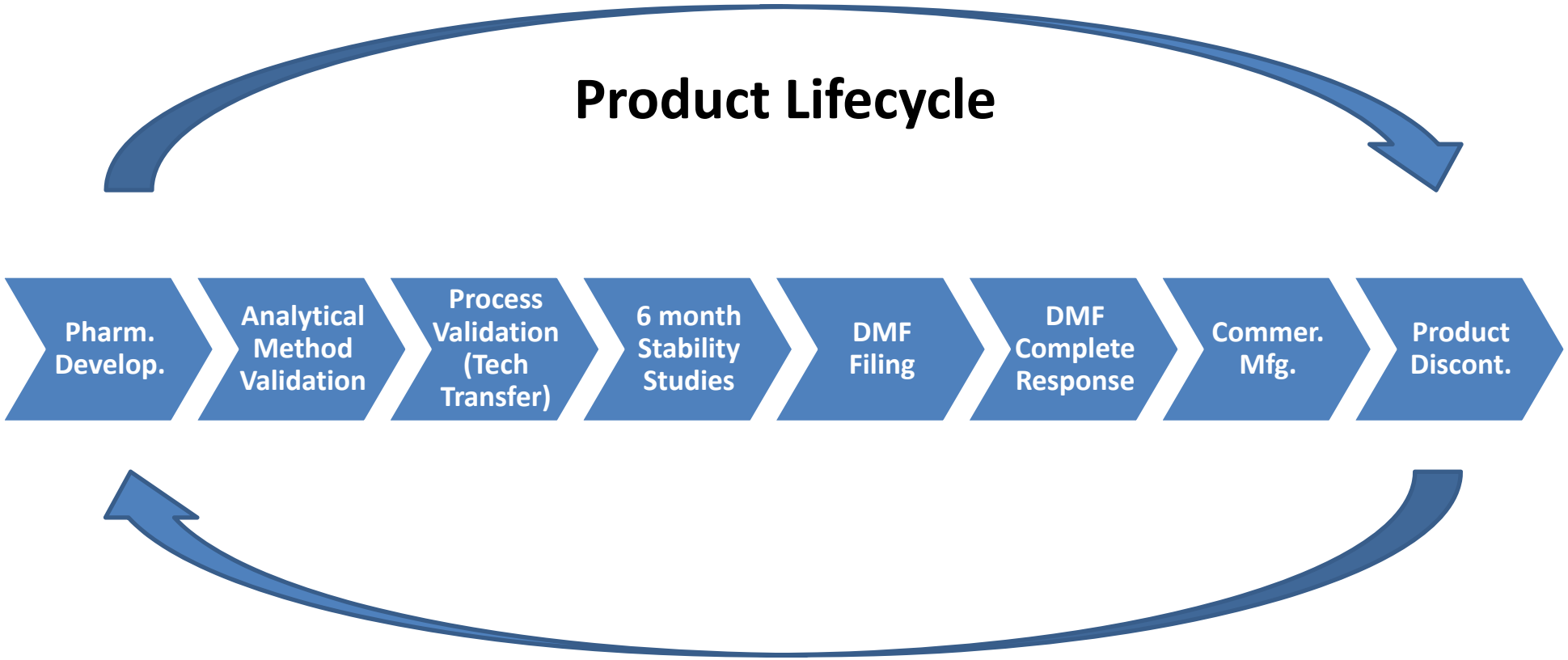
組織溝通與協調之團隊合作經驗

2016-7-21

Product Lifecycle



ICH Quality Guidelines

- Q1 *Stability Testing*
- Q2 *Analytical Validation*
- Q3 *Impurities*
- Q4 *Pharmacopoeias*
- Q5 *Quality of Biotechnological Products*
- Q6 *Specifications*
- Q7 *GMP for API*
- Q8 *Pharmaceutical Development*
- *Q9 Quality Risk Management*
- *Q10 Pharmaceutical Quality System*
- ***Q11 Development and Manufacture of Drug Substances***
- *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management*

Case Study 1. Process Validation

ICH Q10 Pharmaceutical Quality System

- **Achieve Product Realization**
  產品實現
- **Establish and Maintain a State of Control**
  一切在掌控之中
- **Facilitate Continuous Improvement**
  持續改善

API DMFs Under GDUFA-US

Guidance for Industry

Initial Completeness Assessments for Type II API DMFs Under GDUFA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Division of Drug Information at 1-866-405-5367.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2012
Generic Drugs

DMF Review Procedure

If there are deficiencies

- The detailed deficiencies are communicated to the holder.
- The APPLICANT is notified that deficiencies exist in either an Information Request (IR) or a Complete Response (CR) letter.
- The nature of the deficiencies is not communicated to the applicant.

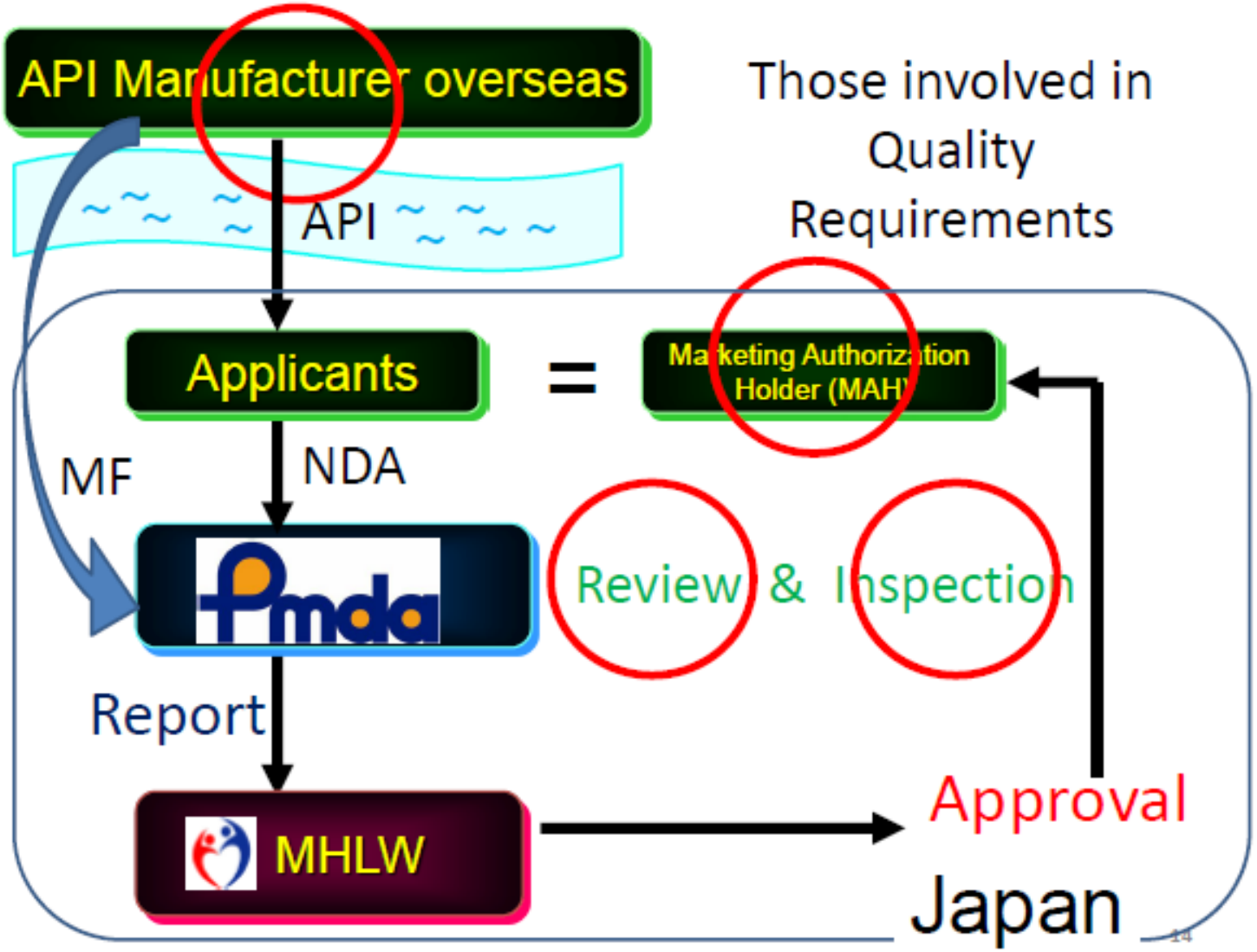
If no deficiencies

- Applicant not notified

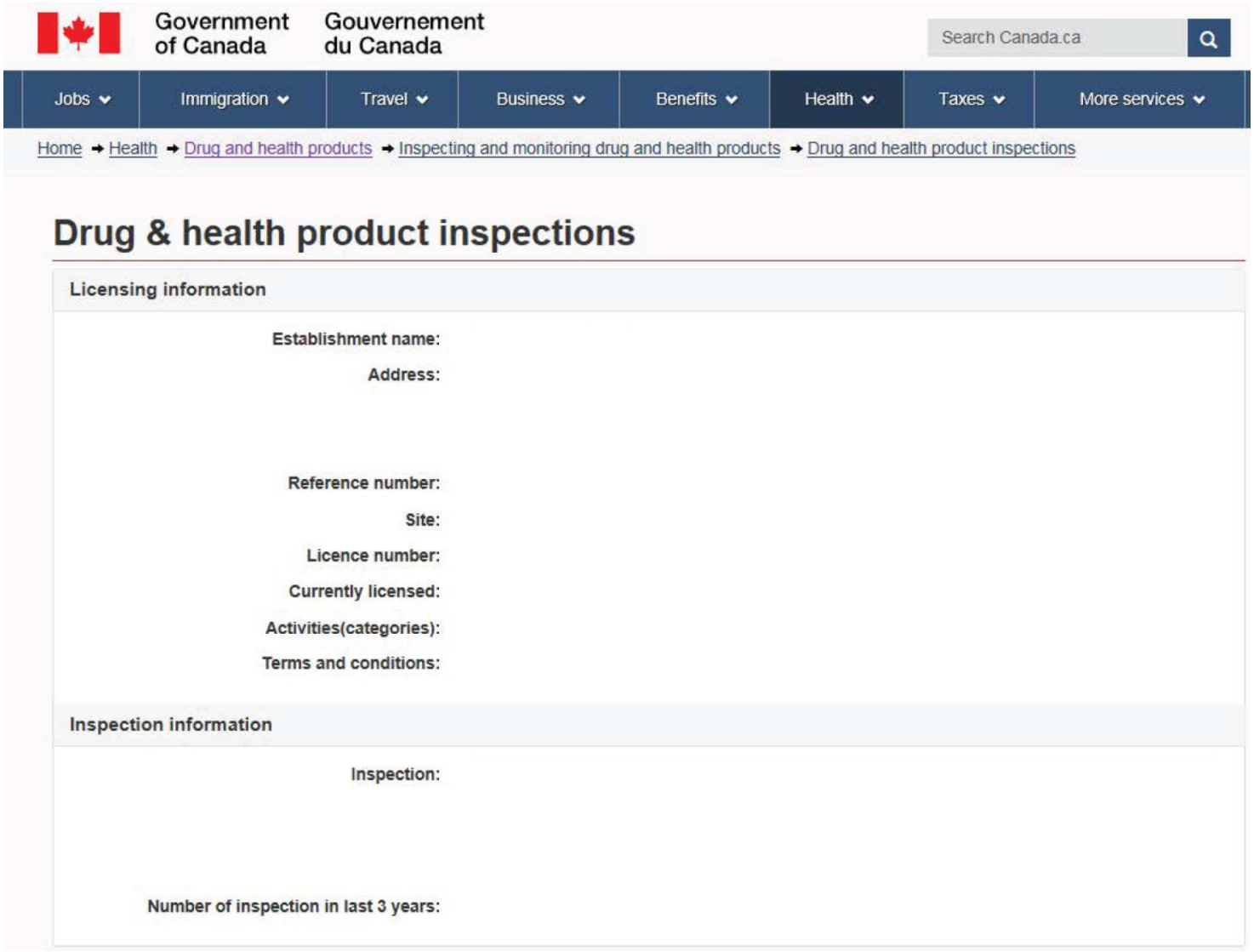
Market Authorization in EU

- Centralized Procedure
- National Marketing Authorization
- Mutual Recognition Procedure
- Decentralized Procedure (2005)

Market Authorization in Japan



Drug & Health Product Inspections in Canada



Drug Establishment License (DEL) Application Form (Section 5.1)

TABLE A: FOREIGN BUILDINGS CONDUCTING API-RELATED LICENSABLE ACTIVITIES

Note: Ensure that macros are enabled before proceeding. Enabling macros will unlock the complete functionality of Table A.

	A	B	C	D	E	F	G	H
	Import Information			API Foreign Building Information				
Action A- Add B- Remove C- Modify	DEL #	Imported As **A- API** **F- Dosage Form**	API name	Foreign Building Name	Street, City, Postal code	Province/ State	Country	GPS # Latitude/Longitude
	101010-A	A	Potassium Chloride	Dow	55 lander st., Baja, 0011-99	PC	Puerto Rico	18.0100799460894/ -66.6156005859375

I	J	K	L	M	N	O	P	Q	R	S
API Foreign Building GMP Status								API Product Information		
Building complies with applicable GMP requirements set out in Part C Div. 2, FDR?	Date first used as Foreign API Source Site	Date of Last Inspection	Inspection Type **A- PIC/S** **B- EDQM** **C- Corporate/ Consultant** **D- Other**	Specify Other	Date of renovations (if applicable)	Has this building been issued a Non-compliant rating in the last 5 years?	Years conducting API-related activities?	Final API Form Class **A- Powder** **B- Crystal** **C- Liquid** **D- Suspension** **E- Sterile Powder** **F- Sterile Crystal** **G- Sterile Liquid** **H- Sterile Suspension** **I- Other**	Specify Other	DIN associated with API
Yes/Oui								N/A	N/A	12345678

DMF in CTD

Info. Source	Module	Open Part	Closed Part
	3.2.S Drug Substance		
	3.2.S.1 General Information		
RD	3.2.S.1.1 Nomenclature	X	
RD	3.2.S.1.2 Structure	X	
ARD / QC	3.2.S.1.3 General Properties	X	
	3.2.S.2 Manufacture		
QA	3.2.S.2.1 Manufacturer	X	
RD	3.2.S.2.2 Description of Manufacturing Process and Process Controls	X	X
RD / QC	3.2.S.2.3 Control of Materials		X
RD / QC	3.2.S.2.4 Controls of Critical Steps and Intermediates		X
RD	3.2.S.2.5 Process Validation and/or Evaluation		X
RD	3.2.S.2.6 Manufacturing Process Development		X
	3.2.S.3 Characterisation		
RD	3.2.S.3.1 Elucidation of Structure and other Characteristics	X	
RD	3.2.S.3.2 Impurities	X	
	3.2.S.4 Control of the Drug Substance		
ARD / QC	3.2.S.4.1 Specification	X	
ARD / QC	3.2.S.4.2 Analytical Procedures	X	
ARD	3.2.S.4.3 Validation of Analytical Procedures	X	
QC	3.2.S.4.4 Batch Analyses	X	
ARD / QC	3.2.S.4.5 Justification of Specification	X	

DMF in CTD-Cont'd

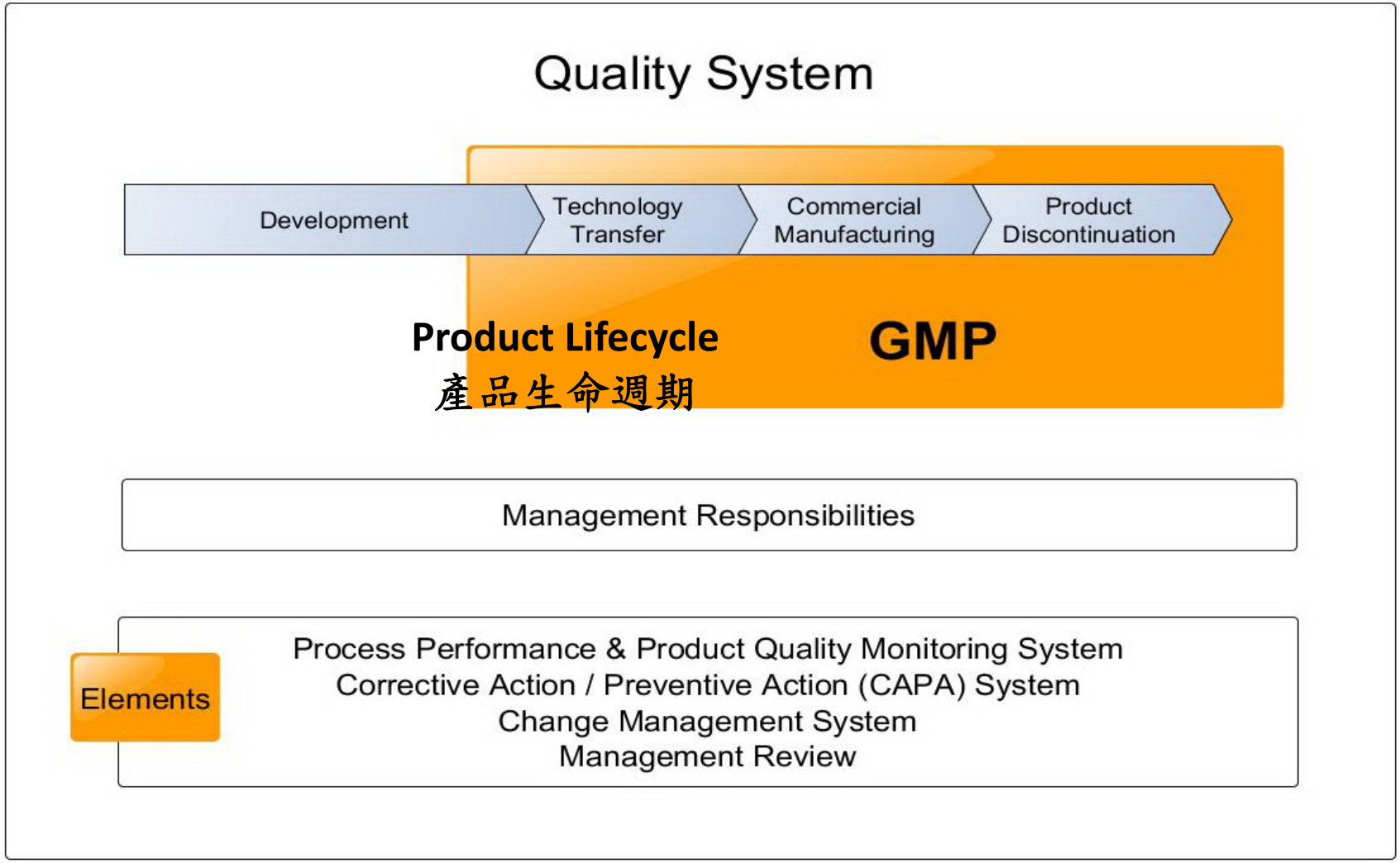
Source	Module	Open Part	Closed Part
ARD / QC	**3.2.S.5 Reference Standards or Materials**	X	
QC	**3.2.S.6 Container Closure System**	X	
	3.2.S.7 Stability		
QC	3.2.S.7.1 Stability Summary and Conclusions	X	
QC	3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment	X	
QC	3.2.S.7.3 Stability Data	X	
	3.2.A Appendices		
QA	**3.2.A.1 BSE/TSE Statement**	X	X
QA	**3.2.A.2 Residual Solvents Statement**	X	X
	3.2.R Regional information		
Production	**3.2.R.1 Executed Batch Records for drug substance**		X

Case Study 2. Deficiency Letter

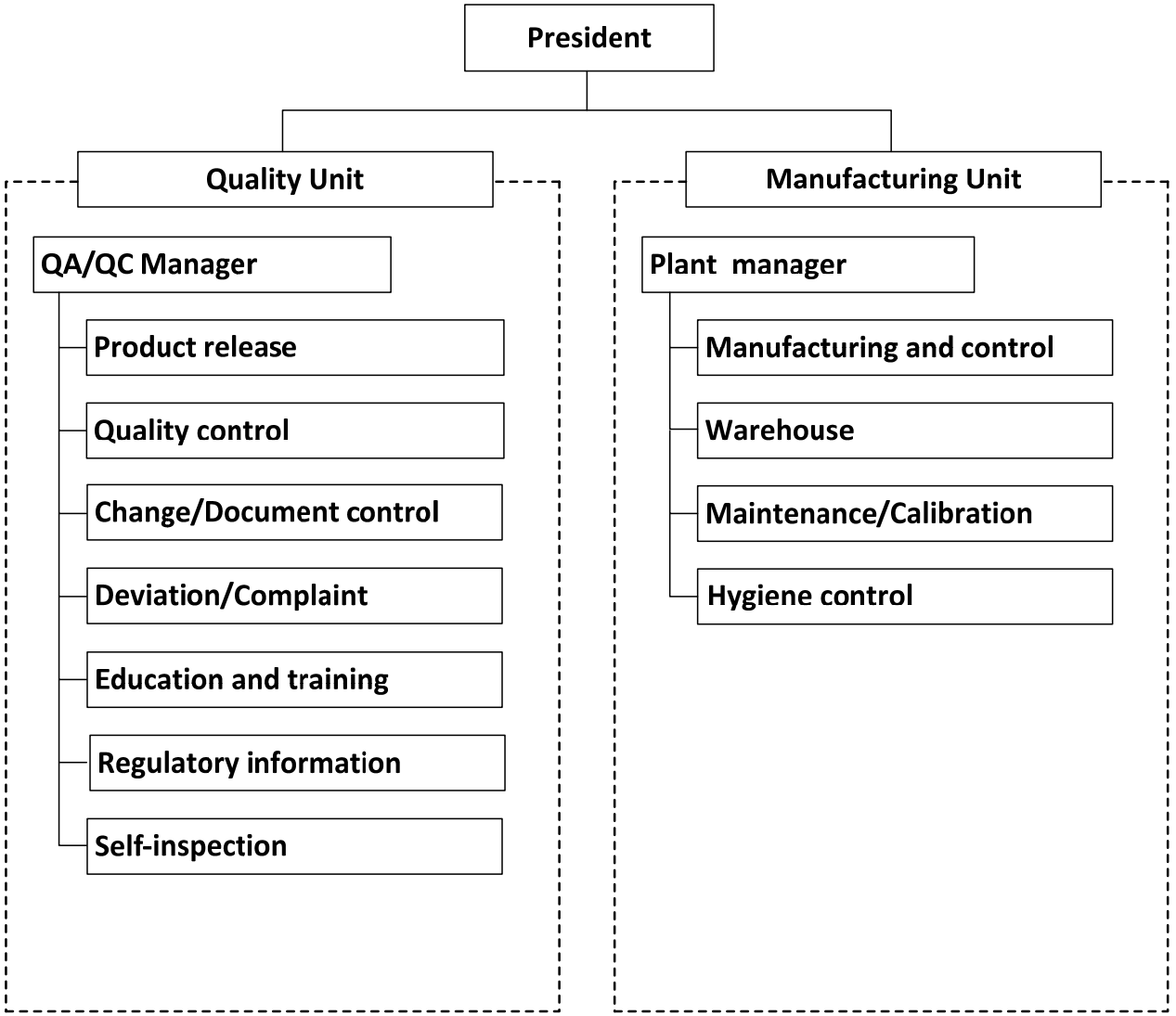
ICH Q10 Pharmaceutical Quality System

- Achieve Product Realization
  產品實現
- Establish and Maintain a State of Control
  一切在掌控之中
- Facilitate Continuous Improvement
  持續改善

ICH Q10 Pharmaceutical Quality System



GMP Organization Chart



Routine Duties of a Qualified Person-Annex 16 to EU Guide to GMP-July 2001

Before certifying a batch prior to release the Q.P. doing so should ensure, with reference to the guidance above, that at least the following requirements have been met:

a) the batch and its manufacture comply with the provisions of the marketing authorisation (including the authorisation required for importation where relevant);

b) manufacture has been carried out in accordance with Good Manufacturing Practice;

c) the principal manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;

Routine duties of a Qualified Person-Annex 16 to EU Guide to GMP-July 2001-Cont'd

d) any deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorisation have been notified to and authorised by the relevant authority;

e) all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;…

Request for Quality Metrics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2015
Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Quality Cultures

FDA acknowledges the importance of quality culture to the overall state of quality of the product, process, and commitment to quality. We also recognize that many companies measure quality culture and encourage this practice. FDA is proposing the following metrics for comment:

- **Senior Management Engagement:**

Proposed Optional Metric 1:

Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither

Quality Cultures-Cont'd

- **CAPA Effectiveness:**

Proposed Optional Metric 2:

A comprehensive corrective action and preventive action program has been identified as a strong indicator of a robust quality.

What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?

Quality Metrics

Quality Metric	
RFT Index	Batch Failure Rate/ Confirmed OOS Rate
	Unconfirmed OOS Rate
	Complaints Rate
Annual Product Review or Product Quality Review on Time Rate	

Request for Quality Metrics-Guidance for Industry (Draft)- July 2015 FDA

Case Study 3. Customer Complaint

Data Integrity and Compliance With CGMP

Guidance for Industry

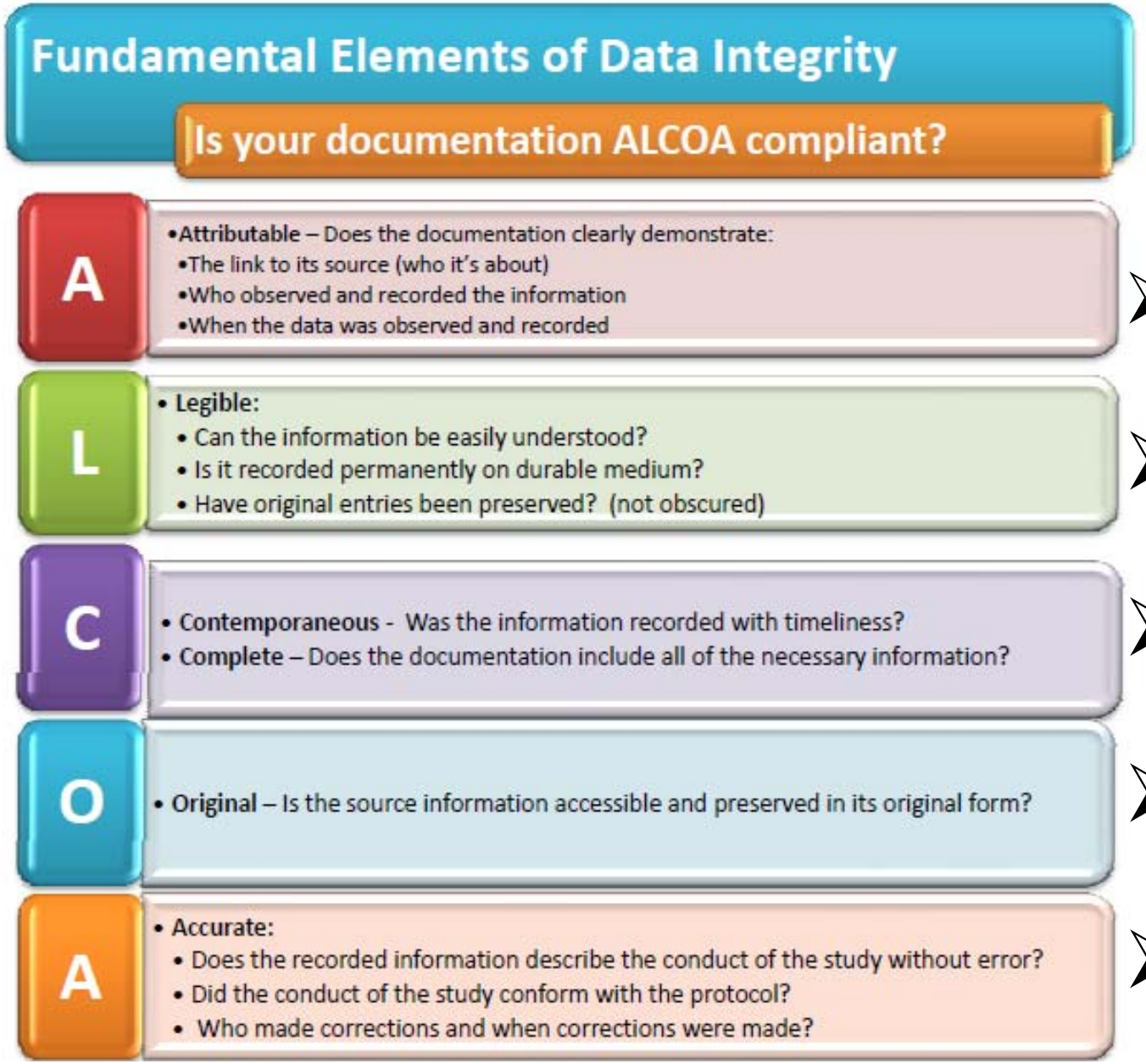
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

April 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Elements of Data Integrity



- 可歸屬
- 可讀的
- 及時的
- 原始的
- 準確的

Warning Letters 2011-2015

- **FDA Warning Letters與原料藥廠相關之件數:**

  2011：12/20

  2012：7/23

  2013：6/21

  2014：11/21 (Hikma, Cadila, Sun, Hospira, Apotex, SKB)

  2015：10/20 (Hisun, Cadila, Sun, Dr. Reddy, Sandoz, Mylan, Hospira, Apotex)

違反歐盟GMP

STATEMENT OF NON-COMPLIANCE WITH GMP

Exchange of information between National Competent Authorities (NCAs) of the EEA following the discovery of serious GMP non-compliance at a manufacturer [1]

Part 1

Issued following an inspection in accordance with :
Art. 111(7) of Directive 2001/83/EC as amended

The competent authority of Czech Republic confirms the following:
The manufacturer: ***HUBEI HONGYUAN PHARMACEUTICAL CO., LTD.***
Site address: ***No. 8 Fengshan Road, Industrial and Economic Development Zone, Luotian County,***

Prohibition of supply
Prohibition of supply is recommended, unless there are not alternative suppliers and there is a risk of shortage.

Suspension or voiding of CEP (action to be taken by EDQM)
CEP suspensed.

Additional comments
This supplier should not be approved in any new/ongoing applications.

2016-01-20

Name and signature of the authorised person of the Competent Authority of Czech Republic

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter: 320-16-06

Via UPS

December 31, 2015

Mr. Hua Bai, CEO
Zhejiang Hisun Pharmaceutical Co., Ltd.
46 Waisha Road
Jiaojiang District
Taizhou City, Zhejiang Province
China 318000

Dear Mr. Bai:

From March 2-7, 2015, investigators from the U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Zhejiang Hisun Pharmaceutical Co., Ltd., 46 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province.

We identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (API).

国内原料药航母-浙江海正药业
被美国FDA枪毙 2016.1.14

对质量卡边或者略微超标的产品“检测直到合格”在国内药企是很普遍的现象，多年都是这么走过来，只是一直没有被曝光而已。

继前几年印度药企被曝数据造假之后，EDQM（欧盟药监局）和美国FDA把监察重点转移到中国，2015年中国多家大中型药企被发现数据完整性缺陷（即分析数据造假）。可笑的是，这些企业甚至狡辩，涉及问题的产品仅销往国内市场，以恳求美国FDA高抬贵手…。

Warning Letter (Hisun)

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of drugs produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you complete all corrections and FDA confirms your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Because of the findings of the FDA inspection described herein, your firm was placed on Import Alert 66-40 on September 9, 2015. If you fail to correct these deviations, FDA may continue to refuse admission of articles manufactured at Zhejiang Hisun Pharmaceutical Co., Ltd., 46 Waisha Road, Jiaojiang District, Taizhou City,

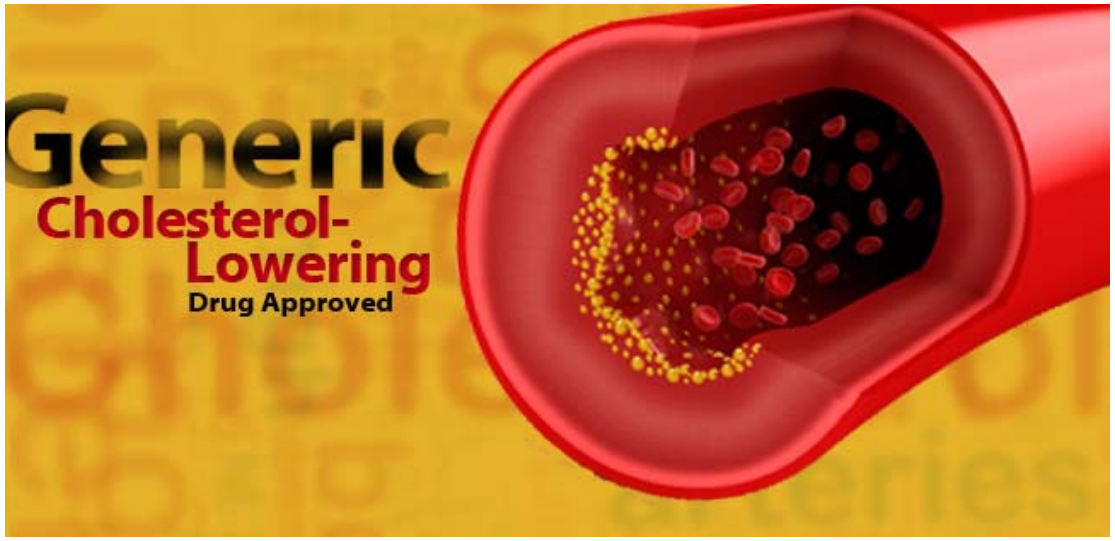
Warning Letters

製劑產品禁止入美國境內

Canada: Apotex 2009-?

India: Ranbaxy 2008-?

(Dewas and Paonta Sahib)



<u>News on Nov. 30, 2011</u>:
Lpitor (atorvastatin calcium, tablets 10, 20, 40, 80 mg)
Produced only in Ohm Laboratory in New Brunswick, NJ

FDA's Actions on Ranbaxy

Consent Decree for Toansa, India, Facility

- **FDA prohibits Ranbaxy's Toansa, India facility from producing and distributing drugs for the U.S. market (1/23/2014)**
- **WL (1/11/2014)**

Import Alert and Consent Decree for Mohali, India, Facility

- **FDA prohibits manufacture of FDA-regulated drugs from Ranbaxy's Mohali, India, plant and issues import alert (9/16/2013)**
- **WL (9/11/2012); WL (12/7/2012)**

Department of Justice (DOJ)Action Against Ranbaxy

- **Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, CGMP Violations and False Statements to the FDA (5/13/2013)**

Consent Decree for Paonta Sahib, Batamandi, and Dewas, India, Facilities and Ohm Laboratories in Gloversville, N.Y. (1/25/2012)

Daiichi Wins $400M in Damage over Ranbaxy Drug Safety Scandal-May 6, 2016 STAT

Eight years after selling its stake in Ranbaxy Laboratories, the family that controlled the generic drug maker has been ordered to pay approximately $400 million in damages to Daiichi Sankyo for concealing information about extensive quality control problems. An arbitration panel on Thursday determined that Malvinder Mohan Singh and Shivinder Mohan Singh hid and concealed facts about operations at Ranbaxy when they sold their shares to Daiichi for $2.4 billion.…The quality control problems, which were disclosed by a former Ranbaxy executive, involved filing false reports to the FDA and improperly testing medicines. After years of scrutiny and investigations, in 2013, Ranbaxy paid $500 million in fines and restitution to US authorities as part of a settlement that included pleading guilty to two charges of violating drug safety laws.

數據完整性顧問的職責

數據完整性顧問應

- 鑑識出工廠在何時段(歷史區間) 開始產生出不正確的數據。
- 指認並面談在此區段前、中、後所雇用的現任員工來鑑定出可能導致不正確資訊的作業、系統、流程及管理模式。
- 指認並面談在此區段前、中、後因故離職的員工以了解他們是否知悉任何不據實以報之相關數據。
- 是否有其他證據來證實面談所收集的資訊。

數據完整性顧問的職責-cont'd

數據完整性顧問應

- 運用公司組織圖及SOPs來識別出不正確數據發生時在位的特定管理人員(**the specific manager who participated in, facilitated, encouraged, or failed to stop subordinates from falsifying data in cGMP records**)，並且決定涉入或知悉數據竄改的中、高階管理層級。
- 確認是否有有任何的管理人員依舊在位操弄cGMP或藥證所需求的數據。
- 擴展你的面談到任何涉及提供不正確數據的其他廠區。
- …

數據完整性的致命問題

- 官方/客戶對公司誠信的懷疑
- 公司內部門間的不信任
- 個人內部的矛盾(自欺欺人)

Back to the Basics

- **“Honesty is the best policy”**
- **“ Make No Mistake…To Err is Human”**
- **“ Mistakes are the stepping stone to learning”**

迷思？

- 犯錯的人不知其所為
- 犯錯的人是必然要歸咎的
- 再教育與警告是改正犯錯的最好措施

PIC/S : Guide to GMP for Medicinal Products (Part I)

Chapter 1. Quality Management-Principle

The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the marketing authorisation and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors.

PIC/S : Guide to GMP for Medicinal Products (Part II)

Chapter 1 Introduction -Scope

This Guide applies to the manufacture of APIs for medicinal products for both human

and veterinary use.

Chapter 2 Quality Management-Principle

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel

GMP Annex 16: Certification by a Qualified Person and Batch Release

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Medicinal products – quality, safety and efficacy

Brussels, 12 October 2015

EudraLex

Volume 4

EU Guidelines for
Good Manufacturing Practice for
Medicinal Products for Human and Veterinary Use

Reasons for changes: The Annex has been revised to reflect the globalisation of the pharmaceutical supply chains and the introduction of new quality control strategies. The revision has been carried out in the light of Directive 2011/62/EU amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of falsified medicinal products. This version also implements ICH Q8, Q9 and Q10 documents, and interpretation documents, such as the manufacturing and importation authorisation (MIA) interpretation document, as applicable. Also, some areas, where the interpretation by Member States has not been consistent, have been clarified.

Deadline for coming into operation: 15 April 2016.

API Supplier Chain Issue-Email
A Notice

“Recently a few of our customers asked for the following details to be provided for all the APIs we supply to them – List of API Key starting materials/intermediates and manufacturer’s names and addresses. With this information the customers want to monitor the suppliers to ensure they do not have Warning Letters and/or Import Alerts… “

Content of the Batch Certificate for Medicinal Products -Appendix II

[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).
2. Batch number of the finished product.
3. Name of the destination country/countries of the batch, at least when within the EU.
4. Certification statement.

I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the EU and [when within the EU] with the requirements of the Marketing Authorisation(s) of the destination country/countries.

5. Name of the Qualified Person certifying the batch.
6. Signature of the Qualified Person certifying the batch.
7. Date of signature.

歡迎指教

中化合成生技股份有限公司
Chunghwa Chemical Synthesis & Biotech Co. (CCSB)