Current Situation of Generic Drugs Assessment, and Expectation in Japan

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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

Reviews and Related Services Conducted for Generic Drugs

Fiscal Year	Applied	Approved	Withdrawn, etc.	Under review
2012	4,077	3,421	190	3,559
2013	3,893	3,504	343	3,605
2014	3,452	3,447	214	3,396
2015	3,502	3,235	281	3,382
2016	3,160	3,192	254	3,096

Note: The figure in "Withdrawn etc." do not include the number of products that were switched to other review categories during the review.

Today's Contents

- Application Form (AF) is a legally binding document in Japan.
- A post-approval regulatory action is required if a marketing authorization holder changes the description in the AF (included MF) .
- AF provides the transparency and flexibility in terms of post-approval changes.
- In change control of AF, scientific justification of the change must be thoroughly explained using CTD at the time of application.

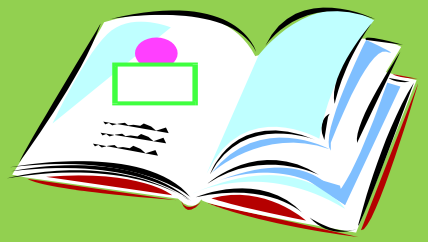
Relationship between AF and CTD Documents in Japan

Approved Matters

Application Form (AF)

Extracted

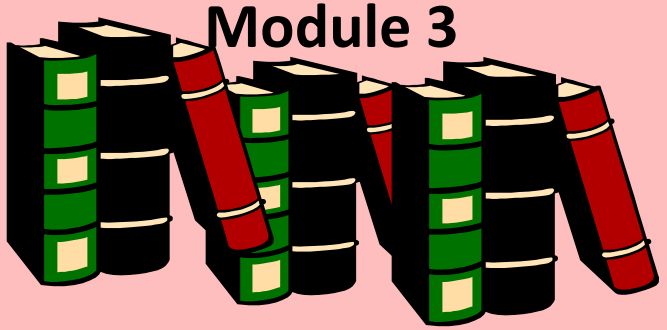
CTD Module 2 (QOS)



Summarized

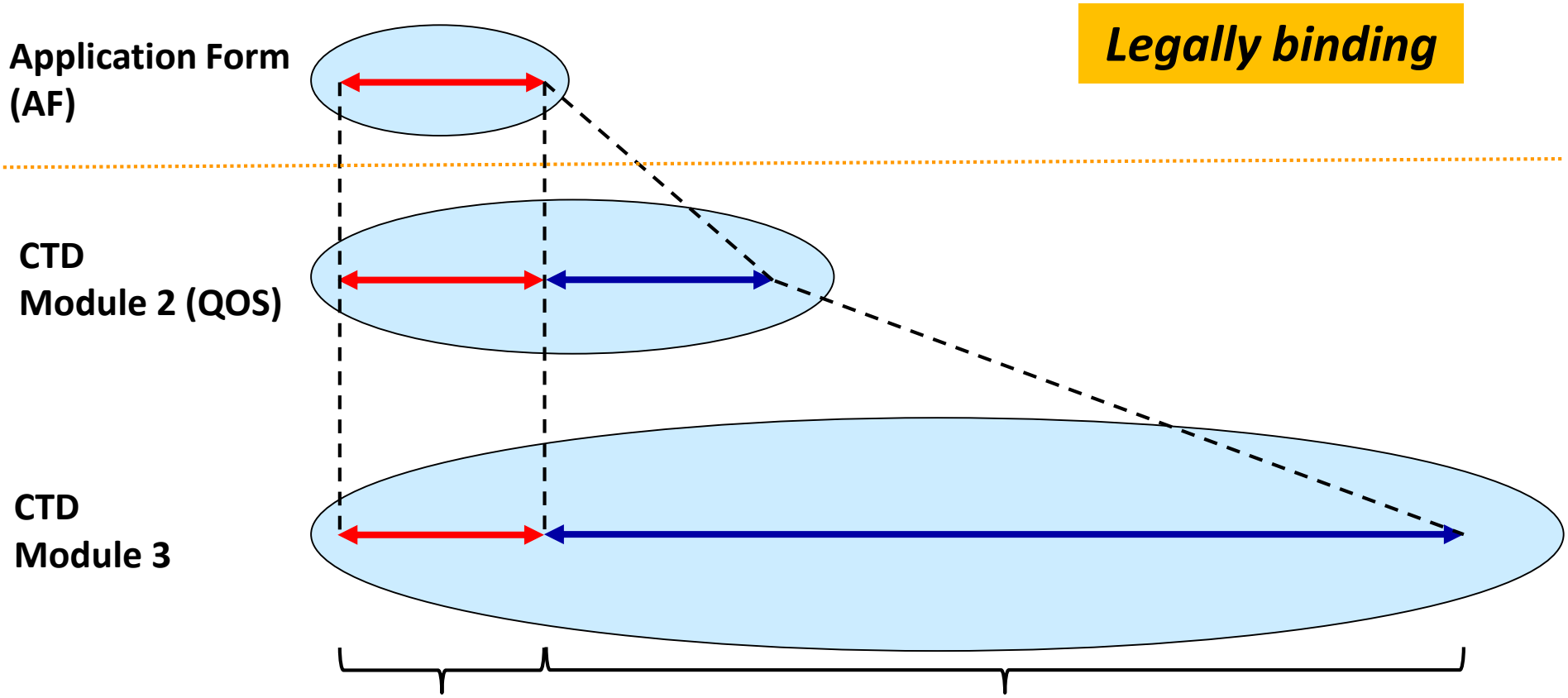
EU, US

CTD Module 3



Japan

Japan's Effective/Efficient/Flexible Quality Regulation



・PCA(Partial change Application)
・MCN(Minor change Notification)

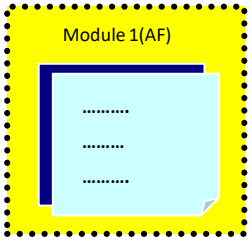
Post-Approval Change Reporting Categories

Impact on quality	Japan	US	EU
High	**Partial change Application** (approval of variation)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	**Minor change Notification** (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**SOP** (Under GMP change control)	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

Matters to be described in Manufacturing Field of AF

All processes from raw materials to packaging process

- A flow diagram of manufacturing process including:
  - Raw materials
  - Charge-in amount
  - Yield
  - Solvent
  - Intermediate materials
  - Process parameter (e.g. Target Value/Set Value)



- A narrative description of manufacturing process
  - Acceptance criteria of the starting material and intermediate materials
  - In process control, Design Space and RTRT etc.

Description of Partial & Minor Change Matters in AF

- Enter items other than target/set values in
  - Nothing : Partial Change Matter
  - “　　” : Minor Change Matter
- Enter target/set values of process parameters and standard charge-in amounts in
  - 《　　》: Partial Change Matter
  - 『　　』: Minor Change Matter

Step 1 (Critical Step)

CP-6『(230kg)』, tetrahydrofuran『(1300L)』, sodium carbonate『(42.4kg)』 are combined. Ethyl chloroformate “158～592kg” is added and the mixture is heated at temperature up to reflux. ・・・・ Water (“25 to 35%” weight per weight of ethanol) is added and the mixture is stirred at 『20℃』.

Acknowledgement : Sakuramil (Sakuramil S2 mock)
http://www.nihs.go.jp/drug/section3/H23SakuramillMock(Eng).pdf

AF system in Japan provides a clear description of post approval change controls

- Transparency
  - We can clearly share the regulatory commitments between applicants and regulators.
- Efficiency
  - Module 2 (QOS) can be a good communication between applicants and regulators.
  - Module 2 (QOS) can facilitate our assessment because Module 2 summarizes the points of reviewing.

Change of Generic drug approval application data to CTD format

- "Handling of documents to be attached with the prescription drugs approval application"
  (PSEHB/ELD Notification No. 0311-3 dated Mar 11, 2016)

  - Basic concept
    In principle, the documents to be attached with the approval application shall be compiled in accordance with the CTD
  - CTD application from March 1, 2017 onward
  - Checking of required items using the attached checklist

⇒ Checklist would be useful for efficient review (shorten review times)

Review in change control of AF

- Trigger
  - Partial change application
- Review documents
  - AF and CTD Module1
  - CTD Module2&3 (e.g. actual data, validation data, stability data)
- Points of reviewing
  - Reasons for the changes
  - Justification of change in the view of the control strategy and the quality attributes
  - Checking based on the current review standards
    (justification of the starting material, impurity management, control of crystal polymorphism, control of residual solvents, use of recovered solvent etc.)
  - Minor change Notification

Points to be considered when creating documents for application (1)

- In the drug product application, objects pertaining to minor change notification and application for approval for partial changes must be mentioned separately
  - The possible impact of description of changes such as manufacturing process on quality
    (As per PFSB/ELD Notification No.0210001 dated Feb 10, 2005)
  - Risk assessment based on the quality attributes

- In partial change application, justification of the change must be explained at the time of application using CTD, in the view of the control strategy

Points to be considered when creating documents for application (2)

- Quality attributes of the active pharmaceutical ingredient (API)
  - Quality attributes of the API is an essential information for explaining the propriety of the control strategy and the manufacturing process
  - Examples
    - Solubility
    - Polymorphic form
    - Related substances and impurities
    - Particle size
    - Stability (influence of light, humidity and temperature)

Points to be considered when creating documents for application (3)

- Describe the pertinent starting material and multiple chemical transformation steps.

- Note that the adequacy of manufacturing process shall not be judged only by the sufficiency of the number of reaction processes.

  → *Justification of the starting material (Ref. ICH Q11)*

  → *Evaluation of the control strategy*

Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents (1)

- "Implementation of Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents"
  (PSEHB/ELD Notification No.0119-1 dated Jan 19, 2016)
- "Procedure After Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents"
  (PSEHB/ELD Notification No.0212-4 dated Feb 12, 2016)
- Minor change Notifications were submitted by 22,297 items (69% of all items) of 479 companies by May 31, 2016

Inspection on Consistency between Actual Manufacturing Practices and Drug Approval Documents (2)

- Reported Cases
  - Change of testing method of critical raw material control points
  - Major manufacturing scale was changed with no information sharing
  - Validation was not conducted for the changes in manufacturing process
  - Analytical procedure is not the method described in AF but alternative method
- Major causes
  - Lack of change controls
  - Lack of communication between applicant, MF folder and in-country caretaker
  - Lack of understanding the Japanese pharmaceutical regulations and the guidance
  - Mistranslation

They can influence the quality !

Consultation Service for Quality

- Simple Consultations (2004-)
  (allowed or required in PFSB/ELD Notification No.0210001 dated Feb 10, 2005)

- Face-to-Face Consultations (2012-)
  - Quality Consultations for Generic Drugs
  (PMDA Notification No.1004003 dated Oct 4, 2011)

- Trial Consultations (2015-)
  (PMDA Notification No.0914001 dated Sep 10, 2015)

- PACMP Quality Consultations for Generic Drugs ***(draft)*** (FY 2018-)
- Change Notification simple consultation for Generic Drugs ***(draft)*** (FY 2018-)
  (PSEHB/ELD, PSEHB/CND Notification No.0309-1 dated Mar 9, 2018)

Simple Consultations

- Consultation cases related to the API
  - Regulatory procedures by changing of..
    - Manufacturing process（charge-in amount, machine, operation orders, scale up, batch mixing, grade of solvent）
    - Specification and analytical procedures（alternative methods, reference standards or materials）
    - Process management
    - Control points and control values of the starting material
    - Re-working/Re-processing
- Points of Response (without data evaluation !)
  - Reasons for the changes
  - Related notifications
  - Quality attributes of the API
  - The possible impact of the change on quality of the API
  - Research on the similar cases

Quality Consultations for Generic Drugs

- Consultation cases related to the API
  - Selection of the starting material
  - Material control
  - Manufacturing control
  - Establishment or change of Specification
  - Retest period
  - Safety evaluation of the impurities from the API

- Issues to be discussed (with data evaluation!)
  - Will the quality will be ensured equal or better than before?
  - Is the proper validation is established to evaluate the quality change?

← Issues to be discussed at the Pre-consultation meetings

Trial Consultations

- Consultations to confirm the change correspond to minor change notification with data evaluation

- 91 consultations were conducted (2015-2017)

- Consultation cases related to the API
  - Extension the shelf life/retest period of API（no commitment）
  - Change of measurement condition/model of NIR
  - Change of the regent used in the analytical procedures
  - Specification change by USP/EP monograph update
  - Change of container

Third Mid-term Plan（FY 2014-2018）

- “Mid-term Plan of the Pharmaceuticals and Medical Devices Agency (PMDA)”
  (Notification No.0331-44 of PFSB, MHLW, dated Mar 31, 2014)

- Enhancement of review system
  - The office of generic drugs was established in Nov 2014.
  - The number of reviewers is to be increased.
- Promotion of streamlining / Establishment of transparent review
  - Encouragement of CTD application.
  - Make a review report.
  - Make use of experience in face-to-face consultations to develop product-specific BE guidance etc.
- Enhancement of consultation service
  - All applications for consultation have been accepted since Nov 2014.
  - New category of consultation is under trial.

Review time for new generic drugs

Targets for shortening review time

- Regarding pharmaceuticals which applications were submitted after April 1, 2004, the target review times for the items approved in respective fiscal years, shall be as shown in the following table. The regulatory authority shall make efforts to achieve these targets with the cooperation of the applicants.
- The review system shall be enhanced to achieve these targets.

- Review time for new application of generic drugs

The following targets shall be achieved at 50% (median) by FY 2018.

Fiscal Year	Regulatory review time (months)	
	Targets	Results
2014	10	6.1
2015		8.2
2016		8.2
2017		-
2018		-

Review time of application for partial change approval (1)

- Targets for shortening review time
  - [1]Review time for partial change application for generic drugs etc. (standard review products)

Targets shall be achieved at 50%(median) by FY 2018, based on the following plan

Fiscal Year	Total review time (months)	
	Targets	Results
2014	15	15.5
2015	14	13.0
2016	13	11.7
2017	12	-
2018	10	-

Review time of application for partial change approval (2)

- Targets for shortening review time
  - Review time for partial change application for generic drugs etc. (excluding the products that fall under “(1)” above)

The following targets shall be achieved at 50%(median) by FY 2018.

	Fiscal Year	Total review time (months)	
		Targets	Results
Partial change (change in procedure of study, etc.)	2014	6	7.3
	2015		6.9
	2016		7.0
	2017		-
	2018		-
Partial change (expedited reviews)	2014	3	4.0
	2015		4.8
	2016		4.3
	2017		-
	2018		-

Current policies, practices and available relevant documents for DS

- "Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law“

  (PFSB/ELD Notification No.021001 dated Feb 10, 2005)

  - referring to filing of the drug substance(DS) manufacture, which recommends for applicants not to register a simple step.

- ICH Q11: "Development and Manufacture of Drug Substances“ dated July 10,2014
  - Implementation of Q11 in Japan has made the starting material (SM) selection more risk-based and applicants have submitted a longer manufacture route.

Thank you for your attention !

http://www.pmda.go.jp/