



# Legacy Data Conversion Issues for Topical Product Studies

Lillian Qiu and Hon-Sum Ko

DDDP, ODE3, CDER, FDA, Silver Spring, MD 20993



## Introduction

- Non-standardized legacy data are common in previous submissions from the pharmaceutical industry to regulatory authorities.
- We conducted legacy data conversion of topical corticosteroid clinical studies into SDTM to facilitate comparison of topical corticosteroids across topical corticosteroid potencies.
- We anticipated that there might be potential issues that could be applicable to therapeutic standards projects for topical drug products.

## Objective

- To convert legacy data from previously submitted topical corticosteroid clinical trials into CDISC SDTM format.
- Discover potential issues to be considered for therapeutic standards projects and highlight what significant information current submissions may be lacking.

## Methods

- We used SAS programming to rename and reformat non-standardized variables in previous submitted clinical datasets, according to an updated CDISC SDTM Implementation Guide (version 3.2).
- We created define file for each study with XML (Extensible Markup Language): listing and explaining all the SDTM domains used in the study, the variables included in each domain, and the controlled terminology used for the variables.
- We validated the converted SDTM datasets by OpenCDISC software.

## Materials

- Legacy data from 10 topical corticosteroid applications containing a total of 59 trials and 732 datasets were converted into SDTM, including safety/efficacy studies, hypothalamic-pituitary-adrenal (HPA) axis studies, and dermal safety studies.

Table 1. Topical Corticosteroid Clinical Trials for CDISC SDTM Conversion

| Steroid Drug       | 1          | 2          | 3                  | 4                  | 5                  | 6          | 7          | 8    | 9          | 10         |
|--------------------|------------|------------|--------------------|--------------------|--------------------|------------|------------|------|------------|------------|
| Year of Submission | 2002       | 2003       | 2004               | 2008               | 2007               | 2006       | 2004       | 2005 | 2008       | 2009       |
| Potency Class      | super-high | super-high | lower mid-strength | lower mid-strength | upper mid-strength | super-high | super-high | mild | super-high | super-high |

## Results

- Legacy clinical data from the submissions were successfully converted into CDISC's SDTM format. Example of sponsor datasets and SDTM datasets:

| DATASET                  | DESCRIPTION OF DATASET                 |                        |
|--------------------------|----------------------------------------|------------------------|
| <a href="#">eff</a>      | Efficacy data for statistical analysis | <a href="#">ae.xpt</a> |
| <a href="#">aecom</a>    | Adverse Event data for stats analysis  | <a href="#">cm.xpt</a> |
| <a href="#">aehdr</a>    | Adverse Events summary data            | <a href="#">da.xpt</a> |
| <a href="#">aes</a>      | Adverse Events data                    | <a href="#">dm.xpt</a> |
| <a href="#">basetest</a> | Baseline Test data                     | <a href="#">ds.xpt</a> |
| <a href="#">conmedh</a>  | Concomitant medication summary data    | <a href="#">ie.xpt</a> |
| <a href="#">conmeds</a>  | Concomitant medication data            | <a href="#">lb.xpt</a> |
| <a href="#">demo</a>     | Demographics data                      | <a href="#">mh.xpt</a> |
| <a href="#">fu1</a>      | Follow-up data                         | <a href="#">mo.xpt</a> |
| <a href="#">fuh</a>      | Follow-up summary data                 | <a href="#">rp.xpt</a> |
| <a href="#">medhx</a>    | Medical History data                   | <a href="#">vs.xpt</a> |
| <a href="#">pd</a>       | Protocol Deviation data                |                        |
| <a href="#">sterm</a>    | Study dosing data                      |                        |
| <a href="#">surgh</a>    | Surgical History summary data          |                        |
| <a href="#">surgical</a> | Surgical History data                  |                        |
| <a href="#">visit1</a>   | Visit 1 data                           |                        |
| <a href="#">visit2</a>   | Visit 2 data                           |                        |
| <a href="#">visit3</a>   | Visit 3 data                           |                        |
| <a href="#">visit4</a>   | Visit 4 data                           |                        |
| <a href="#">visit5</a>   | Visit 5 data                           |                        |

- Many of the issues observed during conversion may not be unique to topical corticosteroid trials, but common among topical dermatologic product clinical trial data.
- a) Controlled terminology issues.
  - In the irritation/sensitization clinical studies for topical corticosteroids, the skin assessment for severity/intensity scale could not be found in the standard severity/intensity grade in Controlled Terminology (CT), e.g.:
    - o There were 7 scales for irritation scoring in the CRF: 'minimal erythema', 'definite erythema', etc. However, there are 3 scales available for severity/intensity scales (MILD, MODERATE, SEVERE) in CT. This issue has not been resolved because there is no standard terminology for skin irritation scoring in CT.
  - The skin evaluations during topical product studies have characteristic assessments. There are no standard terms for them in CT, e.g.:
    - o Plaque induration and scaling assessments in the trials have not been converted to standard terms due to absence of the standard terminology in CT.

## Results (Continued)

- b) Issues concerning laboratory assessment results and reference ranges for LB domain, e.g.:
    - In HPA axis suppression studies, there were no lab results and reference ranges for pre-dose sample evaluations in some visits in the legacy datasets, while there were lab results available for post-dose sample evaluations. However, HPA suppression was determined by both pre-dose and post-dose sample levels.
      - o Resolution is to accommodate the values of pre-dose from the clinical trial study report into a supplemental dataset with excel file. Then importing the values into SAS programming for LB domain conversion.
    - Assessments on the use of alcohol, tobacco, and drug occur before administration of topical products. Alcohol and tobacco usage are supposed to be in SU domain. However, the CRF rarely contains data to be placed in that domain, including substance dosage, form, frequency, etc., for SU domain conversion.
      - o Because the patients were given urine drug tests, with test results being 'Positive' or 'Negative', we captured substance assessment results in LB domain.
  - c) There was inconsistent information between response grades in the legacy dataset and defined response grades in define file, e.g.:
    - Response grades were used to evaluate signs of plaque psoriasis for the entire treatment area during the visits. In the define file, 5 grades, '1', '2', '3', '4', and '5' were given for the response grades, which correspond to 'None', 'Mild', 'Moderate', 'Severe', and 'Very Severe'. However, there were 9 response grades in the legacy dataset. In addition, there was no text description for the intermediate grades (1, 3, 5, and 7) in the CRF, i.e., midpoints between the defined grades (0, 2, 4, 6, and 8).
      - o The ordinal descriptive response grades for signs of plaque induration/scaling, etc. are a use case for topical product studies. The responses, 1, 3, 5 and 7 could not be converted with the standard responses.
  - d) Dosage adjustments in relation to lesion size changes:
    - Treatment dosage depends on severity and size of the skin condition, and accurate measurement is rarely obtainable. For instance, subjects with psoriasis applied the treatment on the lesion, but its dosage changes later due to improvement.
      - o This variability prevents accurate description of dosage as a standard variable in the EX domain.
  - Some conversion challenges are not unique to topical product studies, e.g.:
    - Non-standard terminology has been applied among concomitant medication dosage units in the legacy data, e.g., The term "injection" as a dosing unit is not standard for the variable CMDOSU. Also 'EVERY 5 YEARS', 'TWICE A DAY X7', etc. for dosing frequency per interval (CMDOSFRQ), and 'Inhaled' for route of administration (CMROUTE) are non-standard terms.
    - Absence of relevant details for IE domain.
    - Unavailable RFICDTC (Date/Time of Informed consent) and RFPENDTC (date/Time of End of Participation) in DM domain.
    - Unavailable DAORRES (Assessment Result) in DA domain.
    - AGE in DM domain different from actual age in studies that span for longer than one year.
    - Nonstandard time formats, etc.
- Some of these issues have been resolved, e.g., applying SAS programming to convert standard time variables.

## Conclusions

- Conversion of legacy data from topical corticosteroid clinical trials met with a variety of data issues pertaining to deficiencies, errors, and difficulties in fitting into the standard model.
- There are issues common to dermatological product clinical trials, some of which may require additional considerations, although many of them can be resolved within the current model.
- Experience gained in handling these conversion issues may be helpful in the consideration of therapeutic area standards for dermatologic conditions.

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## Contacts

Aijun (Lillian) Qiu, M.S.  
ORISE Fellow  
FDA/CDER/ODE III  
Phone: (301) 796 0637  
[aijun.qiu@fda.hhs.gov](mailto:aijun.qiu@fda.hhs.gov)

Hon-Sum Ko, MD  
Medical Officer  
FDA/CDER/ODE III  
Phone: (301) 796 3827  
[HonSum.Ko@fda.hhs.gov](mailto:HonSum.Ko@fda.hhs.gov)