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Letter

Establishment of the Global SEND Alliance (G-SEND) in Japan and efficient creation of electronic SEND datasets between CROs

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Abstract: The Standard for Exchange of Nonclinical Data (SEND), adopted by the US Food and Drug Administration (FDA), is a set of regulations for digitalization and standardization of nonclinical study data; thus, related organizations have begun implementing processes in support of SEND. The Global Editorial and Steering Committee (GESC), which provides oversight of the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND), has prepared the SEND Controlled Terminology (CT) for toxicologic pathology. SEND provides electronic data standards created by the Clinical Data Interchange Standards Consortium (CDISC), and CDISC also collaborates in the implementation of SEND. Furthermore, the Pharmaceutical Users Software Exchange (PhUSE), which includes members of the US FDA, has conducted various activities to promote realistic and effective methods to implement SEND. As we reported in 2015, there is a significant variation in the efficiency and quality of SEND data implementation across pharmaceutical companies and contractors (CROs) globally. To address this problem, the Global SEND Alliance (G-SEND) was established in August 2018 to facilitate the coordination and standardization of SEND datasets across CROs in Asia. This paper reports the first method for organizationally and jointly creating consistent SEND datasets between CROs using G-SEND. (DOI: 10.1293/tox.2018-0066; J Toxicol Pathol 2019; 32: 119–126)

Key words: SEND, G-SEND, CDISC, PhUSE, FDA, PMDA

Introduction

Pharmaceutical companies outside the US have reported challenges in adapting SEND procedures[1]. A SEND implementation scheme (Fig. 1) has been proposed as a result. This scheme is an effective method for pharmaceutical companies to create SEND datasets, or to control the creation process, in accord with the SEND Implementation Guide[2], the FDA's Technical Conformance Guide[3], and various additional regulations[4–6]. CROs perform more nonclinical studies than pharmaceutical companies, and as a result, they have handled SEND independent of pharmaceuti-

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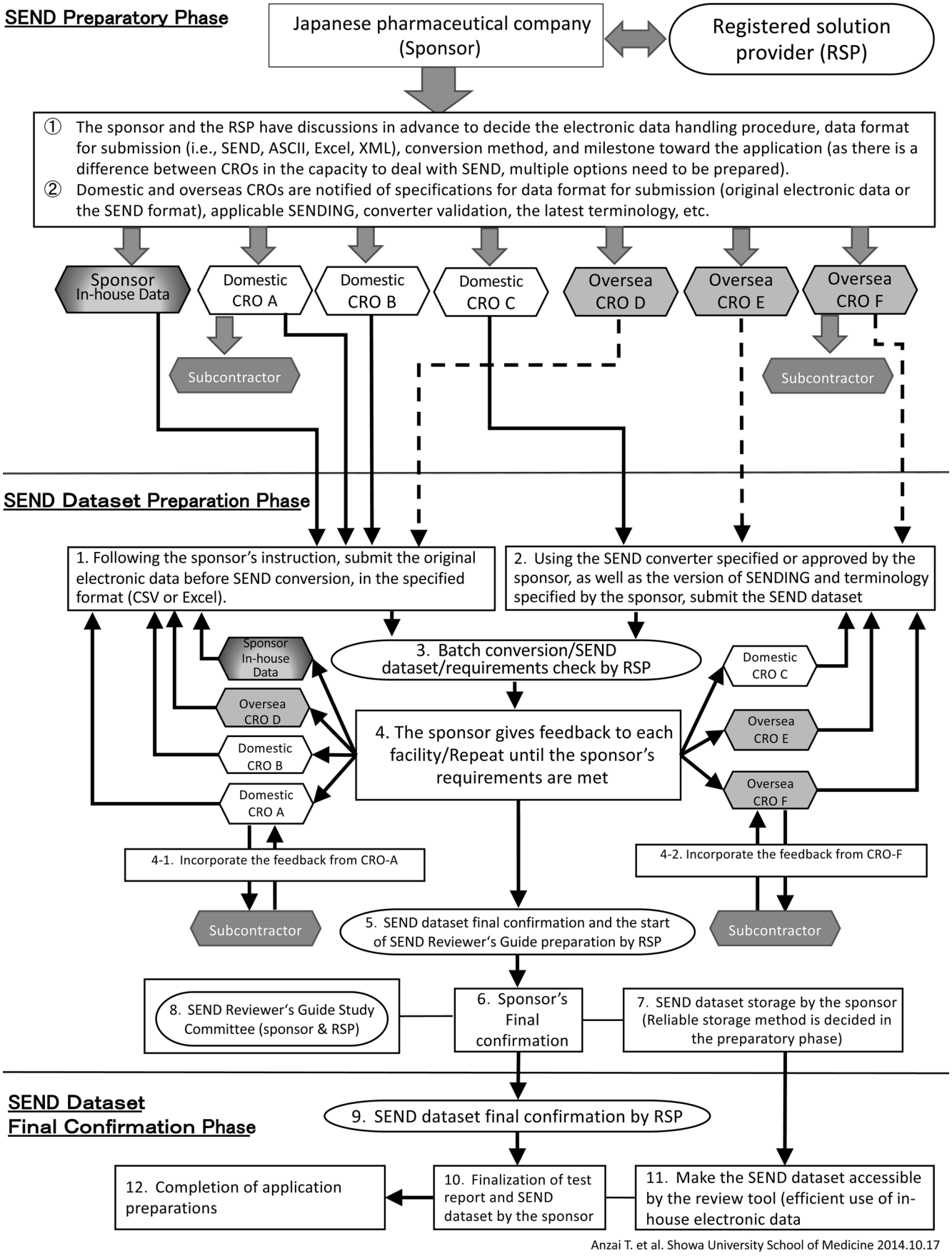

Fig. 1. SEND implementation scheme. Scheme on how non-US pharmaceutical companies can overcome challenges by using RSPs.

cal companies. Under these conditions, inconsistencies in SEND implementation methods and dataset creation have developed across CROs. To resolve this situation, G-SEND was developed as a collaborative process to standardize and implement SEND across CROs globally.

International Regulations Concerning Electronic Data

SEND is the FDA's electronic standard for nonclinical study data and is an extension of the CDISC Study Tabulation Model (SDTM)[7]. STDM is the electronic standard for submission of clinical study case list data to FDA. The objectives of SEND include a shortened period for new drug approval and post-market surveillance, both of which are objectives for SDTM. However, even if clinical and nonclinical study data are available electronically, these objectives cannot be achieved without the appropriate electronic review tools and processes on the part of regulatory authorities. In this context, the FDA is proceeding with electronic standardization of the review process for both clinical and nonclinical studies simultaneously. In Japan, PMDA has started the electronic review process[8] for data from clinical studies in advance of developing such processes for nonclinical study data.

SEND Implementation in Asia and Japan

SEND is a set of FDA regulations relating to the way nonclinical study data must be formatted electronically for new drugs. Accordingly, pharmaceutical companies and CROs in countries or regions where new drugs are being actively developed have started to address SEND implementation in various ways. Japan, Korea, China, India, Taiwan, and Singapore are the principal Asian countries involved in new drug development. As of June 2018, pharmaceutical companies and CROs addressing SEND exist only in Japan and Korea. There are a total of 21 pharmaceutical companies and CROs able to create SEND datasets in Japan and Korea: 19 in Japan and 2 in Korea (Table 1). Of the 16 Japanese pharmaceutical companies able to create SEND datasets, 13 have created SEND datasets jointly with a CDISC SEND Solution Provider (RSP). Korean pharmaceutical companies have not yet been able to achieve SEND dataset creation independently. Two Korean CROs are currently working with SEND; one utilizes an electronic SEND converter but has not yet been able to create compliant SEND datasets appropriate for submission to regulatory authorities.

Success of SEND Trial Submission by Japanese Pharmaceutical Companies, CROs and RSPs

Starting in 2014, the FDA started accepting SEND dataset trial submission. Seven tests of successful SEND trial submissions from Japan occurred in 2015–2016. Four of these tests were sponsored by pharmaceutical companies. Ina Research Inc., a CRO, created SEND datasets, and PDS Life Science, an RSP, submitted on their behalf to FDA. As to the other three tests, Japanese pharmaceutical companies and PDS Life Sciences created SEND datasets and submitted them to FDA as trial submissions. The abovementioned tests were preceded by a reference publication[1]. The process followed for these trial submissions to FDA is outlined in Fig. 1.

Trends for Managing SEND by Pharmaceutical Companies

The pharmaceutical companies that achieved success in the abovementioned FDA SEND trial submissions did not utilize an electronic data conversion system, such as a SEND converter, to create SEND datasets (Table 1). Thus, considering SEND either as an equipment investment case or as a development budget case is important and can impact expenditures significantly. Pharmaceutical companies conduct few in-house GLP tests relative to CROs. Equipment and personnel investments required for GLP tests are large and carry a certain amount of risk. Therefore, the use of RSPs or CROs utilizing a comparatively reduced product development budget has a reduced financial risk. Our research reveals that this point of view has become mainstream in Asia (Table 1).

Table 1. SEND Penetration in Asia

	Japan		Korea	
	Pharmaceutical companies (companies surveyed = 20)	CROs (CROs surveyed= 10)	Pharma/biotech companies (companies surveyed = 7)	CROs (CROs surveyed = 3)
Knowledge about SEND (SEND representatives are allocated)	18 of 20	7 of 10	1 of 7	2 of 3
Experience with SEND data creation	16 of 20 (incl. 13 collaborating with RSP)	3 of 10	1 of 7 (created by RSP)	1 of 3
Experience with FDA trial submission	3 of 20	1 of 10	0	0
Total number of FDA trial submissions	7 studies	4 studies	0	0
Introduction of SEND converter or module	3 of 20	4 of 10	0	1 of 3
Use of solution provider	14 of 20	2 of 10	2 of 7	0

June 1, 2018. Method: direct interview and published data research. Period: from October 2017 to June 2018

Technical Challenges for CROs Relating to SEND

SEND datasets are created by CROs worldwide in conformity with the requirements of the SEND Implementation Guide (IG) and the FDA. These datasets are expected to be consistent across different CROs. However, important differences and inconsistencies in the implementation of SEND currently exist across CROs due to various factors including differences in the interpretation of regulations, work processes, and interpretation of findings. These differences and inconsistencies also apply to the nonclinical Study Data Reviewer's Guide (nSDRG). The nSDRG is an important briefing document for FDA reviewers that is submitted together with SEND datasets for each nonclinical study. For example, the number of pages for nSDRGs for toxicology studies having the same design can differ by a factor of three across CROs even though they all used the same PhUSE-generated nSDRG template[9]. CROs cannot determine by themselves how much information needs to be included in an nSDRG. In many cases, this can result in excessive paperwork for the FDA. This runs counter to the original purpose of nSDRG. Originally, the nSDRG was intended to be a guide read by FDA examiners and was meant to contain concise information. Furthermore, Watanabe and Anzai[10] suggested in 2017 that histopathological knowledge is necessary to create SEND datasets for pathology findings and to accurately apply the required pathology controlled terminology. The involvement of pathologists in each institution is regarded as important. The number of pathologists who are acquainted with SEND remains limited, and this is not just restricted to CROs.

Financial Challenges Related to SEND for CROs

Although SEND dataset creation is performed by CROs, it does not represent their primary focus. Therefore, investment in equipment, including a SEND converter or a new Laboratory Information Management System (LIMS) to create SEND data, represents a significant financial burden. Other challenges include keeping abreast of regulations and implementation best practices, use of up-to-date CT, and availability of trained personnel. Pharmaceutical companies serving as a sponsor require high-quality SEND datasets that are complete, compliant, and ready for submission. SEND dataset creation represents contract work for CROs, with sponsors paying appropriate fees to CROs, leading to an increase in CRO income. On the other hand, a large initial investment and an increase in fixed costs carry a financial risk for many CROs.

Organizational Handling of SEND and the Inauguration of G-SEND

To address SEND challenges faced by CROs, the G-SEND consortium was established along with a workflow model for consistent and compliant SEND dataset creation. There are 20 organizations participating in G-SEND as of December 2018 (Table 2), with two of these organizations serving in a leadership capacity.

The operation of G-SEND is based on its articles of incorporation, with the objective being to consolidate and standardize the SEND process. Members of G-SEND and SEND Center CROs generate individual contracts for data conversion. However, G-SEND is a non-profit voluntary organization and has no relation with individual contracts.

Function of G-SEND

To convert study data to SEND, an individual G-SEND member places a request to the central SEND Center CRO, a subcontractor, as shown in Fig. 2. The SEND Center CRO converts data using TranSEND™, a SEND data converter, and delivers electronic SEND datasets as a draft, or a semi-finished product, to the contractor. The CRO (contractor) conducts quality control and provides finalized SEND datasets to the sponsor. The workload covered by SEND Center CROs varies depending on their capacity; some deliver nearly completed, submission-ready SEND datasets, while others deliver electronically converted data only. The SEND Center CRO requests an RSP to verify and review SEND datasets. Using this process, members of G-SEND can provide more accurate and consistent SEND electronic datasets to customers. In cases where a SEND Center CRO takes on a heavy workload, the CRO can request part of the work be converted using TranSEND™.

Table 2. G-SEND Members

President	Professor, Dr. Dai Nakae, Tokyo University of Agriculture, Setagaya, Tokyo, Japan
Vice President	Dr. Hijiri Iwata, LunaPath Laboratory of Toxicologic Pathology, Hamamatsu, Shizuoka, Japan
Auditor	Dr. Takayuki Anzai, Showa University School of Medicine, Shinagawa, Tokyo, Japan
Auditor	Dr. Hisayoshi Takagi, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu, Shizuoka, Japan

Member company/organization	Number of members	Country
GLP CRO	15	Japan (12) Korea (2) Singapore (1)
SEND Service Provider	3	Japan (2) Korea (1)
IT Vender	1	Switzerland (1)
CDISC Registered Solution Provider	1	USA (1)
Total	20	

As of December 6, 2018.

G-SEND has three types of TranSEND™. A bioanalysis CRO shown in Fig. 3 converts TK/PK data into SEND datasets using TranSEND™. Alternatively, some bioanalysis CROs request that the SEND Center CROs create the TK/PK SEND datasets. In this case, the SEND Center CRO needs to provide data formatting instructions to the bioanalysis CRO before TK/PK data are generated. These processes are as shown in the SEND Preparatory Phase of Fig. 1.

Financial Efficiencies of G-SEND

Utilization of G-SEND provides financial efficiency for CROs. The principal reason for this is that G-SEND is a business model that needs minimal investment in equipment for CROs. Additionally, G-SEND members can obtain updated SEND compliance and implementation information from RSPs. G-SEND members also receive feedback concerning common challenges such as work efficiency and G-SEND solutions, which reduces in-house SEND-related work.

Flexibility of G-SEND Members

G-SEND imposes minimal restrictions on member activity. Members can introduce TranSEND™ and handle operations collectively without having to resort to SEND Center CROs. Members are also free to introduce SEND solutions other than G-SEND. These options can be implemented when the SEND data volume increases, e.g., when the cost of the volume of work outsourced matches the equipment investment. Even if sponsors are capable of creating SEND data, participating in G-SEND as a member provides significant advantages as outlined in this review. It is also important from the perspective of efficiency that CROs work cooperatively across study sites to acquire updated SEND information. For pharmaceutical companies that use a number of CROs, consistency and uniformity of SEND data provided by CROs and G-SEND members brings about substantive benefits.

Effect of G-SEND on Pharmaceutical Companies

The SEND Center CRO exists as a SEND data conversion base commonly used by G-SEND members. Thirty-

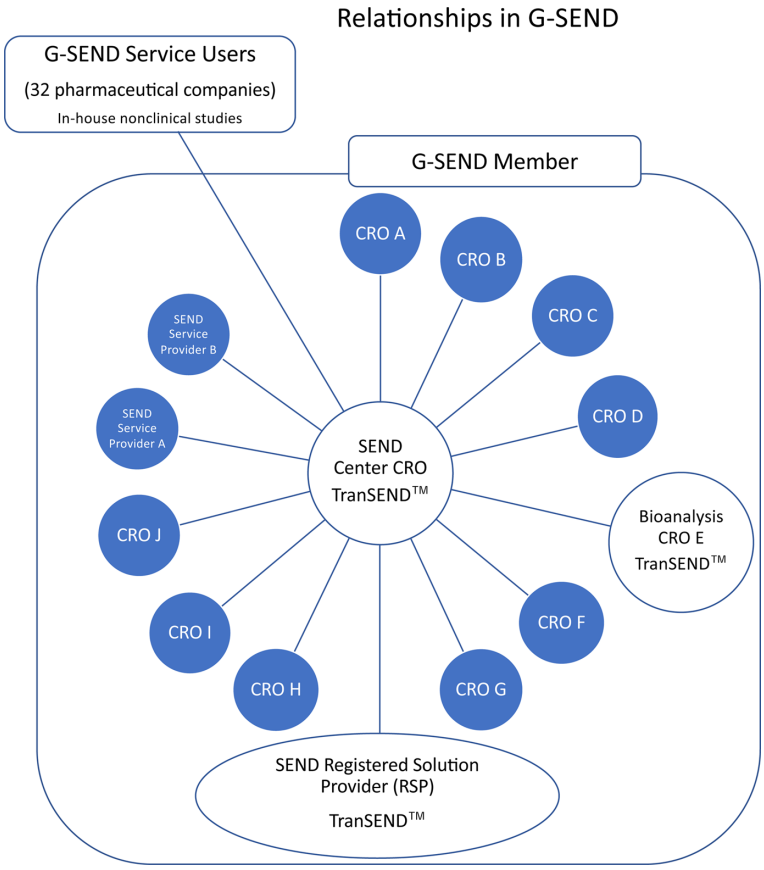

Fig. 2. Relationships in G-SEND. In G-SEND, the SEND Center CRO serves as the SEND data conversion base commonly used by G-SEND members. RSP support to SEND data-based applications to the FDA is available. A SEND Center CRO is entrusted with the creation of SEND data for in-house studies of a pharmaceutical manufacturer.

two pharmaceutical companies who are not part of G-SEND have utilized the SEND Center CRO (Fig. 2). These pharmaceutical companies have made contracts for the creation of SEND datasets for in-house studies. The SEND service employed by many pharmaceutical companies is the same as that provided by CROs and utilized by G-SEND members. The outsourcing of testing to CROs participating in G-SEND provides pharmaceutical companies with SEND datasets. If several CROs belonging to G-SEND are employed, SEND datasets are standardized and coordinated across the CROs of G-SEND, resulting in critical uniformity and consistency. Using the example shown in Fig. 3, if Sponsor A is a G-SEND service user, consistency of SEND datasets for data generated in-house and data generated by outside service providers can be maintained. Assuming that Sponsor A uses a non-G-SEND CRO, they can request an RSP, which provides the common SEND service to create SEND datasets, enabling SEND standardization across CROs.

Cautions to be Considered for G-SEND

G-SEND is a voluntary organization in which a number of peers participate. G-SEND needs to comply with relevant laws, including Japan's Anti-Monopoly Act and the Unfair Competition Prevention Act. As a reference for G-SEND operations, articles concerning the management of Japanese REACH Consortia[11–13] were used. REACH stands for Registration, Evaluation, Authorization and Restriction of Chemicals. REACH was established initially in the EU as a regulation governing chemical substances. REACH Consortia are organizations established to address this regulation in Japan. They include various types of consortia: three consisting of leading chemicals manufacturers in Japan and two comprising members of the Petroleum Association of Japan. Similar to REACH, SEND is currently governed by overseas regulations (FDA). G-SEND is the organization established to address these regulations in non-US countries. Therefore, the REACH consortium is an extremely useful model for G-SEND. Moreover, the G-SEND leadership includes a representative experienced in managing other REACH consortia[11–13], which will facilitate SEND implementation in Japan and other countries in Asia.

PhUSE ISEND

PhUSE is an international nonprofit organization composed of specialists in data management, biostatistics and electronic clinical and nonclinical data in American and Eu-

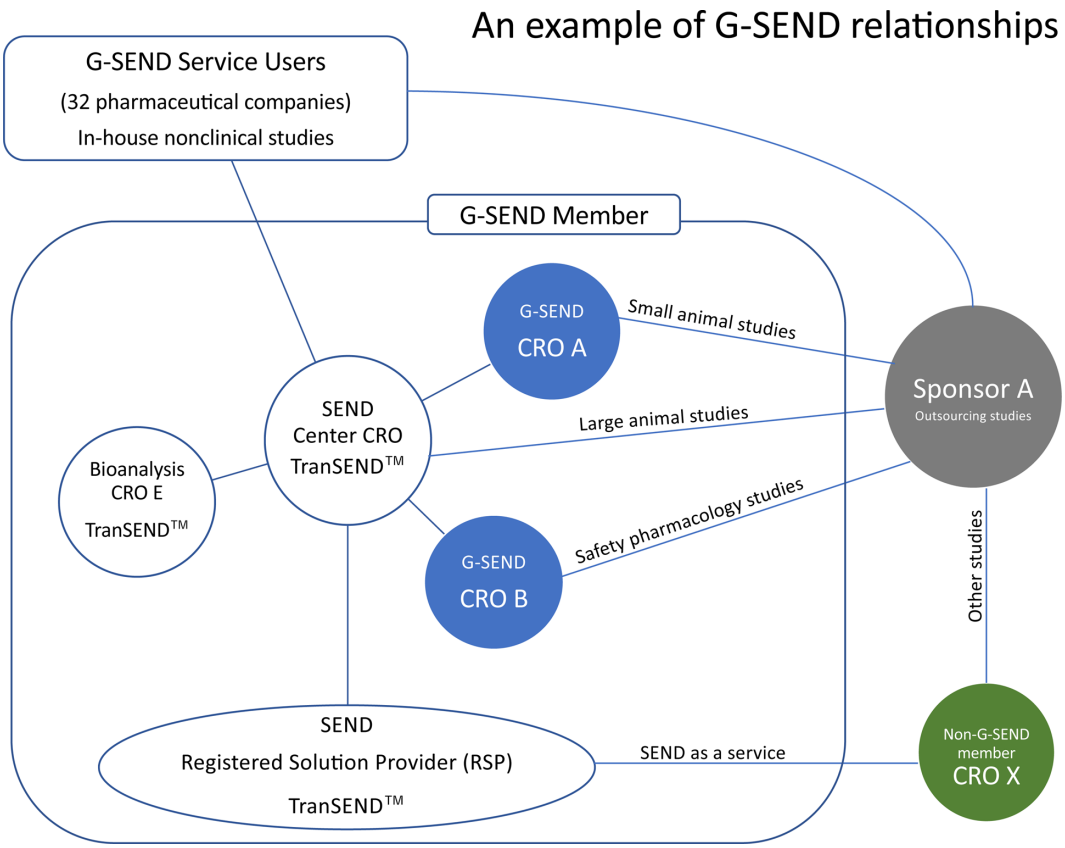

Fig. 3. An example of G-SEND relationships. Sponsor A commissions small animal studies to CRO A, large animal studies to the SEND Center CRO, safety pharmacology studies to CRO B, and other studies to CRO X, which is not a member of G-SEND. Sponsor A requests an RSP, which provides the common SEND service to create SEND data via CRP X, enabling standardization of all test data. If Sponsor A is a G-SEND service user, the consistency of SEND data between in-house studies and outside tests can be maintained.

ropean pharmaceutical and IT companies. PhUSE engages cooperatively with the FDA for both SEND and SDTM. The PhUSE Interorganizational SEND team (ISEND)[14] investigated how pharmaceutical companies and CROs can efficiently cooperate with each other to address SEND. ISEND described three different scenarios: In the first scenario, CROs conduct testing and create SEND datasets. In the second scenario, one CRO conducts the in-life portion of a study and sends plasma samples to a second CRO or to the sponsor, who generate bioanalytical and PK/TK data. A principal CRO then creates the SEND data. The third scenario involves a CRO conducting tests, and an outsourcer (or sponsor) creates SEND datasets. The second scenario is similar to G-SEND in that a number of different CROs are involved. However, ISEND assumes that SEND datasets are jointly created only for tests conducted between CROs, while G-SEND targets all tests. Regardless of joint implementation, its nature is based on a consortium.

Summary-Future Development of G-SEND and a Role for Pathologists

G-SEND is the world's largest utilizer of the common SEND solution. G-SEND is significantly affected by achievements of the SEND Center CRO, which has converted test data from 32 pharmaceutical companies into SEND datasets (Fig. 2 and 3). The worldwide establishment of new SEND Center CROs is considered to be desirable for pharmaceutical companies.

Hereafter, G-SEND aims to provide uniform and high-quality SEND datasets through efficient SEND dataset creation processes between CROs and to standardize the QC method. To achieve these aims, there are quite a few tasks required for pathologists, including the uniform use of controlled terminology. Although pathologists do not need to become specialists in data management, their active involvement in SEND is expected.

Disclosure of Potential Conflicts of Interest: The objectives of the Global SEND (G-SEND) Alliance and/or the article mentioned above are for members to work together to study compliant and more efficient data submission processes for Japanese and international authorities that promote or require the standardization of electronic data for the safety evaluation of pharmaceutical products and other chemical substances. None of the G-SEND members, corresponding authors and co-authors of this article receive any financial support for this article. The purpose of the article and the Alliance is not to recommend any specific products or services. Rather, the Alliance aims to foster cooperation across business communities, academic societies, government, and other relevant organizations in Japan and abroad to make a practical contribution to the solution of existing drug development challenges and advance the development of safe drugs.

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