China submission preparation: lost in translation
Rebecca Moretti & Glauco Cappellini
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
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 pt and angle 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**

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Time</th>
<th>Study Objective (which phase)</th>
<th>Study Design</th>
<th>Subject Population (healthy volunteer or patients, number of subject)</th>
<th>Dosage Regimen (dosage, times and treatment course)</th>
<th>Primary Endpoint(s)</th>
<th>Secondary Endpoint(s)</th>
<th>Progress Situations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Table of Contents

1. Introduction ........................................................................................................................................... 6
2. Summary of the Chinese Pharmacokinetic Study and Comparison with Caucasian Pharmacokinetic Data .................................................................................................................. 7
3. Summary of Clinical Data in Chinese Patients with Asthma ................................................................. 13
   3.1 Summary of Study CHINA01 ........................................................................................................... 13
       3.1.1 Study Design and Demographics ......................................................................................... 13
       3.1.2 Efficacy Results .................................................................................................................. 17
       3.1.3 Safety Results .................................................................................................................... 30
4. Summary of the European Union Pivotal Randomised Clinical Trials in Asthma ............................... 35
   4.1 Summary of Studies CT01, CT02 and CT03 ............................................................................. 35
       4.1.1 Study Design and Demographics ....................................................................................... 35
       4.1.2 Efficacy Results ................................................................................................................ 41
       4.1.3 Safety Results ................................................................................................................... 48
5. Comparison of Study CHINA01 and Study CT03 .............................................................................. 54
   5.1 Comparative Efficacy .................................................................................................................. 54
   5.2 Comparative Safety .................................................................................................................... 59
6. Discussion and Conclusions ................................................................................................................ 64
7. Reference List ...................................................................................................................................... 66
8. Appendix: Study CHINA01 - Post-hoc Analysis Results .................................................................... 68
Regulatory package: Clinical Data

Clinical Data Submission in China

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)

Table of Contents

1. Background and Purposes ................................................................. 3
2. Submission Components of Clinical Trial Data ...................................... 4
   2.1 Study database ............................................................................... 4
   2.2 Analysis database .......................................................................... 5
   2.3 Data definition file ......................................................................... 6
   2.4 Data reviewer’s guide ...................................................................... 7
   2.5 Annotated CRF ............................................................................... 7
   2.6 Programming code ......................................................................... 8
3. Submission Document Format and Conventions ...................................... 8
   3.1 Portable document format ............................................................... 8
   3.2 Extensible mark-up language format ............................................. 8
   3.3 Plain text format ............................................................................ 9
   3.4 Data transport file format .............................................................. 9
   3.5 Dataset split .................................................................................. 9
   3.6 Dataset name, variable name and length ....................................... 9
   3.7 Dataset labels and variable labels ................................................. 10
4. Other Considerations ........................................................................... 10
   4.1 Traceability of trial data ............................................................... 10
   4.2 Data files under eCTD ................................................................... 11
   4.3 Foreign language database ............................................................ 11
   4.4 Communication with regulatory agency ....................................... 12
Clinical data package: required elements

**DATABASES:** SDTM and ADaM

XPT V5 or above* DM and ADSL are mandatory

**ANNOTATED CRF**

aCRF.pdf*

**DATA DEFINITION FILES**

.xml* or .pdf*

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

**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 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.

The CRF text should be identical with the Chinese eCRF translated

Translation of External data Data Transfer Specifications (DTS)

Translation of bookmarks

Translation of all blank eCRF

eCRF English version

aCRF English version

eCRF CHINESE VERSION

aCRF CHINESE VERSION
Clinical data package: annotated CRF

### Demography (DM)

<table>
<thead>
<tr>
<th>1. Date of Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Date of Birth] (DD/MM/YYYY)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Age]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Sex]</td>
</tr>
<tr>
<td>☐ Male</td>
</tr>
<tr>
<td>☐ Female</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Race]</td>
</tr>
<tr>
<td>☐ White</td>
</tr>
<tr>
<td>☐ Asian</td>
</tr>
<tr>
<td>☐ Black</td>
</tr>
<tr>
<td>☐ Other (please specify)</td>
</tr>
<tr>
<td>☐ If other ticked, please specify</td>
</tr>
</tbody>
</table>

(Additional annotations: RACE = “MULTIPLE” and indicator response are in SuppDMQ Qty)
Clinical data package: DATABASES: SDTM

**NMPA requirements**

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

**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

**Chinese translation:**
- dataset label and variable label
- adverse events terms
- generic name of concomitant medications
- medical history in CSR and other documents
**Submission package: DATABASES: SDTM**

<table>
<thead>
<tr>
<th>AESEQ</th>
<th>AESPID</th>
<th>AETERM</th>
<th>AELLT</th>
<th>AELTCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Upper respiratory tract infection</td>
<td>Upper respiratory tract infection</td>
<td>10046306</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Upper respiratory tract infection</td>
<td>Upper respiratory tract infection</td>
<td>10046306</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>Alanine amino acid transferase increased</td>
<td>Alanine amino acid transferase increased</td>
<td>10001551</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>Upper respiratory tract infection</td>
<td>Upper respiratory tract infection</td>
<td>10046306</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>glucose increased</td>
<td>Glucose increased</td>
<td>10018421</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AESEQ</th>
<th>AESPID</th>
<th>AETERM</th>
<th>AELLT</th>
<th>AELTCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>上呼吸道感染</td>
<td>上呼吸道感染</td>
<td>10046306</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>上呼吸道感染</td>
<td>上呼吸道感染</td>
<td>10046306</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>丙氨酸氨基转移酶升高</td>
<td>丙氨酸氨基转移酶升高</td>
<td>10001551</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>上呼吸道感染</td>
<td>上呼吸道感染</td>
<td>10046306</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>葡萄糖升高</td>
<td>葡萄糖升高</td>
<td>10018421</td>
</tr>
</tbody>
</table>
Clinical data package: DATABASES: ADaM

NMPA requirements

- Traceability Analysis ready
- Analysis metadata

Chiesi strategy

- 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

ADaM datasets have been translated from English datasets. They have not been re-created starting from Chinese SDTM.
Submission package: DATABASES: ADaM

<table>
<thead>
<tr>
<th>CMSEQ</th>
<th>CMSPID</th>
<th>CMTRT</th>
<th>ACAT1</th>
<th>ACAT2</th>
<th>CMINDC</th>
<th>CMDECOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 19</td>
<td></td>
<td>Salmeterol Xin...</td>
<td>Asthma</td>
<td></td>
<td>Asthma</td>
<td>FLUTICASONE PROPIONATE;SALMETEROL X...</td>
</tr>
<tr>
<td>2 3</td>
<td></td>
<td>Acarbose Tabl...</td>
<td>Non-Asthma</td>
<td></td>
<td>MH: Type 2 dia...</td>
<td>ACARBOSE</td>
</tr>
<tr>
<td>3 1</td>
<td></td>
<td>Glicazide Mod...</td>
<td>Non-Asthma</td>
<td></td>
<td>MH: Type 2 dia...</td>
<td>GLICLAZIDE</td>
</tr>
<tr>
<td>4 2</td>
<td></td>
<td>Rosiglitazone...</td>
<td>Non-Asthma</td>
<td></td>
<td>MH: Type 2 dia...</td>
<td>ROSIGLITAZONE</td>
</tr>
<tr>
<td>5 9</td>
<td></td>
<td>Thiocit Acid f...</td>
<td>Non-Asthma</td>
<td></td>
<td>MH: Type 2 dia...</td>
<td>THIOCTIC ACID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CMSEQ</th>
<th>CMSPID</th>
<th>CMTRT</th>
<th>CMDECOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 19</td>
<td></td>
<td>沙美特罗替氟普酸和丙酸氟替卡松粉吸入剂250/50 ug</td>
<td>丙酸氟替卡松;替氟普酸沙美特罗</td>
</tr>
<tr>
<td>2 3</td>
<td></td>
<td>阿卡波糖片</td>
<td>阿卡波糖</td>
</tr>
<tr>
<td>3 1</td>
<td></td>
<td>格列齐特缓释片</td>
<td>格列齐特</td>
</tr>
<tr>
<td>4 2</td>
<td></td>
<td>罗格列酮钠片</td>
<td>罗格列酮</td>
</tr>
</tbody>
</table>
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

http://xml4pharma.com/publications/Poster_Jozef_Aerts_Chinese_characters_XPT.pdf
## Clinical data package: Data Definition Files

**NMPA requirements**

<table>
<thead>
<tr>
<th>Data Definition files</th>
<th>Chiesi strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both SDTM and ADaM definition files should be submitted</td>
<td>If external dictionaries are used, sponsor needs to specify the dictionary and its version in data definition file</td>
</tr>
<tr>
<td>Good traceability between data (e.g., between raw data and CRF, analysis data and raw data) needs to be documented in the file to facilitate regulatory review</td>
<td>Data definition file is generally in Extensible Mark-up Language format (XML) or portable document format (PDF) format</td>
</tr>
</tbody>
</table>

**Chinese translation of:**
- description/label and specification of each dataset
- description/label and derivation progress of variables
- values or codes list of efficacy indicators
Clinical data package: Data Definition Files

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)

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.

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.

The sponsor determines which analyses should have analysis results metadata.

<table>
<thead>
<tr>
<th>Table 14.2.1.1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statistical Analyses</strong> Change from Baseline over the Entire Treatment Period in Average Pre-Dose Morning PYY (L/Min)</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
</tr>
</tbody>
</table>

It has been a Chiesi decision to submit ARM to facilitate the package revision.
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
Clinical data package: Programming code

<table>
<thead>
<tr>
<th>Submitted as txt files</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readable with comments</td>
</tr>
</tbody>
</table>
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 activities were delayed by strict Chinese lockdowns, 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.

The Great China Wall, II century before Christ
**Wins**

- **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.

*Gengis Khan*, 1162-1227 after Christ
Wisdoms

- 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!

Confucius, 551-479 before Christ
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