Thursday, May 16, 2013

7:00 A.M. – 4:00 P.M. Registration *Crystal Ballroom Foyer*

7:00 A.M. – 8:00 A.M. Continental Breakfast *Crystal Ballroom Foyer*

8:00 A.M. – 9:30 A.M. *Haverford Baccarat Ballroom*
Plenary Session 3: Raw Material to Tubular Vial
Moderator: Nicholas R. DeBello, *Wheaton Industries, Inc.*

There has been much discussion in recent years surrounding tubular glass. This session will provide an insight into the entire manufacturing process for a tubular glass vial which will include control of raw materials, batching, testing, glass tube forming and fabrication of a tubular glass vial. Each presenter will provide a description of the process which will include the steps that are followed and the controls that are in place to assure the quality of the product through each phase of the process.

8:00 A.M. **Raw Material Control** (Raw Material - Batch - Testing-Melting)
Juan Cerdan-Diaz, PhD, *Nipro Glass Americas*
Mark Fitzgerald, *Nipro Glass Americas*

8:20 A.M. **Glass Tubing Fabrication** (Melting - Forming - Gauging - Packaging)
John McDermott, *Gerresheimer Glass Inc.*

8:40 A.M. **Tubular Glass Vial Forming** (Converting - Gauging - Packaging)
Boris Schmid, *Ompi*

9:00 A.M. Q&A/Discussion

9:30 A.M. Refreshment Break in the Exhibit Hall *Waterford Lalique Suite*

10:15 A.M. – 11:45 A.M. *Haverford Baccarat Ballroom*
Plenary Session 4: Material Science Considerations for Glass Containers
Moderator: Rob Swift, *Amgen, Inc.*

This session includes a case study on the design of experiments work that Alfred University and a glass manufacturer performed on delamination. In addition, the audience will receive an update from USP on its Evaluation of the Inner Surface Durability of Glass Containers Chapter, which provides methods to assess the possibility of a drug product to form glass particles and delamination and to detect their occurrence.

10:15 A.M. **Delamination Case Study**
Carol Rea Flynn, *Gerresheimer Glass Inc.*

10:45 A.M. **Update on USP <1660> Glass Quality Chapter**
Desmond Hunt, PhD, *United States Pharmacopeia (USP)*

11:15 A.M. Q&A/Discussion

11:45 A.M. Lunch *Concours Terrace*

12:45 P.M. – 2:15 P.M. *Haverford Baccarat Ballroom*
Plenary Session 5: Analytical Techniques and Testing Protocols
Moderator: Thomas Schoenknecht, PhD, *Schott AG*

This session will address the increasing interest in industry and regulatory about state of the art inspection technologies capable to visualize stress and tension in glass and sub-visble particles in drug formulations. Such stress measurements for glass are of particular importance as they offer a sensitive method of determining thermal expansion and contraction differences. The session will focus on an imaging measurement system that will help determine the magnitude and orientation of stress by measuring birefringence. Another topic highlighted within the session is measuring glass sub-visible particles in protein drug formulations by analytical techniques.

12:45 P.M. **Imaging Measurement of Stress Birefringence in Pharmaceutical Glass Packages**
Henning Katte, *ilis GmbH*

1:15 P.M. **Glass Particles: Their Detection and Impact on Quality**
John Shabushnig, PhD, *Insight Pharma Consulting, LLC*

1:45 P.M. Q&A/Discussion

2:15 P.M. Refreshment Break in the Exhibit Hall *Waterford Lalique Suite*

3:00 P.M. – 4:30 P.M. *Haverford Baccarat Ballroom*

Plenary Session 6: Integrated Measures to Control Glass Quality during Manufacturing Processes

Moderator: Roger Asselta, *Genesis Packaging Technology*

There is shared responsibility to ensure product quality from pharmaceutical firms as well as container manufacturers. These presentations will illustrate how pharmaceutical firms ensure quality in their manufacturing process as well as how they work to mitigate glass particulates throughout their manufacturing process.

3:00 P.M. Elimination of Glass Damage in Manufacturing Environments
Gregory Pitt, *Eli Lilly and Company*

3:30 P.M. **Detrimental Effects of Transportation and Handling Processes from Dispatch/Supplier to Final Packaging**
Mads Reedtz Espersen, *Novo Nordisk A/S*

4:00 P.M. **Update on the Glass Handling Task Force**
Patrick Begley, *Becton Dickinson*

4:30 P.M. Q&A/Discussion

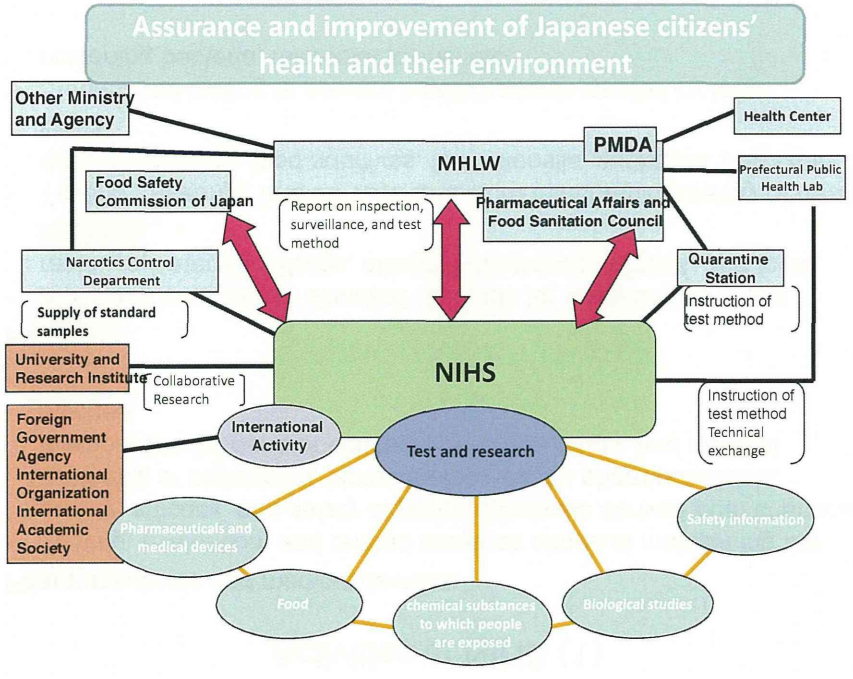
5:00 P.M. Conference Wrap-up
Cesar Matto, CDER/*FDA*

Science and Regulatory Studies at National Institute of Health Sciences Overview of Japanese Regulations, Review, GMP inspection and JP

Yukio Hiyama
Visiting (and retired) Scientist, Division of Drugs
NIHS, MHLW
Seminar at Irish Medicines Board, December 11, 2013

Outline of presentation

- Organization and work relationship
- About NIHS
- Health Science Studies
- Regulatory Sciences Studies
- Pharmaceutical Regulations
- Review process
- GMP inspection process
- JP



History of NIHS

- Established in Tokyo in 1874 as the Tokyo Drug Control Laboratory (later renamed the Tokyo Institute of Hygienic Sciences(in 1883)).
- The oldest national research institute, and now a major organization within the Ministry of Health, Labour and Welfare.
- Engaged principally in the analysis and quality inspection of imported drugs in the beginning.
- The mission of NIHS has been expanded to food and the numerous chemicals in the living environment, so that it serves to control the products that are generated by science and technology to make sure that they truly benefit the general public. In other words, NIHS works to ensure harmony between scientific technology and human beings (Regulatory Science).

Activities of NIHS (1)

Pharmaceuticals and medical devices:

- Testing, evaluation, and related research aimed at maintaining the quality, efficacy, and safety of pharmaceuticals derived from chemical synthesis or organisms, biotechnology-based pharmaceuticals, therapeutics for gene or cell therapy, crude drugs, and medical devices.

Foods:

- Research to establish standard methods for analyzing pesticide residues, veterinary drugs, allergic substances in foods, and food additives.
- Testing, research, and surveys to ensure the chemical safety of newly developed foods, food additives, food utensils, packages, and other items,
- Studies and testing to prevent health hazards caused by food-poisoning bacteria, microbial toxins, etc.

5

Activities of NIHS (2)

Other chemical substances to which people are exposed:

- Testing and research of household products, drinking water, indoor air, etc., from a hygiene-chemistry standpoint
- Simultaneous pass/fail tests of cosmetics, preparation of codes and standards, and testing and research to evaluate the quality and safety of cosmetics and quasi drugs

Biological safety studies:

- Testing and research on chemical substances in pharmaceuticals, foods, food additives, substances found in daily living, etc., using experimental animals, tissues, and cells
- Research on the establishment of testing and evaluation methods.

Safety information on drugs, foods and chemicals:

- Collection of information pertaining to the safety of drugs, foods and chemical substances both in Japan and abroad, maintenance of its own database, and supports of testing and research

6

International Activities: List of international organizations collaborating with NIHS

CAC: Joint FAO/WHO Codex Alimentarius Commission
FAO: Food and Agriculture Organization of the United Nations
FHH: Western Pacific Regional Forum for the Harmonization of Herbal Medicines
IAEA: International Atomic Energy Agency
IARC: International Agency for Research on Cancer
ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPCS: International Program on Chemical Safety
ISO: International Organization for Standardization
JECFA: Joint FAO/WHO Expert Committee on Food Additives
JEMRA: Joint FAO/WHO Expert Meeting on Microbiological Risk Assessment
JICA: Japan International Cooperation Agency
JMPR: Joint FAO/WHO Meeting on Pesticide Residues
OECD: Organization for Economic Co-operation and Development
WHO: World Health Organization
WPRO: Western Pacific Regional Office of WHO

7

MHLW Grant (Health Science) study on Evaluation Methods for Pharmaceutical and Process Development (2004-to date)

- The needs-quality assurance based on science and risk management, gap between desired state and current status, rPAL and ICH
- The group structure- Industry, Academia and Government (NIHS) Joint

(Industry: Nikki-JGC, Pfizer, Powrex, Shionogi, Santen, Takeda and Tanabe 2009 member)

8

List of topics in the Health Science Program (2009)

- Characterization of granulated powders by NIR and Raman imaging(NIHS)
- Characterization of formulations by Teraherz (NIHS)
- Real time monitor of chemical reaction by P-31 NMR and Raman(Santen)
- Real time monitor of MgSt in mixing process by thermal effusivity (Toho University)
- Ultra Performance Liquid Chromatography for PAT (NIHS)
- Tablet hardness and distribution of MgSt in intermediate by SEM and EDAX(Pfizer)
- Development of reproducible dissolution methods with USP stationary basket (Takeda)
- Raman spectrometric application in API crystallization process (Tanabe)
- Survey on bio process monitors(Nikki JGC)
- Quantitative analysis of crystal forms in tablet by XRD (Shionogi)
- Real time process control of coating process (Powrex)

NIR Imaging Analysis on wet granulation process -Dissolution rate- Koide and others(NIHS) since 2005

- Dissolution rate slows when over granulated by high shear mixing process
- NIR imaging method developed

- De-Mixing occurred between friendly componets
- Cause of slowed dissolution is NOTclearly known

International Journal of Pharmaceutics 441 (2013) 135–145

Detection of component segregation in granules manufactured by high shear granulation with over-granulation conditions using near-infrared chemical imaging

Tatsuo Koide[a,*], Takuya Nagato[b], Yoshiyuki Kanou[b], Kou Matsui[b], Susumu Natsuyama[b], Toru Kawanishi[a], Yukio Hiyama[a]

[a] Division of Drugs, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
[b] Powrex Corporation, Osaka Powder Technology Center, 8-121-1 Kitaikmi, Itami 664-0831, Japan

Dissolution rate slows down as granulation progresses :2005

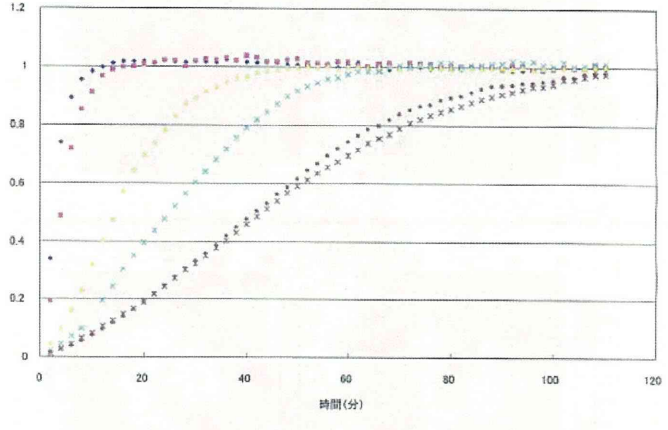


図６．溶出試験（パドル法、溶液：水 900ml 50rpm/min）
◆40:■80:▲120:×160:●200:※240(rpm) 造粒時間５分、打錠圧２ｋN

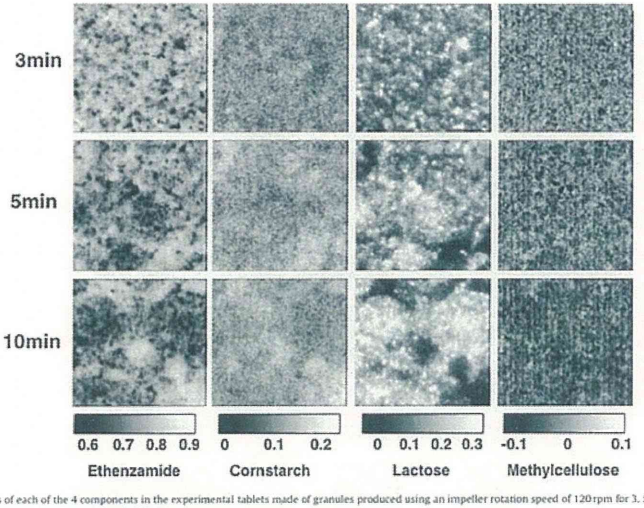


Fig. 3. NIR images of each of the 4 components in the experimental tablets made of granules produced using an impeller rotation speed of 120 rpm for 3, 5, or 10 min. For each of the 4 components, the PLS score bar is shown.

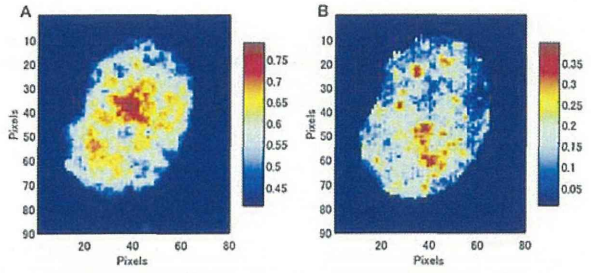


Fig. 10. NIR images of ethenzamide (A) and lactose (B) in granules produced by 5 min of granulation at 40 rpm. For each of the 2 components, the PLS score bar is shown.

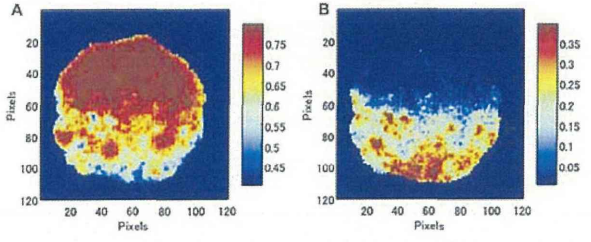


Fig. 11. NIR images of ethenzamide (A) and lactose (B) in granules produced by 5 min granulation at 200 rpm. For each of the 2 components, the PLS score bar is shown.

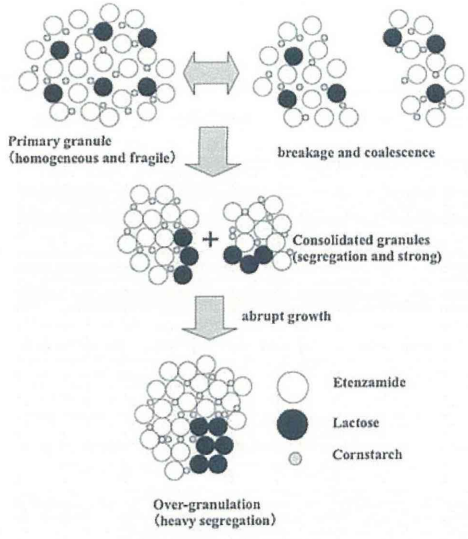


Fig. 12. Proposed model of the segregation process.

Regulatory Science Studies

- Quality System, GMP guidance (2002-2004, 2005-2007,2008-2010,2011-)

QS, Regulations, Product GMP, Information Flow/Tech Transfer, Lab Control, Change Management

- GMP Inspection Policy, Manual(2003-2005, 2006-2008)

Policy, System Base, Inspection Check (Reference) list, Inspection Scenario (Key Questions)

- Manufacturing Process Commitment in Approval Letter

Survey, Technical Elements, Policy, Mock for AL and P2

- Clinical Supply GMP Policy

Pharmaceutical Affairs Law(PAL), ICH Q8/Q9/Q10/Q11 and MHLW Grant **Regulatory Science** Studies

PAL regulation changes	ICH discussion	Regulatory science groups
2002	**2003**	**2002**
Revised PAL published	GMP workshop in Brussels	QS/GMP guidance
	Q8 and Q9 started	**2003** CTD mock
2004	**2004**	Approval matters
PMDA established	Q8 reached step 2	Inspection Policy
New GMP standards	**2005**	**2004** Approval matters
2005	Q9 reached step 2	GMP guideline
Approval matters policy	Q8 and Q9 reached step4	Inspection Policy
Revised PAL enforced	Q10 started	**2005**
Inspection policy published	**2007**	Skip Test guideline
2006	Q10 reached step 2	Inspection Checklist
Product GMP guidance	2008	**2006-2008** P2 /application mock
Sterile process guidance	QIWG Q11 started	Change management system
2012	2011	**2011** Inspection Policy
Inspection Policy revised	QIWG completed	S2 mock
2013	2012	
GMP Standards revised	Q11 reached step4	

Revision of the Pharmaceutical Affairs Regulation (effective April 2005)

- ***Revision of the Approval and Licensing System***
  = From Manufacturing (or Importation) Approval to Marketing Authorization
- ***Enhancement of Post-marketing Measures***
  = To clarify the Market Authorization Holder's (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)

Revision of the Quality Regulation(2005)

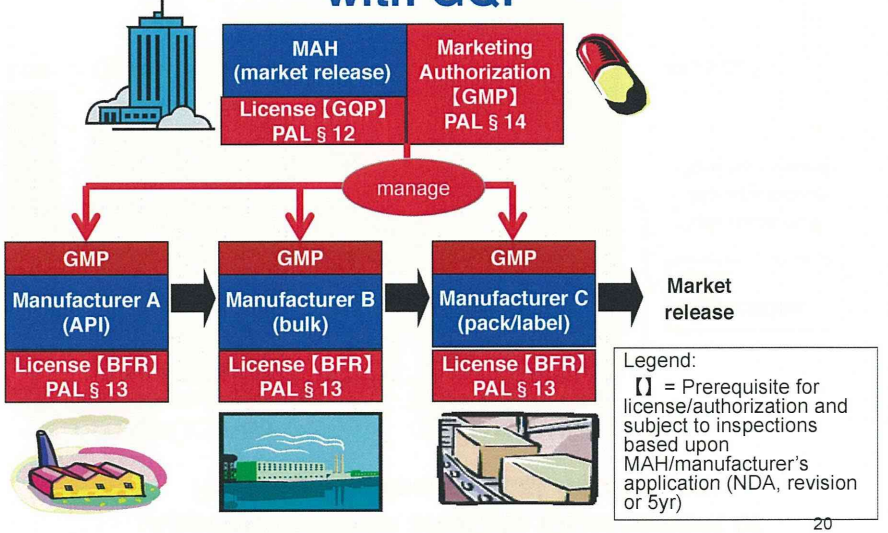
1. **MAH's* responsibility for the Quality management (GQP)** *Marketing Authorization Holder
2. **Requirement Changes in Approval Matters**
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards

* GMP standards revised again in August 30, 2013

1. MAH's responsibility for quality management (GQP)

- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.

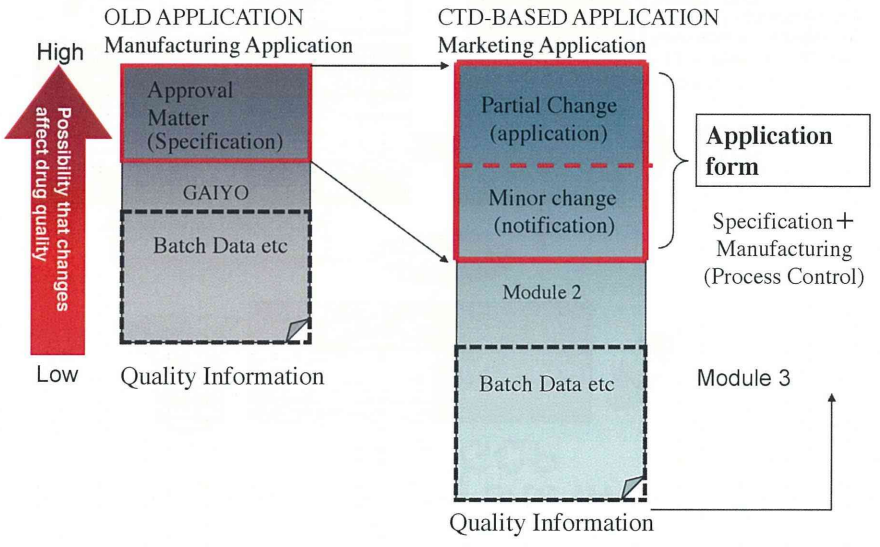
MAH shall ensure GMP compliance of each manufacturing site in accordance with GQP



Revision of the Quality Regulation(2005)

1. MAH's* responsibility for the Quality management (GQP) *Marketing Authorization Holder
2. **Requirement Changes in Approval Matters**
3. Drug Master File system to support CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



Approval Matters

- General name (for drug substance)
- Brand name
- Composition
- Manufacturing process, including control of materials← under PAL(2005)
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

Approval Matters Policy

Notification from Director of Review Management, 0210001 February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale will become approval matters. Principle and quality end point for each manufacturing step will be subject to pre-approval review.
- In-process procedure is pre-approval matter if it replaces final specification test.(RTRt)

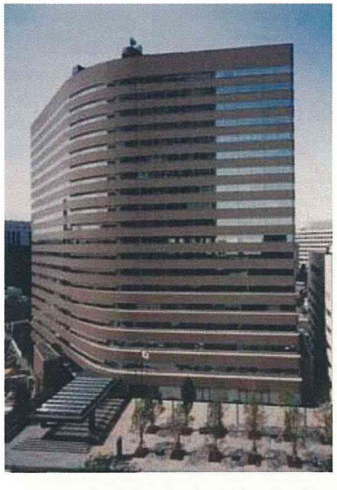
Approval Matters Policy (continued)

- A pilot scale manufacturing processes may be submitted at Application.
- The commercial scale processes will be subject to Pre-approval GMP inspection and the commercial scale must be described in the approval.
- Pre-approval vs. notification classification may be determined through the review process

Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - the evaluation methods which was approved at the time of previous submission might be invalid.
- Change in materials of primary packaging component
- Change in matters for aseptic manufacturing
- Change in specification of intermediate product in case that the test is performed instead of release test of final drug product

Introduction of PMDA



- NAME: Pharmaceuticals and Medical Devices Agency
- Date of Establishment : April 2004
  Established as an Incorporated Administrative Agency (IAA) in April, 2004 by integrating 3 review-related organizations.
- Effective operation under "Mid-Term Plan" for 5 years' activities (09'-13')
- PMDA submits performance report to MHLW annually, and that is evaluated by the "IAA Evaluation Committee" for necessary improvement.

PMDA's 3 major work areas

Review and Audit for Drugs/ Medical Devices Efficacy and Safety
- Clinical Trial Consultation
- Review of Efficacy and Safety
- Conformity Audit for Application Materials of GLP,GCP and GMP/QMS

Post- marketing Safety Operations for Drugs / Medical Devices
- Reinforced Safety Information (Database)
- Scientific Review and Research for Safety Information
- Information Provision (via the Internet), Pharmaceutical Consultation for Consumers

Relief Service for ADR and Other Infectious Disease
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients and HCV positive and HC patients

GMP Inspection System

Pharmaceutical and Food Safety Bureau, MHLW
(manufacturing license, marketing license, marketing authorization, administrative order, pharmacovigilance, license withdrawal, seizure, penalty, etc.)

control over inspectorates, ultimate responsibility

PMDA is partially vested with authority of MHLW(assessment , GMP inspection, information gathering)

Prefectures are vested with part of MHLW's authority to have local autonomy.

PMDA — Inspectorate

Prefectures — 47 Inspectorates

Establishment of GMP Inspectorate Committee

GMP Inspectorate Committee
(representatives from each block, PMDA,MHLW)

MHLW — Committee to investigate harmonization

Secretariat in PMDA

coordination

Instruction

Coordination is basically made within each block: training, internal audit, inspection support, etc.
Support from trainers at PMDA is available

GMP Expert — PMDA GMP group

Trainer

Trainer — Hokkaido and Tohoku block (Pharmaceutical administration in each block)

...i block

7 blocks in total

Overview of GMP on-site inspections by the PMDA

Inspections conducted by the PMDA

Inspection of facilities and equipments

- Licenses for domestic facilities (for biological products etc.) that require a license by the Minister
- Accreditation of foreign manufacturers

GMP compliance inspection

- New drugs
- Biological products etc.
- Drug products manufactured at foreign manufacturing sites

Trends in the Japanese market
- Of accredited foreign manufacturers: approximately 80% are Asian and European.
- Import from major European pharmaceutical companies
- Manufacturing generic drugs in Asian countries

Accreditation of foreign manufacturers: Totals by fiscal year and area

Fiscal 2008 – 2013.3