FDA Warning Letters and Inspections: Lessons Learned and Trends and EMA Australian GCP Inspections

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GCP Refresher Course

SESSION OUTLINE

Part I: The Warning Letter Process – What is a WL and where do I find them?

Part II: Review of Warning Letters Raising Issues on Monitoring

- The Sponsor ‘A’ WL
- The CRO WL
- The Sponsor ‘B’ WL
- Lessons Learned

Part III: Trends in Clinical Investigator (CI) WLs

- Statistics – 2006 to 2014
- Trends & Most Quoted Deficiencies in CI WLs – past years
- More Lessons Learned

Australian FDA Site Inspections

EMA Australian GCP Inspections – the Statistics

And no, its no
~~a Christmas~~
Card!

PART I: FDA Warning Letters – the Three to Four Step Process

- 1. If deficiencies are observed, a Form FDA 483 ('Inspectional Observations') is issued to the auditees at the conclusion of an inspection. The document contains the opinions of the inspector/inspection team [= 'Investigator(s)' in FDA language], and the auditees are required to submit a response to the 483 within 15 working days outlining the corrective and preventive actions (CAPA) they plan to take or have already taken

- 2. Returning from the inspection the (lead)inspector writes an 'Establishment Inspection Report' (EIR), which together with attached copies of all documents obtained during the inspection is submitted to FDA management

- 3. Based on the response received from the auditee and the EIR, management will classify the inspection, and for an OAI, if deemed necessary – often because the CAPA received are not accepted as satisfactory - issue a Warning Letter

Definitions of
FDA Inspection Classifications

NAI	No Action Indicated (no significant findings)
VAI	Voluntary Action Indicated (significant findings)
OAI	Official Action Indicated (major / serious findings)

FDA Warning Letters – the Process – cont.

Definition: "A Warning Letter is an informal advisory to a firm communicating the Agency's position on a matter but does not commit FDA to taking enforcement action. The Agency's policy is that a Warning Letter should be issued for violations which are of regulatory significance in that failure to adequately and promptly take corrections may be expected to result in enforcement action should the violation(s) continue."

Timelines: From Inspection to WL it will take many months – median 7 months [3 – 16] for 23 CI WLs (Part 3); and if applicable *years* to Disqualification etc

4. Possible final outcome for the CI / sponsor: 'clinical hold', disqualification / debarment, and persecution as in fines and even jail-time

   Prior to 'Disqualification' a NIDPOE = '**N**otice of **I**nitiation of **D**isqualification **P**roceedings and **O**pportunity to **E**xplain' [2009-12: 5, 5, 2, and 2 issued]

FDA Warning Letters – the Process – cont.

Sourcing the WLs

The CDER WLs can as part of the Agency's FOI policy be found at:

- **http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm**

On this website you can also sign up to receive monthly updates on recent issued WLs direct to your inbox, but remember that as *FDA covers both **F**ood & **D**rugs, a vast majority of Warning Letters on this website is typically related to the "Food" part (or tobacco).*

Details on the deficiencies for all VAI and OAI classified inspections from 2006 onwards can be found at (from which the metrics in the table under Part 3 of this training session has been extracted):

- **http://www.fda.gov/ICECI/EnforcementActions/Inspectionactivities/default.htm**

PART II: Three Warning Letters of Interest for all Sponsors and CROs

– or *"the study monitor failed to identify…"*

- Issued to Sponsor 'A' - Aug, 2009:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm177398.htm

- Issued to the CRO - Nov, 2009 - *connected to the Sponsor 'A' letter above*:

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm193156.htm

- Issued to Sponsor 'B' – Apr, 2010:

- **http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm208976.htm**

- Similar to the issues in the Sponsor 'A' letter, Sponsor 'C' was in 2007 (23 Oct) issued a WL related to ensuring investigator compliance incl Maria A. K. Campbell MD, committing fraud; and

The Sponsor ‘A’ Letter

This Sponsor Inspection related to 2 studies following submission of an NDA, resulted in a Form FDA 483, which the company responded to, a response regarded unsatisfactory by the Agency

1) **“Failure to ensure proper monitoring of the clinical investigations” [21 CFR 312.50; 312.56(a)]**

- “*you were responsible for ensuring that these studies were adequately monitored for compliance with regulatory requirements*”….(even though the monitoring had been contracted to the CRO):

• Deficiencies in case histories (= *source documents*) – **study drug** administrated to different patients at precisely the same time – [*very detailed with many examples listed!*]

• Study procedures not performed

•Times that **infusions** were delivered to nursing unit not recorded

The Sponsor 'A' Letter – cont. 1

- Storage temperature for reconstituted **study drug** at patients' homes not recorded;

- Temperature recording devise for **drug shipments** showed out-of-range temperatures (refrigerator), but the drug was administrated anyway – stability studies performed retrospectively;

  • **IV** temperature stability worksheets* missing, no insurance that temp. conditions for the **drug** were maintained adequately;
  *) incl. documenting start / finish time & expiry time of infusion

  • Discrepancies in time of delivery of **study drug** to nursing unit versus time of administration of drug to patients;

  • Discrepancies in study records (*CRF*) versus source records – in relation to wound dimensions and **drug accountability.**

All this missed by the CRO monitors – "Study monitors failed to identify…."

The Sponsor 'A' Letter – cont. 2

2) **"Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND" [21 CFR 312.50]**

- Study blinding procedures not correctly followed – including change control not as per GCP, as **correction fluid** was used in source records
- **Dosing** not as per protocol – **drug infusion** order / infusion duration reversed
- Eligibility criteria at enrolment not met – including pregnancy test results not available at enrolment
- Baseline creatinine clearance results not timely available for the un-blinded pharmacist – to be used for **dose** calculations.

Again – "Study monitors failed to identify / ensure……."

The Sponsor 'A' Letter – cont. 3

3) "Failure to secure investigator compliance with the investigational plan and applicable FDA regulations" [21 CFR 312.56(b)]

- Adequate corrective actions not documented in monitoring reports, nor implemented at one site, where the first **study drug dosing** post-patient randomization was delayed for several patients.

4) "Failure to ensure that only investigators who were qualified by training and experience were selected as appropriate experts to investigate a drug" [21 CFR 312.56(a)]

- For one site an investigator was selected, for whom the pre-study monitoring visit report documented that this investigator was not recommended for lack of compliance in completing regulatory documents (incl IRB approvals, lack of diligence in study start procedures and inadequate patient population (e.g. refused to use Spanish ICFs in spite of large population of native Spaniards)), but the CRO monitor was overruled by the CRO supervisor; however the sponsor was responsible for the final approval of the site(s).

The Sponsor ‘A’ Letter – cont. 4

In General:

- The Sponsor ‘A’’s responses to the initial Form FDA 483 were deemed inadequate, e.g. unclear whether infusions were given at the site or at the subjects’ home; and *no* explanation for discrepancies; responses not detailed enough, and did not clarify the initial observations !

‘Good’ example how *NOT* to response to a 483; other examples of what NOT to do:

- Submit the answers *after* the 15 days deadline, or of course not answer at all !
- ‘Pass the Buck’, e.g. to employees of the company / site
- Not properly identifying the possible *causes* for non-compliance
- Not submitting *documentation* of claimed changes in your quality system
- Or provide *unnecessary* documentation, or long, rambling WL responses

The CRO Letter

General Background:

This CRO was contracted by Sponsor ‘A’ for clinical management services, specifically all tasks related to **monitoring**:

- Write monitoring plans; conduct site visits & telephone follow-ups; write monitoring reports; notify sponsor of critical site issues; weekly TCs; tracking of monitoring visits, F/Us, monitoring reports, and protocol violations.

- For site visits the CRO agreed to perform **100% SDV for all data** (*!*), verify Informed Consents, ensure AE reporting, check record retention & adequacy of supplies and ensure proper **drug storage and accountability.**

The CRO Letter – cont.

Background for this Warning Letter – one of the first of it's kind to be issued to a **C**ontract **R**esearch **O**rganisation:

"*US regulations permit the transfer of obligations to a CRO by a sponsor [21 CFR 312.52(a)], and describe the responsibilities in writing that the CRO assumes when obligations are transferred*" = subject to same regulatory action as the sponsor*

The CRO Warning Letter goes on to list the same findings as in the Sponsor 'A' letter, except for the last two (3. & 4.)

And at least 18 times the letter states : "*study monitors failed to identify / document / notice / ensure……*", and "*study monitors should have sought an explanation...*", or "*should have recognized...",* or *"corrective actions by study monitors were inadequate to correct this deficiency...*", or "*conflicting information was not identified by the study monitors...*"

* The updated FDA 'Compliance Program Guidance Manual' [BIMO Program 7348.810, dated March 11, 2011] (= the 'SOP for FDA Inspectors') now directly states: "*When operating under written agreements, the CROs are subject to the same regulatory actions as sponsors for any failure to perform any of the obligations assumed*."

The Sponsor ‘B’ Letter

1) “You failed to ensure proper monitoring of the investigation” [21 CFR 312.50]

- A repeat violation of findings communicated in an ‘untitled letter’ after an inspection 4 years earlier;
- Widespread **overdosing** of paediatric patients (*very detailed*):

  - not discovered by the monitor* (monitors visited the site in total nine days), but by Data Management (*!*);

  - problem found for 2 other studies and 2 additional sites;

  - corrective & preventive actions taken, but deemed by the FDA *too late.*

*)“***Study monitors failed to ensure** *that the investigation was conducted in accordance with the investigational plan. Overdosing at Dr. [*Punjwain*]’s site was neither recognized nor reported by the study monitors in a timely manner*.”

[A WL had already on 4 February 2010 been issued to the Clinical Investigator, Sohail Punjwain MD, detailing these overdosing violations together with other violations.]

The Sponsor 'B' Letter – cont.

2) **"You failed to ensure that the investigations were conducted in accordance with the general investigational plan and protocols contained in the IND" [21 CFR 312.50]**

- Violations observed in **dose** titration, ECG review, lack of a 'rater qualification program', informed consent administration by unqualified staff, hand-written information added to informed consent forms.

3) **" You failed to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particular with respect to adverse events and safe use" [21 CFR 312.55(b)]**

- Lack of documentation to show that all sites conducting the paediatric study received safety reports describing the dosing errors!

SOME LESSONS LEARNED

- The obvious: The importance of *monitoring* – § 5.18 is one of the longest paragraphs in the ICH GCP !
- HA Inspectors have focus on *monitoring* – e.g. the US FDA [as per 21 CFR 312.50 and 312.56(a)] – "*the sponsor must ensure proper monitoring of clinical investigations*"
- *Monitoring* is was the *No. 1 of both critical and major findings* in the 378 **EMA** inspections from 2000 through 2012 (see later slides)
- Some monitors (and auditors) find the drug accountability etc boring, and leave it to last! But the study drug / IMP is of outmost importance -> 75% of issues in these letters deal with the drug: transport, storage / stability, dosing, accountability etc.
- A CRO can*not* 'hide behind' the sponsor / defer responsibility to the sponsor!
- There was a sharp rise in the number of Sponsor / CRO inspections: from 25 and 43 in 2007 and 2008, respectively, to 75 and 62 in 2009 and 2010, respectively

LESSONS LEARNED – cont.

Suggestions for Preventive Measures:

- Training of monitors should include fraud *detection* & investigator misconduct; and site training should include misconduct 'awareness'
- Don't let the 'blind leading the blind' (inexperienced monitors advising inexperienced investigators) and 'audit' your monitors to confirm qualifications, training, experience and competence
- Management must provide support, guidance and oversight of monitors incl. co-monitoring
- Incorporate QUALITY RISK MANAGEMENT *proactively* into your clinical trials
- Implement an effective communication plan between the sponsor, monitor, service providers (where applicable) and investigator

PART III: Clinical Investigator (CI) Inspections by CDER

Year	Total ## of CI Insp.	## of 483s Issued	## of WLs Issued	Protocol Compliance Supervision [312.60]	Records in-adeq or –accurate [312.62(b)]	Drug Accountability [312.62(a)]	IC - not app/sign [50.27(a)]	IC - not obtained [312.50]	IC – excep. do not apply [50.20]
2015	ND	ND	6	4	1	1	-	-	-
2014	452	ND	11	9	4	-	-	3	-
2013	344	ND	9	9	5	1	-	3	(1)
2012	381	164 / 43%	5 / 3.0 %	2	2	-	1	2	-
2011	317	No Data	13	19	7	3	-	4	-
2010	398	282 / 71%	13 >4 %	125	75	36	27	19	9
2009	474	370 / 78%	18 / 3.8%	207	143	57	33	28	13
2008	407	333 / 81%	12 / 2.9%	175	101	49	35	33	-
2007	369	320 / 86%	10 / 2.7%	125	90	32	26	18	6
2006	408	282 / 59%	6 / 1.5%	126	76	29	25	13	

Trends in FDA CI Inspections & WLs

- There was a nearly triple (relative) increase in CI WLs from 2006-2011 – from 1.5 to >4 % of all CI Inspections = seems to be the only trend!
- The number of domestic (US) CI Inspections fairly flat over the same years (average around 385/year), but now decreasing
- The ranging order of the Top 4 deficiency categories remains unchanged
- The FDA conducts more and more CI inspection internationally (98 in 2013) incl. A.-P. and Australia (17 to date), as currently the majority of data are collected “overseas”, but in general fewer of these inspections receive OAI classification (none of the Australian inspections classified OAI!)
- During 2009 and 2010 the FDA has set up offices in China and India, initially to focus on GMP issues (API !) and food ingredients, but next up is GCP !

Most Quoted Deficiencies in the CI WLs

- "***You failed to****...ensure that the investigation was conducted according to the investigational plan* [protocol] or ...*to personally conduct or supervise the clinical investigations*' [nearly all WLs]: e.g. entry criteria violations; delayed review of labs; SAEs not timely reported to sponsor / IRB
- "...*maintain adequate & accurate case stories*...": e.g. records/entries not signed; AEs not reported; dosing decisions not documented; clinical significant labs not commented on; discrepancies between hosp. and study records; "*a mess*"!
- "...*obtain informed consent*..": e.g. changes by hand; obsolete ICF used; verbal consent only
- "...*promptly report to the IRB all changes in the research activity...*": e.g. exemption from sponsor not submitted to IRB; did not tell the IRB that the sponsor had terminated the study* (at least 3 examples in 23 WLs!)

  *) of outmost importance in Australia, as the TGA has "outsourced" the oversight to the HRECs

LESSONS LEARNED

- Preparation of your site for inspections starts when you choose it, assessing whether the PI knows his/her responsibilities and have the resources to conduct the study as in time and qualified staff
- In case of an inspection at one of your sites: if possible support the CI in drafting the response to a 483 in providing realistic and precise CAPA, and ensure its provided within the 15 working days
- Hints: FDA regards “Working” docs as = Source docs; and ‘Notes to File’ not same as SOPs!
- Otherwise see Lessons Learned from Part II of this training session, as most of the reported violations / deficiencies could have been avoided though proper monitoring !

Australian FDA Site Inspections

- **17** in total from 1989 to 2014 (data base searched 8 Jan. 2015)
- (7 in NSW, 6 in Victoria, 2 in QLD, 1 in WA (Perth), and 1 in SA (Adelaide))
- - 8 had 'No deficiencies noted' (NAI)
- - NONE classified as OAI !
- **-** 7 had observations = a Form FDA 483 issued, but no need to respond (VAI*)
  - All cited "*Failure to follow investigational plan*" [= the protocol] (312.50)
  - 2 cited "*Inadequate and inaccurate records*" (312.62)
  - 2 cited "*Inadequate informed consent form*" (50.25)
  - 1 cited "*Failure to report adverse drug reactions*" (312.64)

*) "**V**oluntary **A**ction **I**ndicated. Objectionable conditions were found but problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntary."

EMA Australian GCP Inspections – the Statistics

Nos. of EMA inspections – Pacific* (incl – Australia) or Aus/NZ** of total:

	Non-Routine	Routine	Total
2010	- / ND	**2** / ND	2** / 64
2011	3 / 13	5* / 33	8* / 46 (76% CI)***
2012	- / 22	3** / 49	11 / 71 (83% CI)***
2013	- / 31	3** / 52	10 / 83 (67% CI)***

***) data from '*Annual reports of Good Clinical Practice Inspectors Working Group* 2011, 2012 and 2013, respectively ('23 May 2012 - EMA/INS/GCP/972336/2011', '28 May 2013 - EMA/INS/GCP/627138/2012', and '22 May 2014 - EMA/INS/GCP/123295/2013', respectively). **NOTE**: For all EMA reports & documents: visit www.ema.europa.eu/ema/ , enter search word 'EMA/INS/GCP' and you get GCP/Inspection all 85 related docs.

EMA Australian GCP Inspections – the Statistics – cont.

The '*Inspection report to EMA 2000-2012*'* lists a total of only **4** (four) Routine **GCP Inspections*** conducted for EMA in Australia (none in NZ**)** over those 13 years. Sites (CI, Sponsor, CRO) not specified, but around ¾ of all 398 GCP Inspections conducted are at Investigator Sites.

The 7 major findings (of a total 55 findings - NO critical) are related to the following categories:

- *Protocol Compliance (Selection Criteria):* 4
- *Safeguard of the Safety and well-being of subjects:* 2
- *Reporting in CRF / Diary:* 1

NOTE: no major findings on Monitoring, which overall is No. 1 of both critical and major findings !

*) of '25 March 2014 - EMA/INS/GCP/55482/2012'

EMA Australian GCP Inspections – the Statistics – cont.

Nos. Of Pivotal Trials in MAAs - submitted to the EMA with participation from the ROW region 2005 – 2011* (selected data):

Russia – highest:	222 - 126 ptt. / trial
Australia - 2. highest:	217 - 56 ptt. / trial
India -	148 – 113 ptt. / trial
China -	39 – 206 ptt. / trial
USA	681 – 391 ppt. / trial
Germany	421 – 145 ppt. / trial
Denmark	119 – 91 ppt. / trial

*) '*Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency*' of 11 December 2013 – EMA/INS/GCP/676319/2012

Please share experience w/ HA inspections – anyway Always Be Prepared QUESTIONS ??