



Health Care Inspectorate
Ministry of Health, Welfare and Sport

Good Clinical Practices (GCP) in developing settings: The promotion of the international harmonization for the respect of ethical principles, human rights and justice

On behalf of the **Clinical Trials Unit**

of the

**Health Care Inspectorate,
The Netherlands**

Presenter: Dr. Willem R. Verweij
Senior Inspector (for Clinical Trials)

11 – 14 June- 2012, Mwanza

14 June 2012, GCP in developing settings, Mwanza

For
justified
confidence
in good
care



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Ministry of Health, Welfare and Sport

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Inspections:

Findings and grading,
outcomes, critical
issues and decisions

14 June 2012, GCP in developing settings, Mwanza



Health Care Inspectorate The Netherlands

Health Care Inspectorate
Ministry of Health, Welfare
and Sport (Dutch: VWS)

4 regional offices:

- The Hague (*Prog. 8* + 'Rijswijk')
- Amsterdam
- Zwolle
- 's Hertogenbosch

1 Knowledge and Training Centre:

- Utrecht (also most staff)





IGZ (Health Care Inspectorate)

The Netherlands Health Care Inspectorate (*IGZ*)

≈ 490 employees

10 programs (8 – Pharmaceutical Products)

Program 8 consists of:

- GMP/GDP
- GCP (5 + 1 Inspectors)*
- PhV (2 + 2 Inspectors)*
- Blood and Tissues
- Opiates
- Marketing and Promotion of Medicines ('advertisement' for medicines on prescription is not allowed in The Netherlands)

* + supporting assistance (Program Officer (1 GCP, 1 PhV))



The perspective / 'disclaimer'

This presentation, coming from a Dutch inspector, will reflect the international (ICH-GCP), European and partly national perspective, definitions, requirements and authority/ jurisdiction, focus on studies with medicinal products and keeping in mind :

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA

Be aware of additional (inter-)national or continental legislation and regulations.

Note:

Within the regions for which the ICH-GCP Guideline is used as a unified standard to facilitate the mutual acceptance of clinical data by the regulatory authorities, differences do exist as to the legal status of and/or reference to this Guideline.



What are inspection findings ?

All **non-compliances** against;

- Legal requirements (National + international)
- Standards

Most of them **could, will have** or **(will) have had**:

- Impact on Subject Rights and Safety and/or Quality and integrity of the Study Data (the two 'pillars' of ICH-GCP)

Or be the result of **insufficient/inadequate Response and/or Corrective- and Preventive Action** (implementation + follow-up)



..... not all findings are equally 'important'

Based on their actual or potential impact

and taking into account the 'COMPLETE PICTURE'

Findings are generally graded:

Minor - Major - Critical

In addition, there might be: **Comments / Remarks**



Gradings of Findings (EMA, GCP-IWG)

Critical Finding Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Major Finding Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Minor Finding Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.



Critical Findings, a closer look

Critical Finding

Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents.

Fraud belongs to this group

Note: pattern → 'whole picture', Fraud <= => Legal



Critical Findings, cont'd

Possible consequences:

- Rejection of data (+ withdrawal of approved applications)
- Legal action required (Fraud)
- 'Black-listed'
- Re-inspections (after implementation CAPA)

DIRECT ACTION often required.



Major Findings, a closer look

Major Finding

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.

Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

Note: pattern → 'whole picture'



Major Findings, cont'd

Possible consequences:

- Rejection of (part of) the data / sites
- Rejection of the complete application (% affected)
- Legal action required
- 'Marked' (< 'Black-listed')
- Re-inspections (after implementation CAPA)



Minor Findings, a closer look

Minor Finding

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Again: → 'whole picture' (... the sum might be equal)



Minor Findings, cont'd

Possible consequences:

- Observations classified as minor, indicate the need for improvement of conditions, practices and processes
- (country specific other consequences)

Having an inspection with NO findings is not likely to 'exist'; work involving humans 'is likely to lead' to human errors.



Practical implications / consequences

Since :

- › 'complete picture'
- › often extra documentation is taken (during the inspection) to analyse further back at the Agency / Inspectorate
- › findings / issues might have to be discussed with colleague inspectors or assessors:

'NO' Grading will be provided at the site during the exit-meeting

EXCEPTION: Clear CRITICAL issues (direct action required)



Inspection Report

- › Text body (including administrative data)
 - Description of observed non-compliances
 - Formulating finding (according to ICH-GCP)
 - Referring to / mentioning of specific article(s)
 - (Additional info, comments, explication, impact)



In practice:

Based on the total number and the grading of the findings Inspectors state in their Inspection Report:

- A GCP-compliance statement
- An 'advise' to the assessors with regard to the acceptance of the (inspected) data in the process of a Marketing Authorisation Application (MAA).



Final decision / consequence on MAA

Based on **ALL INPUT**,

including the IR, but also the complete Application Dossier (e.g. CSR) (+ Assessment Report(s), answers to LoQ's etc.)

in most countries in Europe, **the assessors** (or CHMP for centralised products) finally decide on a MA.

In case of 'negative advise' from the inspectors or serious issues, 'generally' inspectors are contacted (TC, mail, etc.)

Note: This is now part of the new EMA Inspection Procedure



Critical Findings, general

Still (frequently *) critical findings on EMA inspections

All aspects of trials/systems

Variable 'orientation' / scope of inspection
(now also routine (vs triggered) inspections internationally)

Differences between traditional, innovative pharmaceutical products, biological products, generics, ATMPs, commercial sponsors and academic / Investigator Initiated Trials (IIT) ?

* On TRIGGERED inspections



Example of a critical finding: but first:

- The COMPLETE PICTURE is **essential**
- Despite harmonisation and definitions differences between inspectors and countries MIGHT (still) be there

..... and more examples in the practice session ☺



Study on BioEquivalence of a ('new') generic

- Relative small group of subjects (32 – 48)
- Relative simple protocol (2 times a single dose, 1 – 2 week(s) in between, regular blood sample (cannula), recording (S)AE's AND: VITAL SIGNS including ECG's (pre and post study))

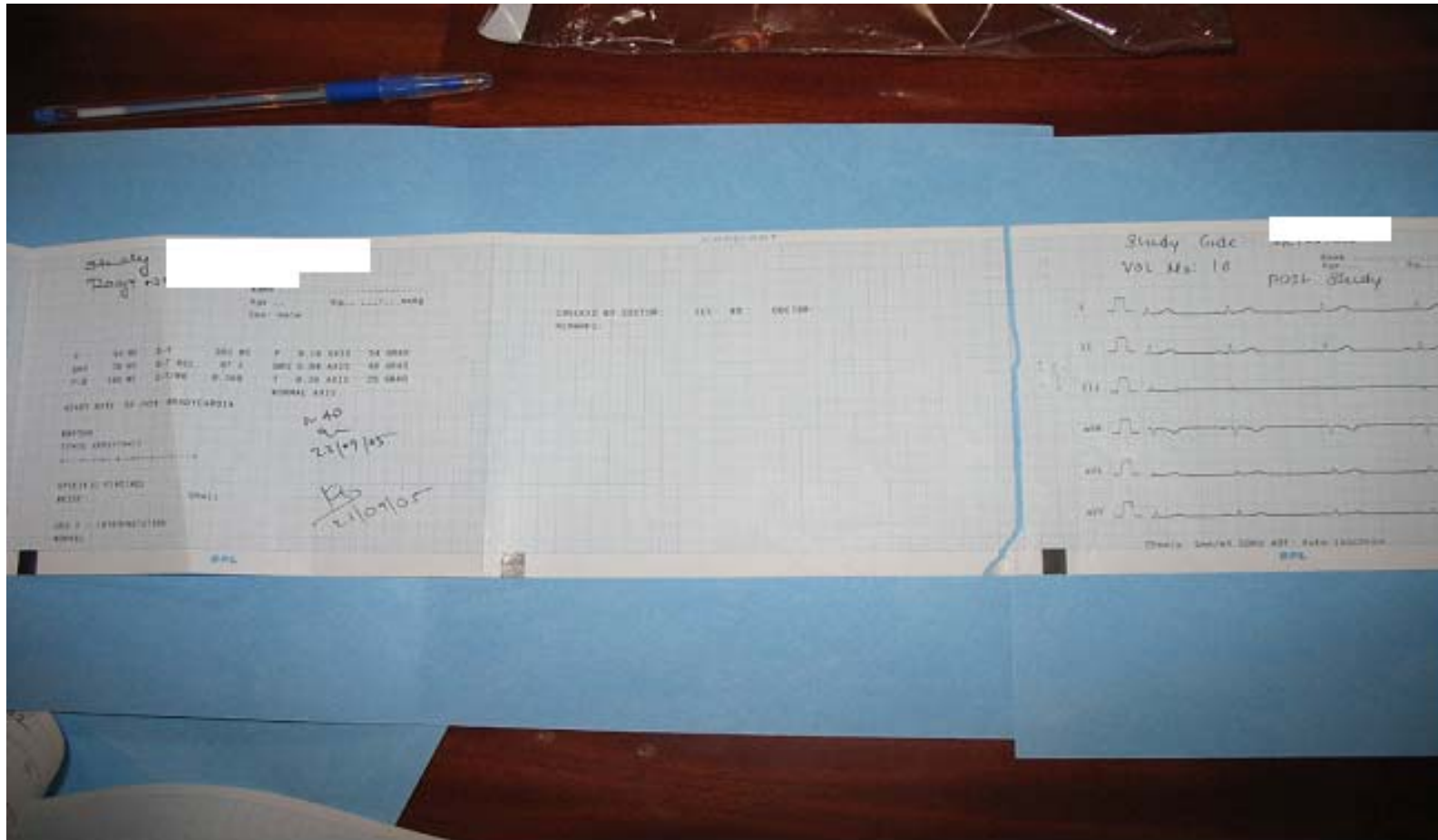
Note: Taking an ECG ~ 4 (- 5) minutes per subject,
so: 32 subjects → > 2 hours

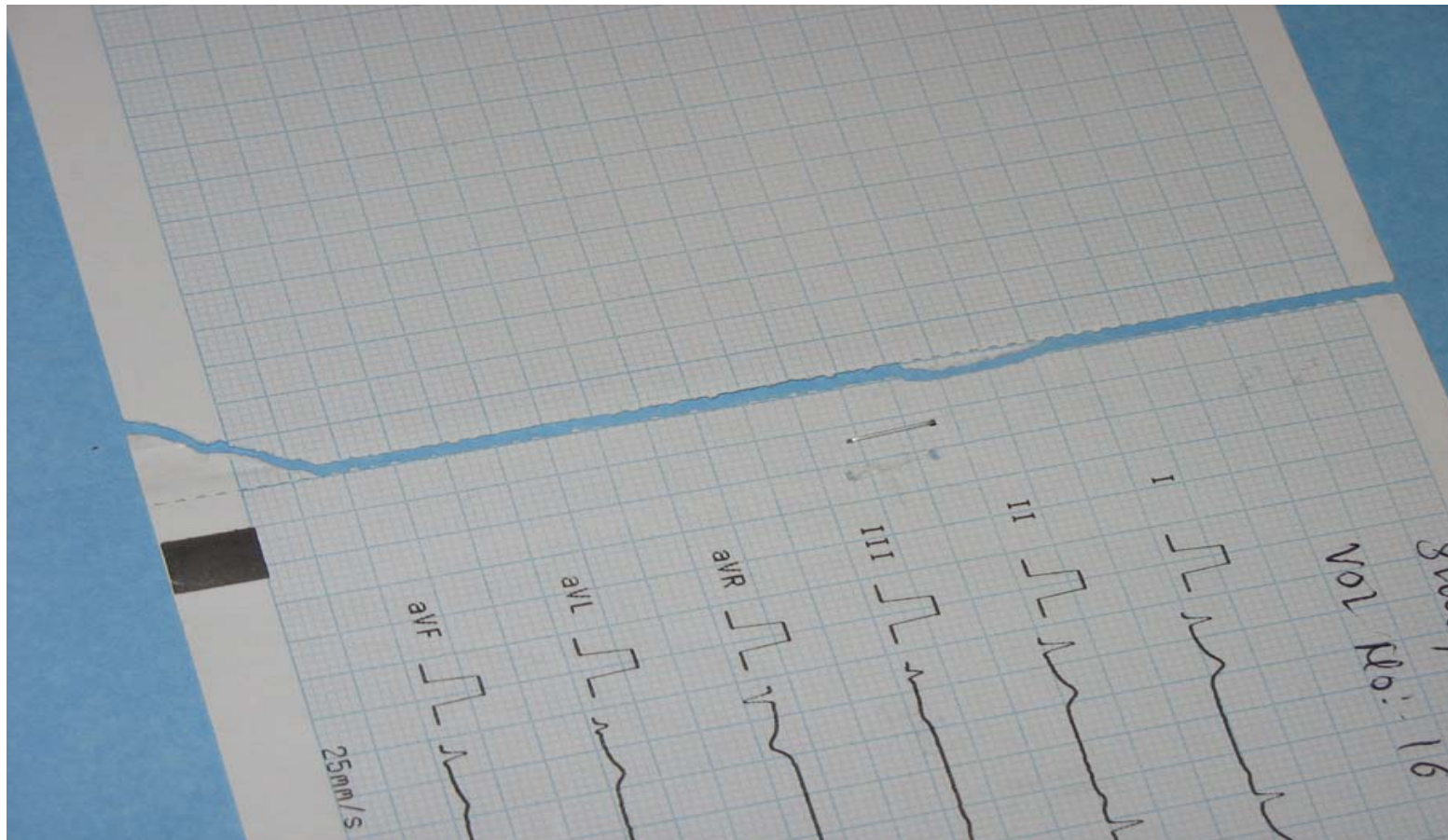


What did we find ?

- Some quite characteristic ECG's
- More 'examples' (copies ???) of those ECG's
- ECG's having been taken , 30 **seconds** apart
- 'Identical' ECG's from different subjects and both from before and after the study

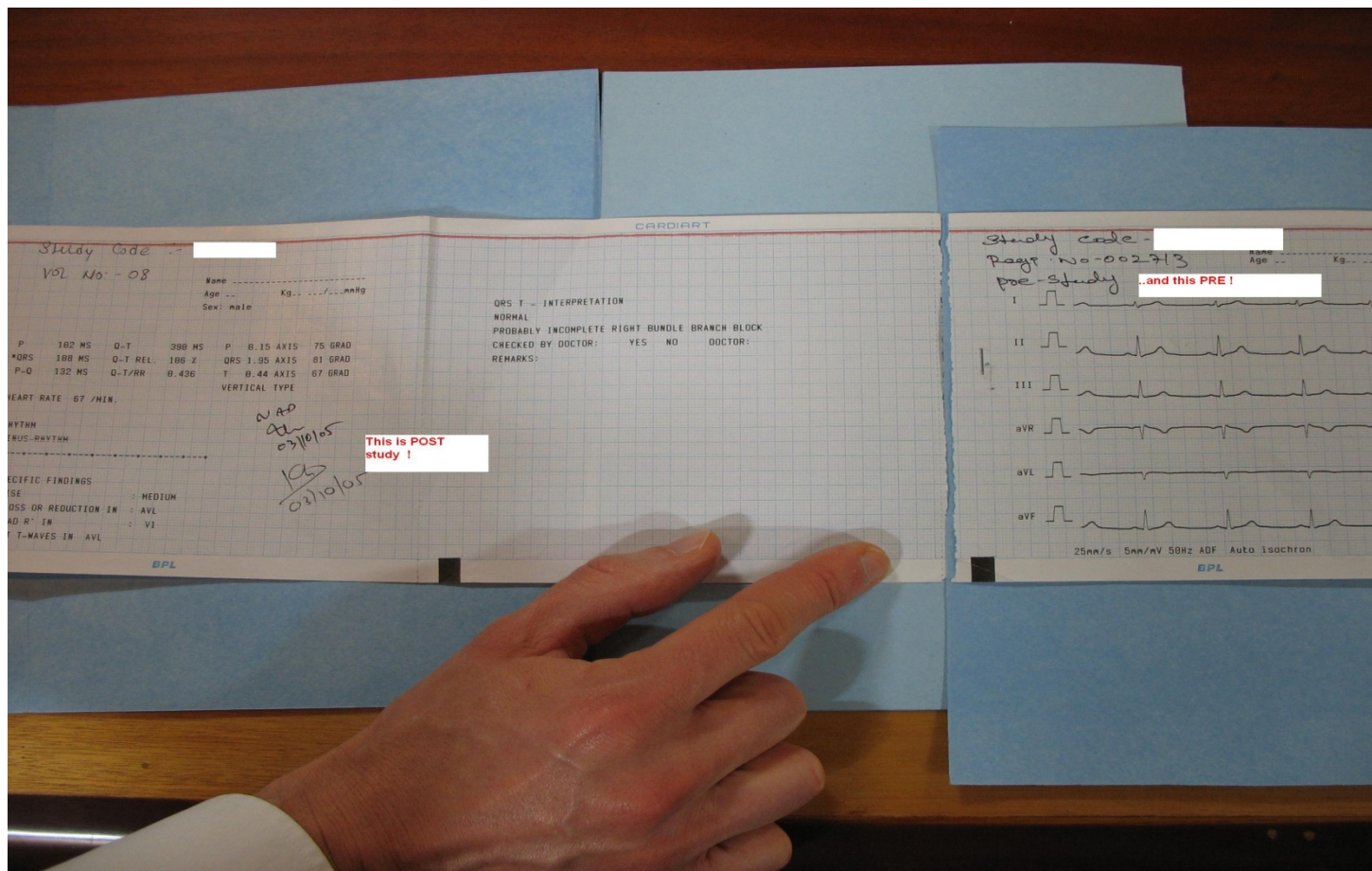
Note: Study numbers (+ 'pre' and 'post') manually added





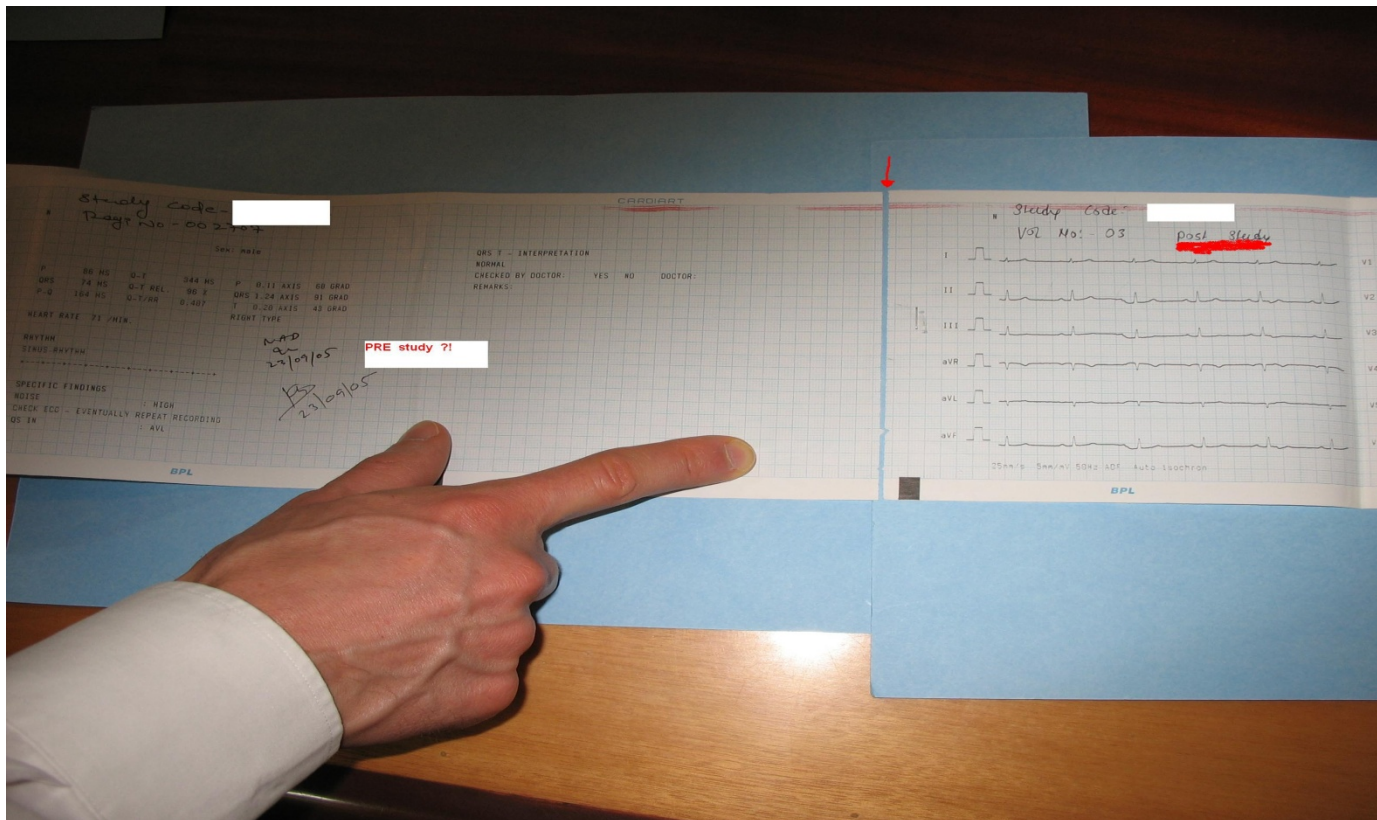


..... and some more





..... and more





So.....

Clear example of FRAUD (/ MISCONDUCT)

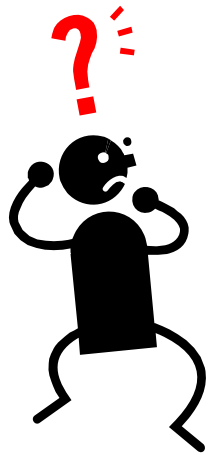
- But:
- How to communicate this to the inspectee ?
 - How to formulate this in the IR ?
 - What are the (potential) consequences / (product efficacy vs integrity of the (rest of the) data
- ➔ More in the practice session



In this case:

- MAA (for other countries) original dose: NOT approved
 - Withdrawal of ALL already marketed dosings based on this same dossier in different EU countries
 - CRO 'blacklisted' → mandatory inspection(s) for next applications (+ review of previously approved products / dossiers)
- (- this CRO, as such, no longer exists; taken over, new management, new procedures, better control, ...)

BTW: This product as such has 'no' influence on cardio vascular parameters



QUESTIONS





Thank you for your attention

On behalf of The Clinical Trials Unit
of the Health Care Inspectorate
The Netherlands

Questions or further information:

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or put your questions to
gcp@igz.nl

(Or, of course, the organising committee)