二極化する日本のSEND対応

SEND Experiences are Bipolar in Japan

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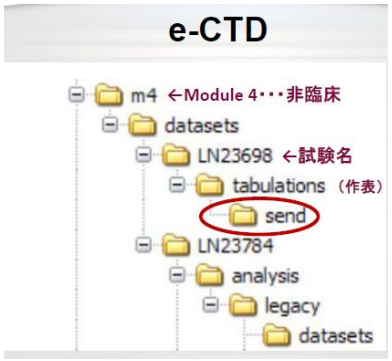
August 4th, 2016

- Data conversion （converter）
- SEND terminology (INHAND etc.)
- Data mapping (SEND specialist)
- Study Data Reviewers Guide (SEND Specialist)



FDA Electric Submission Gateway

SEND is the nonclinical implementation of SDTM, the standard electronic format for clinical regulatory submissions to FDA. SEND, SDTM, and the associated Controlled Terminology have been developed by CDISC.

Needs for SEND

When	From whom	Why
Application for FDA (IND, NDA)	FDA	Requirements of regulatory authorities
Cut time to market	All stakeholders	Increased profit for pharmaceutical companies, faster delivery of new drugs to patients
Data trading in a joint development or licensing-in/licensing-out	Trading partners	Prompt data evaluation enables faster value judgment and increases the added value of data
Preparation for SEND regulations of many countries around the world	Authorities of each country	Future requirements
Establishment of data warehouse	Sponsor companies	Bioinformatics, Rapid access to data

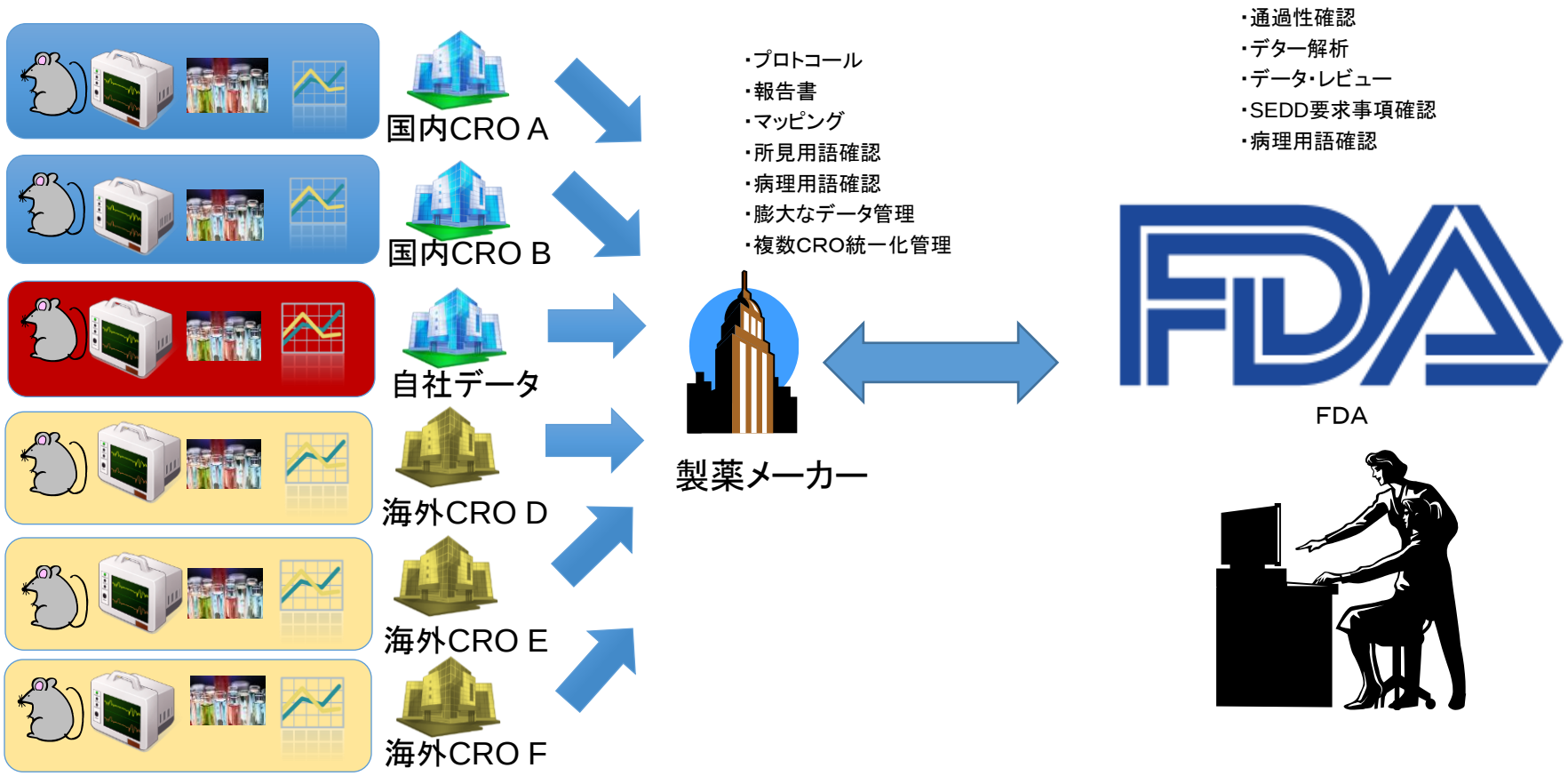
Step-by-step approaches by INHAND (GESC), FDA, CDISC, and EVS	
Phase Ⅰ **2012–2014**	・Classify and define the terms used in SEND ・Position INHAND terminology as SEND terminology and perform a proper mapping
Phase Ⅱ **in progress**	・Appoint experts on different areas to the committee to hear their opinions and update requests regarding INHAND terminology, and coordinate the process of updating terms ・Develop a framework of future activities in partnership with various academic journals including goRENI (global open Registry Nomenclature Information system). Also, work with the FDA and other organizations that are working on the development of SEND terminology
Phase Ⅲ **2013–2015**	・Develop the terminology of non-rodent species. Do that not by organ but species-by-species ・Set up expert panels for each of the following: dogs, monkeys, rabbits, and miniature pigs. Each panel member compiles the terminology in a manuscript

Challenges in responding to SEND in Japan and other non-US countries and ways to manage them

Challenge 1　　Differences in study entrustment

Generally, most pharmaceutical companies that are based or have headquarter functions in the US conduct safety tests of drugs at their own research facilities and CROs. Accordingly, in iSEND, the assumption is that roles for SEND are shared among US-based CROs. This can be considered a **region-based model** in which US pharmaceutical companies apply to the US authority using US CROs. Meanwhile, in Japan, the situation varies greatly.

SEND 対応の現状



Most Japanese pharmaceutical companies often use more than one Japan-based CRO as well as CROs based in Europe and the US for the development of one product. This means they need to conform the data created in multiple countries and facilities to the SEND requirements. In these cases, not all the commissioned CROs can necessarily use SEND or use it in a manner that meets the client's needs.

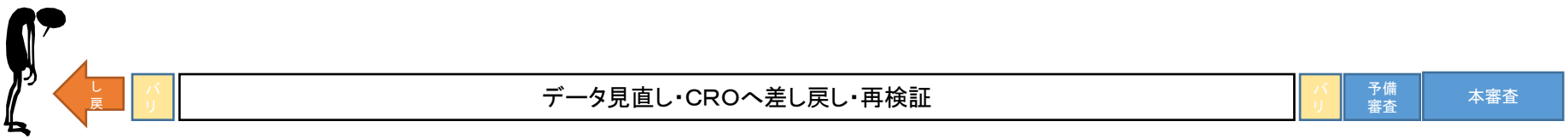
Risk of application rejection

The largest risk associated with SEND is that of a refusal to file (RFP) from FDA. FDA clearly states that it will return the SEND dataset to the applicant if FDA's validation system identifies errors. This means applications may be returned before they are reviewed. Therefore, application materials, including the SEND dataset and accompanying Reviser's Guide, need to be complete. If the application is returned, the launch of a product will be delayed, causing a significant loss.

Upon receipt of a submission, FDA tries to complete the validation process within a specified period of time. If FDA receives a SEND dataset that contains validation errors, it may return the dataset to the sponsor for correction. Some validation errors can prevent analysis by FDA. For this reason, the FDA is strict about the integrity of datasets and does not hesitate to return incomplete ones.

Risk of application rejection

今までの審査



今までより開発が遅れる会社

今までより更に早く開発できる会社

Challenge 2 Reliability of SEND datasets

Pharmaceutical companies take full responsibility for the reliability of SEND datasets. CROs bear Good Laboratory Practice (GLP) responsibilities for the reliability of raw data or original electronic data, but currently not for the reliability of the SEND data converted from the original data. Obviously, CROs assume no responsibility, in terms of both laws and GLP, for the preparation of applications or the compatibility of electronic data with FDA's screening tool. Therefore, SEND datasets are not recommended to be submitted by CROs for application without verification. This point is sufficiently discussed in the iSEND.

Challenge 3 Flexibility of CROs

If a CRO is using a widely used converter for SEND, the program will be updated as needed to deal with the addition of CTs and the requirements of FDA, which are expected to increase in the future. However, if the CRO is using a self-developed program, the sponsor always needs to verify that the program is accurate and updated. In any case, since CROs bear GLP responsibilities for the original data, the important thing is how they can submit the original data in an electronic format to meet the sponsor’s needs. Sponsor pharmaceutical companies should confirm how flexible commissioned CROs can be in the submission of before-conversion original data in the proper electronic format, rather than requesting them to submit the dataset in the SEND format.

二極化している日本のSEND －製薬企業とCRO－

日本のCRO

CRO A社

STAGE 6 ➡ 恒常的にFDA申請データセットを作成し通過させている

STAGE 5 ➡ FDAトラ 過できる

STAGE 4 ➡ データセット 正ができる

STAGE 3 ➡ SDRGが作成 科学的な判断ができる)

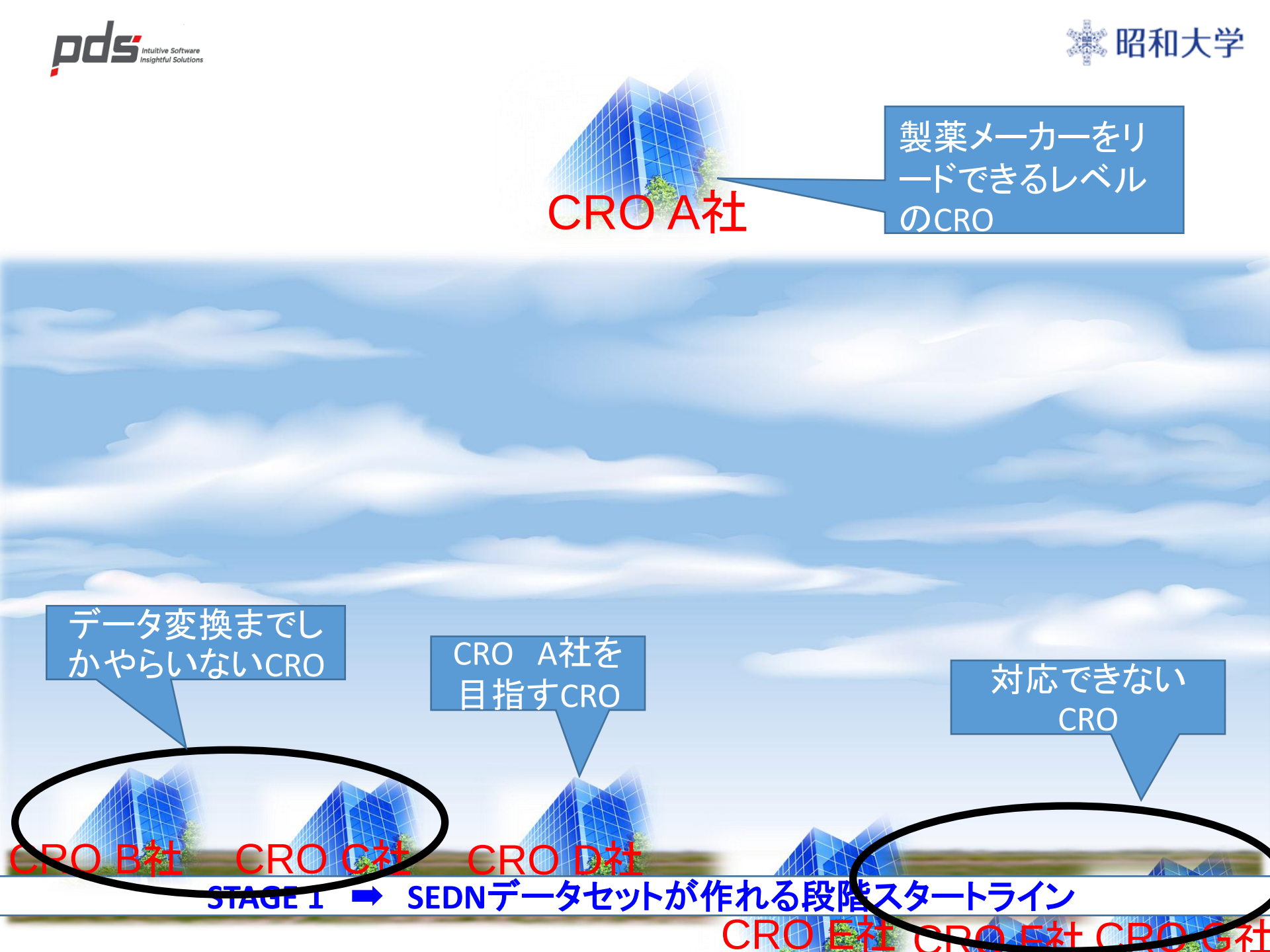
STAGE 2 ➡ データセ 証と科学的検証ができる

極端な力量差がある

CRO B社　CRO C社　CRO D社

STAGE 1 ➡ SEDNデータセットが作れる段階スタートライン

CRO E社　CRO F社　CRO G社


CRO A社
製薬メーカーをリードできるレベルのCRO
データ変換までしかやらないCRO
CRO　A社を目指すCRO
対応できないCRO
CRO B社
CRO C社
CRO D社
STAGE 1 ➡ SEDNデータセットが作れる段階スタートライン
CRO E社
CRO F社
CRO G社

Proof-of-Concept終了した日本の製薬企業

Parma A社　Parma B社　Parma C社　Parma D社　Parma E社

極端な経験値の差が生じる

自社（内製）データについて実[illegible]るCROやCDISC-RSPと共同でFDAトライアル申請を[illegible]の手続・作業の手順書化等の検証が終了している。ま[illegible]（外製）データについても同様のパイロットが終了してい[illegible]

成功企業の共通点➡ 自社[illegible]換装置を買ったり、システムのアップグレードなどは時間[illegible]るいは経済性に余裕がない。

Stage 0　情報収集段階

情報収集段階　多数の企業がこの段階

Efficient ways for Japanese pharmaceutical companies to respond to SEND

Given the current situation in Japan, it is difficult to imagine a scenario in which both pharmaceutical companies and CROs have sufficient knowledge of SEND and a capacity to manage it. In addition, as discussed earlier, a region-based scenario is not applicable to Japanese pharmaceutical companies.

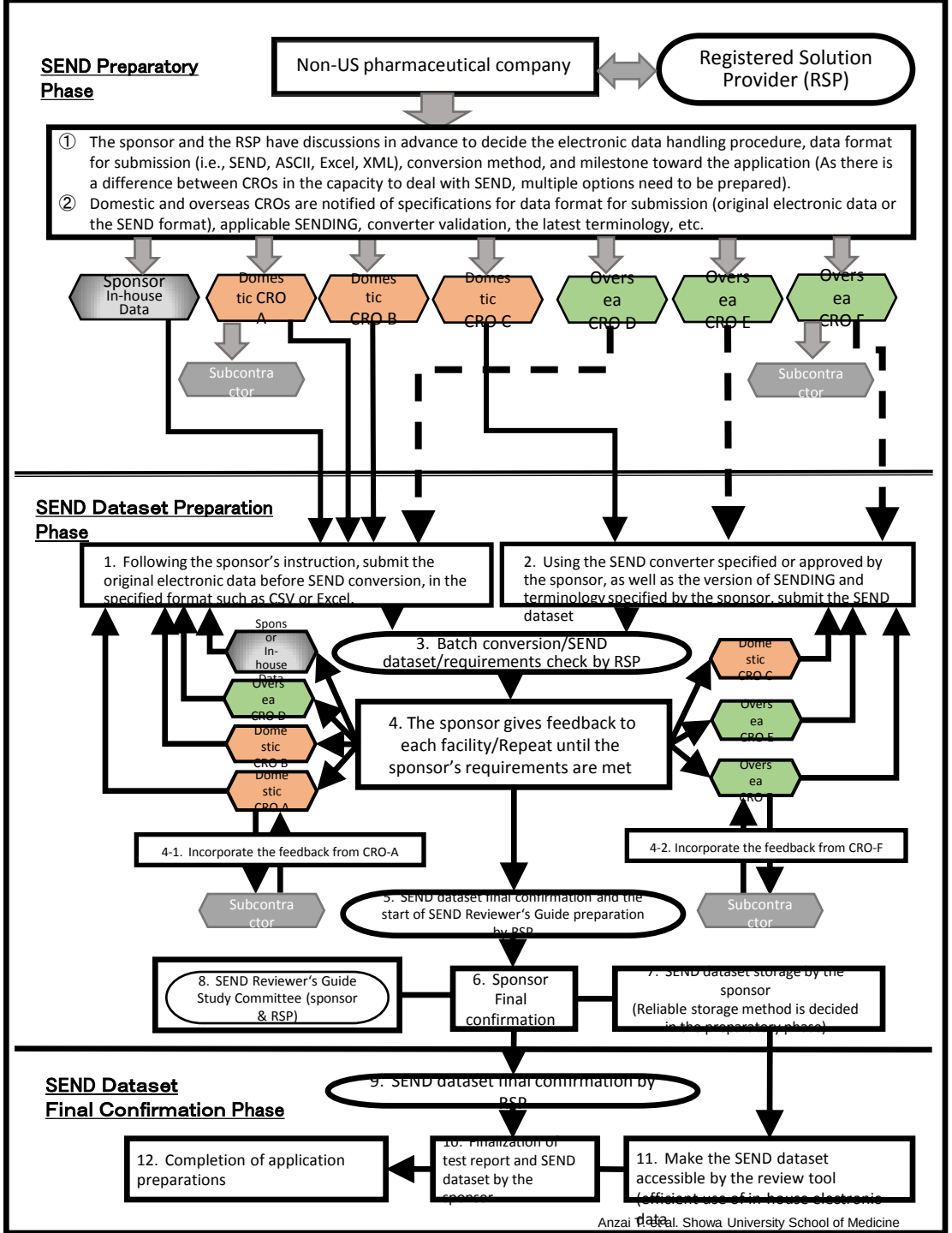
The next Fig. 1 (SEND compliance scheme in Japan and other non-US countries) illustrates how Japanese or other non-US countries' pharmaceutical companies can overcome challenges by using RSPs. One of this scheme's characteristics is that the phases from SEND dataset preparation to final confirmation are described based on the use of CROs with different nationalities and capacities to use SEND.

Fig. 1
SEND compliance scheme in Japan and other non-US countries

Anzai. T. et al. “Responses to the Standard for Exchange of Nonclinical Data (SEND) in non-US countries”

Journal of Toxicol Pathol. 2015 Apr;28(2):57-64. doi: 10.1293/tox.2015-0007. Epub 2015 Apr 1.

会場に論文別刷があります。



P06-002

FDA SEND in Non-US Countries

Responses to the Standard for Exchange of Nonclinical Data (SEND) in Non-US Countries

T. Anzai[1,2], L. Kaufman[3], R. Aerni[4], F. Mura[4], M. Schuster[3], R. Buchanan[3], M. Wasko[3]

[1]PDS Pathology Data Systems, Hamamatsu, Japan [2]Showa University School of Medicine, Tokyo, Japan [3]PDS Life Sciences, NJ USA, [4]PDS Pathology Data Systems, Switzerland

Introduction

The Standard for the Exchange of Nonclinical Data (SEND), adopted by the US FDA, is part of a set of regulations and guidances requiring the submission of standardized electronic study data for nonclinical and clinical data submissions. Thus, non-US countries must consider and develop approaches to SEND that meet their needs. This poster summarizes the real issues in non-US countries concerning with SEND (Fig. 1), and details a compliance scheme (Fig. 2) illustrating how pharmaceutical companies can complete a large amount of work up to an FDA application with the effective utilization of CROs and solution providers.

Needs for SEND (Table 1)

Compared with other regulations, SEND is unique because pharmaceutical companies can use it for various purposes, which can be broadly divided into five categories.

Table 1 Needs for SEND

When	From whom	Why
Application for FDA (IND, NDA, BLA)	FDA	Requirements of regulatory authorities
Cut time to market	All stakeholders	Increased profit for pharmaceutical companies, faster delivery of new drugs to patients
Data trading in a joint development or licensing-in/licensing-out	Trading partners	Prompt data evaluation enables faster value judgment and increases the added value of data
Preparation for SEND regulations of many countries around the world	Authorities of each country	Future requirements
Establishment of data warehouse	Sponsor companies	Bioinformatics, Rapid access to data

Fig. 1 Current situation of SEND in non-US countries

Challenges in responding to SEND in Japan and other non-US countries and ways to manage them

As Fig. 1 shows, most Japanese pharmaceutical companies often use more than one Japan-based CRO as well as CROs based in Europe and/or the US for the development of one product. This means they need to conform the data created in multiple countries and facilities to the SEND requirements. In these cases, not all the commissioned CROs can necessarily use SEND or use it in a manner that meets the client's needs. Another aspect that needs to be taken into account is the analyses and tests contracted out by CROs to subcontractors.

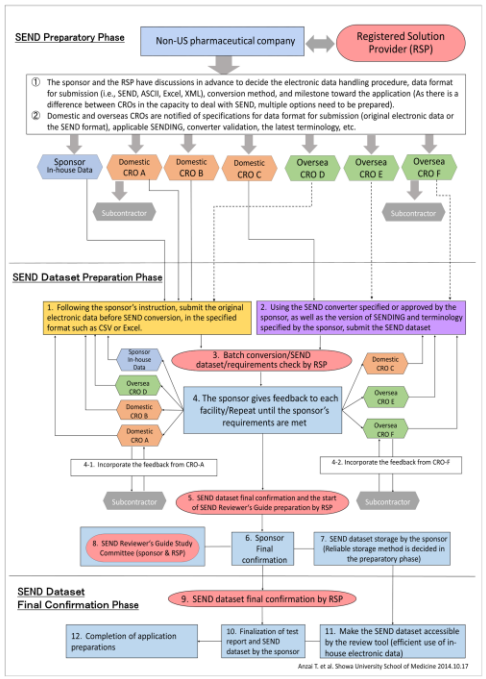


Fig. 2 SEND compliance scheme in Japan and other non-US countries

Efficient ways for Non-US pharmaceutical companies to respond to SEND

Fig. 2 illustrates non-US countries' pharmaceutical companies can overcome challenges by using CDISC Registered Solution Providers (RPSs). One of this scheme's characteristics is that the phases from SEND dataset preparation to final confirmation are described based on the use of CROs with different nationalities and capacities to use SEND.

SEND Preparatory Phase

In the SEND preparatory phase in Fig. 2 (top), the sponsor pharmaceutical company consults with an RSP to summarize the proper requirements while taking into account each CRO's capacity to comply with SEND (Fig. 2, SEND Preparatory Phase ① and ②).

SEND Dataset Preparation Phase

The SEND dataset preparation phase in Fig. 2 (middle) starts with classification of the data, which were received from CROs into two forms according to their response ability to SEND capacities (Steps 1 and 2). Steps 2 and 3, Steps 1,3 and 4, or Steps 2-4 are repeated until the sponsor's requirements are met.

SEND Dataset Final Confirmation Phase

The SEND dataset final confirmation phase in Fig. 2 (bottom) is an important phase in which the sponsor verifies the compatibility of the SEND dataset with the FDA's screening system. The RSP or sponsor submits the SEND dataset before finalization to FDA for a trail submission, in which the FDA's validation tools are used to verify that no compliance errors are found in the dataset that will interfere with processing and analyzing the electronic data (Step 9).

Storage and browsing of the SEND dataset

The dataset before finalization, which was stored in the SEND dataset final confirmation phase in Fig. 2 (Step 7), or the finalized dataset needs to always be accessible by the sponsor or RSP with the dataset review tool (Step 11).

Conclusion

The largest risk associated with SEND is that of a refusal to file from FDA. FDA clearly states that it will return the SEND dataset to the applicant if FDA's validation system identifies errors. Even if an application with a SEND dataset is returned for reexamination, CROs and vendors will not be held responsible. It is obviously the applicant pharmaceutical company that takes on the responsibility and associated risks. The largest challenge related to SEND is how pharmaceutical companies can avoid these risks in an adequate manner. Therefore, we think the compliance scheme (Fig. 2) explained in this scheme is a very practical way to deal with SEND in Japan or other non-US countries.

FDA SEND in Non-US Countries

T. Anzai[1,2], L. Kaufman[3], R. Aerni[4], F. Mura[4], M. Schuster[3], M. Wasko[3]

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Conclusion

Even if an application with a SEND dataset is returned for reexamination, CROs and vendors will not be held responsible. It is obviously the applicant pharmaceutical company that takes on the responsibility and associated risks. The largest challenge related to SEND is how pharmaceutical companies can avoid these risks in an adequate manner. Although I think the compliance scheme explained in this paper is a very practical way to deal with SEND in Japan or other non-US countries, it is only one of many ways. With increased response capacities of pharmaceutical companies in the future, more efficient ways should be devised.

Conclusion

The biggest advantage of SEND is its potential to decrease the examination time, which means, a faster time to market. Although it will not be officially introduced until December 2016, FDA is already accepting submissions with SEND and SDTM datasets, and it has expressed that these standardized formats are preferred., Many pharmaceutical companies are using this system, and this is probably because SEND and SDTM are viewed not as a regulatory requirement but as a business strategy tool. Pharmaceutical companies now need strategic thinking to avoid the risks involved in using SEND as well as to enjoy its benefits.

SEND関連団体の活動

2）FDA-PhUSEの役割

PhUSEとCDISCとFDA

２）SEND関連団体の活動

第４回 浜松毒性試験フォーラム

第一部　毒性試験における様々な動物種とその有用性・将来展望
第二部　いよいよ直線待ったなし FDA SEND

日　時：　2016 年 10 月 21 日（金）　10：30～　(受付 10：00～)
会　場：　TKP 浜松アクトタワーCC ホール A　(アクトタワー25 階)

講　師

小川久美子	国立医薬品食品衛生研究所
下井　昭仁	株式会社イナリサーチ
高木　久宜	日本エスエルシー株式会社
安藤　友紀	医薬品医療機器総合機構
星野裕紀子	医薬品医療機器総合機構
正田　俊之	日本たばこ産業株式会社
吉池　通晴	第一三共株式会社
齊藤　祥子	株式会社スリーエス・ジャパン
Reto Aerni	PDS　Pathology Data System

2）SEND関連団体の活動

第二部　いよいよ直前 待ったなし FDA SEND ～成功実例と失敗しないポイント～		
時刻	演題（仮題）	演者
12:40～	臨床試験における次世代電子審査の進展状況と展望 座長：中江 大 先生　東京農業大学	安藤友紀　先生 医薬品医療機器総合機構 PMDA
13:20～	非臨床試験における次世代電子審査の進展状況と展望 座長：安齋享征 先生 昭和大学医学部/FDA-PhUSE SDRG 委員/PDS Ltd.	星野裕紀子　先生 医薬品医療機器総合機構 PMDA
14:00	**第4回 浜松毒性試験フォーラム　で検索**	会社
14:30～	Coffee Brake	
14:40～	スポンサーと CRO による SEND 導入成功事例 座長：岩田 聖 先生　ルナパス毒性病理研究所	吉池通晴　先生 第一三共株式会社 堀川真一　先生 株式会社イナリサーチ
15:20～	SEND 対応状況とソリューションプロバイダーの役割 座長：　義澤克彦　先生 関西医科大学	齋藤祥子 先生 株式会社ｽﾘｰｴｽ･ｼﾞｬﾊﾟﾝ
15:50～	FDA が求める Study Data Standardization Plan(SDSP)とは 座長：　千葉 修一 先生　中外製薬株式会社	レト・アーニ Reto Aerni PDS Pathology Data Systems PDS：CDISC ゴール会員企業
16:30～	パネルディスカッション　～浜松言いたい放題～　（18:00 まで） 総合座長：　大石裕司　先生（大阪市立大学・関西医科大学・ルナパス毒性病理研究所）	

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Thank you!