Statistical Programming

e-Data Submission Overview in US/EU/Japan/China

PhUSE Single Day Event 2017, Shanghai, China

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Nov 3, 2017

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Disclaimer

- All information provided in this slides is provided for information purposes only

- Views expressed in this presentation are those of the speaker and not necessarily of Novartis

Acknowledgement

- This slides referenced a presentation made by **Marjorie Nowak** a lot
- Marjorie Nowak is an expert in Novartis focusing on development, maintenance, training and support of data standards, e-Data submission packages and related tools, processes, trainings and guidelines to ensure the compliance with health authority agencies' latest requirements

Biography

- Yi (Eason) Yang joined Novartis in 2010 and is currently the global lead of statistical programming team for Entresto® (LCZ696)

Agenda

- eCTD
- Data Standards
- Deliverables
- Meetings to Discuss Data Standards With the HAs
- Submission Process

Acronyms

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use	**CFDA**	China Food and Drug Administration
FDA	Food and Drug Administration	**CDE**	Center for Drug Evaluation
CBER	Center for Biologics Evaluation & Research	**eCTD**	Electronic Common Technical Document
CDER	Center for Drug Evaluation and Research	**NDA**	New Drug Application
OSI	Office of Scientific Investigations	**ANDA**	Abbreviated New Drug Application
BIMO	Bioresearch monitoring	**BLA**	Biologics License Applications
EMA	European Medicines Agency	**IND**	Investigational New Drug
CHMP	Committee for Medicinal Products for Human Use	**DMF**	Drug Master Files
PRAC	Pharmacovigilance Risk Assessment Committee	**SEND**	Standard for Exchange of Nonclinical Data
CAT	Committee for Advanced Therapies	**SDTM**	Study Data Tabulation Model
MAA	Marketing Authorization Application	**ADaM**	Analysis Data Model
CP	Centralized Procedure	**SDSP**	Study Data Standardization Plan
DCP	Decentralized Procedure	**ARM**	Analysis Results Metadata
MRP	Mutual Recognition Procedure	**SDRG**	Study Data Reviewer's Guide
NP	National Procedures	**ADRG**	Analysis Data Reviewer's Guide
PMDA	Pharmaceuticals and Medical Devices Agency	**GCP**	Good Clinical Practice
MHLW	Ministry of Health, Labour and Welfare	**GLP**	Good Laboratory Practice

eCTD

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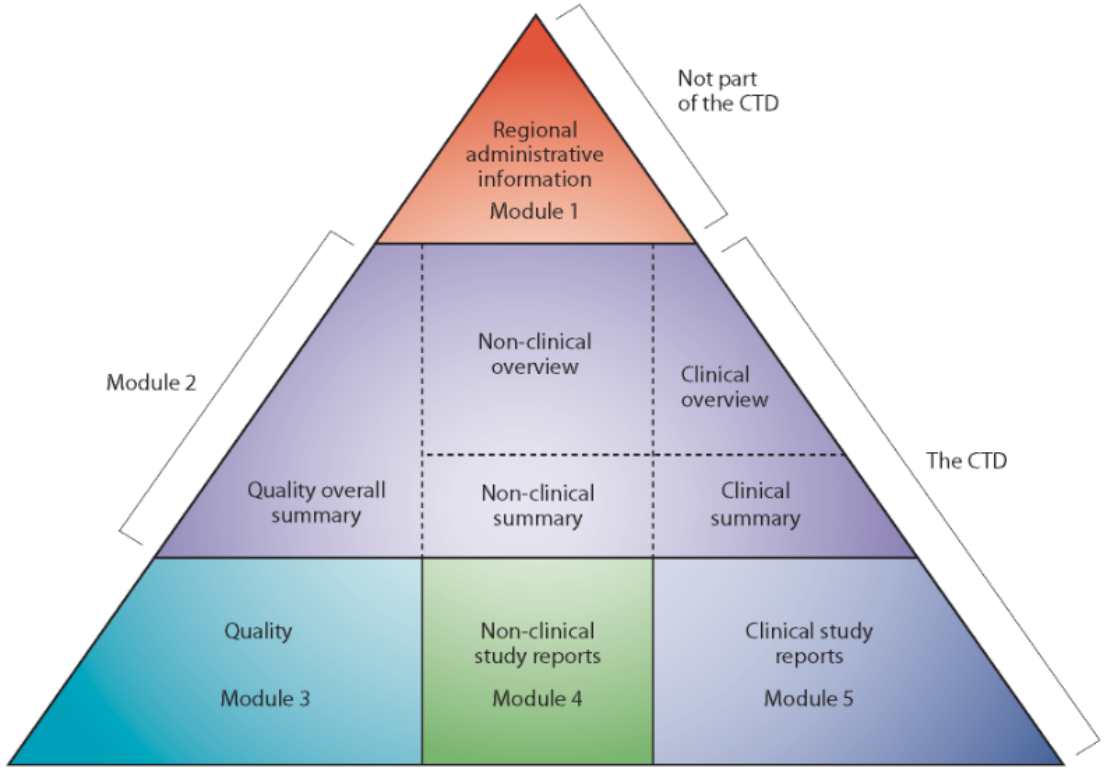
CTD: an ICH Harmonized format for submission to Competent / Regulatory Authorities



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

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eCTD advantages

- Supporting a better, more comprehensive review
- Providing for a more effective review process
- Promoting standardization
- Promoting operational efficiency

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eCTD in US

- The eCTD is the **standard** format for submitting applications, amendments, supplements, and reports to FDA's CDER and CBER

- After the dates listed below, eCTD requirements for submissions to CDER and CBER will go into effect and submissions that **do not use eCTD will not be filed or received**
  - ✓ **May 5, 2017: NDAs, ANDAs, and BLAs**
  - ✓ **May 5, 2018: INDs and DMFs**

Please refer to the eCTD Guidance for the complete details to meet the eCTD requirement

eCTD in EU

- Since **June 2003**, applicants have had the option of submitting an eCTD in parallel with the paper submission

- Timeline of implementation of **mandatory** use of eCTD format for regulatory submissions
  - ✓ **Jan 1, 2009: Centralized Procedure (CP)**
  - ✓ **Jul 1, 2015: New MAA* in Decentralized Procedure (DCP)**
  - ✓ **Jan 1, 2017: New MAA* in Mutual Recognition Procedure (MRP)**
  - ✓ **Jan 1, 2018: All regulatory activities in European procedures (DCP/MRP)**
  - ✓ **Jul 1, 2018: New MAA* in National Procedures (NP)**
  - ✓ **Jan 1, 2019: All regulatory activities in National Procedures (NP)**

**MAA=Marketing Authorization Application*

eCTD in Japan

- Japan began accepting eCTD submissions for marketing applications in **2004**. Paper copies of the submissions were also required

- Regulations changed in **2009**, and paper replicas of Modules 3, 4 and 5 were no longer required if applicants submitted an original eCTD

- With the requirement to electronically submit clinical study data, all necessary documents and data in an application, **in principle, should be submitted in accordance with eCTD**

eCTD in China

- **2010年09月25日**: 关于**按CTD格式**撰写化学药品注册申报资料有关事项的通知 （国食药监注[2010]387号）

- **2010年09月30日**: 国家食品药品监督管理局发布《**化学药品CTD格式申报资料撰写要求**》

- **2010-10-11**: SFDA issues Requirements on **Application Dossiers in CTD Format for Pharmaceutical Products**

- **2017年3月23日**: 深化改革、鼓励创新，全国药品注册管理工作会议在京召开

  .....四是改革受理模式，**加快推进电子通用技术文档（eCTD）系统建设**逐步实现化学仿制药的网上集中申报.....

Data Standards

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Study data for submission to CDER and CBER

- CDER and CBER strongly encourage IND sponsors and NDA applicants to consider the implementation and use of study data standards as early as possible in the product development life cycle so that data standards are accounted for in the design, conduct, and analysis of studies

- Sponsors whose studies start after the dates listed below **must** submit data in the data formats supported by FDA and listed in the **FDA Data Standards Catalog**
  - ✓ **Dec 17, 2016: NDAs, ANDAs, BLAs, and subsequent submissions to these types of applications**
  - ✓ **Dec 17, 2017: INDs**

For exemptions and the definition of "study start date", see the Guidance for Industry, Providing Regulatory Submissions in Electronic Format—Standardized Study Data (PDF - 131 KB)

Current versions of data standards

- Currently supported study data standards:
  - ✓ **SEND**
  - ✓ **SDTM**
  - ✓ **ADaM**
  - ✓ Case Report Tabulation Data Definition Specification (**Define-XML**) for the metadata that accompany SEND, SDTM, and ADaM datasets

- These study data standards were developed as part of a collaboration between FDA, CDISC, and other stakeholders

For detailed CDISC submission instructions, see the Study Data Implementation Guides

Updates of data standards

- FDA has the following procedures for updating standards
  - ✓ FDA will **periodically** publish its intent to begin supporting new standards and new versions of current standards
  - ✓ FDA will give **at least one year's** notice before a new version of a standard is required
  - ✓ For entirely new standards, the notice **will be at least two years**
  - ✓ FDA is supporting efforts to develop clinical terminology standards for **particular therapeutic areas** within the SDTM. The SDTM will be updated periodically to include new and revised standards for specific therapeutic areas

To learn more about how FDA identifies and develops study data standards, see CDER Study Data Standards Research and Development.

There is a need to define data formats

- CDISC **recommended** but not mandatory yet
  - ✓ Data shall be published in the format they have been submitted and evaluated - **no conversion** of formats
  - ✓ Data should be **human readable and searchable**, with consistent formats
  - ✓ Patient-level data should be accompanied by associated documentation that allows a rapid and clear understanding of the data and how to process it. This documentation, which includes **metadata**, should ideally be **machine readable**
  - ✓ Formats should be chosen so that data is readable with open source, non-proprietary software: It would be easier for Industry in general if these requirements are the **same as FDA's**

To learn more about the EMA's recommendation of study data standards, see Final advice to the European Medicines Agency from the clinical trial advisory group on Clinical trial data formats

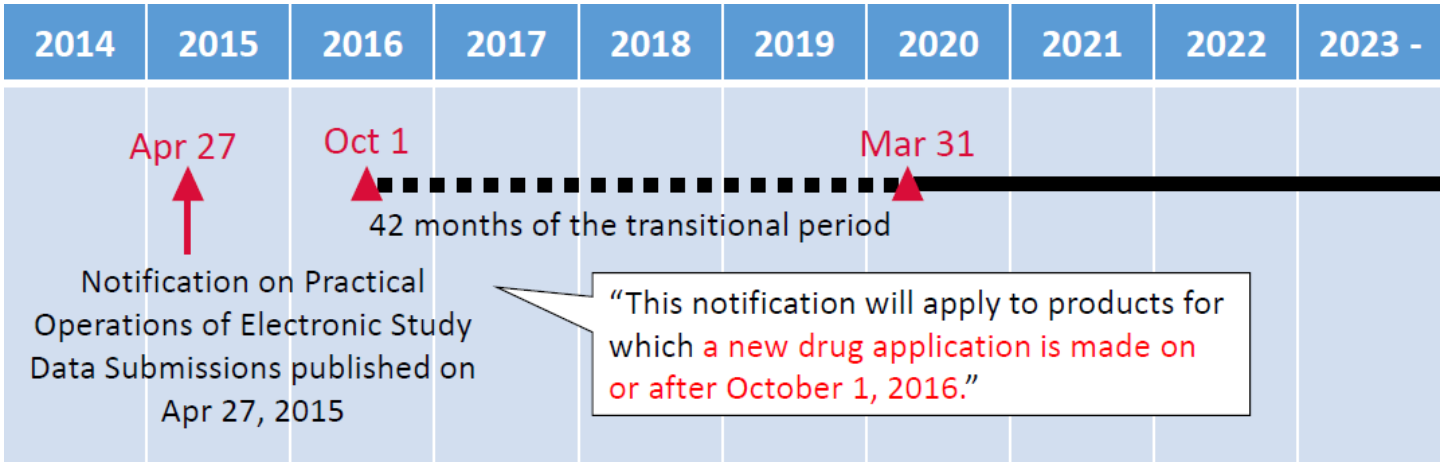
Formats recommended

- **SDTM**, **ADaM** and **Define-XML** is recommended is for all these to be submitted to the Agency
- **SDTM-annotated CRF** would also be very useful for data re-analysis
- Harmonization of formats such as CDISC SDTM and ADaM is **desirable**. This exercise shall be progressively implemented in a collaborative way between CDISC and EMA to ensure consistency and versioning control
- It was acknowledged that CDISC implementation guides can be interpreted in different ways by Applicants, therefore **EMA and FDA** requirements in relation to these guides should be **consistent**
- EMA guidance on formats may not follow the evolution of CDISC modifications at the same rhythm if it imposes too much burden on applicants. This will reduce the potential for re-formatting should a newer version be required

Initiation timing of submission of e-study data

- The initiation date of submission of e-study data is **October 1, 2016**

- There is a transitional period of 42 months from **October 1, 2016** to **March 31, 2020**
  - ✓ PMDA accepts the legacy submission and partial data submission (hybrid submissions) during the transition period



After April, 2020

- **All** required study data need to be submitted in **CDISC** format
- **No waivers** are allowed on this point
- Studies in legacy format need to be **converted**
- Closed or completed studies will require data **converted** to CDISC-compliant if study meets e-study data submission criteria

Data Standards

- **2016年07月29日**：总局关于发布临床试验数据管理工作技术指南的通告（2016年第112号）
  - ✓ 国际发达监管机构如美国FDA、日本医药品医疗器械综合机构（PMDA）将强制要求递交符合CDISC标准的电子数据，可见**CDISC**标准已越来越得到业内的认可和广泛使用，成为临床试验数据的**国际“通用语言”**
  - ✓ 为了提高临床试验数据质量以及统计分析的质量和效率，方便数据的交流与汇总分析，在新药上市注册申请时，**建议采用CDISC标准**递交原始数据库和分析数据库

To learn more about the CFDA's technical guide of study data standards, see 2016年第112号通告附件

Deliverables

focus on data and programming related deliverables

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Deliverables

	FDA	EMA	PMDA	CFDA
SDSP	✓ **Should**		✓ **Preferable**	
Annotated CRF (pdf)	✓ **Mandatory**	✓ **Not routinely requested**	✓ **Mandatory**	✓ **Mandatory**
Source and Analysis datasets: SDTM/ADaM (xpt)	✓ **Mandatory** since Dec 17, 2016 for NDAs/ANDAs/BLAs ✓ **Mandatory** since Dec-17, 2017 for INDs	✓ Not routinely requested but CDISC format **recommended**	✓ **Mandatory** since Apr 1, 2020	✓ **Recommended**
Pinnacle 21 checks	✓ **FDA specific rules** (FDA rejection criteria not yet implemented)	✓ **Recommended** to use FDA rules	✓ **PMDA specific rules** (PMDA rejection criteria implemented)	✓ **Recommended** to do the same as for FDA
SDRG/ADRG (pdf)	✓ **Recommended**	✓ Not routinely requested but **recommended**	✓ **Mandatory**	

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Deliverables

	FDA	EMA	PMDA	CFDA
Define-XML	✓ **Mandatory**	✓ Not routinely requested but **recommended**	✓ **Mandatory**	✓ **Not yet Required** but require a text file containing brief introduction of the deliverables to describe what is in the package
Programs	✓ **Should** for the programs used to create the ADaM datasets ✓ **Should** for the programs associated with primary and secondary efficacy analyses	✓ **Not routinely requested**	✓ **Mandatory** for the programs used to create the ADaM datasets ✓ **Mandatory** for programs used for analyses	
Site inspection	✓ OSI BIMO clinical data and listings (PDF)	✓ Listings (PDF) (similar to FDA) and corresponding data in XLS	✓ Listing summary of # of patients having at least 1 AE with suspected relationship to study drug by site	✓ Self-inspection ✓ Source data listings by site on-site inspection

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Meetings to Discuss Data Standards With the HAs

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Meetings with FDA

- **Type A Meeting**
  - ✓ Help an otherwise stalled product development program proceed
  - ✓ Occur within 30 days of FDA receipt of a written meeting request
- **Type B Meeting**
  - ✓ Pre-IND meetings
  - ✓ End-of-Phase I meetings
  - ✓ End-of-Phase II and Pre-Phase III meetings
  - ✓ Pre-NDA/BLA meetings
  - ✓ Occur within 60 days of FDA receipt of a written meeting request
- **Type C Meeting**
  - ✓ Any meeting other than a Type A or Type B
  - ✓ Occur within 75 days of FDA receipt of a written meeting request

Data standards discussion

- Sponsors and applicants may use established **Type B meetings** to discuss the SDSP and to raise data standardization issues (if any) related to NDAs and BLAs
  - ✓ Initial discussions about which data standards to use for study data should take place as early as possible during drug development, especially for safety data, but should in any event occur **no later than the end of phase II**
  - ✓ Discussions about nonclinical SDSP may be initiated **at the pre-IND stage** and should continue throughout development
  - ✓ In general, **Pre-NDA/BLA meetings** is considered **too late** to initiate data standardization discussions

Data standards discussion

- Sponsors and applicants may also request a separate **Type C meeting** to discuss substantive data standardization issues for NDAs and BLAs
  - ✓ E.g., a sponsor's desire to use a therapeutic area standard in SDTM format that is not currently supported by FDA
  - ✓ The request should include adequate information to identify the appropriate FDA staff necessary to discuss the proposed agenda items

- Sponsors and applicants may submit technical questions related to data standards at any time to the **technical support team**
  - ✓ Contact CDER at cder-edata@fda.hhs.gov
  - ✓ Contact CBER at cber.cdisc@fda.hhs.gov

Meetings with EMA

- Pre-submission meeting (6-7 Months before submission)
  - ✓ Discuss **final practical & regulatory aspects** of upcoming application
  - ✓ Clarify **application-specific issues** not addressed on the EMA website
  - ✓ Useful step to ensure that application will **meet all requirements for validation**
  - ✓ **Strongly recommended**, even for experienced users of the centralized procedure
  - ✓ Reconfirm various administrative/procedural/legal issues; requirements may have changed

- Pre-submission meetings are the **best opportunity** for applicants to obtain procedural and regulatory advice from the Agency

Meetings with PMDA

- The applicant must discuss and confirm with the PMDA on the scope of the submission of electronic study data and the planned date of a new drug application, in principle, at the meeting prior to pre-NDA consultation and also by utilizing **clinical trial consultations** and **consultation on data format** of the submission of electronic study data, if necessary

Meetings with PMDA

- Clinical trial consultations (roughly $1,400 to $70,000)
  - ✓ Pre-Phase I consultation
  - ✓ Pre-Early Phase II consultation
  - ✓ Pre-Late Phase II consultation
  - ✓ End-of-Phase II consultation
  - ✓ **Pre-NDA consultation**
  - ✓ .....
- Pre-NDA consultation
  - ✓ PMDA will **not** discuss the contents of the data
  - ✓ PMDA will **confirm** whether the results of the consultation on the data format for the submission of electronic study data correctly reflected
- To confer with the PMDA on the scope of the submission of electronic data of ISS/ISE, applicants **must** use the clinical trial consultation, not the consultation on data format of submission

Meetings with PMDA

- Consultation on data format meeting (free)
  - ✓ Anytime from beginning of Phase II to a few months prior to NDA
  - ✓ Provide the **necessary explanation for violations** for the submission of electronic study data
  - ✓ Confirm the **details** of such datasets, including file types to be submitted, etc
  - ✓ Sponsors or applicants can request multiple consultations until data submission

- Preliminary meeting (free)
  - ✓ Usually 1 to 3 months before NDA
  - ✓ **Final version of Attachment 8** (Supporting Document on Consultation on Data Format of Submission of Electronic Study Data) has to be submitted

- Attachment 8
  - ✓ Reflect the **results** of the consultation on the data format for the submission of electronic study data
  - ✓ Should be **submitted** when sponsors or applicants apply for the Pre-NDA consultation
  - ✓ When the NDA is submitted, the PMDA will **check** submitted data based on the Attachment 8

Meetings with CFDA

- 药审中心与申请人的沟通交流一般可分为以下几种类型
  - ✓ 双向预约式沟通交流
  - ✓ 查询式沟通交流
  - ✓ 问询式沟通交流
  - ✓ 开放式沟通交

- 双向预约式沟通交流申请，根据品种研究进程和注册申请的不同阶段可分为以下五种类型
  - ✓ 临床前（Pre-IND）申请—基本完成非临床试验研究，但尚未提出临床研究申请阶段的申请
  - ✓ 临床（IND）申请--已提出临床研究申请阶段的申请
  - ✓ 完成I期临床后（End of phase I）申请--已批准进行临床研究，并已经完成I期临床研究阶段的申请
  - ✓ 完成Ⅱ期临床后（End of phase Ⅱ）申请--已批准进行临床研究，并已完成Ⅱ期临床研究阶段的申请
  - ✓ 生产（NDA）申请--完成临床研究，并提出生产注册申请阶段的申请

药品审评中心与注册申请人沟通交流质量管理规范（试行）.docx

Submission Process

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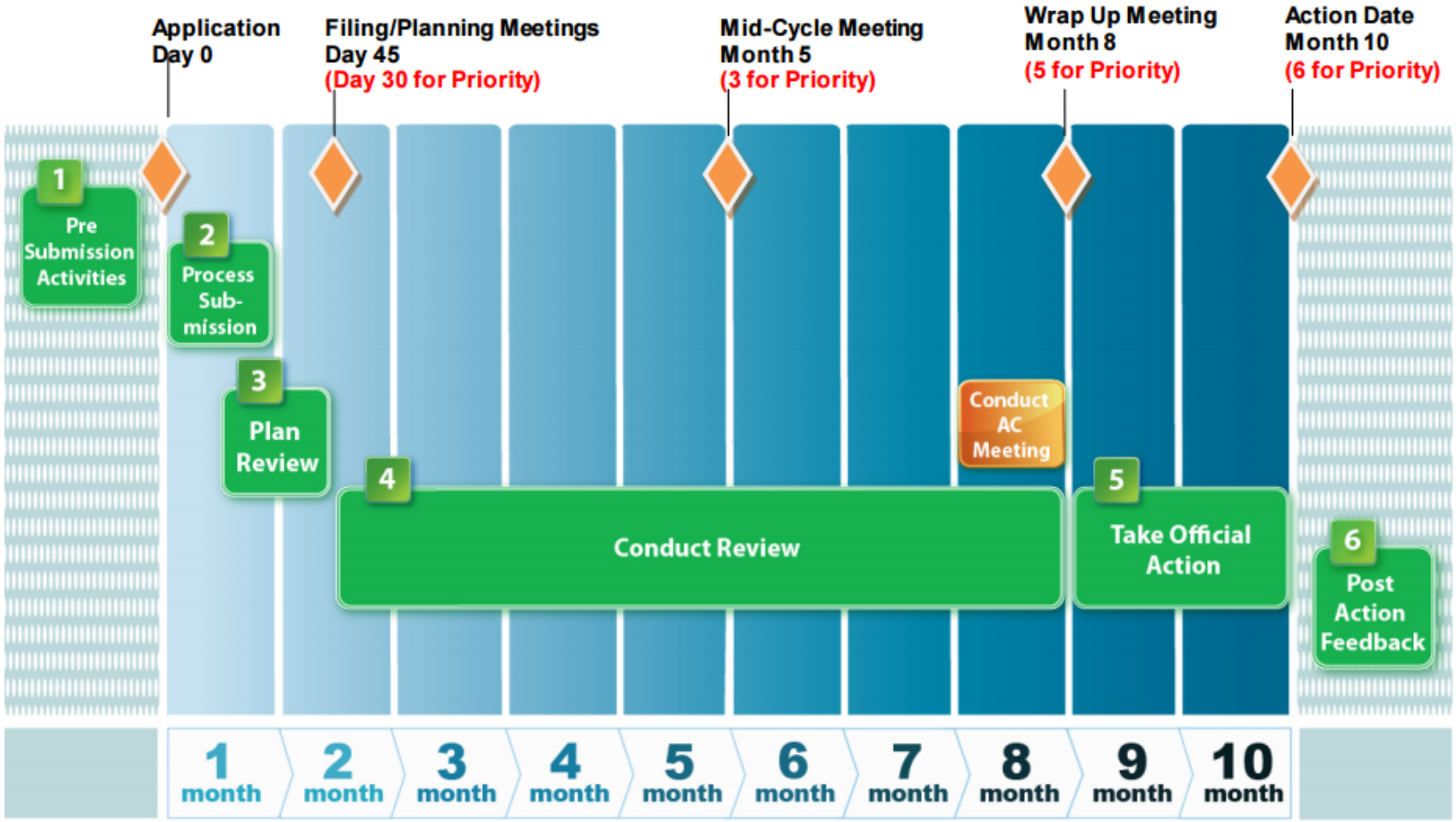
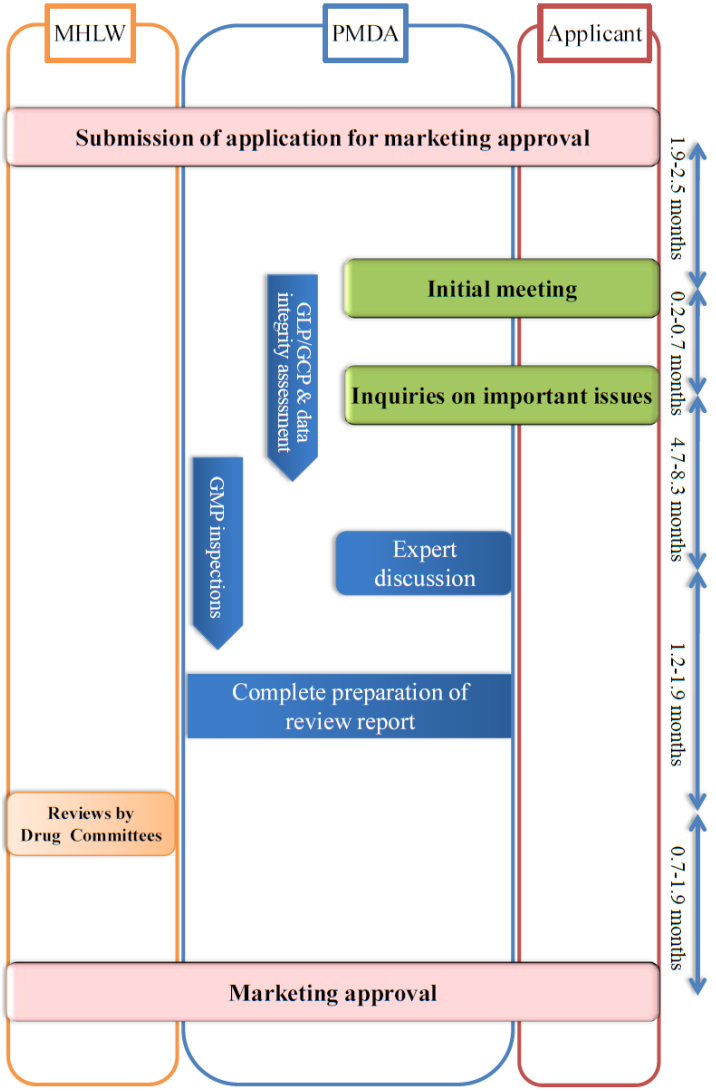
US Submission



EU Submission

Timing	Action	Objective
18 to 7 months before submission of MAA	**Submission of eligibility request**	Provide justification and find out whether a product can be evaluated under the centralized procedure
7 months before submission of MAA	**Notification of intention to submit an application**	Notify the Agency of the intended submission date according to EMA procedural timetables
	Appointment of rapporteurs	The CHMP and the PRAC appoint (co-)rapporteurs to conduct the scientific assessment
6 to 7 months before submission of MAA	**Pre-submission meetings**	Obtain procedural and regulatory advice from the Agency (Marketing authorization application pre-submission meeting request form)
Submission of MAA	**Submission and validation of the application**	Applicants should use the eCTD format and submit the application through the eSubmission gateway or web client
Up to 210 active days of assessment	**Scientific evaluation**	The CHMP evaluates MAA submitted through the centralized procedure. The PRAC provides input on aspects related to risk management and the CAT on advanced therapy medicines
	CHMP scientific opinion	After the evaluation, the CHMP must issue a scientific opinion on whether the medicine may be authorized or not. EMA sends this opinion to the European Commission, which issues the marketing authorization. The Agency then publishes a summary of the committee's opinion
Within 67 days of receipt of CHMP opinion	**European Commission decision**	Legally binding decision

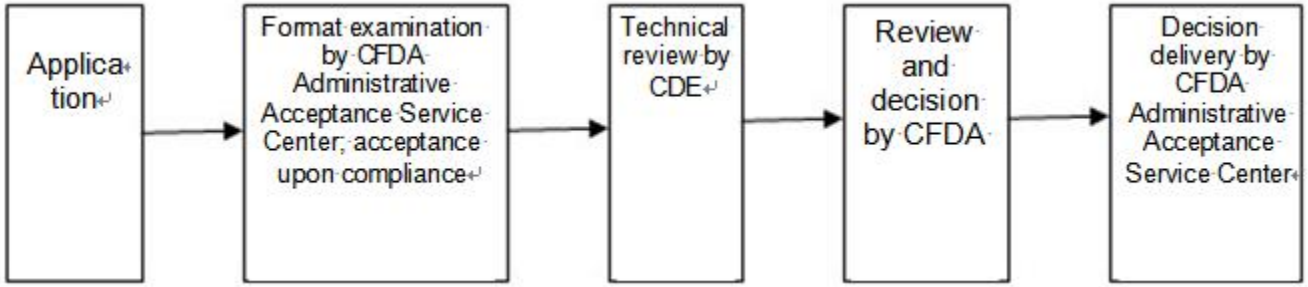
Japan Submission



- The review time from receipt of an application to approval is
  - ✓ **12 months** for standard review products
  - ✓ **9 months** for the "Orphan Drug Designation"

- During this review, there are two big periods of PMDA questions
  - ✓ The first one is after Initial meeting
  - ✓ The questions received are mostly of general nature (e.g. clinical)
  - ✓ The second one is after GCP compliance check but before the Expert discussion
  - ✓ The questions received require a substantial programming involvement which should be planned ahead

China Submission



Timing	Actions
5 days from the date of receipt of application dossiers	**Acceptance by CFDA**
30 days from the date of acceptance	**Application dossiers transferred to CDE**
90/80[1] days from the date of application dossiers transferred to CDE **30/20[1] days** for supplementary dossiers[2]	**Technical review by CDE**
20 days from technical review by CDE extension of **10 days** with competent leader's consent	**Review and decision by CFDA**
10[1] days from decision by CFDA	**Decision delivery by CFDA**

- Only working days is counted
- 1: Days after slash is for products approved of special approval process
*- 2: Supplementary dossiers should be submitted within **4 months** from the notice*

Appendix

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Guidances and Support

- Development & Approval Process (Drugs)
  - ✓ Guidance Documents for Drug Applications
  - ✓ Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products
  - ✓ Electronic Regulatory Submission and Review
  - ✓ FDA Review Desktop Guide

- Electronic Common Technical Document (eCTD)
  - ✓ Submit Using eCTD
  - ✓ eCTD Guidance
  - ✓ eCTD Resources
  - ✓ eCTD Important Notices
  - ✓ eCTD Submission Standards
  - ✓ eCTD Technical Conformance Guide
  - ✓ Specifications for eCTD Validation Criteria
  - ✓ Recent FDA eCTD Presentations

Guidances and Support

- Study Data for Submission to CDER and CBER
  - ✓ Guidance for Industry — Providing Regulatory Submissions in Electronic Format — Standardized Study Data
  - ✓ Study Data Standards Resources
  - ✓ Data Standards in the Drug Lifecycle
  - ✓ Data Standards and Terminology Standards for Information Submitted to CDRH
  - ✓ CDER Data Standards Program
  - ✓ CDER / CBER Study Data Standardization Plan Recommendations
  - ✓ Study Data Standardization Plan Checklist Recommendations (SDTM, ADaM and CDASH)
  - ✓ FDA Data Standards Catalog
  - ✓ Technical Rejection Criteria for Study Data
  - ✓ Study Data Technical Conformance Guide
  - ✓ FDA Business Rules
  - ✓ FDA Validator Rules

Guidances and Support

- eSubmission
  - ✓ Final HMA eSubmission Roadmap
  - ✓ eSubmission Roadmap (visual representation)
  - ✓ Annex 2 to the HMA eSubmission Roadmap on the implementation of mandatory use of eCTD format for regulatory submissions
  - ✓ Guidance for e-submissions to EMA
  - ✓ The CMDh Best Practise Guide for use of eCTD in MRP/DCP
  - ✓ eCTD Validation Criteria
  - ✓ eCTD Validation Criteria Q&A
  - ✓ Variations in eCTD format Q&A document

- Marketing authorization
  - ✓ Final advice to the European Medicines Agency from the Clinical Trial Advisory Group on clinical-trial-data formats

Guidances and Support

- Electronic Data Promotion
  - ✓ Basic Principles on Electronic Submission of Study Data for New Drug Applications
  - ✓ Question and Answer Guide Regarding “Basic Principles on Electronic Submission of Study Data for New Drug Applications
  - ✓ Notification on Practical Operations of Electronic Study Data Submission
  - ✓ Question and Answer Guide Regarding “Notification on Practical Operations of Electronic Study Data Submissions”
  - ✓ Technical Conformance Guide on Electronic Study Data Submissions
  - ✓ PMDA Data Standards Catalog
  - ✓ Study Data Validation Rules
  - ✓ FAQs on Electronic Study Data Submission (Excerpt)

Guidances and Support

- Regulatory submission
  - ✓ On the Standard Review Timeline for New Drug Applications

- Recent Presentation on CDISC by PMDA Staffs
  - ✓ PMDA Update
  - ✓ CDISC Implementation in PMDA
  - ✓ Advanced Review with Electronic Data and CDISC Implementation in PMDA
  - ✓ Our Way to CDISC Submissions - An Update 12 Months Later
  - ✓ CDISC standards and data management-The essential elements for advanced Review with Electronic Data
  - ✓ Overview of CDISC Implementation at PMDA
  - ✓ Japan PMDA and CDISC Standards

Guidances and Support

- Regulatory Guide
  - ✓ Approval for clinical trials of imported (incl. from Hong Kong, Macao and Taiwan) chemicals
  - ✓ 关于按CTD格式撰写化学药品注册申报资料有关事项的通知
  - ✓ 总局关于发布临床试验数据管理工作技术指南的通告（2016年第112号）
  - ✓ 药品审评中心与注册申请人沟通交流质量管理规范（试行）

Q & A

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Thank you

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