Clinical Data e-Submission Updates in China

John Wang, Director, Programming, dMed Pharmaceutical Co., Ltd.
Stanley Wei, Group Head of Data Management and Innovation, Novartis
Victor Wu, EVP, Data Science, Beijing Data Science Express Consulting Co., Ltd.
Zibao Zhang, VP Business Development, dMed Pharmaceutical Co., Ltd.

TUE 26 JAN
9:00-10:30AM ET

Today’s Agenda

1. Housekeeping
2. Presenter Introductions
3. Feature Presentations
4. Question & Answer Session
5. Upcoming Learning Opportunities + Resources

Housekeeping

Housekeeping

- You will remain on **mute** for the entirety of the webinar
- There will be a Q&A after all of the presentations are finished
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  - To access – make sure that you create a login for the CDISC website if you haven't already
  - If you are employed by a CDISC member organization, please ensure you use your employer-issued email address with your employer's domain name, so we can verify membership for the purpose of applying discounts to purchasing event tickets, online courses, and more!
  - Public Review webinars are also available to stream on the relevant public review page on our website

Content Disclaimer

- The purpose of this webinar is to provide examples of implementation and should not be considered official recommendations by CDISC unless otherwise stated in the presentation.
- This webinar is not an authorized CDISC course, is not developed or delivered under CDISC Operating Procedures, and should not replace a published standard. Please refer to the latest published standards for the most authoritative implementation information.

Our Presenters

- John Wang, Director, Programming, dMed Pharmaceutical Co., Ltd.
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CDISC 2021 Webinar

By Zibao Zhang, John Wang, Stanley Wei, and Victor Wu

2021-01-26

Speakers and Panelists

- **Zibao Zhang**, VP Business Development, dMed pharmaceutical Co., Ltd. Dr. Zhang is past Chair of China CDISC Coordinating Committee (C3C), and Vice Chair of China Clinical Data Standardization Steering Committee with China CDE, NMPA since 2012. Zibao had provided multiple CDISC trainings to the industry, regulatory agency and academic since then.
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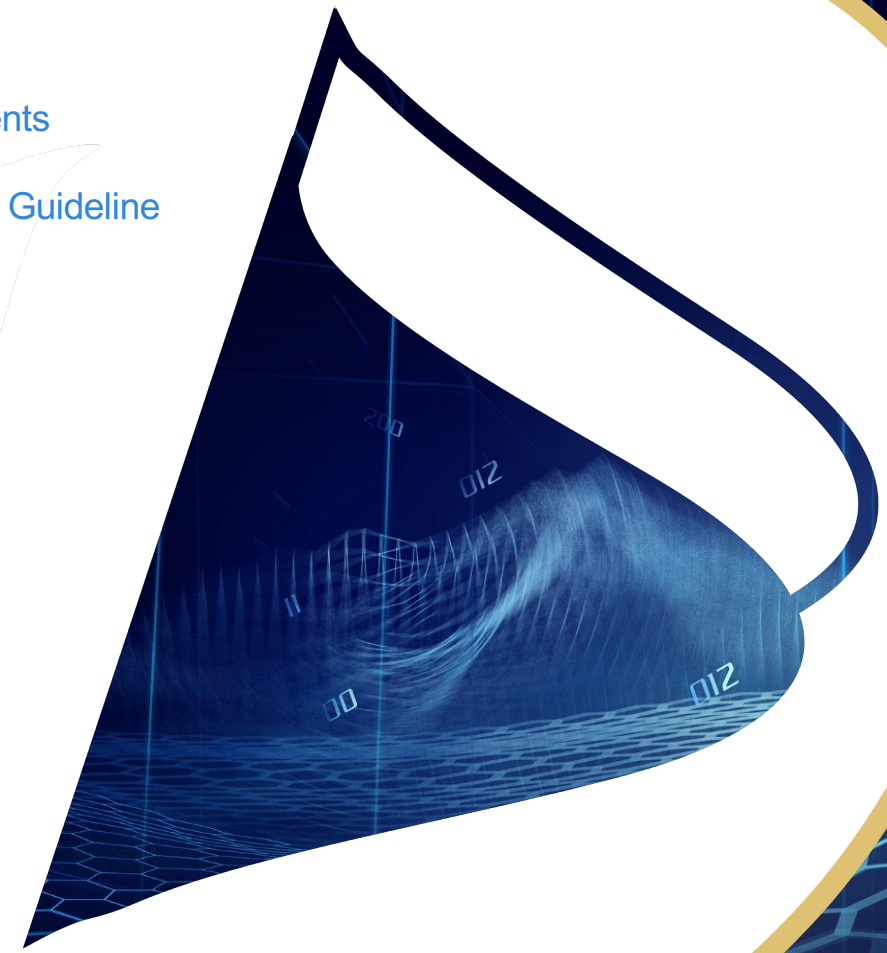
CONTENTS



dMed 缔脉

01

Related Regulatory Requirements

Requirements of Clinical Data Submission in China

- 2007：Provisions for Drug Registration《药品注册管理办法》
  - database submission was required in NDA
- 2016：Guideline on Clinical Data Management Plan & Report and Statistical Analysis Plan & Report. 《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》
  - Raw database and analysis database and meta data should be submitted (with xpt format)
- 2016：Technical Guidance on Data Management《临床试验数据管理工作技术指南》
  - …Suggested to adopt CDISC standards to submit raw database and analysis database.
- 2019-10 Requirements on Clinical Trial Database and Related Materials in eCTD, Public Review 《eCTD中临床试验数据库及相关资料的申报要求（征求意见稿）》
  - 原始数据库与分析数据库：数据集、数据说明文件、数据审阅说明、注释CRF raw database, analysis database and related materials
  - 文件夹结构 clinical data and document folder structure
  - 接收CDISC数据 acceptation of CDISC standards
- 2020-07-20 Clinical Trial Data Submission Guideline (Provisional)《药物临床试验数据递交指导原则（试行）》
  - submit clinical trial data following CDISC standards

Final Guideline Published 2020-07-20, Effective 2020-10-01

当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

Clinical Trial Data Submission Guideline (Provisional)

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。

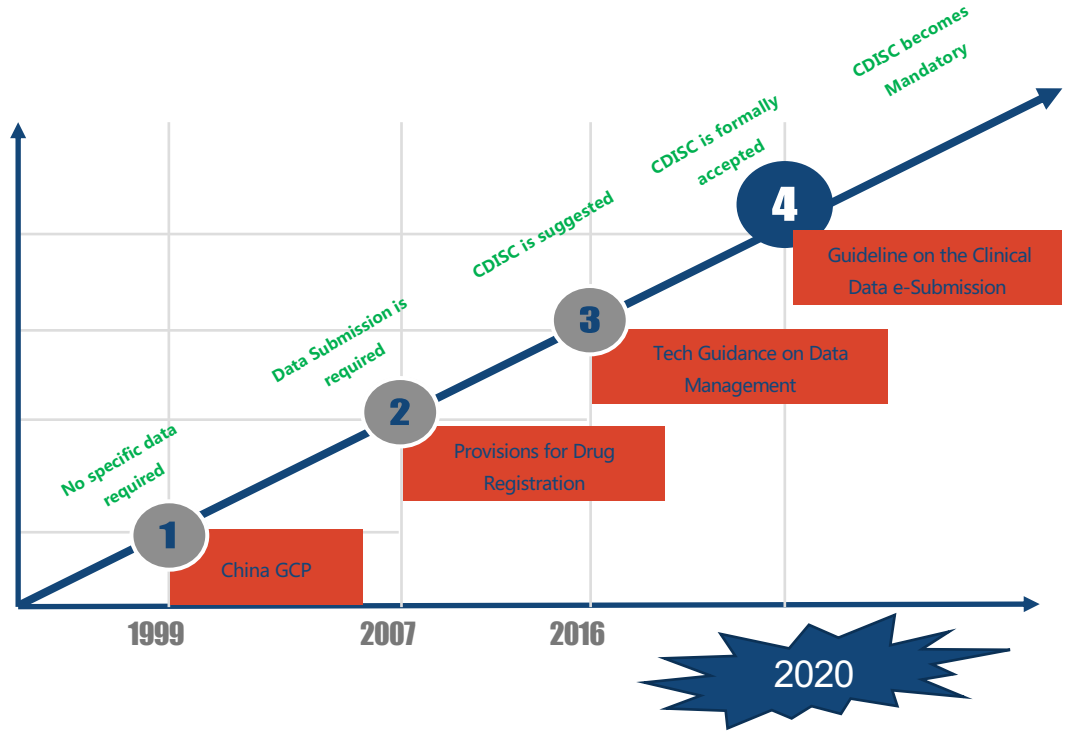
国家药品监督管理局药品审评中心

2020年7月20日

附件 1：	《药物临床试验数据递交指导原则（试行）》.pdf

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

Clinical Data Submission in China (*Yesterday, Today and Tomorrow*)



02

Highlights of Provisional e-Sub Guideline

Final Guideline Published 2020-07-20, Effective 2020-10-01

当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

Clinical Trial Data Submission Guideline (Provisional)

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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。

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

China eSubmission Guideline (Provisional, 2020-07-20) -- Table of Contents

1. Background and Purpose
2. Clinical Data, Documents and Data Definitions
3. Formats
4. Other Considerations
5. References

目录

1) Raw Database
2) Analysis Database
3) Data Definitions
4) Reviewer's Guides
5) Annotated CRF
6) Programs Code

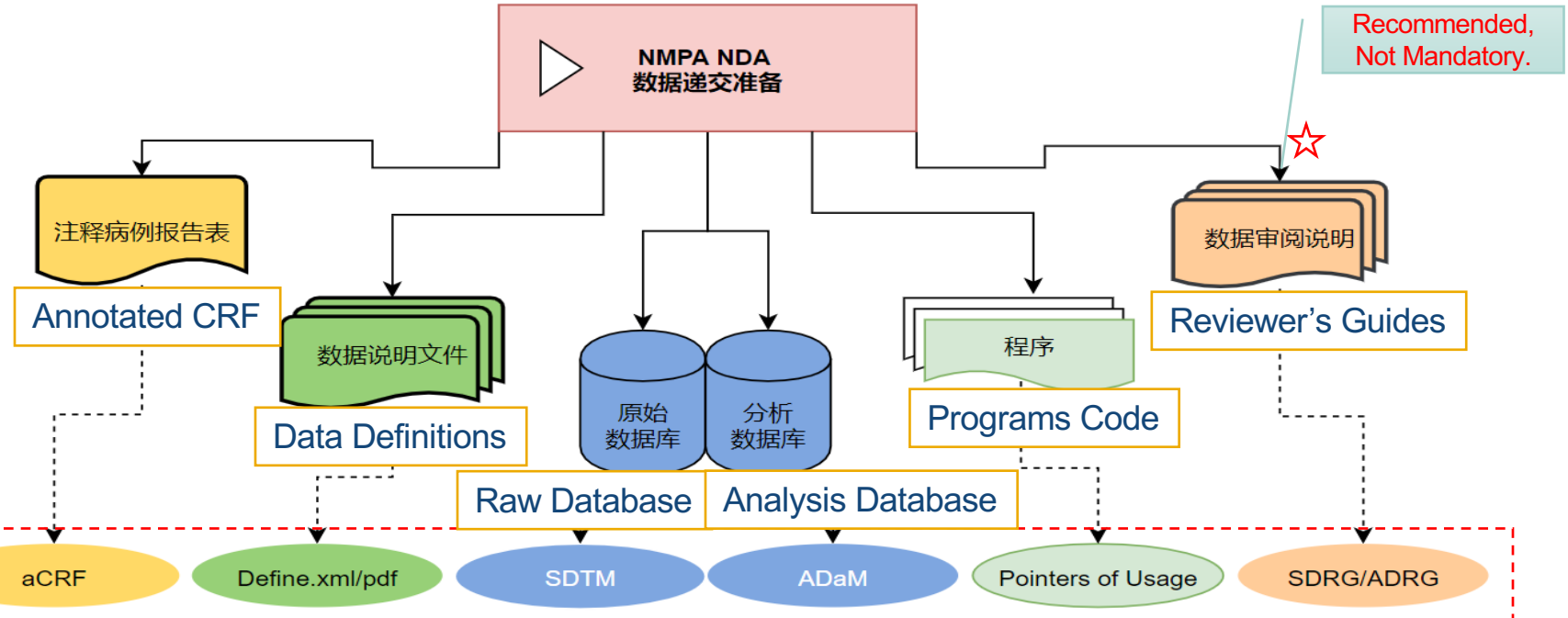
Foreign Database

"The package should be in Chinese mainly"

（三）外文数据库

临床试验数据相关的申报资料应以中文为主，

NMPA/CDE 《Clinical Trial Data Submission Guideline (Provisional)》 2020-10-01



*"**鼓励**申办方参照临床数据交换标准协会（Clinical Data Interchange Standards Consortium, CDISC）标准递交临床试验数据及相关的申报资料。随着临床试验数据标准的发展以及对其认识与实践的提高，本指导原则会酌情修订完善。"*

"CDISC standards are recommended to use for data submission…, this guideline will be updated when the progresses are made in data standards and practice"

Raw Database vs Analysis Database

原始数据库通常包含多个原始数据集，原始数据集应按主题进行组织并命名，数据集通常以两个英文字母组成的代码命名，如人口学（dm）、不良事件（ae）、实验室检查（lb）等数据集。临床试验中常见的原始数据集命名详见附录 1。

所有递交的原始数据集必须包含研究标识符（STUDYID）变量；反映各受试者观测结果的数据集（如附录 1 中的 dm、ae、lb 等数据集）中还必须包含受试者唯一标识符（USUBJID）变量；另外，受试者标识符（SUBJID）变量必须包含在 dm 数据集中。常用到的标识符举例说明如下：

如果申办方参照 CDISC 标准递交数据，则可将原始数据标准模型（Study Data Tabulation Model，SDTM）数据库视为原始数据库。

- Legacy Data and non standard variables naming
- 3 Basic Principles for Analysis Data

附录 1：常用原始数据集

表 1 常用原始数据集及命名

数据集	命名	递交要求
人口学	dm	必须递交
病史	mh	如适用
不良事件	ae	如适用
既往与合并用药	cm	如适用
暴露	ex	如适用
受试者分布	ds	如适用
问卷与量表	qs	如适用
方案偏离	dv	如适用
实验室检查	lb	如适用
心电图	eg	如适用
生命体征	vs	如适用
临床事件	ce	如适用
体格检查	pe	如适用

Data Definitions

递交的原始数据库和分析数据库必须有相应的数据说明文件。数据说明文件是一份用来描述递交数据的文件，至少应包含递交数据库中各数据集名称、标签、基本结构描述及每一数据集中各变量的名称、标签、类型、来源或衍生过程。

数据说明文件是监管机构审评时准确理解递交数据内容最重要的文件之一。申办方应确保每个变量的编码列表和来源都有清晰的定义，并且易于查找。如果使用外部词典，需要在数据说明文件中指明所用的词典及版本。需要通过数据说明文件建立起数据间良好的可追溯性（如：原始数据集与 CRF、分析数据集与原始数据集之间），以便于监管机构的审阅。申办方需要在数据说明文件中提供相关细节，尤其是和衍生变量相关的详细说明，必要时可使用关键程序代码辅助说明。

- File format（define.xml or define.pdf）
- Descriptions of data and also variable derivation and algorithm
- Traceability
  - External files, like datasets, aCRF, data reviewer guides, etc.
  - Internal links: datasets, variables, value list, format and codelists, etc.
  - Variable's Origin: Protocol, Assigned, Derived.
- Searchable
  - Hyperlinks, bookmarks, etc.

Programs Code

申办方需要递交的程序代码包括但不限于：分析数据集中衍生变量的衍生过程、疗效指标分析结果的生成过程等。申报资料中递交的程序代码应当易懂、可读性强，建议提供充分的注释、避免外部(宏)程序调用。程序代码一般采用 TXT 文件。

“申办方根据具体临床试验数据特点及复杂程度，若需要，可按照药物研发与技术审评沟通交流的相关管理办法，与审评机构就临床试验数据库及相关资料的递交进行沟通，以方便审评人员快速、准确地理解申办方递交的临床试验数据。”

- ADaM programs
- Primary endpoints analysis programs
- Avoid macros if possible.
- Emphasize the re-creation of analysis results; no format requirement.
- Recommend to include the description to each Program and clear comments.
- *Programs should be executable or not (?)*
- Communication with reviewers are recommended

Data Reviewer's Guides

为了帮助审评人员更好地理解与使用递交的数据，鼓励申办方递交数据审阅说明。数据审阅说明是对数据说明文件的进一步补充，其内容包括但不限于研究数据使用说明、临床总结报告与数据之间的关系、研究文档（如试验方案、统计分析计划、临床总结报告等）中部分关键信息、所递交程序代码的使用说明、数据集所用编码（如 utf-8、euc-cn 等）及其它特殊情形说明等。数据审阅说明并不旨在取代数据库的数据说明文件，而是通过文档描述的方式来帮助审评人员更准确、高效的理解与使用所递交的数据库、相关术语、程序代码及数据说明文件信息等。数据审阅说明应采用 PDF 文件。

- Recommend to submit reviewer guides, but not mandatory yet.
- No specific format requirement yet. Suggest to use the templates from PhUSE:

  https://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide
  https://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer%27s_Guide

- Dataset encodings
- How the big datasets are split, then combined
- How the programs codes are used.

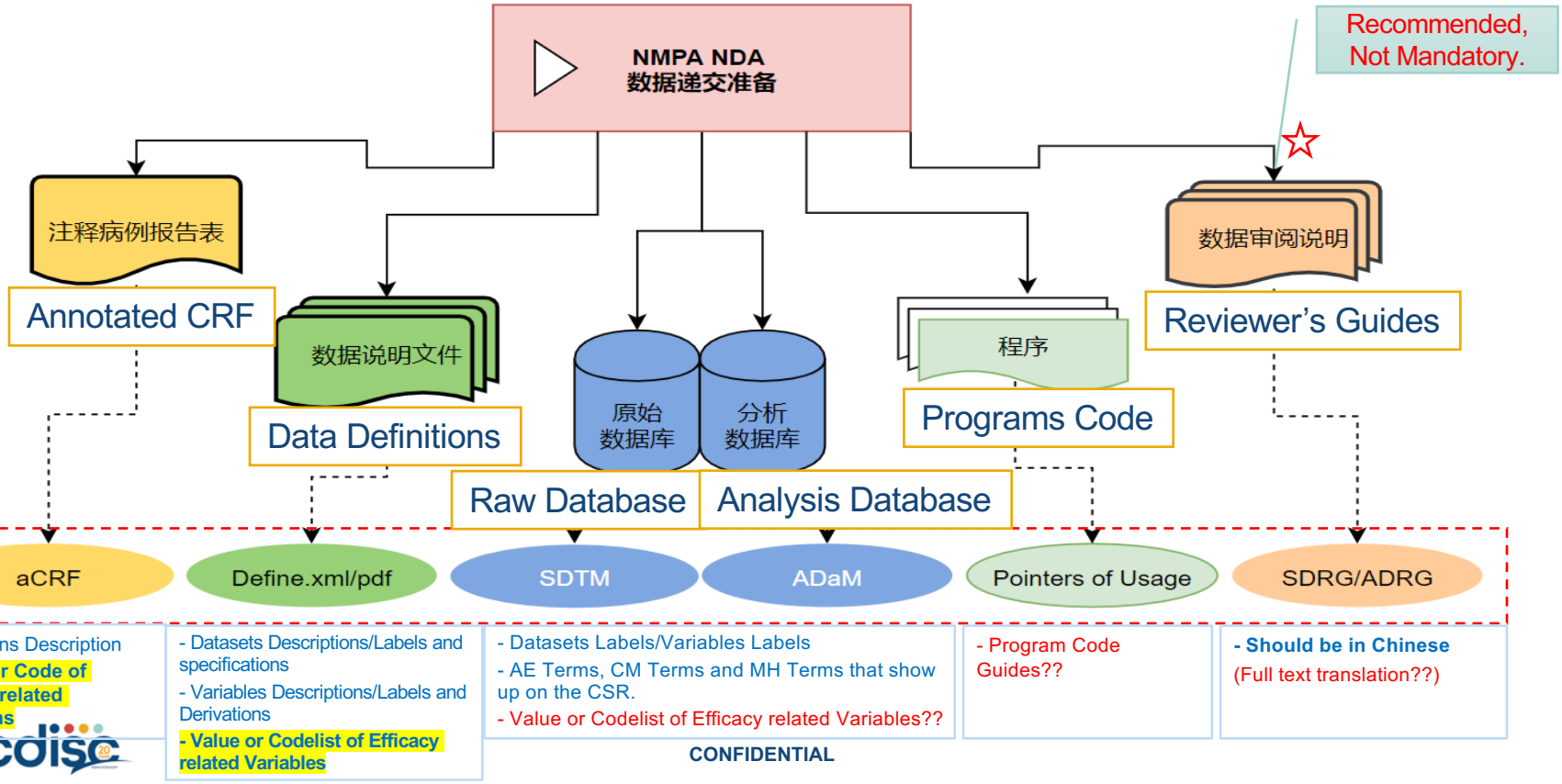
Other Considerations

- Validation Rules and Validation Reports
  - Pinnacle21 Chinese Support
  - OpenDV (for Chinese datasets)
  - Openchecks (for Chinese datasets)
- Datasets encoding
- SAS Transport Format and version (SAS XPORT V5/V8), unintelligible text or gibberish (乱码) for Chinese chars in SAS viewer
- Dataset splitting, variable length and label length, etc.
- eCTD requirements such as study tagging file, and folder structure
- ... ...

03

Foreign Database

Minimal Requirements for Translation of Foreign Database



Other Considerations in Foreign Database

- Translation Terms consistency in different documents, including:
  - Protocol, CRF, Datasets, Data Definitions, Data Reviewer's Guides, CSR, etc.
- Qualifiers' labels in SUPPQUAL (SUPP--)
- Handling of non matching Chinese Terms in WHODRUG
- Different versions or formats of Medication Dictionaries (e.g. WHODRUG)
- Translation of the primary parameters and analysis endpoints in the datasets
- ... ...

Other Considerations in Foreign Database

- Building of Translation Library
  - CRF Questions Library
  - Questionnaires, Rates and Scales Library
  - Datasets and Variables Chinese Labels Library
  - Derivation Logics Library
  - English-Chinese Medication Library
  - Terms and Codelists Chinese Library

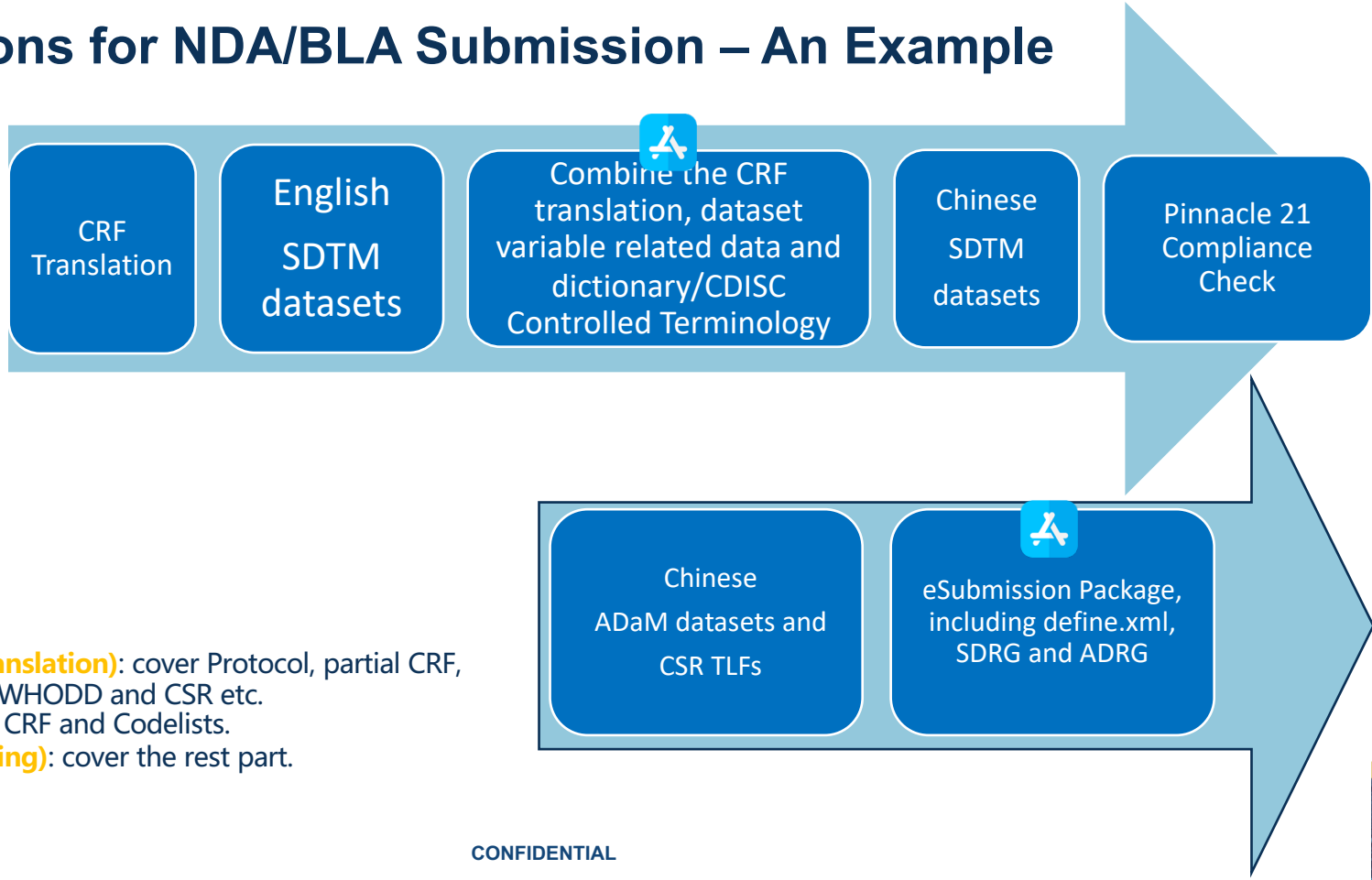
- Cooperation across multiple functions, planning early, and working in parallel …

dMed Solutions for NDA/BLA Submission – An Example

CRF translation review and free-text parts translation
Solution 1 (Medical Translation)

Label and codelist translation
Solution 2 (DM)

Dictionary translation, including preferred name in WHODrug, etc.



Solution 1 (Medical translation): cover Protocol, partial CRF, Medical Coding PN for WHODD and CSR etc.
Solution 2 (DM): cover CRF and Codelists.
Solution 3 (Programming): cover the rest part.

04

Summary

eSubmission Requirements Comparison: China vs US and Japan

China NMPA	US FDA	Japan PMDA
CDISC Recommended	CDISC Mandatory	CDISC Mandatory
aCRF *(minimal Chinese required)*	aCRF	aCRF
Data Definition (XML or PDF)	Define.xml	Define.xml
Reviewer's Guides Recommended	Reviewer's Guides Mandatory	Reviewer's Guides Mandatory
No Automation Tools yet	Automation Tools Available	No Automation Tools yet
No Conformance Rules yet	Strict Conformance Checking	Strict Conformance Checking
No Codelist Standards yet	NCI Terminology	NCI Terminology
Minimal Chinese Requirements (Complete Chinese later on)	Full English	Full English

Summary

1. eSubmission Guideline, a good start for embracing the global standards.
2. Start small, part of rules from global; More rules later on.
3. Foreign Database, minimal Chinese translation requirements.
4. Reviewer oriented principle.
5. Industry solution is ready.

References:

- http://www.cde.org.cn/news.do?method=viewInfoCommon&id=7a43c3abfde95950 (China eSub Guideline)
- https://www.cdisc.org/translations/chinese (CDISC Standards Chinese translation)

Acknowledgements

The slide deck was prepared based on the contributions from C3C members – Stanley Wei, John Wang and Victor Wu.

05

Q & A

Q&A Panelists

- **Zibao Zhang**, VP Business Development, dMed pharmaceutical Co., Ltd. Dr. Zhang is past Chair of China CDISC Coordinating Committee (C3C), and Vice Chair of China clinical data standard steering committee with China CDE, NMPA since 2012. Zibao had provided multiple CDISC trainings to the industry, regulatory agency and academic since then.
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Contacts

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Victor Wu victor.wu@datascie.com


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THANK YOU.

Audience Questions

What are the differences between data submission to FDA and NMPA?

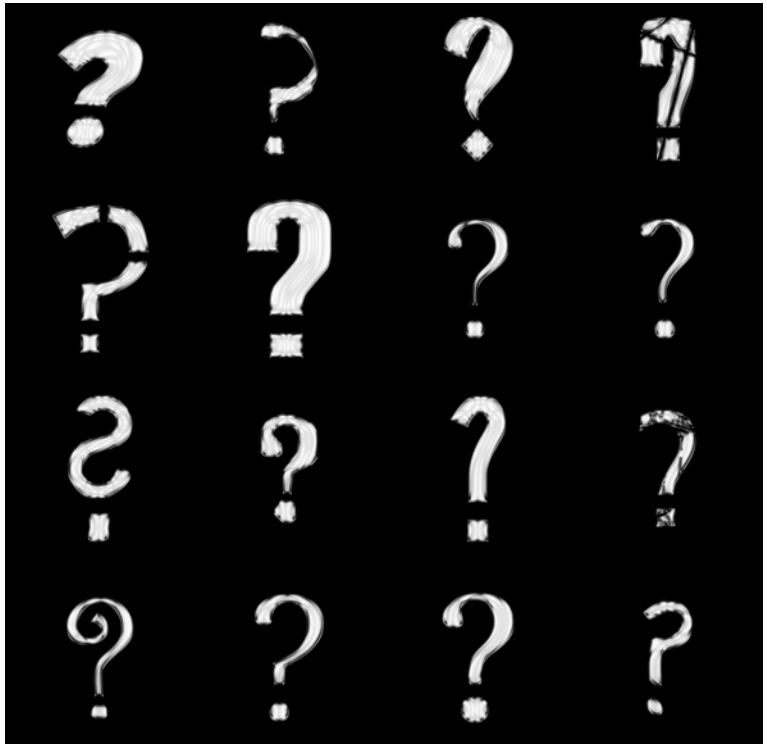
Audience Questions

Is there any foreseeable impact on the submission of clinical data for medical device in China?

Audience Questions

Where do Chinese Authorities currently stand on CDISC Compliance? How rigid are they regarding compliance?

Audience Questions



Does the guidance apply to any typeof submission e.g. drugs, biological compounds, vaccines, devices, etc. ?

Audience Questions

How do you think about contribution from AI in the future?

Audience Questions

For the translation, should all item questions be translated in Chinese?

Audience Questions

What kind of obstacles could you expect in Traditional Chinese Medicine study with CDISC Standard?

Audience Questions

Does NMPA accept all valuation results from P21, OpenDV, and OpenChecks?

Audience Questions

On one of the slides that compared FDA, PMDA and NMPA submissions, what is meant by 'automated tools'?

Audience Questions

For global study, is it possible to only translate analysis results in Chinese, but not every single dataset? it's like the reviewers reproduce the output by English datasets, and then compare the results with Chinese translation version directly.

Upcoming Learning Opportunities

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- Register at: https://learnstore.cdisc.org/
- Contact us at: training@cdisc.org

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2 FEB	Navigating the CDISC Learning System and Our Many Training Offerings
4 FEB	Public Review Webinar: COVID-19 Therapeutic Area User Guide Update
23 FEB	What's Different about SDTM for Clinical and Non-Clinical Trials (registration coming soon!)
Coming Soon	QRS "Office Hours"; CDASH "Office Hours"; ADaM "Office Hours"; CDISC Library Update
Visit https://www.cdisc.org/education/webinars for information on additional Public Training events.	

Thank You!

Questions, comments, concerns? Email bklinke@cdisc.org

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