Challenges and Opportunities for NDA Filing in China – DM/STAT Perspective

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General Requirements from China NDA Filing (1)

注册分类

1. 未在国内外上市销售的药品。
2. 改变给药途径且尚未在国内外上市销售的制剂。
3. 已在国外上市销售但尚未在国内上市销售的药品。
4. 改变已上市销售盐类药物的酸根、碱基（或者金属元素），但不改变其药理作用的原料药及其制剂。
5. 改变国内已上市销售药品的剂型，但不改变给药途径的制剂。
6. 已有国家药品标准的原料药或者制剂。

General Requirements from China NDA Filing (2)

（一）综述资料

1.药品名称。

2.证明性文件。

3.立题目的与依据。

4.对主要研究结果的总结及评价。

5.药品说明书、起草说明及相关参考文献。

6.包装、标签设计样稿。

（二）药学研究资料

7.药学研究资料综述。

8.原料药生产工艺的研究资料及文献资料；制剂处方及工艺的研究资料及文献资料。

9.确证化学结构或者组份的试验资料及文献资料。

10.质量研究工作的试验资料及文献资料。

11.药品标准及起草说明，并提供标准品或者对照品。

12.样品的检验报告书。

13.原料药、辅料的来源及质量标准、检验报告书。

14.药物稳定性研究的试验资料及文献资料。

15.直接接触药品的包装材料和容器的选择依据及质量标准。

General Requirements from China NDA Filing (3)

（三）药理毒理研究资料

16.药理毒理研究资料综述。

17.主要药效学试验资料及文献资料。

18.一般药理学的试验资料及文献资料。

19.急性毒性试验资料及文献资料。

20.长期毒性试验资料及文献资料。

21.过敏性（局部、全身和光敏毒性）、溶血性和局部（血管、皮肤、粘膜、肌肉等）刺激性等特殊安全性试验资料和文献资料。

22.复方制剂中多种成份药效、毒性、药代动力学相互影响的试验资料及文献资料。

23.致突变试验资料及文献资料。

24.生殖毒性试验资料及文献资料。

25.致癌试验资料及文献资料。

26.依赖性试验资料及文献资料。

27.非临床药代动力学试验资料及文献资料。

General Requirements from China NDA Filing (4)

（四）临床试验资料

28.国内外相关的临床试验资料综述。

29.临床试验计划及研究方案。

30.临床研究者手册。

31.知情同意书样稿、伦理委员会批准件。

32.临床试验报告。

- 申请注册分类1～5的品种，按照《申报资料项目表》的要求报送资料项目1～30（资料项目6除外）；临床试验完成后报送的资料项目包括重新整理的综述资料1～6、资料项目12和14、临床试验资料28～32以及重新整理的与变更相关的资料和补充的资料，并按申报资料项目顺序排列。

  对于注册分类1的品种，临床试验完成后应根据临床期间进行的各项研究的结果，重新整理报送资料项目1～30的全部资料。

  同时申请注册属于注册分类3的原料药和属于注册分类6的制剂的，其原料药的注册申请应当符合申报生产的要求。
- 申请注册分类6的药品，按照《申报资料项目表》的要求报送资料项目1～16和28～30。需进行临床试验的，在临床试验完成后报送资料项目28～32以及其他变更和补充的资料，并按申报资料项目顺序排列。

Requirements for CSR in China (2005/03)

正文加上以下附件：

1. 伦理委员会批准件
2. 向受试者介绍的研究信息及受试者的知情同意书样本
3. 临床研究单位情况及资格，主要研究人员的姓名、单位、资格、在研究中的职责及其简历
4. 临床试验研究方案、方案的修改内容及伦理委员会对修改内容的批准件
5. 病例报告表（CRF）样本
6. **总随机表**
7. 试验用药物检验报告书及试制记录（包括安慰剂）
8. 阳性对照药的说明书，受试药（如为已上市药品）的说明书
9. 试验药物包括多个批号时，每个受试者使用的药物批号登记表
10. 20%受试者样品测试的色谱图复印件，包括相应分析批的标准曲线和QC样品的色谱图复印件、受试者个体的药—时曲线
11. 严重不良事件及主要研究者认为需要报告的重要不良事件的病例报告
12. **统计分析报告**
13. 多中心临床试验的各中心小结表
14. 临床研究主要参考文献的复印件

Key Messages from the Requirements

- No data package is required
- For the CSR, based on current CSR guideline, even line listing is not required
  - Traceability link will not be available
  - CFDA will not be able to replicate sponsor's analysis directly
  - Sensitivity analysis by CFDA is not a possibility based on the submitted materials

With this, can we take it easy after the reports are done?

药物临床试验数据自查核查工作的公告(7/22)

1. **核对锁定的数据库与原始数据一致性，统计分析以及总结报告数据与原始记录及数据库的一致性；数据锁定后是否有修改以及修改说明等。**
2. 生物样本分析测试仪器（如HPLC、LC-MS/MS）等主要的试验仪器设备运行和维护、**数据管理软件稽查模块（Audit trail）的安装及其运行等。**
3. 各临床试验机构受试者筛选、入组和剔除情况，受试者入选和排除标准的符合情况，抽查核实受试者参加临床试验的情况。
4. **临床试验方案违背例数、剔除例数、严重不良事件例数等关键数据**；医院HIS系统等信息系统中的受试者就诊信息、用药及检查化验的临床过程情况等。
5. 试验药物和对照药品的生产或购进、检验、运输、保存、返还与销毁以及相关票据、记录、留样等情况。
6. 生物样本的采集过程及运送与交接和保存等记录；生物样本分析方法确证，生物样本分析过程相关的记录以及样本留样情况。
7. 有关方在临床试验项目中主要职责的落实情况、合规情况。

Key Messages from Recent Announcements

- Grandfather rule may not always apply
  - For example, the Data Management guideline published on 2012/03/12 was the first guideline to mention key concepts such as user access control and audit trail. However, in the self-inspection notification, this becomes a mandatory requirement regardless as long as the trial is on the self-inspection list.
- Traceability concept is noted (数据库, 原始数据, 统计分析以及总结报告数据)
- Certain validity concept about statistical methodology is mentioned (方案违背例数、剔除例数、严重不良事件例数)

Will there be further, more stringent inspection guideline in the future? How should we prepare for potential change?

A look at Some Key FDA Data Submission Requirements

- Need individual study CSRs with SAP, TLF as attachments among other attachments. For Chinese CSR requirements, only SAR is an required appendix.
- Prefer to have data in standard formats (and soon to be requirements):
  - For CDISC, 2016/12/17 for most NDAs, ANDAs, BLAs.
  - For MedDRA, 2016/12/17 for most NDAs, ANDAs, BLAs.
  - For WHO Drug, 2018/03/15 for most NDAs, ANDAs, BLAs
- Data packages always need to come with define package. Full traceability is available
- Analysis data sets need to be one-proc-away from results. FDA can easily verify the key results or conduct additional analysis.
- Integrated analysis are usually required.

Some Issues That We Have Seen in Existing Practice

- Many study protocols have existing statistical issues.
- Lots of analysis are not fully pre-planned. The SAPs are too simple and lacking the details to guide implementation.
- Some institutes or CROs do not have a validation procedure for results.
- For the analysis process, some institutes or CROs do not have a step for analysis data sets. Lots of data handling steps are embedded in the programs.
- Programs are often developed without any specifications.
- Some programs are not archived or kept after conclusion of a project.

Points to Consider When Implementing a Company Strategy

- Basic principles need to be maintained: traceability, statistical principle.
- Quality target should be maintained.
- Record retention policy (paper and electronic).
- Cost of implementation

Overall Proposal for Implementation (1)

- Need to care about the Data Manage platform
- Statistical
  - The statistical principle needs to be clear and correct starting from the protocol. At least the primary analysis for the primary endpoint must be in the protocol
  - SAP should expand the methodology of the protocol. And then, provide sufficient details to enable the implementation.
  - Important to check for conventional analysis rather establish new analysis methodology – multivariate analysis usually should not be the primary analysis.
  - Only design meaningful analysis items
  - TLF shells should be developed to provide clear indication about what outputs are expected.

Overall Proposal for Implementation (2)

- Must have analysis data sets as the intermediate step, with pre-specified analysis data set specification. The analysis data sets will make most analysis as specified in the SAP and TLF shells one-proc-away.
- Suggest to make SDTM optional for now.
- Double programming QC should become a norm for analysis data sets and key analysis items.
- Statisticians should review TLF outputs thoroughly to make sure the analysis intentions are met, the analysis assumptions are valid, the outputs are logically valid, and need to be able to interpret the results.
- Good archival SOPs – need to prepare to reproduce the results many years after the study closure.

Overall Proposal for Implementation (3)

- Clear process with minor increase of cost
- Need to have all the key materials ready, in case higher submission standards are required in the future
  - Data standards such as strict SDTM/ADaM
  - Integrated analysis
  - Define package
  - E-submission
  - etc.

Further Discussion