

Challenges in Legacy Data Mapping to SDTM Exposure Domains for Topical Drug Studies



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Introduction

- Data regarding study drug exposure are critical in assessing drug safety and efficacy.
- Our experience in legacy-data conversion for topical dermatologic drug studies reveals that many submission datasets do not provide sufficient information for reliable assessment of actual exposure. There may also be issues in representation of collected exposure data into SDTM Exposure (EX) and Exposure as Collected (EC) domains in their submissions. For example:
 - Some dermal safety studies combine exposure to drug and UV light irradiation to evaluate local toxicity. There are multiple patch tests with different ingredients or drug strengths at various randomized application sites in each subject.
 - To evaluate systemic toxicity, e.g., in hypothalamic-pituitary-adrenal axis (HPA) suppression studies, exposure may involve study drug and test stimulant (e.g., ACTH).
 - In clinical trials, the actual dose per administration is often estimated, and varies with lesion size/location change.
- We present our resolutions for the challenges of accurate mapping with current Exposure domain variables through three typical scenarios from topical drug studies.

Methods

- Employing 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).
- Validation of the converted SDTM datasets was performed by OpenCDISC software.

Materials

Three typical scenarios - (a) local safety testing, (b) systemic toxicity studies and (c) clinical trials of topical drugs:

- Example of Exposure dataset for a 4-day, randomized study to evaluate photo-irritation potential of Drug A at 0.25% and 0.05% strength vs. vehicle (Placebo). Study drug was applied to 6 sites (3 irradiated and 3 non-irradiated) on skin of back daily, followed by light exposure through a patch test design.
- Example of randomized, open-label study to assess the potential for adrenal suppression of Drug X (0.1% of cream) as compared to Drug X (0.05% of lotion) when applied to affected lesion areas of subjects with psoriasis, twice daily for 14 days. The study involved ACTH (cosyntropin) Stimulation Test to measure how well adrenal glands respond to adrenocorticotrophic hormone (ACTH) after treatments.
- Example of clinical trial for a topical therapy for 14 consecutive days. At the Week 1 and 2 visits, study professionals reviewed the subject's daily diary and collected all used and unused medication containers. Each container of study medication dispensed to the subjects was weighed before dispensing and again upon return: weights were recorded in the CRF.

Results

- Upon the scenario of photo-irritation study, SDTM EX domain was converted as shown below. To resolve the incomplete presentation of exposure data in EX domain, UV light exposure as a treatment was presented under EXTRT, with EXCAT distinguishing the several treatment categories. EXLOC was used for sub-sites of the applications. The standard patch test provided accurate dosage for each application for the EXDOSE and EXDOSU.

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXDOSFRM
A01	EX	01-101	1	DRUG A 0.05%	STUDY MEDICATION	1	PATCH	PATCH
A01	EX	01-101	2	PLACEBO	CONTROL	1	PATCH	PATCH
A01	EX	01-101	3	DRUG A 0.25%	STUDY MEDICATION	1	PATCH	PATCH
A01	EX	01-101	4	DRUG A 0.05%	STUDY MEDICATION	1	PATCH	PATCH
A01	EX	01-101	5	PLACEBO	CONTROL	1	PATCH	PATCH
A01	EX	01-101	6	DRUG A 0.25%	STUDY MEDICATION	1	PATCH	PATCH
A01	EX	01-101	7	UV IRRADIATION	MED DETERMINATION	216	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	8	UV IRRADIATION	MED DETERMINATION	270	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	9	UV IRRADIATION	MED DETERMINATION	338	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	10	UV IRRADIATION	MED DETERMINATION	423	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	11	UV IRRADIATION	MED DETERMINATION	529	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	12	UV IRRADIATION	MED DETERMINATION	661	$\mu\text{W}/\text{cm}^2$	UVA/UVB
A01	EX	01-101	13	UV IRRADIATION	TREATMENT	661	$\mu\text{W}/\text{cm}^2$	UVB
A01	EX	01-101	14	UV IRRADIATION	TREATMENT	661	$\mu\text{W}/\text{cm}^2$	UVB
A01	EX	01-101	15	UV IRRADIATION	TREATMENT	661	$\mu\text{W}/\text{cm}^2$	UVB
A01	EX	01-101	16	UV IRRADIATION	TREATMENT	661	$\mu\text{W}/\text{cm}^2$	UVB
A01	EX	01-101	17	UV IRRADIATION	TREATMENT	60	$\mu\text{W}/\text{cm}^2$	UVA
A01	EX	01-101	18	UV IRRADIATION	TREATMENT	60	$\mu\text{W}/\text{cm}^2$	UVA
A01	EX	01-101	19	UV IRRADIATION	TREATMENT	60	$\mu\text{W}/\text{cm}^2$	UVA
A01	EX	01-101	20	UV IRRADIATION	TREATMENT	60	$\mu\text{W}/\text{cm}^2$	UVA

ROW(CONT)	EXLOC	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
1	SITE1-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
2	SITE2-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
3	SITE3-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
4	SITE1-NIR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
5	SITE2-NIR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
6	SITE3-NIR OF SKIN OF BACK	TREATMENT PHASE	2009-11-29T08:39	2009-11-30T08:30	1	2
7	SITE1 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	
8	SITE2 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	
9	SITE3 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	
10	SITE4 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	
11	SITE5 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	
12	SITE6 OF SKIN OF BACK	MED PHASE	2009-11-29T08:35		1	

Results (Continued)

ROW(CONT)	EXLOC	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
13	SITE1-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
14	SITE2-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
15	SITE3-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
16	CONTROL SITE OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
17	SITE1-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
18	SITE2-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
19	SITE3-IR OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	
20	CONTROL SITE OF SKIN OF BACK	TREATMENT PHASE	2009-11-30T08:30		2	

- In the example of HPA axis suppression study, there is an important time factor in the injection of the stimulant in relation to blood draw (cortisol levels before and 30 minutes after administration of a stimulant, ACTH (cosyntropin)). To complete EX domain conversion, cosyntropin should be counted as a treatment under EXTRT and captured under EXCAT as stimulant. The EC domain is not shown since it would be exact duplicate of EX domain (shown as below).

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXDOSFRQ	EXDOSFRM
B01	EX	01-101	1	DRUG X 0.1%	STUDY MEDICATION	3500	mg	BID	CREAM
B01	EX	01-101	2	COSYNTROPIN	STIMULANT	0.25	mg	ONCE	INJECTION
B01	EX	01-102	1	DRUG X 0.1%	STUDY MEDICATION	3700	mg	BID	CREAM
B01	EX	01-102	2	COSYNTROPIN	STIMULANT	0.25	mg	ONCE	INJECTION
B01	EX	01-103	1	DRUG X 0.05%	STUDY MEDICATION	2800	mg	BID	LOTION
B01	EX	01-103	2	COSYNTROPIN	STIMULANT	0.25	mg	ONCE	INJECTION

ROW(CONT)	EXROUTE	EXLOC	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
1	TOPICAL	SKIN	TREATMENT PHASE	2012-01-08T11:30	2012-01-23T08:55	1	14
2	IV	ARM	TREATMENT PHASE	2012-01-23T08:58		1	
3	TOPICAL	SKIN	TREATMENT PHASE	2012-01-09T10:30	2012-01-24T08:30	1	14
4	IV	ARM	TREATMENT PHASE	2012-01-24T08:39		1	
5	TOPICAL	SKIN	TREATMENT PHASE	2012-01-09T10:45	2012-01-24T08:40	1	14
6	IV	ARM	TREATMENT PHASE	2012-01-24T08:45		1	

- In the example of the clinical trial, the actual dose per administration varies with lesion size/location change. To address the challenge, dosing information for topical applications may be collected as a volume of a dosing of study medication with a known concentration for convenient measurement. For example, for a protocol-specified dose of 3 g per application twice per day, a subject would be dosed 5 mL of a formulation at 60 g/dL per application two times daily. The CRF may be designed to collect the volume dosed, which could be represented in EC, while EX could contain the dose in mg for the active drug substance which was represented by "API" (active pharmaceutical ingredient).

ex.xpt

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRQ
AB	EX	01-101	1	DRUG Y API	3000	mg	BID

ec.xpt

STUDYID	DOMAIN	USUBJID	ECSEQ	ECTRT	ECDOSE	ECDOSU	ECDOSFRQ
AB	EX	01-101	1	DRUG Y SOLUTION 60%	5	mL	BID

Meanwhile, the subjects should be encouraged to accurately complete dosing information in diaries for entry into case report forms (CRFs). The investigators should review and discuss the diary, which may result in adjustment of treatment dose and a potentially better outcome. The diary can be visible reminder for completion and subsequent medication application.

Conclusions

- We have presented the challenges and proposed solutions in converting legacy data into SDTM EX and EC domains in topical drug studies. It may require sponsors' additional considerations when mapping collected drug exposure data to SDTM EX and EC domains according to CDISC SDTMIG v3.2.
- The remedies for deficiencies in data collection and data management can be addressed up front, in the design of protocol and the CRFs. This will ensure that one obtains the most accurate picture of study drug exposure.
- Experience gained in conversion here may be helpful in the consideration of therapeutic area standards and industry EX domain submissions for dermatologic conditions.

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