China submission preparation: lost in translation

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IX Italian CDISC UN Day – 12 May 2023

- Setting the scene
- Regulatory package
- Regulatory package: details
- Clinical data package: required elements
- Clinical data package: required elements details
- Walls
- Wins
- Wisdoms

Setting the scene

Class V
Imported Drugs

Safe and effective, but lack of data on Chinese population

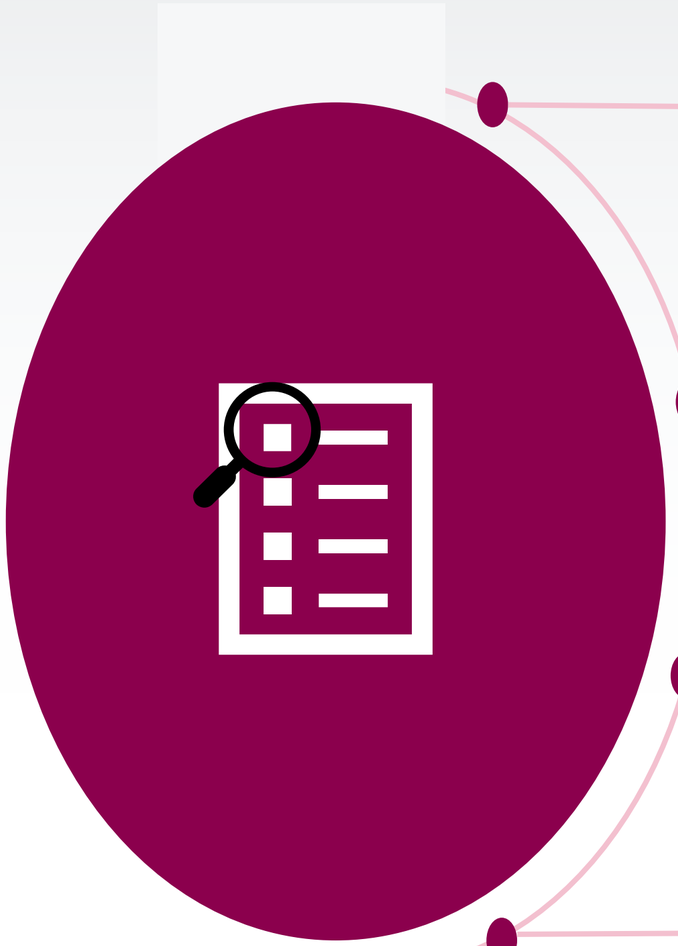
(ethnic sensitivity)

PK

Efficacy and Safety

Source:
Drugs marketed overseas but not marketed in China – Clinical technical requirements
https://www.cde.org.cn/zdyz/opinioninfopage?zdyzIdCODE=4832fe1bef75686610c58cc092e0f911&rddt=1
http://english.nmpa.gov.cn/2020-11/18/c_568155.htm

Regulatory package



1. CTD Clinical Modules
2. Clinical Study Reports of Chinese studies
3. Additional documents on clinical development in China
4. Clinical Data Package

CTD: Common technical document

Regulatory package: details

- Common Technical Document (CTD) clinical modules as they have been submitted in the rest of the world, but translated in Chinese.
  - CTD is a common standard for exchanging regulatory information between industry and agency; the clinical modules of the eCTD includes PK, efficacy and safety overviews and summaries

- Clinical Study Reports for Chinese Studies:
  - Written in English and then translated in Chinese

- Additional documents on clinical development in China
  - Summary on NDA Application
  - Ethnicity comparison

Translation is required for all!!!!!

Regulatory package: Summary of NDA Application

- Template provided by the Agency upon request
- Brief, 30-page long document
- Condensed description of clinical development outside from China
- Detailed summary of clinical studies conducted in China, including main design features and results
- Brief comparative description of results of Chinese vs. non-Chinese trials, focusing on main, key messages

Clinical Data Submission Template for NDA Application (Imported, Domestic)

General requirements: The text is written in Song typeface, 12 pt, 1.5 times line spacing; the tables are in Song typeface, 10.5 pt and single spacing. The words of the whole text should be controlled within 30 pages (including tables).

1. Overview

2. Briefly describe the situations of all the completed clinical studies of the product

2.1. Content of all the completed clinical studies

Study No.	Study Time	Study Objective (which phase)	Study Design	Subject Population (healthy volunteer or patients, number of subject)	Dosage Regimen (dosage, times and treatment course)	Primary Endpoint (s) Secondary Endpoint(s)	Progress Situations

2.2. Results of the completed clinical studies

2.3. Overall evaluation of the completed clinical trials

3. Situations of the clinical studies finished in China

3.1. Pharmacokinetic studies

3.2. (II) Randomized controlled clinical trials which support marketing in China

3.2.1. Summary:

4. Comparative analysis of the results of the clinical trials finished in China and results of all the clinical trials finished abroad (this item can be skipped if it has been included in "3")

Explanations for the leaflet

Regulatory package: Ethnicity comparison

- Strongly suggested to support and extend the Summary NDA application
- Neither formal template nor length limits
- Extended, detailed description clinical development outside from China
- Detailed comparative discussion of results of Chinese vs. non-Chinese trials focusing on:
  - Pharmacokinetics
  - Efficacy
  - Safety

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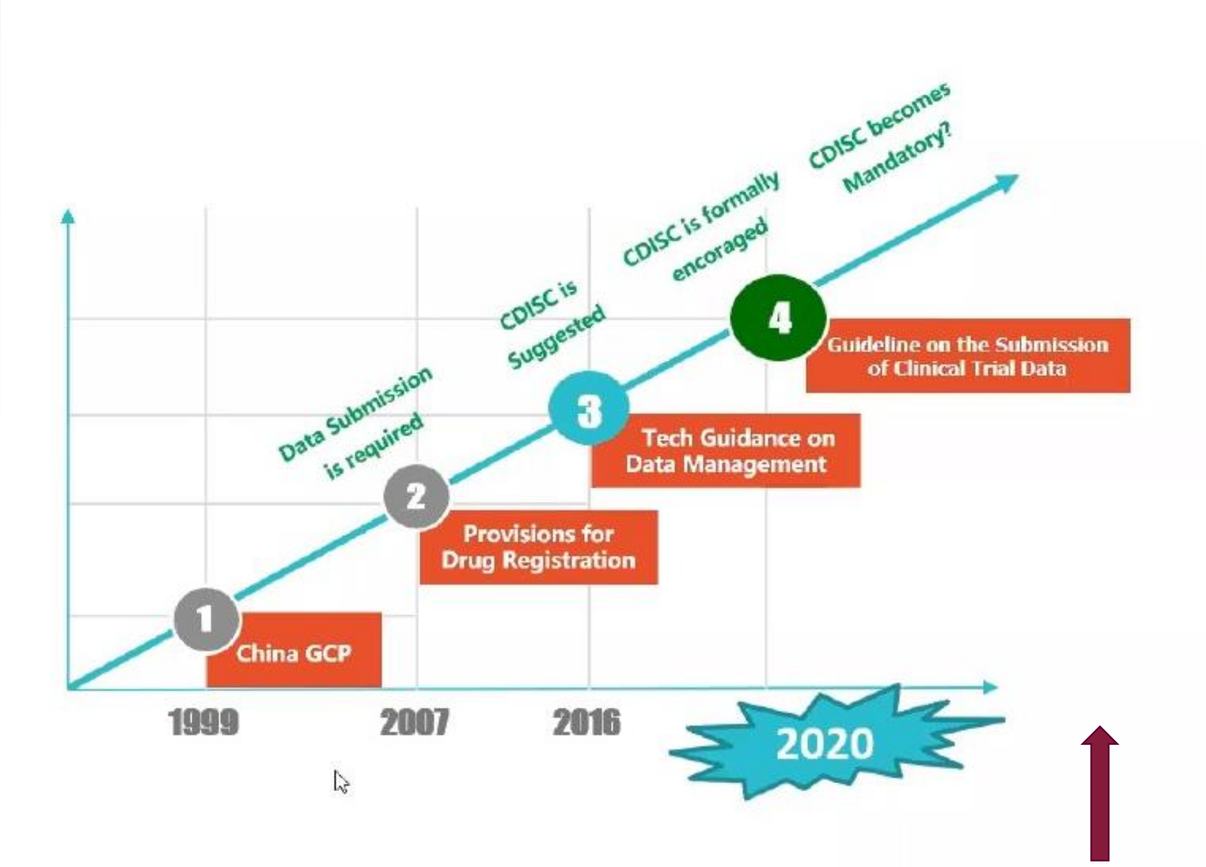
Regulatory package: Clinical Data

Clinical Data Submission in China



2023: CHINA NDA submission

Source: https://data42.cn/c3c/webinar/20200527/C3C_NMPA.mp4

Guideline on the Submission of Clinical Trial Data (Jul 2020)

- Aligns technical requirements for clinical data package supporting submission with international CDISC standards:
  - SDTM -> strongly encouraged
  - ADaM -> recommended

- Details on:
  - Components of the data package
  - Format and conventions
  - Additional details

Source:
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）（cde.org.cn）

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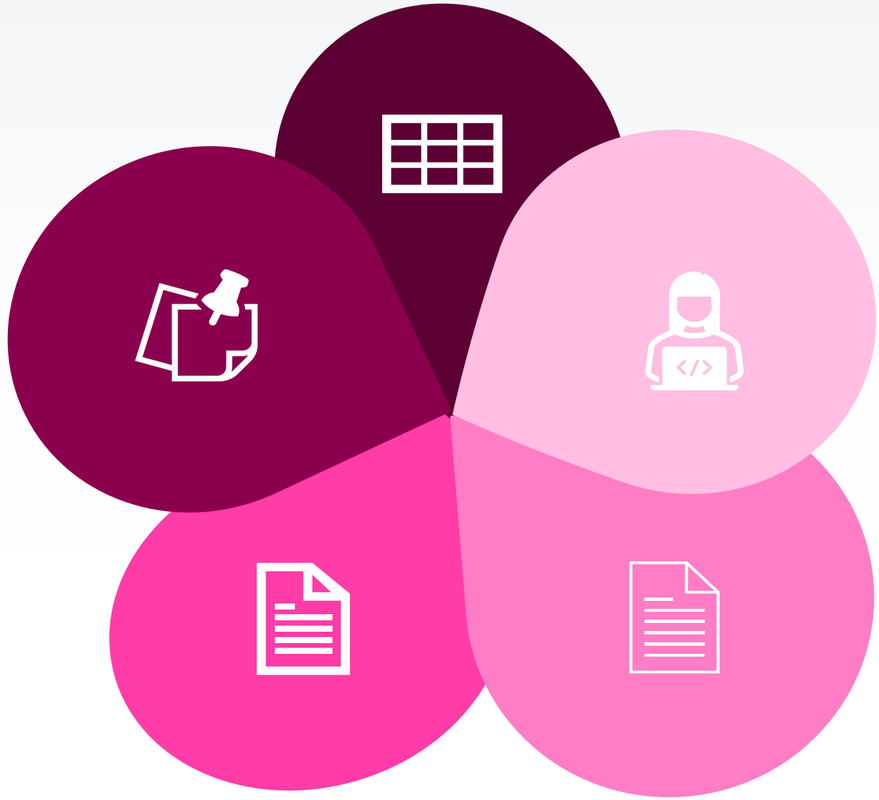
Clinical data package: required elements

DATABASES: SDTM and ADaM

XPT V5 or above* DM and ADSL are mandatory



ANNOTATED CRF

aCRF.pdf*

PROGRAMMING CODE

Not needed for SDTM
Readable and understandable
Do not include external program calls; Avoid to use nested macros.
.txt as the file extension

DATA DEFINITION FILES

.xml* or .pdf*
.pdf is not required when .xml is used for submission

DATA REVIEWER'S GUIDE

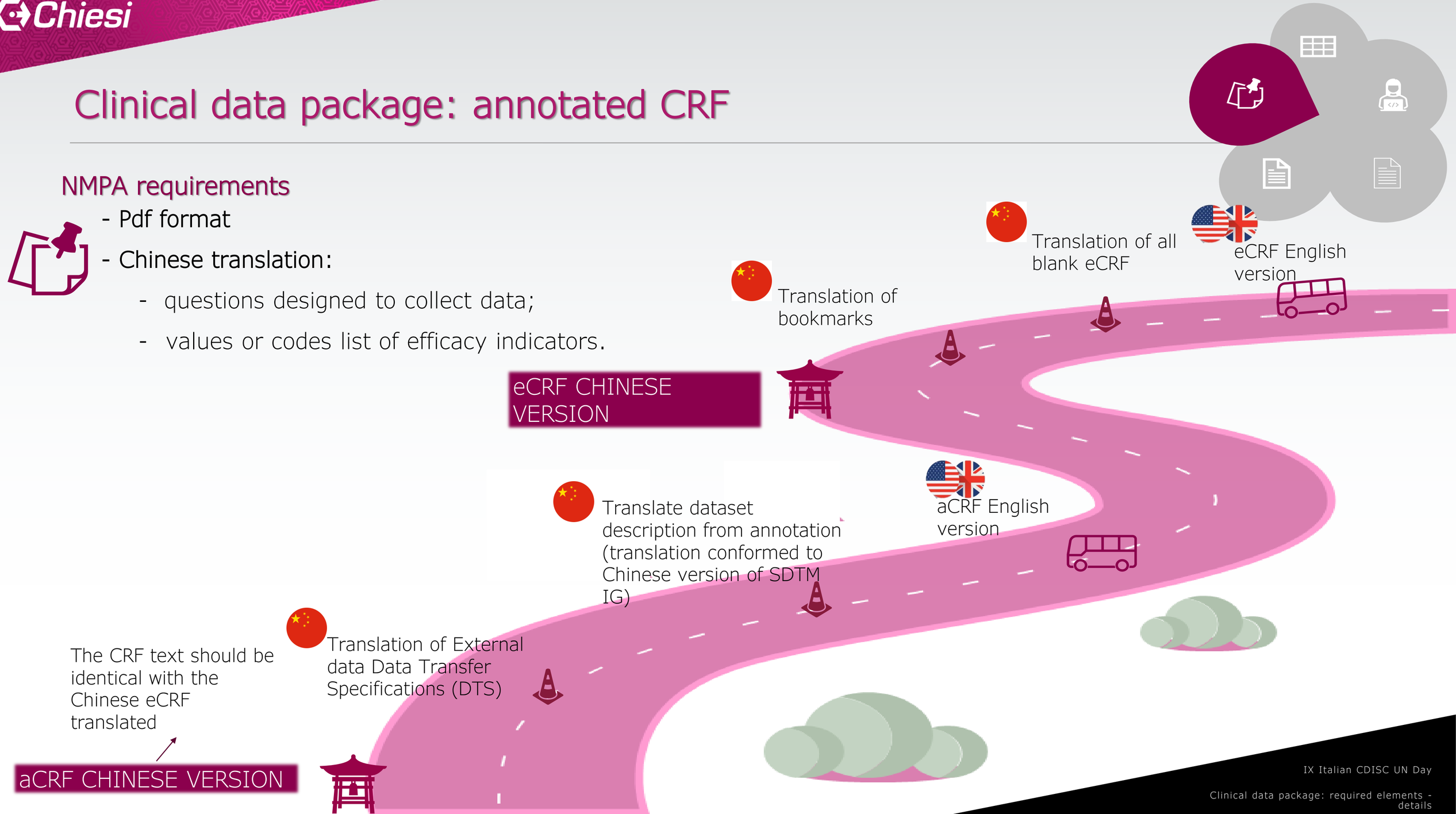
.pdf*
ADRG recommended but not mandatory

**Chinese translation requirement for foreign language database*

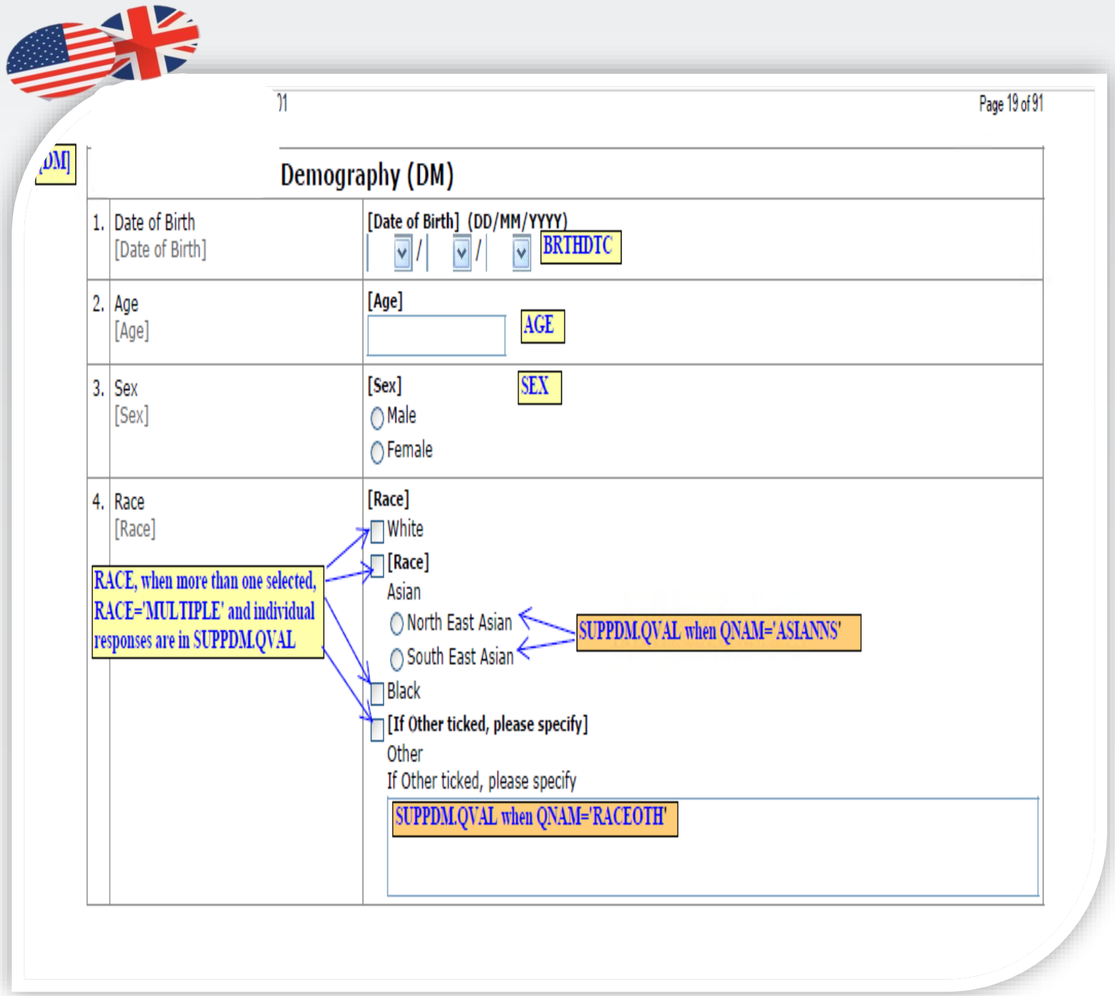
Clinical data package: annotated CRF

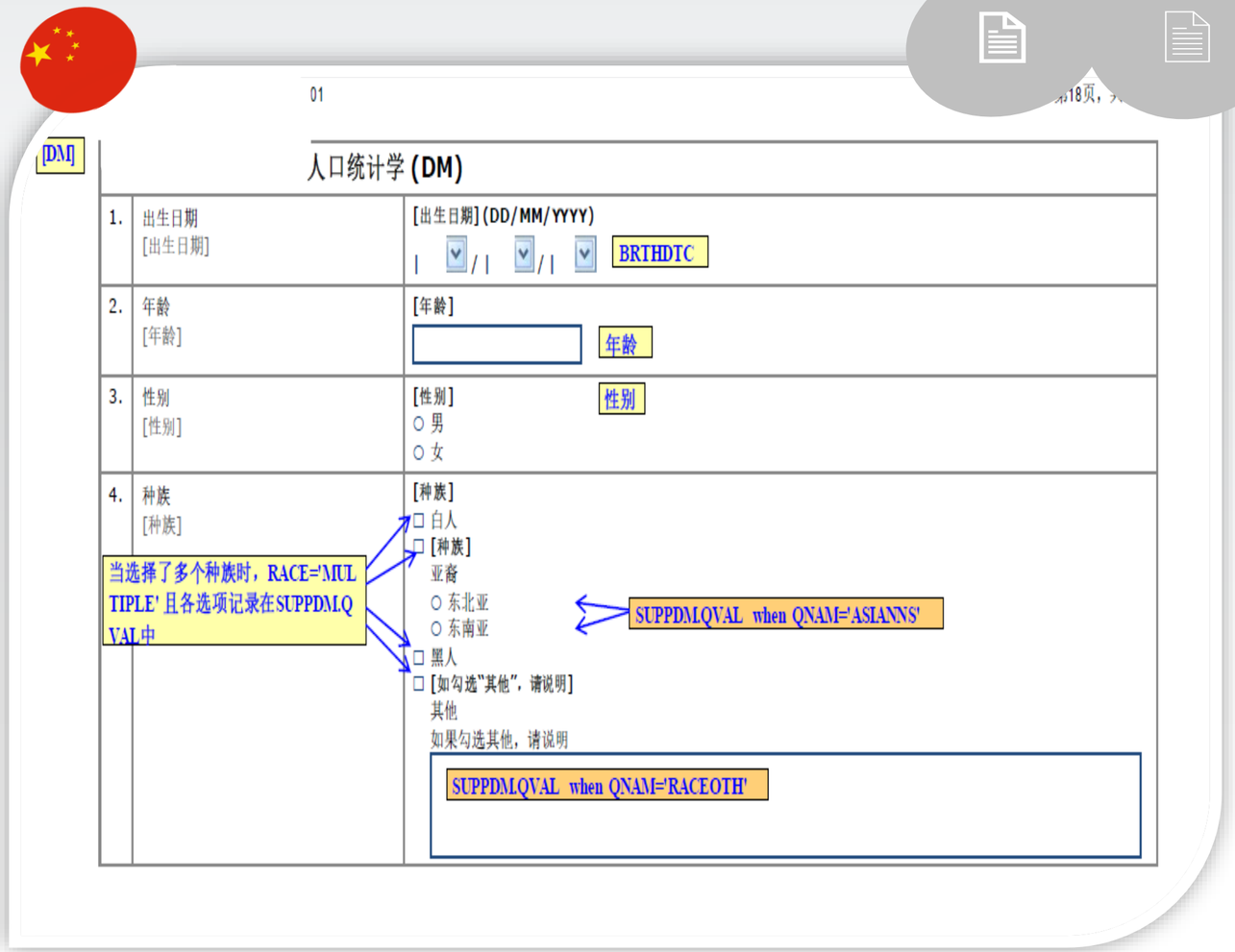
NMPA requirements

- Pdf format
- Chinese translation:
  - questions designed to collect data;
  - values or codes list of efficacy indicators.



Clinical data package: annotated CRF





Clinical data package: DATABASES: SDTM

NMPA requirements

Raw data not to be submitted	Sponsor is encouraged to submit SDTM according CDISC	Chinese translation

Chinese translation:

- dataset label and variable label
- adverse events terms
- generic name of concomitant medications
- medical history in CSR and other documents

Chiesi strategy

Dataset and variable labels taken from Chinese version of SDTM IG.

Starting from codes in AE, CM and MH Chinese verbatim and coding terms have been merged

Submission package: DATABASES: SDTM

AESEQ	AESPID	AETERM	AELLT	AELLTCD
1	1	Upper respiratory tract infection	Upper respirator...	10046306
2	2	Upper respiratory tract infection	Upper respirator...	10046306
1	7	Alanine amino acid transferase increased	Alanine aminotr...	10001551
2	11	Upper respiratory tract infection	Upper respirator...	10046306
3	9	glucose increased	Glucose increased	10018421

AESEQ	AESPID	AETERM	AELLT	AELLTCD
1	1	上呼吸道感染	上呼吸道感染	10046306
2	2	上呼吸道感染	上呼吸道感染	10046306
1	7	丙氨酸氨基转...	丙氨酸氨基转...	10001551
2	11	上呼吸道感染	上呼吸道感染	10046306
3	9	葡萄糖升高	葡萄糖升高	10018421

Clinical data package: DATABASES: ADaM

NMPA requirements

Traceability

Analysis ready

Analysis metadata

Sponsor is encouraged to submit ADaM according CDISC

Chinese translation

Chinese translation:

- dataset label and variable label
- adverse events terms
- generic name of concomitant medications
- medical history in CSR and other documents

Chiesi strategy

Dataset and variable labels taken from Chinese version of ADaM IG.

ADaM datasets have been translated from English datasets → They have **not** been re-created starting from Chinese SDTM

Submission package: DATABASES: ADaM

CMSEQ	CMSPID	CMTRT	ACAT1	ACAT2	CMINDC	CMDECOD
1	19	Salmeterol Xin...	Asthma		Asthma	FLUTICASONE PROPIONATE;SALMETEROL X...
2	3	Acarbose Tabl...	Non-Asthma		MH: Type 2 dia...	ACARBOSE
3	1	Gliclazide Mod...	Non-Asthma		MH: Type 2 dia...	GLICLAZIDE
4	2	Rosiglitazone...	Non-Asthma		MH: Type 2 dia...	ROSIGLITAZONE
5	9	Thioctic Acid f...	Non-Asthma		MH: Type 2 dia...	THIOCTIC ACID

CMSEQ	CMSPID	CMTRT	CMDECOD
1	19	沙美特罗昔萘酸和丙酸氟替卡松粉吸入剂250/50 ug	丙酸氟替卡松;昔萘酸沙美特罗
2	3	阿卡波糖片	阿卡波糖
3	1	格列齐特缓释片	格列齐特
4	2	罗格列酮钠片	罗格列酮

Clinical data package: DATABASES

NMPA databases general requirement

If dataset needs to be split because the file size does not meet submission requirements, sponsor can just submit the split dataset, details to be included in reviewer's guide

Chiesi strategy

NO INDICATION OF SUBMISSION REQUIREMENTS
→ FDA REQUIREMENTS HAVE BEEN CONSIDERED FOR THE SUBMISSION

Points of attention

Additional challenges in Chinese translation:
- Chinese character = 3 bytes
- English character = 1 byte (generally)

→ Length of variable might exceed the limit imposed by SAS xport format and CDISC requirements
→ Chinese characters need UTF-8 encoding

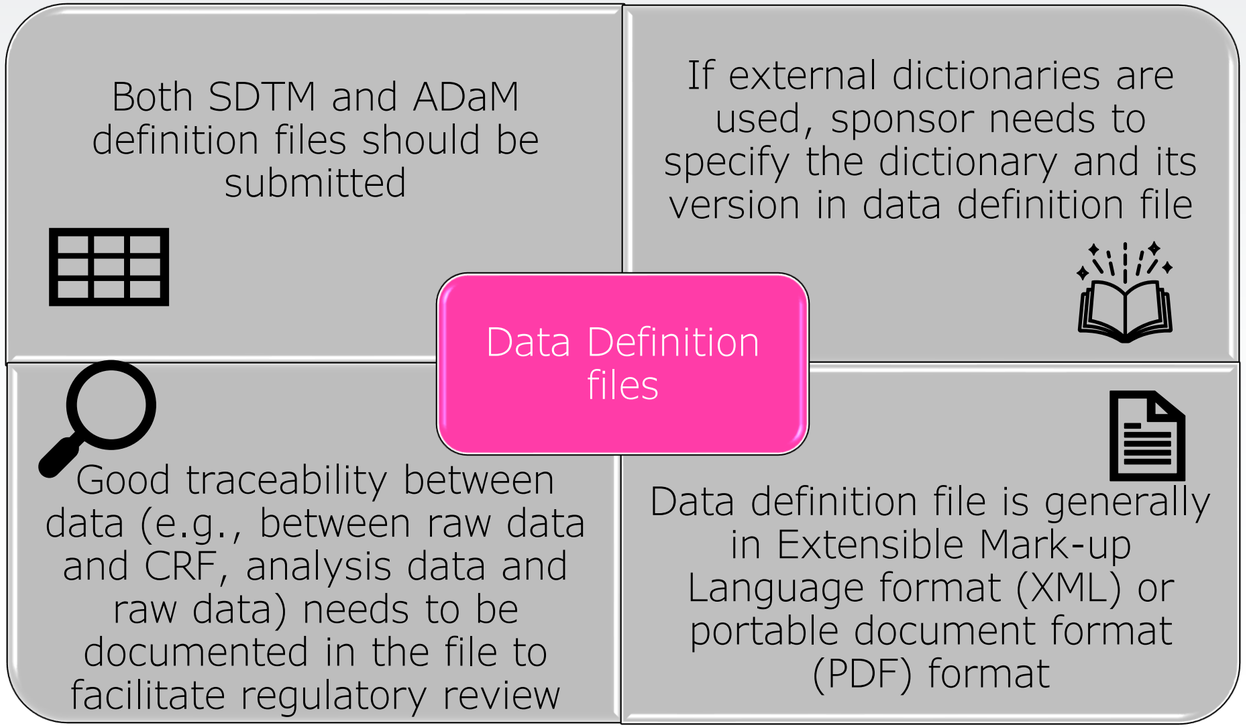
1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM v1.4 / SDTM IG v3.2
Controlled Terminology	CDISC Controlled Terminology dated 2018-12-21
Data Definitions	define.xml v1.0
Medications Dictionary	WHO Drug Dictionary IQ2018Q3* * WHO Drug Dictionary version Q1 2020 has been used for translation, since this was the first Chinese version available. In case a Chinese term was not available within the Q1 2020 version, then the current English term has been displayed.
Medical Events Dictionary	MedDRA v23.1

http://xml4pharma.com/publications/Poster_Jozef_Aerts_Chinese_characters_XPT.pdf
https://www.lexjansen.com/phuse-us/2021/dh/PAP_DH12.pdf

Clinical data package: Data Definition Files

NMPA requirements



Chinese translation of:

- description/label and specification of each dataset
- description/label and derivation progress of variables
- values or codes list of efficacy indicators

Chiesi strategy

English SDTM and ADaM data definition files have been completely translated in Chinese

Clinical data package: Data Definition Files

DM (人口学) - SPECIAL PURPOSE

相关补充修饰语数据集: SUPPDM (DM补充限定符)

变量	标签/描述	类型	角色	长度或显示格式	受控术语或ISO格式	来源/源/方法/注释
STUDYID	研究标识符	text	Identifier	15		Protocol
DOMAIN	域名缩写	text	Identifier	2	SDTM Domain Abbreviation [31 术语]	Assigned 两个字符的域名缩写。
USUBJID	受试者唯一标识符	text	Identifier	24		Derived USUBJID由STUDYID和SUBJID连接组成，用'_'分隔，例如，'
SUBJID	受试者标识符	text	Topic	8		CRF Annotated Case Report Form [80]

Define-XML文档的创建日期/时间: 2023-03-20T13:06:57Z

Define-XML版本: 2.0.0

样式表版本: 2018-11-21

标准	ADaM-IG 1.1
研究名称	
研究概要	在哮喘得到控制的患者中对比Fost
协议名称	一项在哮喘得到控制的患者中对比I
元数据名称	

分析结果元数据-概要

Table 14.2.1.1.2 Statistical Analysis:Change from Baseline over the Entire Treatment Period in Average Pre-Dose Morning PEF (L/Min).ANCOVA Model (Intention-To-Treat Set)

按治疗组在模型中考虑的受试者的数量 (n)

整个治疗期给药前早晨PEF均值相对基线的变化

POINTS OF ATTENTION: the pagination in aCRF has changed due to translation (one page became 2 for instance), page numbering in SDTM define has been updated accordingly

Define.xml and data have been validated through P21 community with CDISC engine

Clinical data package: Analysis Results Metadata (ARM)

NMPA Data definition files requirements

Analysis Results Metadata include statistical displays (text, tabular or graphical presentation of results) or inferential statements such as p-values or estimates of treatment effect.

Analysis results metadata are not needed or even advisable for every analysis included in a clinical study report or submission. The sponsor determines which analyses should have analysis results metadata.

Table 14.2.1.1.2

显示	Statistical Analysis:Change from Baseline over the Entire Treatment Period in Average Pre-Dose Morning PEF (L/Min).ANCOVA Model (Intention-To-Treat Set)
分析结果	按治疗组在模型中考虑的受试者的数量 (n)
分析参数	PARAMCD = "PEFAMETP" (整个治疗期早晨给药前PEF均值 (L/min))
分析变量	ADPEF.TRT01P (阶段01计划治疗)
分析原因	SPECIFIED IN SAP
分析目的	PRIMARY OUTCOME MEASURE
数据参考（包括选择标准）	ADPEF [PARAMCD = "PEFAMETP" and BASE ≠ missing and CHG ≠ missing and ITTFL = "Y" and REGION1 ≠ "missing" and SEX ≠ "missing"]
文献资料	意向治疗(ITT)分析集中包含的受试者的唯一计数，其中每个治疗组内协变量（基线值）未缺失，固定效应（区域和性别）未缺失，并且从随机治疗期开始日期后第二天的早晨时段到随机治疗期结束日期的早晨时段之间的时间间隔内至少有一个可评估的访视间期。 SAP第9.1.1节 [35] SAP第14节 [58]
编程语句	[SAS version 9.4] proc sql; select distinct TRT01P, count(distinct USUBJID) as n from ADPEF where ITTFL="Y" and PARAMCD="PEFAMETP" and missing(CHG)=0 and missing(BASE)=0 and REGION1 and SEX group by TRT01P; quit; t14_2_1_1_2

Chiesi strategy

It has been a Chiesi decision to submit ARM to facilitate the package revision

ARM not mentioned in Chinese guideline

ARM to be provided for submitted programs

Submit ARM for primary and key secondary endpoints with inferential analyses

Submission package: Reviewer's guide

NMPA requirements

- Should be submitted in Chinese

- Supplement to data definition files for the reviewers

- Provides information in addition to what we have in data definition file

- Submitted in .pdf

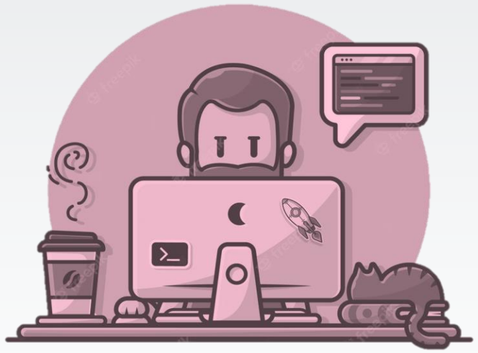
Chiesi strategy

Both English SDTM and ADaM reviewer's guides have been translated

分析数据审阅指南

目录

Clinical data package: Programming code



Submitted as txt files		
Readable with comments	Understandable	No external macro calls

Walls

The Great China Wall, II century before Christ

- Tight timelines: We joined the race when cars were already at full speed and we had to catch up very quickly
- COVID-19 pandemic: trial execution and data cleaning activites were delayed by strict Chinese lock-downs, increasing pressure on study team
- Chinese requirements: evolving regulations with continuous updates and China-specific activities (e.g. GCP Officer data QC)
- It is not all about translation: Chinese SDTM IG and ADaM IG should be applied and consistency between documents should be ensured

Wins

Gengis Khān, 1162-1227 after Christ

- Information sharing: Multiple internal trainings to maximize lessons learnt from previous China regulatory experiences
- Strong internal know-how on FDA package preparation
- Cross-functional team work is the key:
  - Close cooperation between clinical, regulatory and affiliate teams to ensure full alignment on the strategy
  - Constant support to translation, regulatory and medical writers CROs to ensure consistency
- One package ready to be submitted in May and other two submissions planned this year in China

Wisdoms

Confucius, 551-479 before Christ

- Plan ahead:
  - Define internal standards for Chinese data submission
- Chinese authority will accept the package without additional requests:
  - This will increase our confidence on the next two submissions planned this year in China
- Chinese Guideline to be more and more aligned with requirements from other countries
- …and a dream: that in the mid term Chinese authority will not longer ask the translation of the database!

A big big thank to..

- Chiesi stat programming team:
  - Paola Vaghi
- Chiesi clinical team:
  - Emanuele Calabrò, Eva Topole, Florence Zuccaro, Cissy Zhu and Gianluigi Poli
- Chiesi regulatory team:
  - Adele Sansone and Jessica Coretti
- Chiesi affiliate team:
  - Jingjing Liu