COMMON GCP INSPECTION FINDINGS FOR 2014

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Health Sciences Authority

OUTLINE

- GCP Inspection Framework
- Classification of GCP Inspection Findings
- Common GCP Inspection Findings for 2014
- Quality Improvement Initiatives for 2014

GCP Inspection Framework

66!

- Launched in Sep 2009;
- Completed 66 GCP Site Inspections to date:
  - 2009-2010 : 13 (Protocol-specific)
  - 2011 : 15 (Protocol-specific), 1 (Systems on ICF and IP)
  - 2012: 10 (Protocol-specific), 1 (Systems on ICF and IP)
  - 2013: 10 (Protocol-specific)
  - 2014: 15 (Protocol-specific), 1 (Systems on ICF and IP)

Objectives of GCP Inspection

- To safeguard the Rights, Safety and Well-Being of trial subjects.
- To verify the Quality and Integrity of the clinical trial data submitted to the Regulatory Authority.
- To assess Compliance to protocol and applicable regulations, guidelines and standard operating procedures for clinical trials.

Classification of GCP Inspection Findings

~ adopted from EMEA SOPs on GCP Inspection.

- **Critical:** 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**: 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.

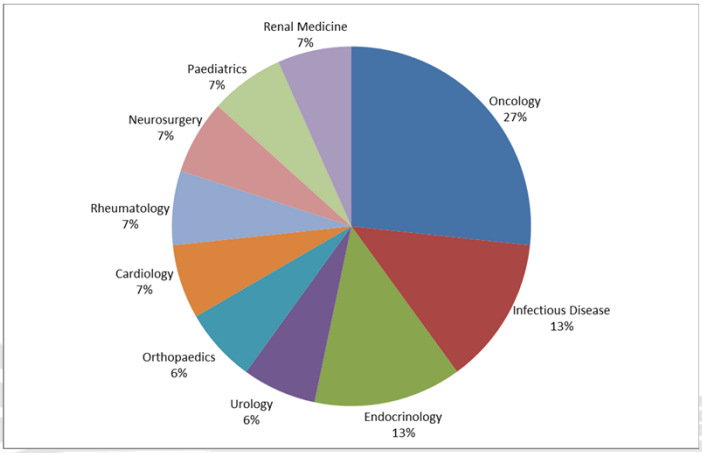
Classification of GCP Inspection Findings

~ adopted from EMEA SOPs on GCP Inspection.

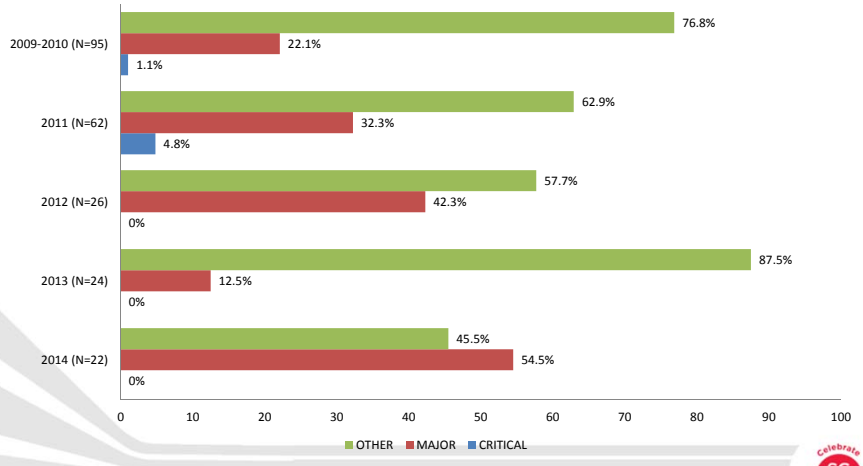
- **Other**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.
- **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

GCP Inspections in 2014

- Distribution of Therapeutic Areas (N=15)



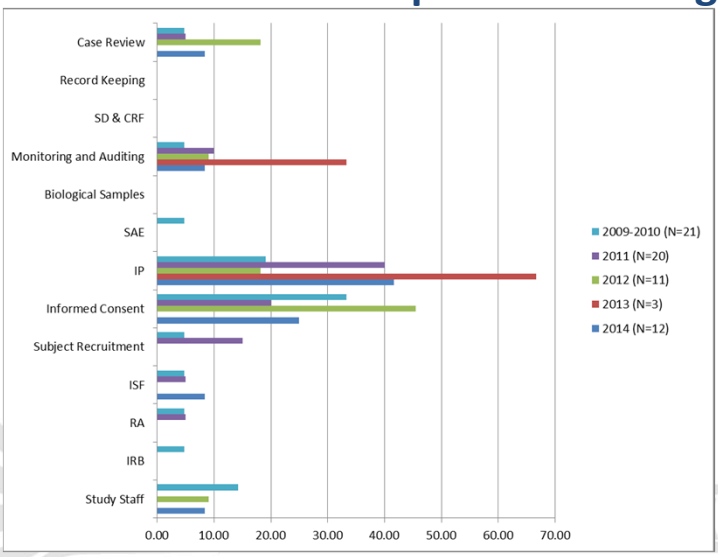
Distribution of GCP Inspection Findings



GCP Site Inspections (2014)
CRITICAL GCP Inspection Findings

- None ☺

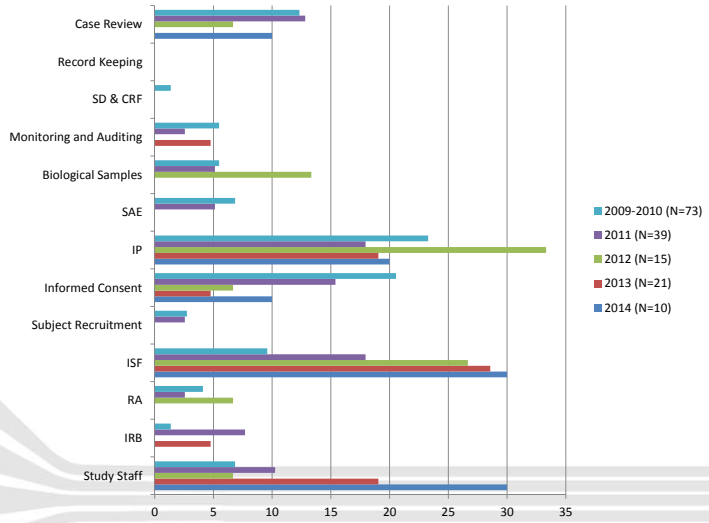
GCP Site Inspections (2014)
MAJOR GCP Inspection Findings



MAJOR
GCP Inspection Findings (2014)

- Investigational Product
- Informed Consent

GCP Site Inspections (2014)
OTHER GCP Inspection Findings



OTHER

GCP Inspection Findings (2014)

- Study Staff
- Investigator Site File
- Investigational Product

CASE STUDIES

Study Overview

- **Protocol:** A Phase 2, randomised, placebo-controlled study to compare the safety and efficacy of ABC Vaccine for Hepatitis B.
- **Sponsor :** Care Bear Hospital
- **Site:** Care Bear Hospital
- **Principal Investigator :** Dr John Doe
- **Sub-investigator:** Ms Jane Tan (Post-grad medical student)

SIGNATURE SHEET

PROTOCOL TITLE: A Phase 2, randomised, placebo-controlled study to compare the safety and efficacy of ABC Vaccine for Hepatitis B.

PROTOCOL NO.: ABC | **PRINCIPAL INVESTIGATOR: Dr John Doe** | **SITE NAME: Care Bear Hospital**

Name of Study Staff	Study Role*	Delegated Study Responsibilities	Start Date	End Date	Initials of Study Staff	Signature of Study Staff	Authorization by Principal Investigator (Signature and Date)	CV collected (Tick)
Dr John Doe	Principal Investigator	1,2,3,4,5,6,7,8,9, 10,11,12,13,14,15,16	1 Dec 2014		J. D.	JDoe		☑
Ms Jane Tan	Sub-investigator	1,2,3,4,11,12,13,14, 15,16	1 Dec 2014		J. T.	Jane		☑
								☐
								☐

LIST OF STUDY RESPONSIBILITIES*

1. Subject Screening	6. Reviewing ECG Results	11. Obtaining Vital Signs and Demographics	16. Managing study supplies
2. Obtaining Informed Consent	7. Signing Case Report Forms	12. Making data entries and corrections into CRFs	17. Randomization
3. Confirming Subject Eligibility	8. Signing off Data Queries	13. Investigational Product Management	18. Others:
4. Performing Physical Examination	9. Safety Reporting	14. Handling Biological Samples	19. Others:
5. Reviewing Laboratory Results	10. Communicating with IRB and HSA	15. Maintaining Investigator Site Files	20. Others:

*Responsibilities 1-9 should be delegated to a locally registered medical doctor or dentist, whilst the remaining responsibilities may be delegated to other study staff.

To be signed by Principal Investigator at Site Closing Visit:

I confirm that the individuals listed are authorised and qualified by education, training and experience to conduct the study responsibilities assigned. The overall assurance for the quality and accuracy of all study data is my responsibility as the Principal Investigator.

Name of Principal Investigator | Signature | Date

Version Date: 1 Dec 2014 | Page 1

SCENARIO 1
Subject 001/B-T

Ben Tan	Jan	5/12/2014
Name of Subject	Signature	Date
Name of Parent / LAR	Signature	Date
Name of Witness	Signature	Date
Jane Tan	Jane	5th Dec 2014
Name of Person Obtaining Consent	Signature	Date

ICF dated 1 Dec 2014

17

SCENARIO 1 - ANSWER
Subject 001/B-T

Ben Tan	Jan	5/12/2014
Name of Subject	Signature	Date
	Jane Tan was not adequately qualified to obtain informed consent for Subject 001/B-T. [Ref: SGGCP 4.3.1, 4.8.7]	
Name of Parent / LAR	Signature	Date
Name of Witness	Signature	Date
Jane Tan	Jane	5th Dec 2014
Name of Person Obtaining Consent	Signature	Date

ICF dated 1 Dec 2014

18

OBTAINING INFORMED CONSENT

- Locally registered medical doctor / dentist
- Authorised by the Principal Investigator
  - Sign Signature Sheet

SCENARIO 2A
Subject 002/X-M

Name of Subject	Signature	Date
小明	明	5/12/2014
Name of Parent / LAR	Signature	Date
Nicole Lim	Nicole	5 Dec 2014
Name of Witness	Signature	Date
Dr John Doe	J Doe	5th Dec 2014
Name of Person Obtaining Consent	Signature	Date

ICF dated 1 Dec 2014

SCENARIO 2B
Subject 003/TBH

Name of Subject	Signature	Date
Tan Boon Hao		5/12/2014
Name of Parent / LAR	Signature	Date
小明		5/12/2014
Name of Witness	Signature	Date
Dr John Doe	J Doe	5th Dec 2014
Name of Person Obtaining Consent	Signature	Date

ICF dated 1 Dec 2014

SCENARIO 2B - ANSWER
Subject 003/TBH

Name of Subject	Signature	Date
Tan Boon Hao		5/12/2014
Name of Parent / LAR	Signature	Date
小明		5/12/2014
Name of Witness	Signature	Date
Dr John Doe	J Doe	5th Dec 2014
Name of Person Obtaining Consent	Signature	Date

Impartial witness for informed consent of Subject 003/TBH was inappropriate, as the impartial witness had required an impartial witness for her informed consent when she had been enrolled as Subject 002/X-M for the same clinical trial . [Ref: Medicines (CT) Regs 11(5) and SGGCP 4.8.9].

ICF dated 1 Dec 2014

SCENARIO 3

Subject 004/WLL

王丽丽	丽	5 Dec 2014
患者姓名	患者签名	日期
患者的合法授权代表姓名	患者的合法授权代表签名	日期
Deepa Singh	Deepa	5/12/2014
公正见证人姓名	公正见证人签名	日期
Dr John Doe	JDoe	5th Dec 2014
获取同意人姓名	获取同意人签名	日期

ICF dated 1 Dec 2014

23

SCENARIO 3

Subject 004/WLL

王丽丽	丽	5 Dec 2014
患者姓名		
患者的合法授权代表姓名		
Deepa Singh	Deepa	5/12/2014
公正见证人姓名	公正见证人签名	日期
Dr John Doe	JDoe	5th Dec 2014
获取同意人姓名	获取同意人签名	日期

Impartial witness for informed consent of Subject 004/WLL was inappropriate, as the impartial witness was unable to read the Mandarin informed consent form dated 1 Dec 2014 [Ref: Medicines (CT) Regs 11(5) and SGGCP 4.8.9].

ICF dated 1 Dec 2014

24

IMPARTIAL WITNESS FOR INFORMED CONSENT

SGGCP Section 1.26

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Choice of impartial witness:

- ❑ Family member / friend
- ❑ Clinic staff (non-study staff)
- ❑ Lay person from the street

Role of impartial witness:

- ❑ Accurate explanation
- ❑ Understood
- ❑ Voluntary participation

SCENARIO 5

A Randomization Plan
from
http://www.randomization.com

```
68001. Placebo
68002. Active
68003. Placebo
68004. Active
68005. Placebo
68006. Active
68007. Active
68008. Active
68009. Placebo
68010. Active
68011. Placebo
68012. Placebo
```

12 subjects randomized into 2 blocks
To reproduce this plan, use the seed 9097
along with the number of subjects per block/number of blocks
and (case-sensitive) treatment labels as entered originally.
Randomization plan created on Wednesday, 3 December, 2014 4:08:09 PM

SCENARIO 5 - ANSWER

A Randomization Plan
from
http://www.randomization.com

68001. Placebo
68002. Active
68003. Placebo
68004. Active
68005. Placebo
68006. Active
68007. Active
68008. Active
68009. Placebo
68010. Active
68011. Placebo
68012. Placebo

12 subjects randomized into 2 blocks
To reproduce this plan, use the seed 9097
along with the number of subjects per block/number of blocks
and (case-sensitive) treatment labels as entered originally.
Randomization plan created on Wednesday, 3 December, 2014 4:08:09 PM

Lack of quality systems in the Master Randomisation List [Ref: SGGCP 2.13]:
(a) Lack of traceability to the study protocol.
(b) Lack of documentation of who had generated the Master Randomisation List.
(c) Lack of traceability to the names of the actual IP used in the clinical trial.

SCENARIO 6
Subject 001/B-T

- **Source Document Template (Abstract):**

Subject ID: *001/B-T* Visit 1 Date: *5 Dec 2014*
Date of birth: *1 Oct 1974* Gender: Male / ~~Female~~
Informed Consent Date: *5 Dec 2014*
Was subject eligible for enrollment? Yes / ~~No~~

1 mL ABC vaccine / ~~placebo~~ administered via IM on 5 Dec 2014.

SCENARIO 6 - ANSWER
Subject 001/B-T

- **Source Document Template (Abstract):**

Subject ID: *001/B-T* Visit 1 Date: *5 Dec 2014*
Date of birth: *1 Oct 1974* Gender: Male / ~~Female~~
Informed Consent Date: *5 Dec 2014*
Was subject eligible for enrollment? Yes / ~~No~~

1 mL ABC vaccine / ~~placebo~~ administered via IM on 5 Dec 2014.

Lack of quality systems in source document template as there was no document control and it was not possible to attribute who had captured the source data [Ref: SGGCP 2.13]

Treatment assignment had been unblinded in Source Document Template for Subject 001/B-T [Ref: SGGCP 2.10 and 4.7].

29

SCENARIO 7
Prescription for Subject 001/B-T

CARE BEAR HOSPITAL
88 CARE BEAR ROAD, SINGAPORE 226688

Protocol ABC
Subject ID: 001/B-T

DRUG NAME	DOSE AND FREQUENCY
IM ABC Vaccine / Placebo	*1 mL stat*

5th Dec 2014	*Dr John Doe*	*J Doe*
DATE	**DOCTOR'S NAME**	**DOCTOR'S SIGNATURE**

30

SCENARIO 7 - ANSWER
Prescription for Subject 001/B-T

CARE BEAR HOSPITAL
88 CARE BEAR ROAD, SINGAPORE 226688

Protocol ABC
Subject ID: 001/B-T

DRUG NAME	DOSE AND FREQUENCY
IM ABC Vaccine / Placebo	1 mL stat

5th Dec 2014	Dr John Doe	JDoe
DATE	DOCTOR'S NAME	DOCTOR'S SIGNATURE

Lack of subject identifiers in prescription [Ref: SGGCP 2.13]

31

SCENARIO 8

INVESTIGATIONAL PRODUCT (IP) DISPENSING AND ACCOUNTABILITY LOG

PROTOCOL TITLE: A Phase 2, randomised, placebo-controlled study to compare the safety and efficacy of ABC Vaccine for Hepatitis B.

PROTOCOL NO.: ABC | INVESTIGATIONAL PRODUCT: ABC / PLACEBO | PRINCIPAL INVESTIGATOR: DR JOHN DOE | SITE NAME: CARE BEAR HOSPITAL

IP RECEIPT FROM PHARMACY					IP DISPENSING TO SUBJECT				IP RETURN TO PHARMACY FOR DESTRUCTION				VERIFICATION BY MONITOR	
Date IP received from Pharmacy	Treatment Kit No.	Lot No.	Expiry Date	IP received by (Initials)	Date IP dispensed	Subject ID	Vol. of IP dispensed	IP Dispensed by (Initials)	Date returned	No. of syringes returned	Initials	Date	Initials	Date
1 Dec 2014	68001	A246	Dec 2015	JT	5 Dec 14	001/ B-T	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68002	A246	Dec 2015	JT	5 Dec 14	002/ X-M	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68003	A246	Dec 2015	JT	5 Dec 14	003/ TBH	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68004	A246	Dec 2015	JT	5 Dec 14	004/ WLL	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68005	A246	Dec 2015	JT										

Version Date: 1 Dec 2014 Page 1

32

SCENARIO 8 - ANSWER

INVES[illegible]IONAL PRODUCT (IP) DISPENSING AND ACCOUNTA[illegible]LOG

PROTOCOL TITLE: A [illegible]-2, randomised, placebo-controlled study to compare the safety and efficacy of ABC Vaccine for Hepatitis B.

PROTOCO[illegible]: ABC | INVESTIGATIONAL PRODUCT: ABC / PLACEBO | PRINCIPAL INVESTIGATOR: DR JOHN DOE | SITE NAME: CARE BEAR HOSPITAL

IP RECEIPT FROM PHARMACY					IP DISPENSING TO SUBJECT				IP RETURN TO PHARMACY FOR DESTRUCTION				VERIFICATION BY MONI[illegible]	
[illegible]ate IP received from Pharmacy	Treatment Kit No.	Lot No.	Expiry Date	IP received by (Initials)	Date IP dispensed	Subject ID	Vol. of IP dispensed	IP Dispensed by (Initials)	Date returned	No. of syringes returned	Initials	Date	Initials	Date
1 Dec 2014	68001	A246	Dec 2015	JT	5 Dec 14	001/ B-T	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68002	A246	Dec 2015	JT	5 Dec 14	002/ X-M	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 Dec 2014	68003	A246	Dec 2015	JT	5 Dec 14	003/ TBH	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 Dec 14
1 [illegible] 2014	68004	A246	Dec 2015	JT	5 Dec 14	004/ WLL	1 mL	JD	5 Dec 14	1	JT	5 Dec 14	CS	10 D[illegible]
1 Dec 2014	6800[illegible]	[illegible]246	Dec 2015	JT										

Lack of quality systems in the IP Dispensing and Accountability Log as it was maintained electronically [Ref: SGGCP 2.13].

Version Date: 1 Dec 2014 Page 1

33

Quality Improvement Initiatives

- Training
- CTB FAQs on HSA website
- Engaging stakeholders
- Observation of GCP Site Inspections
- Upstream consultation on IP management
- Sharing of Best Practices
- ICH E6 Workgroup
- Template Forms Repository
- Review of Serious Breaches

34

Commentary

DIA DEVELOP INNOVATE ADVANCE

General Principles for the Education and Training of GCP Inspectors: The Outcome of Discussions by International Regulatory Experts in the Discussion Group on ICH E6 guideline

Yoshiaki Uyama, PhD[1], Eriko Yamazaki, MS[1], Katherine Clark, BSc (Hons) PhD[2], Chao-Yi Wang, MSc[3], Endang Woro, MSc[4], Foo Yang Tong, BSc(Pharm)[5], Sumitra Sachidanandan, BSc(Pharm)(Hons)[5], Ana Rodriguez, PhD[6], Hojin Oh, PharmD[7], Kamaruzaman Saleh, BPharm(Hons), MSc, PhD[8], Joyce Cirunay[9], Akanid Wapeewuttikorn, BSc(Pharm), MSPH(Epidemiology)[10], Evgeny Rogov, MD, PhD, JD[11], Khaled W. Alshahwan, MPharm[12], Ileana Herrera, MD[13], Joseph Mthetwa, BSc (HONS) Pharmacology, MSc (Med), D.Clin.Med, A.D. Edu.[14], Fortunate Fakudze, BSc., BPHARM (Hons)[15], and Tomoko Osawa, PhD[1]; on behalf of the E6 Discussion Group under the International Pharmaceutical Regulators Forum

Abstract

In response to the globalization of drug development, regulatory inspection of Good Clinical Practice (GCP) has recently been conducted not only by International Conference on Harmonisation (ICH) regions but also non-ICH regions. To promote the international implementation of GCP, consistent understanding and interpretation of its concept among regions are important. This article summarizes the background and past activities of the E6 Discussion Group, established under the Regulators Forum.

Supplementary material for this article is available on the journal's website at http://dir.sagepub.com/supplemental.

[1]Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
[2]Therapeutic Goods Administration, Department of Health, Woden, Australia
[3]Food and Drug Administration, Taiwan, Chinese Taipei
[4]The National Agency of Drug and Food Control, Jakarta Pusat, Indonesia
[5]Health Sciences Authority, Singapore
[6]European Medicines Agency, London, UK
[7]Ministry of Food and Drug Safety, Cheongju, Korea
[8]National Pharmaceutical Control Bureau, Ministry of Health Selangor Darul Ehsan, Malaysia
[9]Food and Drug Administration, Muntinlupa City, Philippines
[10]Food and Drug Administration, Nonthaburi, Thailand
[11]Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor), Moscow, Russia
[12]Saudi Food and Drug Authority, Riyadh, Saudi Arabia
[13]Ministry of Health, San José, Costa Rica
[14]Southern African Development Community Secretariat, Gaborone, Botswana
[15]Ministry of Health, Mbabane, Swaziland

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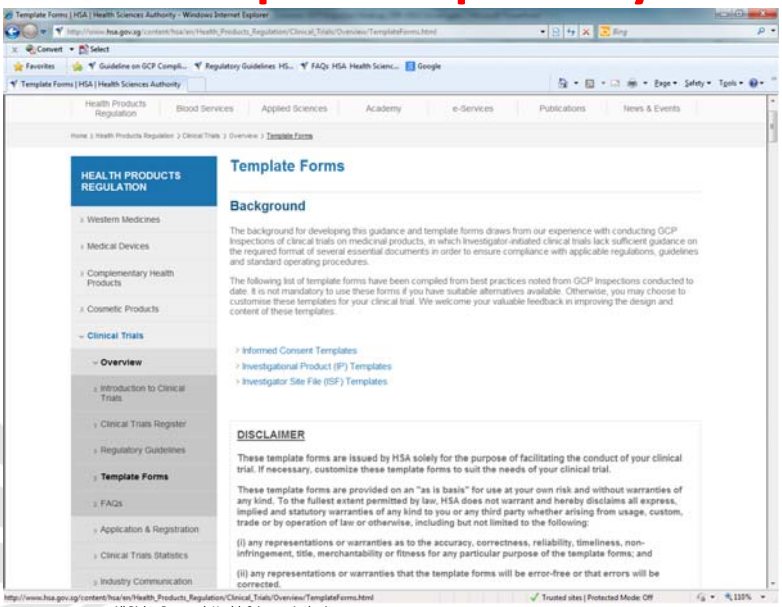
ICH E6 WORK GROUP

Template Repository



THANK YOU!

We welcome your queries!

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37