Good Laboratory Practice (GLP) Case Studies

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CDER Inspections of Good Laboratory Practice, Animal Rule, and Bioavailability/Bioequivalence Study Sites – July 20, 2022

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Learning Objectives

- List the most commonly cited observations from GLP inspections
- Describe the handling of protocol deviations in GLP studies
- Describe the current issues encountered in GLP study reports translated into English

Most Common Noncompliance Observations from GLP Studies

- 21 CFR 58.35(b)(5): QAU failed to determine that protocol and SOP deviations were made without proper authorization and documentation
- 21 CFR 58.33(b): Study director failed to assure that all experimental data were accurately recorded and verified
- 21 CFR 58.81(b): SOPs have not been established
- 21 CFR 58.35(b)(6): QAU did not review the final report
- 21 CFR 58.51: Archives
- 21 CFR 58.113(a)(1): Formulation analysis

Observations Discussed Today

- Protocol deviation
  - 21 CFR 58.35(b)(5)
- Report translation/data accuracy
  - 21 CFR 58.35(b)(6), 58.33(b), 58.185(c), and 58.185(a)(12)

Case #1 – Protocol Deviation

Case #1 – GLP Toxicology Study

- Test system, Dose Groups
  - Cynomolgus macaque, experimentally naïve
  - 3 males/3 females in the control group
  - 5 males/5 females in low, mid and high dose groups
- Intravenous slow bolus
- Dosing twice a day (AM and PM) for 4 days; once a week thereafter
- 28 days, 14-day untreated recovery period

Case #1 – GLP Toxicology Study

- Assessments included
  - Ophthalmology
  - Electrocardiography
  - Body weight
  - Clinical observations
  - Clinical pathology (hematology, clinical chemistry, coagulation)
  - Necropsy (macroscopic findings)
  - Histopathology (microscopic findings)

Case #1 – GLP Toxicology Study

Study Day 2

- High dose females showing clinical signs of toxicity after AM dose; clinical signs increase in severity for 3 of the 5 females after the PM dose
- No males or lower dose females showing signs
- Controls remain normal
- Clinical pathology of affected animals show signs of dehydration

Case #1 – GLP Toxicology Study

Study Day 3 AM

- High dose females show clinical signs of toxicity after AM dose; more severe than seen on Day 2
- High dose males showing similar but minimal clinical signs of toxicity
- No lower dose males or females showing signs; controls normal
- Affected animals show clinical pathology results consistent with dehydration and renal impairment

Case #1 – GLP Toxicology Study

Study Day 3 Noon

- High dose females still showing clinical signs of toxicity
- Study Director & clinical veterinarian decide to stop dosing all high dose females
- Study Director creates Protocol Amendment to stop dosing high dose females and sends to Sponsor for signature per facility SOP
- Study Director sends email to technical staff alerting them to stop dosing all high dose females

Case #1 – GLP Toxicology Study

Study Day 3 at 4 PM

- All animals except the high dose females are dosed per the study protocol.
- Clinical conditions of three high-dose females continue to deteriorate and animals are euthanized in moribund condition.

Case #1 – GLP Toxicology Study

Study Day 4

- All animals except the high dose females are dosed per the study protocol.
- Sponsor signed and returned the Protocol Amendment to the Study Director
- Study Director signed the Protocol Amendment
- Protocol Amendment is distributed to study staff

Case #1 – GLP Toxicology Study

Study Days 5-28; Recovery Period

- All remaining animals are dosed per the study protocol
- Male high dose animals show clinical signs of toxicity however they remain minimal; no clinical signs during the recovery period
- No other animals show clinical signs of toxicity
- Clinical pathology assessments show evidence of renal impairment in mid- and high-dose males and females

Case #1 – GLP Toxicology Study

Necropsy and Histopathology

- All remaining animals survive to scheduled study termination.
- No test article-related findings at necropsy
- Histopathology shows evidence of dose-dependent renal epithelial cell damage with casts

Poll Question #1

In the study described, did a protocol deviation occur?

A. No, the Protocol Amendment covered the change in dosing

B. No, the Study Director email covered the change in dosing

C. Yes, the change in dosing was not covered by the Protocol Amendment

D. No, the stopped dosing was due to animal welfare

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Pause for Discussion

Case #1 – GLP Toxicology Study

Correct Answer will be reviewed

Case #1 – GLP Toxicology Study

Observation

The quality assurance unit failed to determine whether any deviations from approved protocols or standard operating procedures had been made without proper authorization and documentation.

Reference 21 CFR 58.35(b)(5)

Case #2 – Translation/Report Accuracy

Case #2 – Translation/Report Accuracy

- The number of GLP studies conducted in foreign countries and submitted to the FDA is increasing
- Many reports from non-English speaking countries are translated from their native languages
  - China, Korea, Japan, Taiwan
- FDA/CDER review divisions have concerns related to the accuracy of translated documents

Case #2 – Translation/Report Accuracy

English translation of the final study report does not accurately reflect the raw data reported in the studies

- Misspellings/typographical errors
- Inaccurate translation
- Omissions: paragraphs or an amended report
- Mislabeled parameters
- Wrong tables
- Table formatting errors

Case #2 – Translation/Report Accuracy

Inconsistency between GLP regulations followed

- Original Compliance Statement and translated Compliance Statement report difference regulations followed

No consistent practice on signatures/dates on translated reports

- Translated study report was not signed and dated
- Study Director's name was printed on translated version by translator
- Translated study report was signed/dated by the Study Director

Case #2 – Translation/Report Accuracy

- English proficiency is often limited for staff, including Study Directors and QAU staff
  - Cannot review/verify accuracy of translation
- No SOPs in place or did not follow SOPs for translation process
  - Translation performed by bilingual staff
  - Translation performed by Study Director
  - Contract the translation procedure to friends
  - Study director and QAU not able to check accuracy of translation

Case #2 – Translation/Report Accuracy

- Some non-OECD member foreign firms have studies conducted in compliance with their own GLP regulations
  - Originally performed for submissions in their countries
  - New firms did not know FDA's expectations
- For a non-OECD member country, studies conducted for US submission should be conducted following US GLP regulations
- Review divisions sometimes ask for OSIS inspection background for their decision making

Case #2 – Translation Deficiency 1

- Inaccurate data with the translated report

Case #2 – Translation Deficiency 1

续表 15：

测定时间	组别	剂量（g/kg.bw）	Ca（mmol/L）	LDH（U/L）	GLB（g/L）	TBA（umol/L）	CysC（mg/L）	GLDH（U/L）
给药前（n=10）	明胶对照组	—	2.75±0.08	90.70±21.94	25.12±1.93	5.24±1.34	0.64±0.27	5.16±1.12
	低剂量组	1.125	2.73±0.07	116.25±39.84	24.92±2.11	4.96±1.28	0.64±0.37	5.04±0.91
	中剂量组	2.250	2.72±0.07	115.55±41.42	25.94±3.35	4.51±1.81	0.70±0.45	4.86±1.12
	高剂量组	4.500	2.74±0.06	107.45±44.35	26.04±2.06	4.76±1.02	0.66±0.25	5.04±1.34
给药2周（n=10）	明胶对照组	—	2.69±0.05	115.60±33.68	23.79±1.81	4.80±1.09	0.38±0.05	5.10±1.00
	低剂量组	1.125	2.68±0.10	133.20±64.84	24.03±1.70	5.87±5.11	0.39±0.04	4.69±2.35
	中剂量组	2.250	2.67±0.10	148.20±85.94	26.13±2.40	4.08±0.33	0.37±0.03	4.70±1.83
	高剂量组	4.500	2.66±0.07	107.60±41.81	26.24±3.62	4.87±1.09	0.37±0.02	21.82±37.98
给药4周（n=10）	明胶对照组	—	2.68±0.06	99.90±36.86	25.01±2.08	4.39±0.86	0.31±0.06	6.49±2.21
	低剂量组	1.125	2.69±0.10	117.90±48.54	25.82±2.38	4.21±0.35	0.43±0.13◆	7.23±3.86
	中剂量组	2.250	2.68±0.09	113.90±42.54	27.91±3.13◆	4.09±0.23	0.38±0.08◆	9.05±3.96
	高剂量组	4.500	2.68±0.08	110.30±41.81	28.17±2.01◆	4.71±2.54	0.34±0.06★	10.31±8.26
恢复4周（n=4）	明胶对照组	—	2.77±0.05	146.00±46.18	28.40±2.30	4.20±0.73	0.52±0.13	7.08±2.02
	低剂量组	1.125	2.82±0.13	137.25±22.10	27.45±3.17	4.18±0.41	0.72±0.15	6.60±1.70
	中剂量组	2.250	2.72±0.05	188.75±78.05	31.58±4.58	3.98±0.78	0.50±0.17	4.08±2.21
	高剂量组	4.500	2.79±0.06	211.00±60.40	29.08±3.69	5.88±3.51	0.68±0.24	7.80±1.83
恢复6周（n=4）	明胶对照组	—	2.59±0.04	144.75±41.11	28.45±3.76	4.30±0.29	0.88±0.24	7.25±2.39
	低剂量组	1.125	2.62±0.08	176.50±55.02	26.18±2.24	4.42±0.26	0.86±0.12	7.58±3.38
	中剂量组	2.250	2.52±0.06	226.00±65.25	29.20±4.86	4.38±0.22	0.77±0.08	4.30±1.77
	高剂量组	4.500	2.60±0.09	210.00±43.43	26.90±1.06	5.22±1.44	0.86±0.25	5.40±1.82

统计学分析：◆与明胶对照组比较有显著性差异($p<0.05$)；★与低剂量组比较有显著性差异($p<0.05$)；

注：1. 给药前各指标 $\bar{x} \pm s$ 为给药前第 1、2 次检测值平均值统计结果；

2. n 为各组动物数；

Case #2 – Translation Deficiency 1

Table 15 (contd.):

Testing time	Groups	Final dose (g/kg.bw)	Ca (mmol/L)	LDH (mmol/L)	GLB	TBA (mmol/L)	CK-MB (mmol/L)	CysC (U/L)	GLDH (mmol/L)
Before administration (n = 10)	Gelatin	—	2.75±0.0	90.70±21.9	25.12±1.	5.24±1.3	0.64±0.	5.16±1.12	2.75±0.
	Low-dose	1.125	2.73±0.0	116.25±39.	24.92±2.	4.96±1.2	0.64±0.	5.04±0.91	2.73±0.
	Middle-do	2.250	2.72±0.0	115.55±41.	25.94±3.	4.51±1.8	0.70±0.	4.86±1.12	2.72±0.
	High-dose	4.500	2.74±0.0	107.45±44.	26.04±2.	4.76±1.0	0.66±0.	5.04±1.34	2.74±0.
Week 2 of administration (n = 10)	Gelatin	—	2.69±0.0	115.60±33.	23.79±1.	4.80±1.0	0.38±0.	5.10±1.00	2.69±0.
	Low-dose	1.125	2.68±0.1	133.20±64.	24.03±1.	5.87±5.1	0.39±0.	4.69±2.35	2.68±0.
	Middle-do	2.250	2.67±0.1	148.20±85.	26.13±2.	4.08±0.3	0.37±0.	4.70±1.83	2.67±0.
	High-dose	4.500	2.66±0.0	107.60±41.	26.24±3.	4.87±1.0	0.37±0.	21.82±37.	2.66±0.
Week 4 of administration (n = 10)	Gelatin	—	2.68±0.0	99.90±36.8	25.01±2.	4.39±0.8	0.31±0.	6.49±2.21	2.68±0.
	Low-dose	1.125	2.69±0.1	117.90±48.	25.82±2.	4.21±0.3	0.43±0.	7.23±3.86	2.69±0.
	Middle-do	2.250	2.68±0.0	113.90±42.	27.91±3.	4.09±0.2	0.38±0.	9.05±3.96	2.68±0.
	High-dose	4.500	2.68±0.0	110.30±41.	28.17±2.	4.71±2.5	0.34±0.	10.31±8.2	2.68±0.
Week 4 of recovery (n = 4)	Gelatin	—	2.77±0.0	146.00±46.	28.40±2.	4.20±0.7	0.52±0.	7.08±2.02	2.77±0.
	Low-dose	1.125	2.82±0.1	137.25±22.	27.45±3.	4.18±0.4	0.72±0.	6.60±1.70	2.82±0.
	Middle-do	2.250	2.72±0.0	188.75±78.	31.58±4.	3.98±0.7	0.50±0.	4.08±2.21	2.72±0.
	High-dose	4.500	2.79±0.0	211.00±60.	29.08±3.	5.88±3.5	0.68±0.	7.80±1.83	2.79±0.
Week 6 of recovery (n = 4)	Gelatin	—	2.59±0.0	144.75±41.	28.45±3.	4.30±0.2	0.88±0.	7.25±2.39	2.59±0.
	Low-dose	1.125	2.62±0.0	176.50±55.	26.18±2.	4.42±0.2	0.86±0.	7.58±3.38	2.62±0.
	Middle-do	2.250	2.52±0.0	226.00±65.	29.20±4.	4.38±0.2	0.77±0.	4.30±1.77	2.52±0.
	High-dose	4.500	2.60±0.0	210.00±43.	26.90±1.	5.22±1.4	0.86±0.	5.40±1.82	2.60±0.

Statistical analysis: There was significant difference between ◆ and gelatin control group ($p<0.05/0.01$); there was significant difference between ★ and low-dose group ($p<0.05/0.01$);

Note: 1. $\bar{x} \pm s$ before administration was the statistical results of average value measured 2 times before administration; 2. n is the number of animals in each group.

Case #2 – Translation Deficiencv 1

表 17　Beagle 犬给药前和给药 2、4 周及恢复 4、6 周血液学各指标组间比较结果（$\bar{x}\pm s$）

测定时间	组别	剂量（g/kg·bw）	WBC（10^9/L）	NEU（10^9/L）	LYM（10^9/L）	MONO（10^9/L）	EOS（10^9/L）	BASO（10^9/L）	NEU（%）	LYM（%）	MONO（%）
给药前（n=10）	明胶对照组	—	11.18±1.98	6.36±1.74	3.75±0.45	0.53±0.09	0.42±0.18	0.08±0.03	55.66±7.06	34.56±6.15	4.80±0.93
	低剂量组	1.125	10.12±2.02	5.74±1.42	3.26±1.07	0.48±0.08	0.54±0.26	0.06±0.02	56.48±7.42	32.27±6.31	4.87±0.80
	中剂量组	2.250	10.36±2.18	5.97±1.50	3.21±0.87	0.58±0.15	0.49±0.20	0.06±0.02	57.10±6.04	31.34±5.88	5.70±1.21**
	高剂量组	4.500	11.17±2.12	6.62±1.47	3.51±1.00	0.47±0.09	0.47±0.20	0.07±0.02	58.94±7.00	31.66±6.73	4.20±0.54▲▲
给药 2 周（n=10）	明胶对照组	—	10.33±3.08	5.82±2.22	3.57±0.78	0.50±0.18	0.31±0.12	0.09±0.04	55.25±6.82	35.48±5.60	5.02±1.71
	低剂量组	1.125	9.46±1.67	5.37±0.80	3.12±0.84	0.47±0.05	0.40±0.31	0.07±0.02	57.10±4.73	32.75±4.28	5.07±0.81
	中剂量组	2.250	10.51±2.66	6.38±2.22	3.20±0.81	0.56±0.13	0.26±0.18	0.08±0.02	59.60±9.05	31.29±8.15	5.39±0.95
	高剂量组	4.500	12.43±5.72	8.07±5.15	3.42±0.77	0.56±0.28	0.26±0.14	0.07±0.03	61.91±9.18	30.14±8.78	4.49±0.52
给药 4 周（n=10）	明胶对照组	—	10.58±2.36	6.27±1.96	3.22±0.79	0.59±0.18	0.39±0.13	0.08±0.05	58.33±7.51	31.28±7.84	5.74±1.73
	低剂量组	1.125	8.91±1.94	5.11±1.14	2.95±1.19	0.46±0.13	0.30±0.19	0.06±0.03	57.81±7.16	32.64±7.47	5.32±1.52
	中剂量组	2.250	9.74±1.74	5.66±1.37	3.07±0.99	0.63±0.18	0.27±0.19	0.07±0.03	57.90±8.75	31.68±8.74	6.57±2.10
	高剂量组	4.500	11.30±4.71	7.08±4.00	3.28±0.83	0.61±0.29	0.22±0.14	0.08±0.03	60.53±7.39	30.86±7.33	5.38±0.89
恢复 4 周（n=4）	明胶对照组	—	13.38±3.59	8.30±3.11	3.99±0.31	0.61±0.26	0.29±0.08	0.14±0.09	60.58±8.39	31.45±8.66	4.45±0.74
	低剂量组	1.125	10.20±2.68	5.36±0.99	3.96±1.49	0.38±0.06	0.38±0.32	0.08±0.03	53.50±6.23	38.12±4.95	3.82±0.74
	中剂量组	2.250	11.11±1.79	6.08±0.75	3.95±1.39	0.55±0.06	0.39±0.20	0.09±0.02	55.35±7.66	34.98±7.72	5.05±1.00
	高剂量组	4.500	12.00±2.38	6.92±1.61	4.08±1.47	0.49±0.12	0.38±0.27	0.09±0.02	57.82±7.85	33.88±8.12	4.08±0.46
恢复 6 周（n=4）	明胶对照组	—	10.65±1.51	6.38±1.40	3.28±0.61	0.50±0.11	0.34±0.15	0.10±0.07	59.48±7.87	31.30±7.92	4.72±0.48
	低剂量组	1.125	11.26±3.62	6.64±2.09	3.70±1.31	0.48±0.13	0.34±0.27	0.07±0.02	59.18±5.09	32.95±5.15	4.28±0.31
	中剂量组	2.250	10.27±2.58	5.71±1.67	3.67±1.43	0.52±0.09	0.27±0.13	0.08±0.01	55.58±9.26	35.58±8.91	5.15±0.69
	高剂量组	4.500	10.91±1.46	6.51±0.38	3.52±1.23	0.40±0.08	0.37±0.25	0.08±0.02	60.20±6.15	31.82±7.00	3.73±0.73*▲▲

统计学分析：*与明胶对照组比较有显著性差异（$p<0.05$）；*与低剂量组比较有显著性差异（$p<0.05$）；▲▲与中剂量组比较有显著性差异（$p<0.01$）；

注：1. 给药前各指标 $\bar{x}\pm s$ 为给药前第 1、2 次检测值平均值统计结果；

2. n 为各组动物数；

Case #2 – Translation Deficiency 1

Table 17 Inter-comparision results of hematology indicators before administration, at week 2 and 4 of administration, and at week 4 and 6 of recovery ($\overline{x}$ ±s)

Testing time	Groups	Final dose (g/kg.bw)	WBC (10^9/L)	NEU (%)	LYM (%)	MONO (%)	EOS (%)	BASO (%)	RBC (10^12/L)	HGB (g/L)	HCT (%)	MCV (fL)
Before administration (n=10)	Gelatin control group	—	11.18±1.98	6.36±1.74	3.75±0.45	0.53±0.09	0.42±0.18	0.08±0.03	55.66±7.06	34.56±6.15	4.80±0.93	11.18±1.98
	Low-dose group	1.125	10.12±2.02	5.74±1.42	3.26±1.07	0.48±0.08	0.54±0.26	0.06±0.02	56.48±7.42	32.27±6.31	4.87±0.80	10.12±2.02
	Middle-dose group	2.250	10.36±2.18	5.97±1.50	3.21±0.87	0.58±0.15	0.49±0.20	0.06±0.02	57.10±6.04	31.34±5.88	5.70±1.21◆★	10.36±2.18
	High-dose group	4.500	11.17±2.12	6.62±1.47	3.51±1.00	0.47±0.09	0.47±0.20	0.07±0.02	58.94±7.00	31.66±6.73	4.20±0.54▲▲	11.17±2.12
Week 2 of administration (n = 10)	Gelatin control group	—	10.33±3.08	5.82±2.22	3.57±0.78	0.50±0.18	0.31±0.12	0.09±0.04	55.25±6.82	35.48±5.60	5.02±1.71	10.33±3.08
	Low-dose group	1.125	9.46±1.67	5.37±0.80	3.12±0.84	0.47±0.05	0.40±0.31	0.07±0.02	57.10±4.73	32.75±4.28	5.07±0.81	9.46±1.67
	Middle-dose group	2.250	10.51±2.66	6.38±2.22	3.20±0.81	0.56±0.13	0.26±0.18	0.08±0.02	59.60±9.05	31.29±8.15	5.39±0.95	10.51±2.66
	High-dose group	4.500	12.43±5.72	8.07±5.15	3.42±0.77	0.56±0.28	0.26±0.14	0.07±0.03	61.91±9.18	30.14±8.78	4.49±0.52	12.43±5.72

Case #2 – Form 483 Observation

- The quality assurance unit failed to review the final study report to assure that such report accurately described the methods and standard operating procedures, and that the reported results accurately reflected the raw data of the study

- The study director failed to assure that all experimental data were accurately recorded and verified.

  – Reference 21 CFR 58.35(b)(6), 21 CFR 58.33(b)

  – The English translation of the final reports does not accurately reflect the raw data reported in the Chinese version of the report.

Case #2 – Other Translation Observations

- Corrections or additions to a final report shall be in the form of an amendment by the study director
  - Reference 21 CFR 58.185(c)
  - Report amendments were not translated
- A final report shall be prepared for each nonclinical laboratory study and shall include the signed and dated report of each of the individual scientist or other professionals involved in the study
  - Reference 21 CFR 58.185(a)(12)
  - Signed pathology report not attached to the translated final reports

Case #2 – Translation Deficiency 2

- Inadequate handling of signatures and dates
- Study Director and QAU signatures and dates left blank
- Compliance statement signature and date left blank

Case #2 – Translation Deficiency 3

- Inadequate handling of signatures and dates
- Study Director and QAU signatures and compliance statement dated when the report was translated

Case #2 – Translation Deficiency 4

- Compliance statement implies compliance with 21 CFR part 58

Questions for Consideration

- Who should do the translation?
  - Contract to a professional translator?
  - Study Director or QAU staff?
  - Laboratory staff?
  - Friend?
- Is a certificate of translation or a statement from the translator about the translation needed?
- What do the dates and signatures mean on translations of study reports?

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Pause for Discussion

Expectations

- SOP for study translation process is available and followed
- Translation performed by a qualified translator
- If possible, translated study report should be accompanied by a signed certificate of translation
  - Signed/dated statement from the translator
    - the translation is an accurate representation of the original document
    - who performed the translation and the date of the translation

Expectations

- Translated reports
  - Should not contain signatures
  - Should contain the typed names (Study Director, QAU, Test Facility Management) and dates of the original document
- Review division may request BOTH the original document (native language) and translated documents
- Poorly translated documents may be brought to the GLP team's attention by the review divisions for follow-up

Resources

- FDA GLP Regulations – 21 CFR Part 58
  - Good Laboratory Practice for Nonclinical Laboratory Studies
    - describes requirements for conducting and reporting nonclinical laboratory studies
- Compliance Program
  - Good Laboratory Practice Program 7348.808
    - general inspectional focus; minimum information that must be obtained during an inspection
    - http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133765.pdf

Summary

- OSIS serves as one of the last sets of eyes for authenticating data, and to provide assurance that the data supporting regulatory decisions are reliable
- The case studies presented today highlight two of the common noncompliance observations from GLP studies – failure to identify and issue protocol deviations when required and issues observed in English translations of final study reports from GLP studies
- GLP regulations provide the framework to ensure the quality and integrity of data from nonclinical studies so any noncompliance may impact the quality of the data submitted for review
- Valid nonclinical safety data are essential to hazard identification and risk assessments for clinical trials

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Questions?

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Closing Thought

Remember that the quality, integrity and regulatory compliance of GLP nonclinical studies that you submit have a direct impact on the welfare of study subjects and public health as a whole.


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