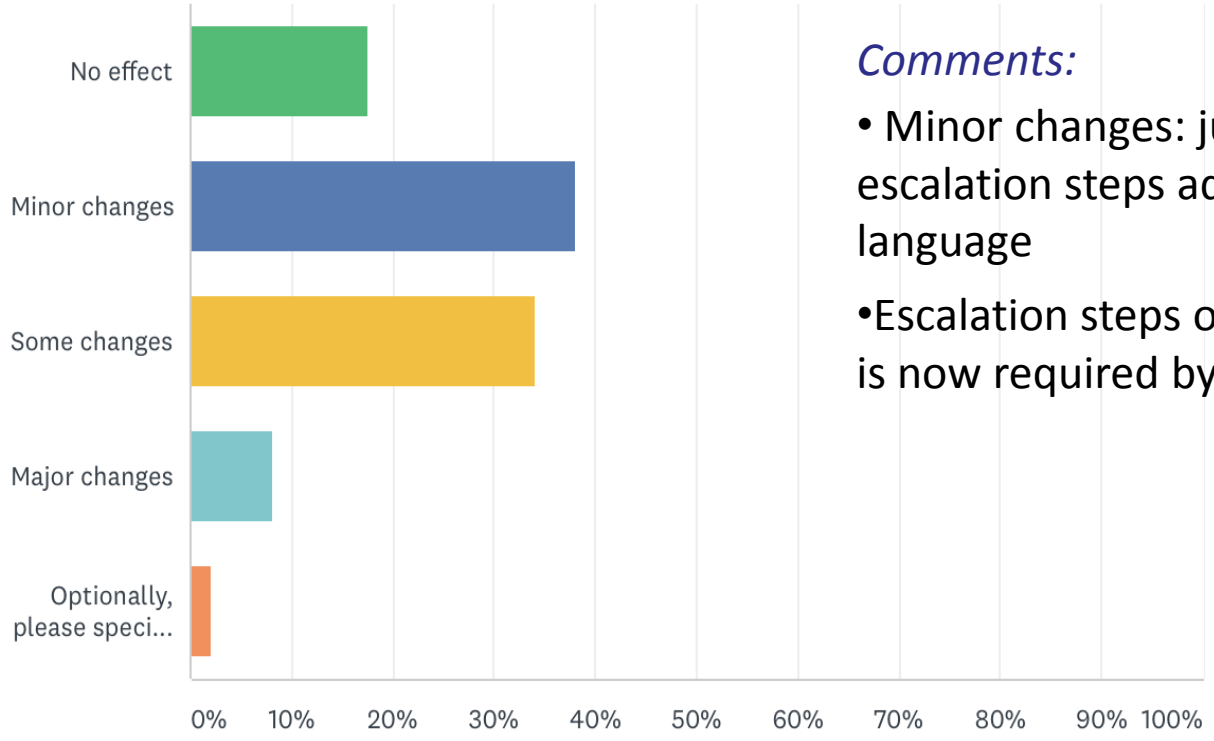


	Germany	BUKaN
No effect	**17%**	**36%**
Minor changes	35%	23%

Specific questions

What effect will the implementation of the definition of dose escalation steps have on your current practices?

Beantwortet: 97 Übersprungen: 28



Comments:

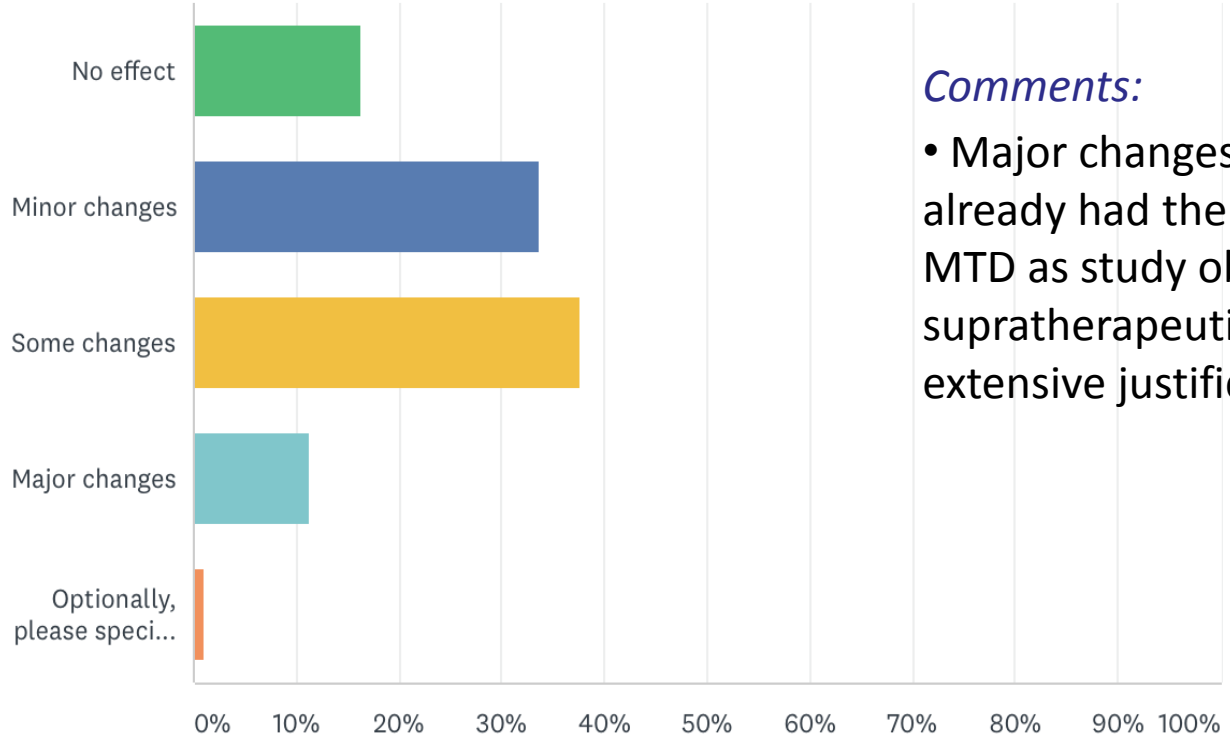
- Minor changes: justification on escalation steps added to protocol language
- Escalation steps of 2-fold maximum is now required by the EC

No remarkable differences Germany vs. BUKaN for ‘minor changes’, ‘some changes’

Specific questions

What effect will the implementation of the definition of maximum exposure have on your current practices?

Beantwortet: 98 Übersprungen: 27



Comments:

- Major changes: although we already had the habit of declining MTD as study objective, now supratherapeutic exposures need extensive justification in the protocol

No remarkable differences Germany vs. BUKaN for ‘minor changes’, ‘some changes’

Specific questions

What effect will the implementation of the guidance for transitioning from SAD to MAD have on your current practices?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
No effect		26.53%	26
Minor changes		33.67%	33
Some changes		30.61%	30
Major changes		8.16%	8
Optionally, please specify the key changes:	Responses	1.02%	1

No remarkable differences between Germany and BUKaN

Comments:

- Some changes: more emphasis that exposure (rather than dose) is already covered by preceding SAD cohorts

Specific questions

What effect will the implementation of the guidance on sentinel dosing have on your current practices?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
No effect		22.45%	22
Minor changes		25.51%	25
Some changes		34.69%	34
Major changes		14.29%	14
Optionally, please specify the key changes:	Responses	3.06%	3

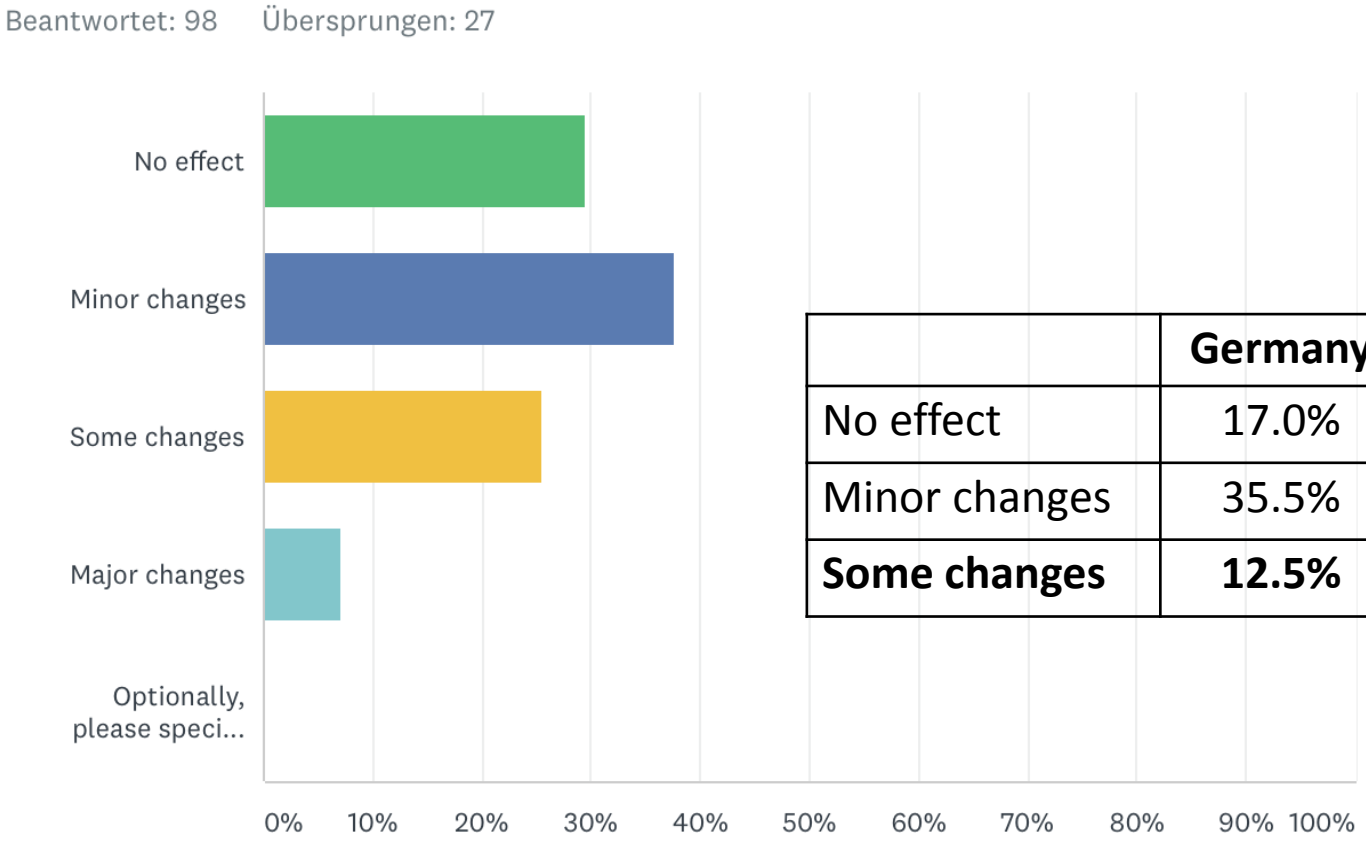
No remarkable differences between Germany and BUKaN

Comments:

- Sentinel dosing in MAD, Timeline
- Some changes: justification needed in protocol why no sentinel in MAD cohorts. In exceptional cases sentinel also in MAD

Specific questions

What effect will the implementation of the guidance on stopping rules have on your current practices?



	Germany	BUKaN
No effect	17.0%	24.5%
Minor changes	35.5%	22.5%
Some changes	**12.5%**	**24.5%**

Specific questions

Overall, what level of change do you expect in your current practices for FIH and early phase trials with the implementation of the revised guideline?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
No effect		9.28%	9
Minor changes		41.24%	40
Some changes		38.14%	37
Major changes		7.22%	7
Optionally, please specify the key changes:	Responses	4.12%	4

No remarkable differences Germany vs. BUKaN

Specific questions

Overall, what level of change do you expect in your current practices for FIH and early phase trials with the implementation of the revised guideline?

Comments:

- As an Educational Supervisor minor effects on judgement over quality of advice to my trainee
- Some changes. Overall it depends on the interpretation of the Competent Authority and the question if they see this as a rule or a guideline from which can be deviated if justified
- Not applicable at the moment
- All together result in major changes

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Impact on European Union / Innovation

Overall, what impact will the implementation of the revised guideline have on the European Union?

ANTWORTOPTIONEN	BEANTWORTUNGEN	
Very negative	2.06%	2
Rather negative	11.34%	11
Neutral	45.36%	44
Rather positive	29.90%	29
Very positive	5.15%	5
Optionally, please specify: Responses	6.19%	6

	Germany	BUKaN
Neutral	29%	38%
Rather positive	17%	28%

BUKaN more positive?
(66% vs. 46%)

Impact on European Union / Innovation

Overall, what impact will the implementation of the revised guideline have on the European Union?

Comments:

- This will depend more on the timelines of the new portal and submission process than on the revised guideline.
- It will increase the burden of doing FIH trials, but enhance the safety for the subjects
- Depending on the interpretations by the competent authorities
- Can't say
- The problem it tries to resolve (off target activity) is untouched
- That guideline is badly written, the contents are not clear, there's a mix of several study types, and the fact that advertising for umbrella protocols is made is really disadvantageous. Overall, the impact of that guideline is very negative

Impact on European Union / Innovation

Overall, do you think that the implementation of the revised guideline could have consequences on innovation?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
Yes		40.00%	38
No		60.00%	57
Optionally, please specify:	Responses	0.00%	0
TOTAL			95

No remarkable differences Germany vs. BUKaN

Impact on European Union / Innovation

Overall, do you think that the implementation of the revised guideline could have consequences on innovation? YES:

ANTWORTOPTIONEN		BEANTWORTUNGEN	
Very negative		5.00%	2
Rather negative		42.50%	17
Neutral		15.00%	6
Rather positive		32.50%	13
Very positive		0.00%	0
Optionally, please specify:	Responses	5.00%	2

Numbers too small for subgroup analyses

Comments:

- Can't say
- On biotechs

Impact on European Union / Innovation

Further comments or thoughts?

- The guidance itself leaves many options, so should be OK to conduct trials in innovative or conservative ways. The problem will be is how regulators will interpret the guidance. While at the EMA stakeholder meeting on numerous occasions it was indicated the guidance is not law, we know some regulators will be interpreting the guidance quite literally or conservatively, that would be a significant risk

Impact on European Union / Innovation

Further comments or thoughts?

- This questionnaire has not covered my class of input to FIH studies. So my answers are not helpful in my opinion
- A Q&A document would be helpful, elucidating the ways of justification of e.g. not using sentinel dosing (especially in the MAD), and use of supra-therapeutic exposure.
- We are implementing already a lot of things implied in the guidelines

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Interpretation – Conclusions

- No representative survey – spotlight from a group of highly motivated and educated stakeholders; majority located in western parts of Europe
- All FIH stakeholders are represented in the survey, especially those asking for approval of CTAs
- 88% of stakeholders have a high level of experience in FIH trials, 72% conducted >10 FIH trials over 10 years
- Most types of FIH trials have been covered by the survey: >70 - >80% for 1st in class / SME / Biologicals / Well-known substances

Interpretation – Conclusions

➢ The requirements of the revised EMA FIH guideline is 'Very clear' for 31%

Summary of 'No changes' plus 'Minor changes'

Impact nonclinical requirements	57.5%
Need for PK/PD data for dose escalation decision	53.0%
Selection of starting dose	**73.5%**
Definition of dose escalation steps	55.5%
Definition of maximum exposure	50.0%
Transitioning from SAD to MAD	50.0%
Sentinel dosing	48.0%
Impact on stopping rules	**68.0%**
Level of change in current practice	50.5%

Areas requiring discussion, explanation and resolution

Summary of 'No effect' <20%

Level of change in current practice	**9.3%**
Need for PK/PD data for dose escalation decision	17.4%
Definition of dose escalation steps	17.5%
Definition of maximum exposure	16.3%

Summary of 'Major changes' >10%

Impact nonclinical requirements	10.1%
Need for PK/PD data for dose escalation decision	11.2%
Definition of maximum exposure	11.2%
Sentinel dosing	**14.3%**