Practices Sharing of Submitting data to NMPA

ClinChoice

ClinChoice K.K. Sanae Fujita

2023/12/08

Agenda

- Who we are /ClinChoiceとは
- Pharma Regulation in China /中国の薬事規制
- CDISC Regulation comparison/CDISCの各局規制比較
- Example /例：中国NDA用の試験データの作成業務

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More than 25 years of operating history worldwide, with 15 Years of experience in China, to serve both local, regional and global customers for the development of innovative drugs, biologics and medical devices

Global CRO headquartered in China with **4,000+ employees** located in 55 cities and 8 countries across the globe

Established in
1995

Headquartered in
Shanghai, China &
Philadelphia, USA

International expansion:
Merger with **FMD, K&L, iMED Global**

Recognized by world-class investors
Lilly Asia Venture /Goldman Sachs / Legend/Apricot/ Yuanbio Venture/ Sherpa, etc.

Global employees
3,800+

Provide service in
8 countries, 55 cities
China, US, India, Philippines, Armenia, Japan, UK, Canada

Management team are from
Top Global CRO & Pharma

With full CRO service
PM / CRA / SSU / PMA / CTA
MA / RA / PV / HGRAC / FSP
Biometrics / QCT / QA / SMO

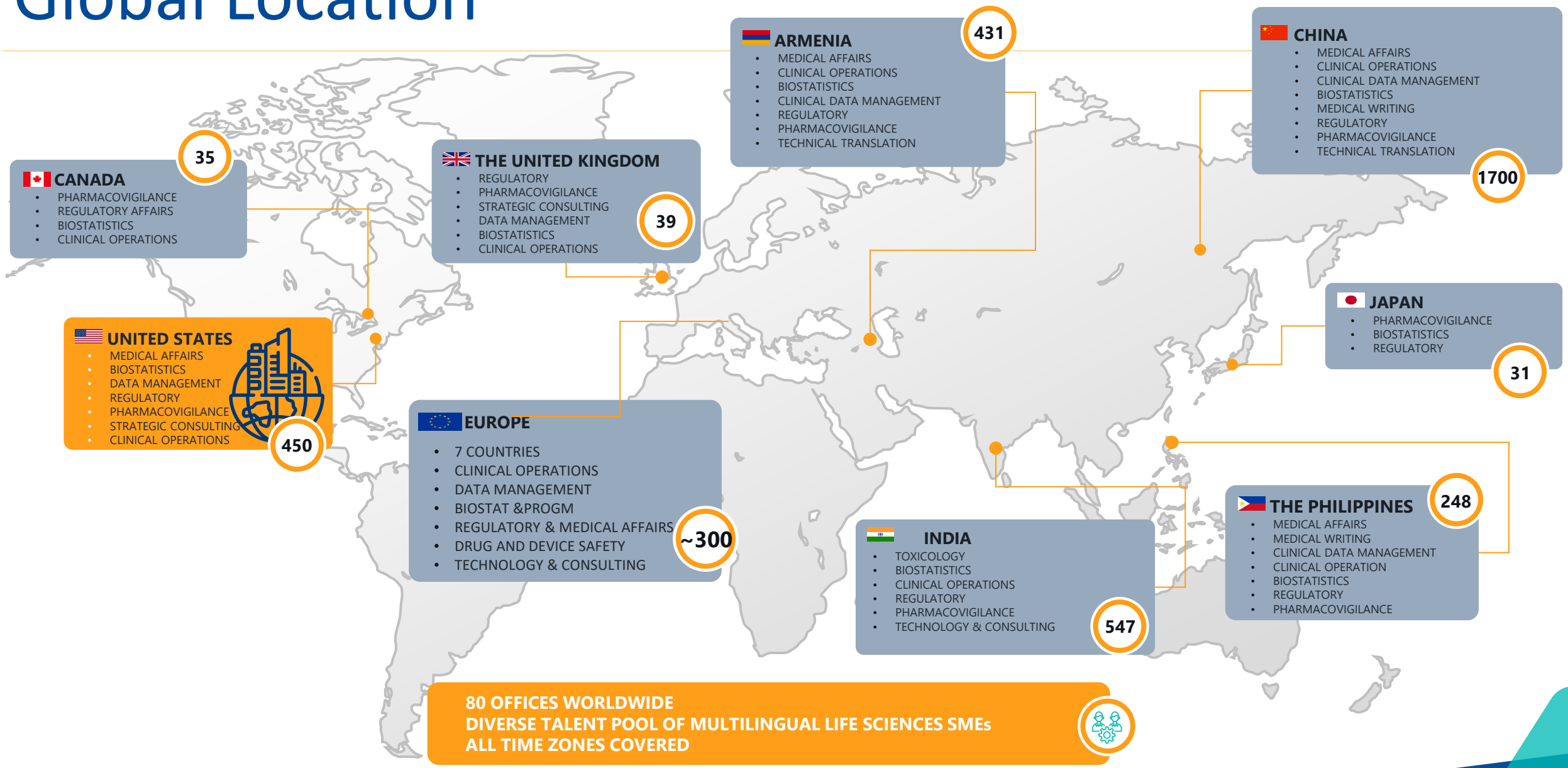
Completed over
1000 + clinical full-service studies

Completed
~ 500 Chinese traditional drug studies

Phase 1 capacity with
~200 beds **&** **~ 180** studies

Cooperated with
300+ bioteches **&** **600+** projects

Global Location



80 OFFICES WORLDWIDE
DIVERSE TALENT POOL OF MULTILINGUAL LIFE SCIENCES SMEs
ALL TIME ZONES COVERED

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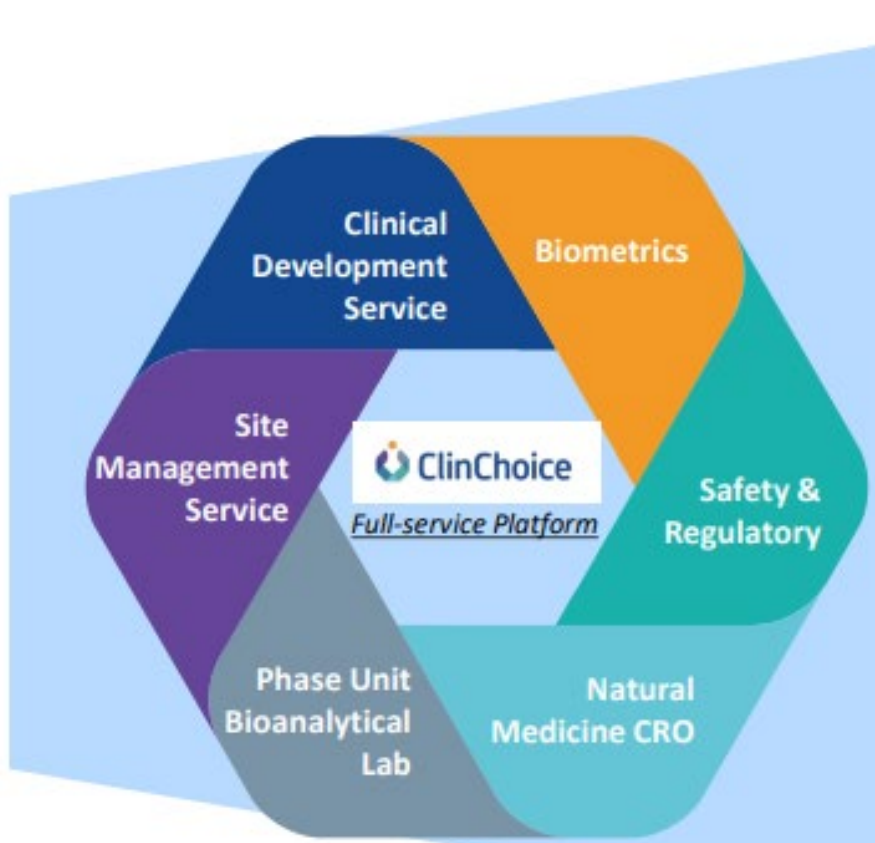
Partner of Choice for Multinational and Emerging Biopharma



- Project Management
- Clinical Operations
- Site Strat -up
- Quality Control
- Training (for CO)
- Biostatistics
- Data Management
- Analysis Programmer
- Medical Affairs
- Regulatory Affairs
- Human Genetic Resource Administration
- Pharmacovigilance
- Quality Assurance

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Supported NDA/BLA data submission to FDA/NMPA

Therapeutic Area	Approved	Need more development work	Ongoing	Suspended	
Cardiovascular	3				3
Neurology/CNS	11	1			12
Dermatology	2				2
Gastroenterology	2				2
Metabolism and Nutrition	3		3		6
Oncology	6		3	4	13
Oncology	2				2
Urology		1			1
Women's Health	1				1
Respiratory	4		1		5
Endocrine			1		1
Vaccines	3				3
Immunology	2				2
Infections and Infectious Diseases	1		1		2
Total	**40**	**2**	**9**	**4**	**55**

Submitted 55 products with accepted by FDA, 40 products were approved.

国家药品监督管理局
National Medical Products Administration

Therapeutic Area	Submitted	Approved
Infections and Infectious Diseases	4	4
Respiratory	1	
Psychiatric Disorders	1	1
Immunology	1	1
Dermatology	1	
Gastroenterology	1	1
Hematology	1	
Vaccines	2	1
Metabolism and Nutrition	7	6
Devices/Diagnostics	3	3
Oncology	3	2
Total	**25**	**19**

Approved 19 products, including 8 products with priority approval.

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Pharma Regulation in China

Pharma Regulation in China /中国の薬事規制

2019

Drug Administration Law of the People's Republic of China

中华人民共和国药品管理法

2020.7.1

Drug registration management practices

药品注册管理办法

药品生产质量管理规范

2020.7.1

Good Manufacturing Practice (GMP)

药物临床试验登记与信息公示管理规范

2020.7.1

Code of Practice for the Administration of Drug Clinical Trial Registration and Information Publication

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NMPA Guides

- July 27, 2016. 药物临床试验数据管理与统计分析的计划和报告指导原则
  Guidelines for Planning and Reporting of Data Management and Statistical Analysis in Clinical Trials
- July 27, 2016. 药物临床试验数据管理工作技术指南
  Technical Guidelines on Data Management in Clinical Trials
- June 01, 2017. 关于补交“临床试验数据库”资料的通知
  Notification of the submission of "Clinical Trial Data"
- Oct 09, 2019. eCTD中临床试验数据库及相关资料的申报要求
  Reporting Requirements for Clinical Trial Data and Related Information in the eCTD
- Jul 20, 2020. 发布《药物临床试验数据递交指导原则（试行）》的通告
  Notice of Release of Guidelines for Submission of Clinical Trial Data (for Trial Implementation)
- Sep 30, 2021. 关于实施药品电子通用技术文档申报的公告
  Announcement on the implementation of the drug electronic general technical document declaration
- Nov 4, 2022. 公开征求《关于药品注册申请实施电子申报的公告（征求意见稿）》等文件意见
  Public Consultation on the Announcement on the Implementation of Electronic Filing for Drug Registration Applications (Draft for Comment) and Other Documents

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CDISC starts in October 2020

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA
NMPA CDE
此页面上的内容需要较新版本的 Adobe Flash Player。
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国家药监局药审中心关于发布《药物临床试验数据递交指导原则（试行）》的通告（2020年第16号）

发布日期：20200720

为规范药品注册申请人递交药物临床试验数据及相关资料，配合新修订的药品注册申报资料要求，提高药品审评效率，药审中心组织制定了《药物临床试验数据递交指导原则（试行）》（见附件）。根据《国家药监局综合司关于印发药品技术指导原则发布程序的通知》（药监综药管〔2020〕9号）要求，经国家药品监督管理局审核同意，现予发布。

化学药品、生物制品自2020年10月1日起实施。中药实施日期按国家药监局发布中药注册分类及申报资料要求的通告中相关规定执行。

特此通告。

国家药品监督管理局药品审评中心

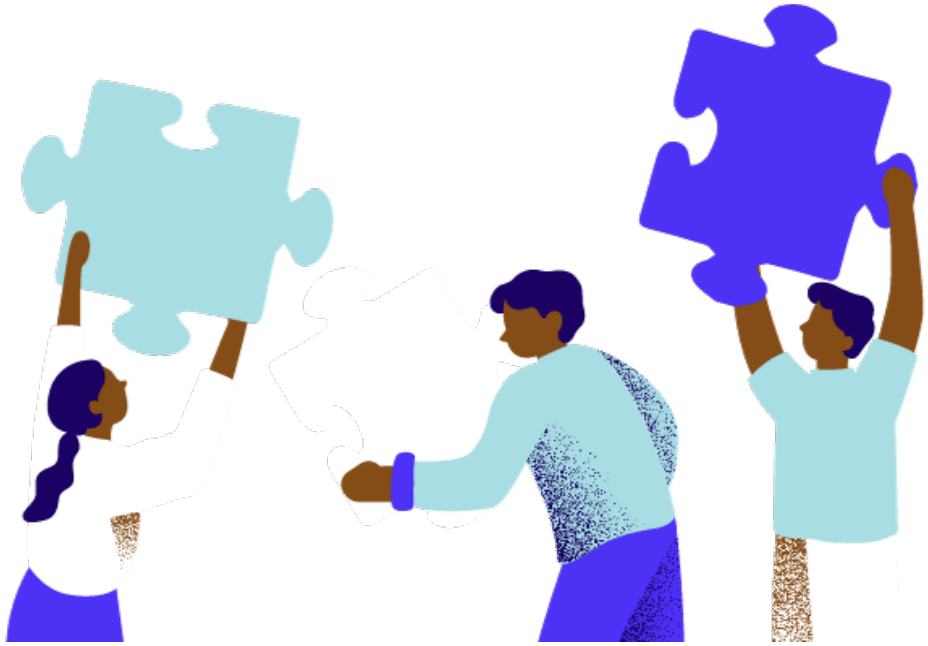
http://www.cde.org.cn/news.do?method=viewInfoCommon&id=7a43c3abfde95950

Summary of these guides

Subtitle

- Raw data and analytical data are recommended to be submitted in XPT version 5 (XPT V5) or above.
- Sponsors are **encouraged** to submit clinical trial data in accordance with CDISC standards.
- Data description files must be submitted, either in XML or PDF format.
- Data reviewer's guide are encouraged and should be in PDF format.
- The annotated case report form aCRF should be in PDF format, and the program code should be in TXT format.

Collaboration with China RA team

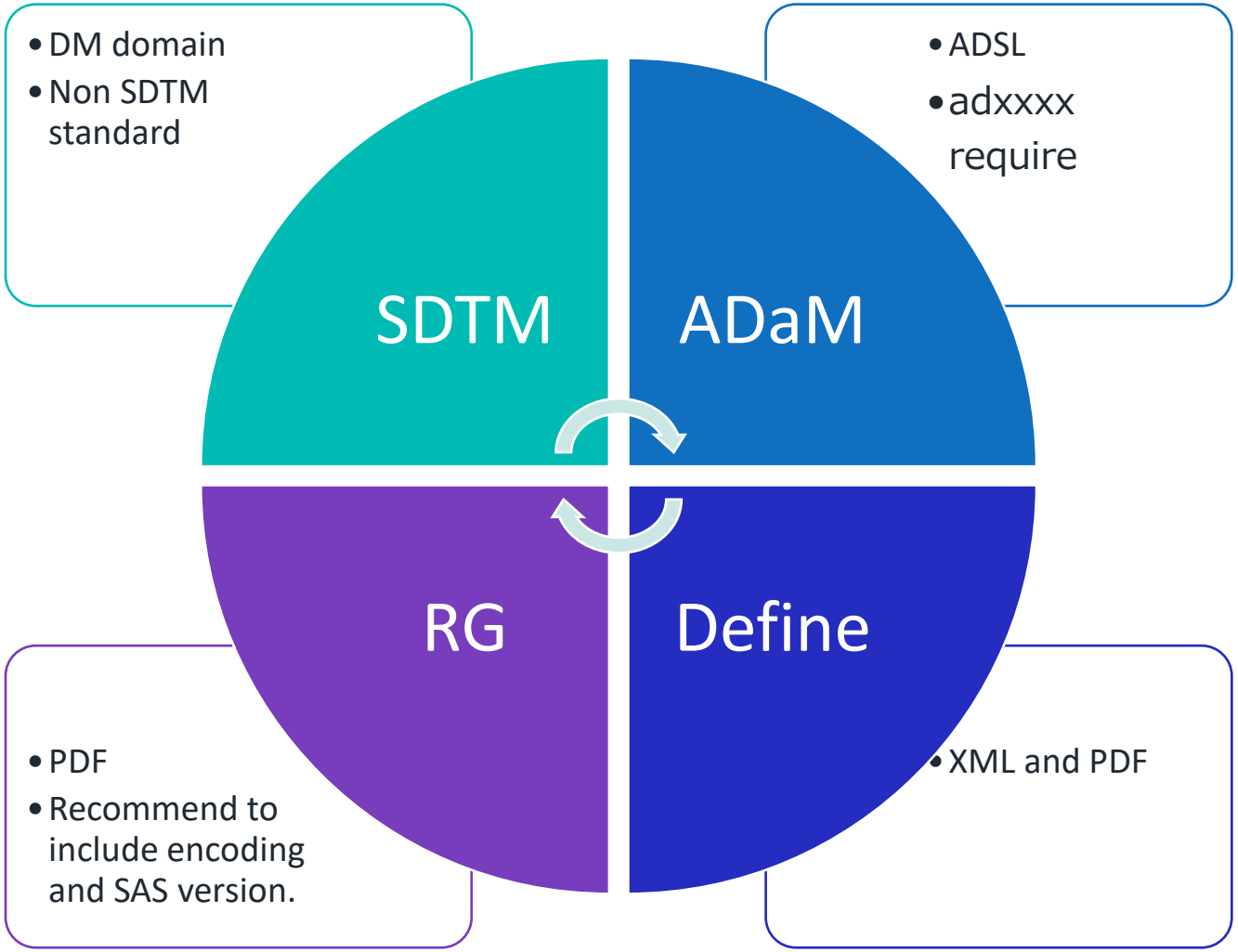


- The relationship allows the Chinese to ask about the Japanese regulatory system and the Japanese to feel free to ask about the Chinese regulatory system **at any time.**
- There are projects to support foreign expansion **in both country.**
- Gap analysis, which originally could only be carried out after translation, can be carried out **without perfect translation** (if it is simple.)

CDISC Regulation comparison

Characteristics of Chinese Regulations

The NMPA took a cue from the FDA's strategies and methods and added some uniqueness in its data submissions.



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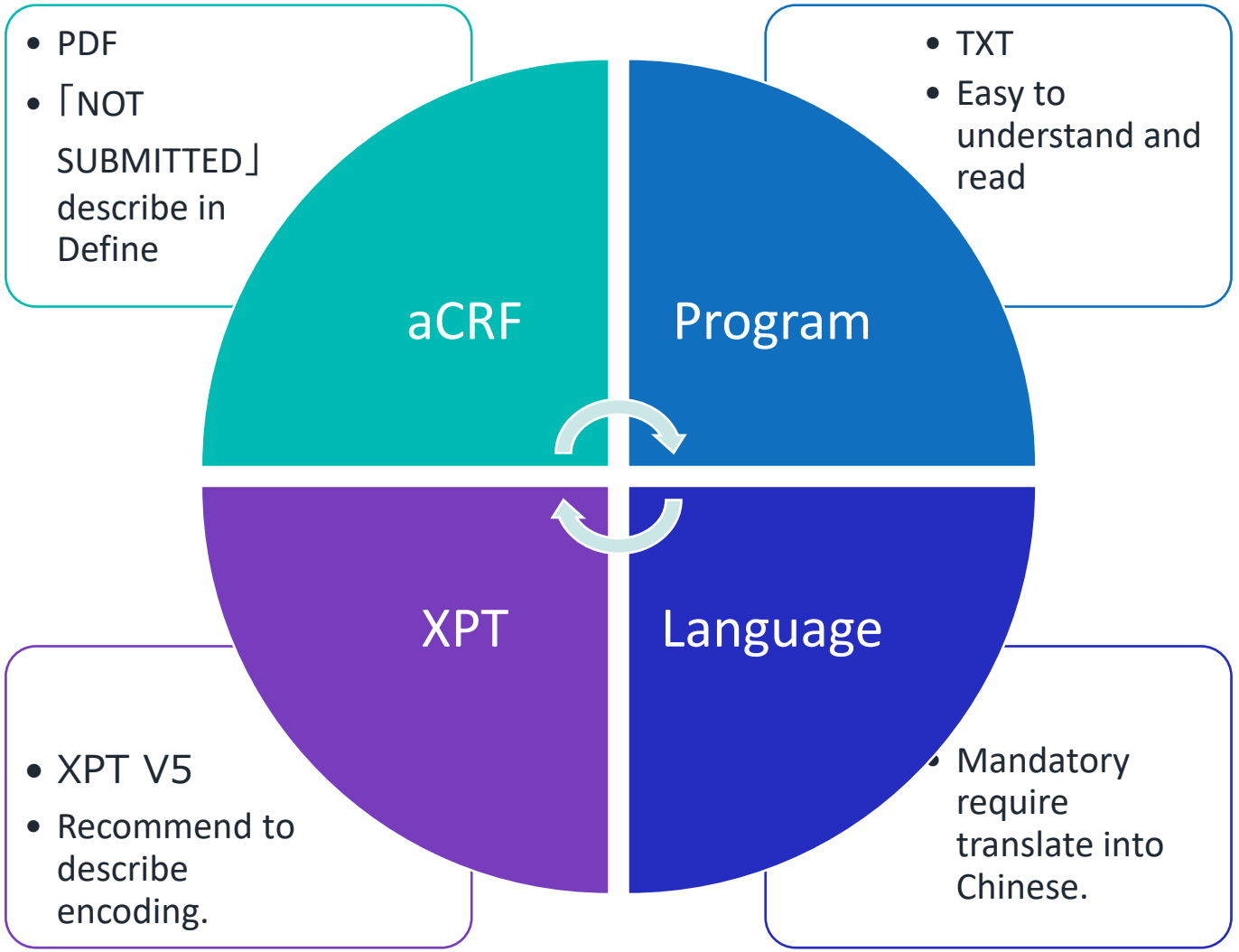
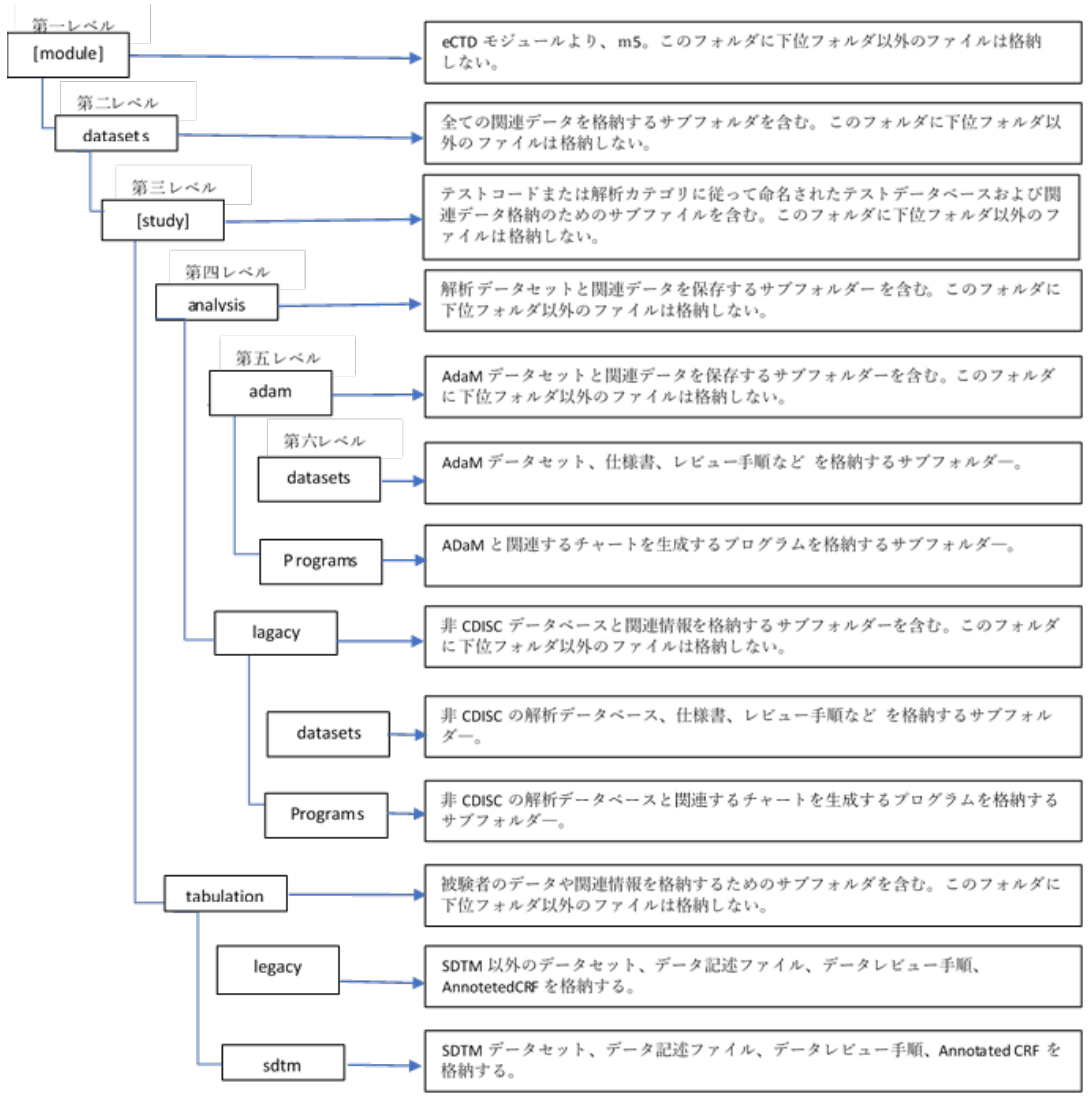


Difference between FDA , NMPA, and PMDA

Item	FDA	NMPA	PMDA
File Size for XPT	5GB	4GB	10 GB
XPT version	V5	V5 or above	V5
Dataset Standard	CDISC	CDISC standard is recommended	CDISC
Define	XML	XML or PDF	XML
Language	English	Chinese	English and Japanese

M5 folder



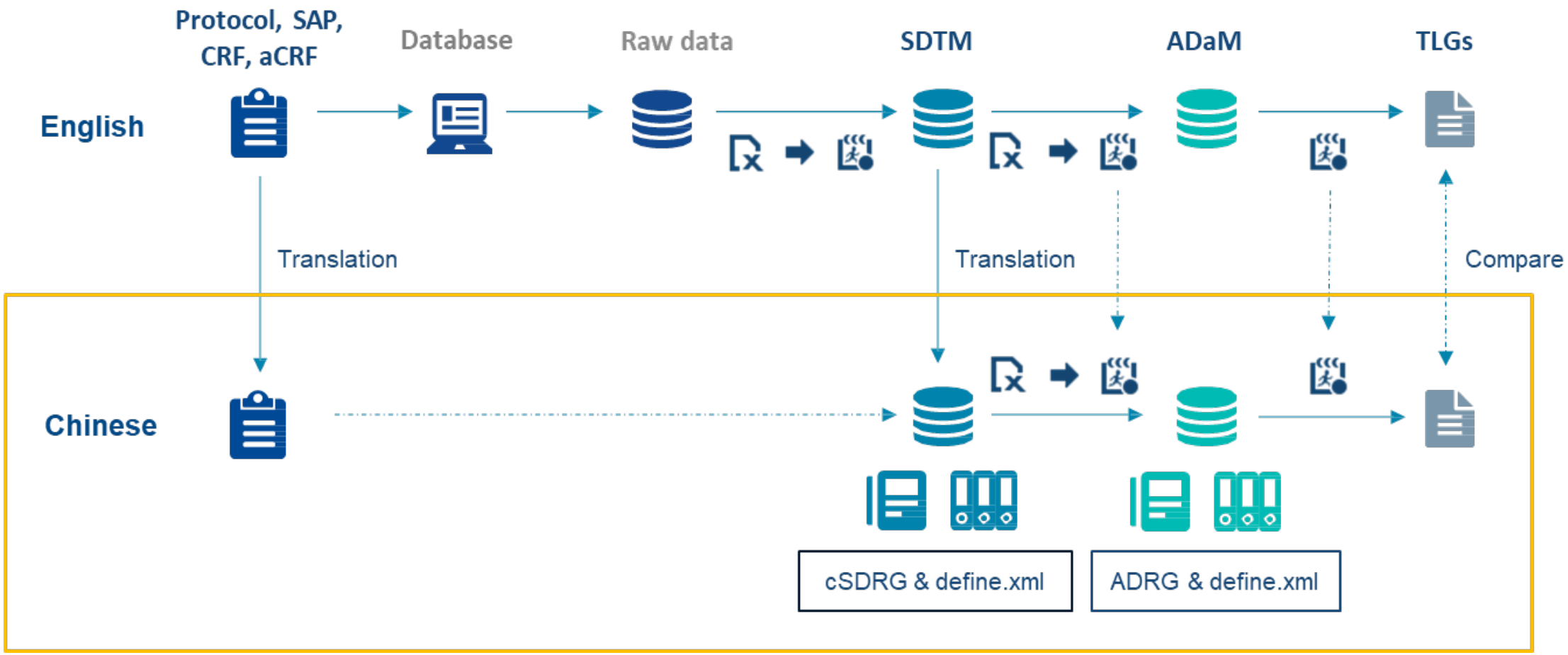
The eCTD compliant folder structure is recommended.

The basic structure is the same as in Japan.
Since Chinese can be used for labels, we do not have folders like adam_j or sdtm_j.

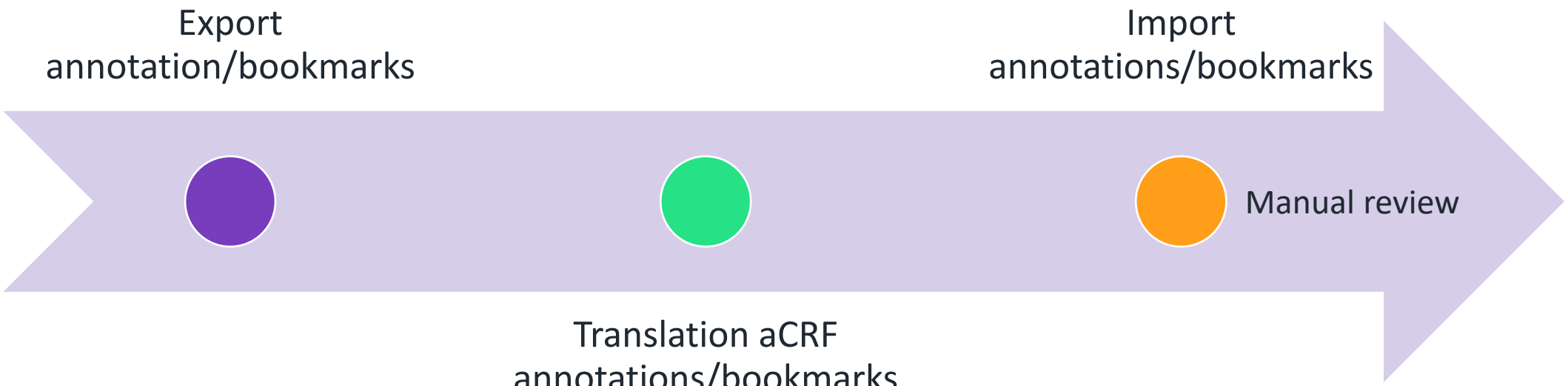
Tips

- The variable label must be 40 bytes, but one Chinese character is not necessarily one times one, but depending on the encoding, one character can be 1 to 4 bytes, which can exceed 40 bytes. (variable names ≤ 8 bytes, Variable labels ≤ 40 bytes, Variable length ≤ 200 bytes)
- P21E supports Chinese data sets, but detailed validation rules are still under construction. Therefore, it is necessary to refer to the guidelines to create data that meets the requirements.
- Not only do the variables have to be in Chinese, but if translated from English, they cannot be checked for consistency in each data set or document. If treatments, drugs, etc. are not coded, it is extremely difficult to have consistency in translation.

Key process to prepare for NMPA submission



aCRF translation



- Central Dictionary
- Update page number
- Manual review

SDTM dataset translation

- Dataset label
- Variable label
- Code list
- Free text

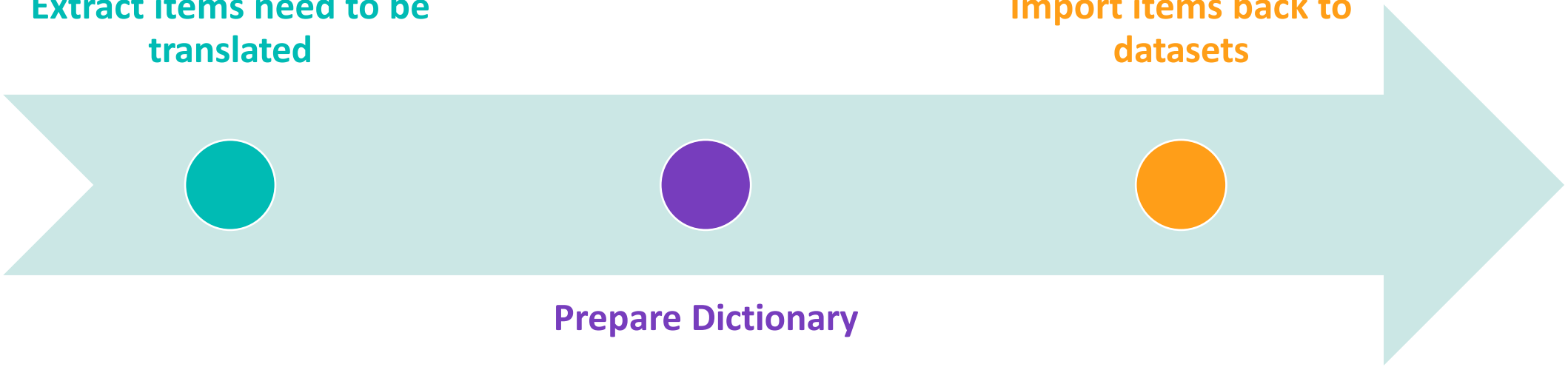
Extract items need to be translated

Prepare Dictionary

- SDTM IG Metadata
- ADaM IG Metadata
- ADaM IG OCCDS metadata
- Controlled terminology Chinese translation

Import items back to datasets

- Encoding
- Double programming
- P21&CCSCC
- Compare with origin dataset



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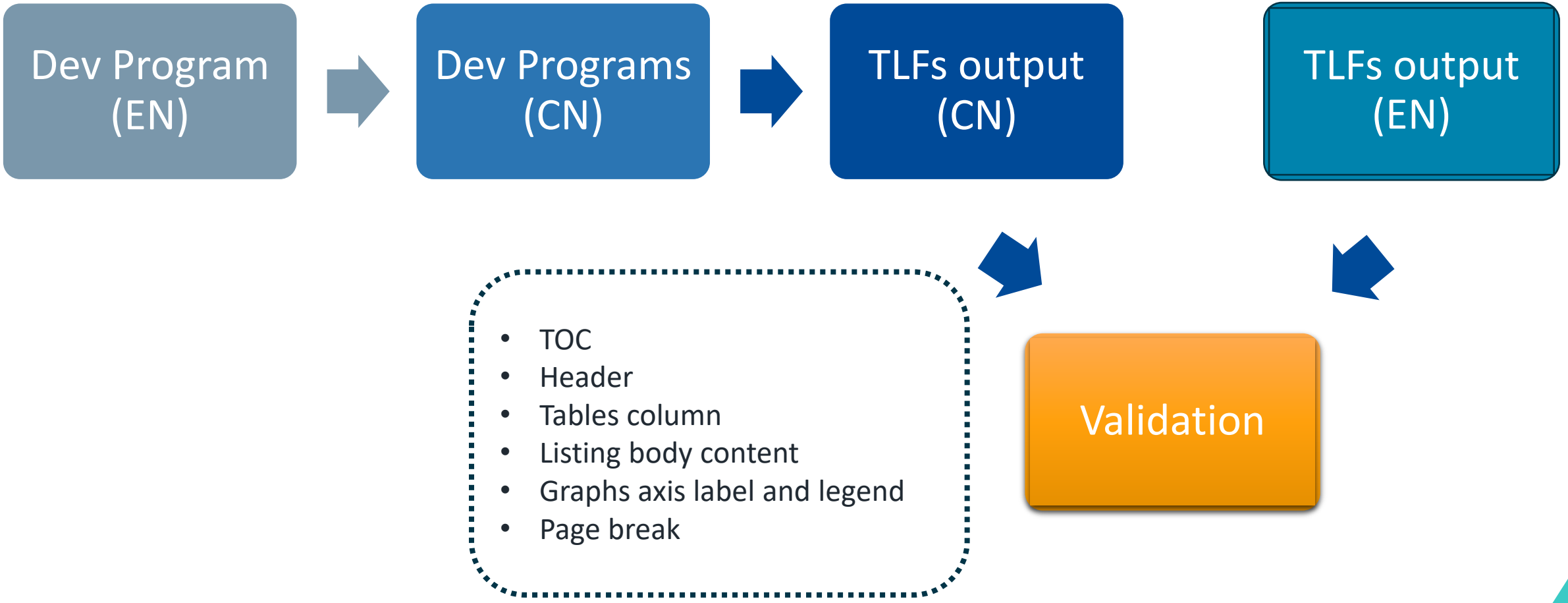
TLFs translation



A past project experience

A past project experience

Purpose:
NDA data creation from very old Japanese study data.

History:
A Japanese pharmaceutical company did not have China branch office. They contracted with a local Chinese regulatory consultant for the application and was informed that a CDISC data set was required.

They asked for help but the RA consultant did not know the guidelines related to data at all.

The sponsor need a CRO that can handle Japanese data and understand Chinese regulations.

A past project (cont.)

What we did (summary):

1. Waiting for Chinese translation of CSR
2. aCRF translation
3. CSR and aCRF consistency check
4. Update CSR
5. SDTM/ADaM/Spec define recreate in Chinese
6. Select reproduced TLFs with sponsor
7. Create program and program description document

A past project (cont.)

What we did (detail):

Item	Task
Raw dataset (RDS)	Create SDTM followed by Chinese regulation
Analysis dataset (ADS)	Create ADaM followed by Chinese regulation
Program	・Identify what needs to be submitted ⇒Analysis dataset program ⇒Programs that create TLFs ・The program code must include comments that promote understanding. ・The macro code must also be submitted. ・The version of the software and the system environment must be explained.
Define	・SPEC with hyperlink added is acceptable as define PDF
Other documents	・Create RG-style documents to help reviewers quickly understand the content and structure of the clinical trial database
Form of Submission	・raw dataset, analysis dataset, define, program in separate folders ・sas dataset: xpt　(xpt V5) ・Spec: Excel ・aCRF: PDF ・Program: txt

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A past project (cont.)

Schedule

- The project was scheduled to be handled in two months, including the year-end and New Year holidays, but then a serious problem was found in the RAW data, requiring an additional two months of work time.

- Four months after the project started, the application was successfully submitted to the Chinese authorities.

- However, the inquiry was received within one week. The application was completed with the creation of an additional document "程序代码说明文件" (program code description file that written in Chinese) on the same day.

Key to success

- Need to understand China regulations even you are a programmer.
- Try to join in project discussions **from the beginning!**
- Creating electronic application data is **not just translation.** The amount of drug codes and adverse events in the data makes it very difficult to be consistent with the documentation.
- It may be necessary to update the CSRs because modifying the data would be punishable as data falsification, including the CRO who did the work.

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