

**P-186**

# **Issues of SEND reliability extracted by questionnaire**

## **アンケートにより抽出された、SENDの信頼性保証に対する課題**

○Daisuke SASAKI<sup>1,2</sup>, Ryo OKUMURA<sup>1,3</sup>, Akiyoshi KURIHARA<sup>1,4</sup>, Tomokazu SHIGEYAMA<sup>1,5</sup>, Terukazu KITAHARA<sup>1,6</sup>

<sup>1</sup> Japan Society of Quality Assurance, <sup>2</sup> Astellas Pharma Inc, <sup>3</sup> Kissei Pharmaceutical Co., Ltd.,

<sup>4</sup> Taisho Pharmaceutical Co., Ltd., <sup>5</sup> Shin Nippon Biomedical Laboratories, Ltd., <sup>6</sup> Instem Japan K.K.

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# **The Japanese Society of Toxicology**

## **COI Disclosure**

The authors have no conflicts of interest directly relevant to the content of this Poster.

Presenting author: Daisuke Sasaki

# Abstract

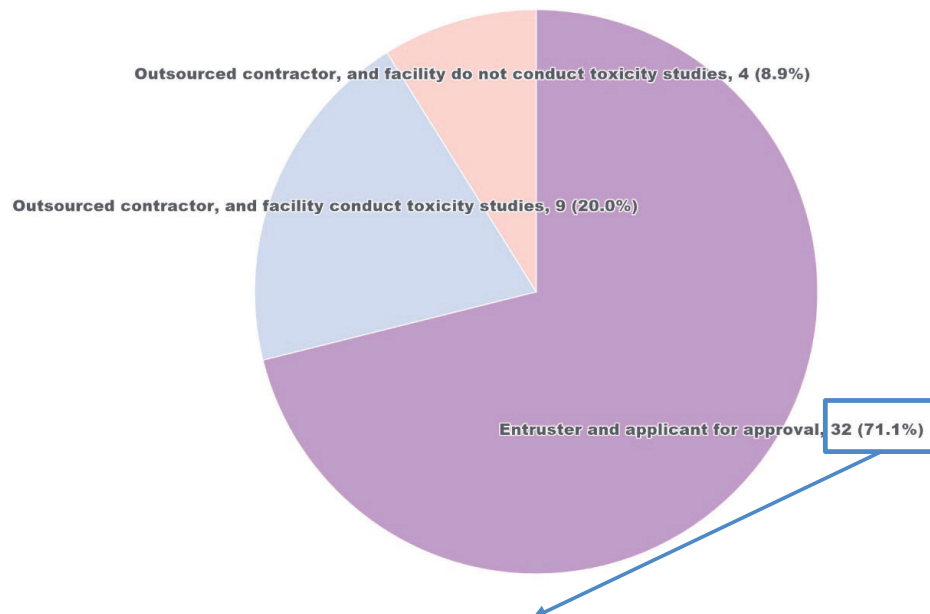
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- For NDA, BLA, and IND submission to FDA in the United States, SEND data is required for nonclinical safety studies of general toxicity, carcinogenicity, and safety pharmacology (respiratory and cardiovascular) studies. In addition, the requirements for the SEND are still continuously changing. Under the circumstances, it is necessary to submit SEND data to the FDA without any defects in order to promptly provide patients with new drugs.
- In order to ensure the reliability of SEND data, Japan Society of Quality Assurance (JSQA) analyzed the flow of SEND data creation, identified the risks in ensuring reliability, and proposed the points to consider and countermeasures for preparing SEND data based on the ISO9001 by International Organization for Standardization.
- In the current presentation, we would like to discuss the points that should be particularly focused on to ensure the reliability for the SEND data based on the results of the questionnaire in each member company of JSQA GLP Division.

# Sample size for questionnaire

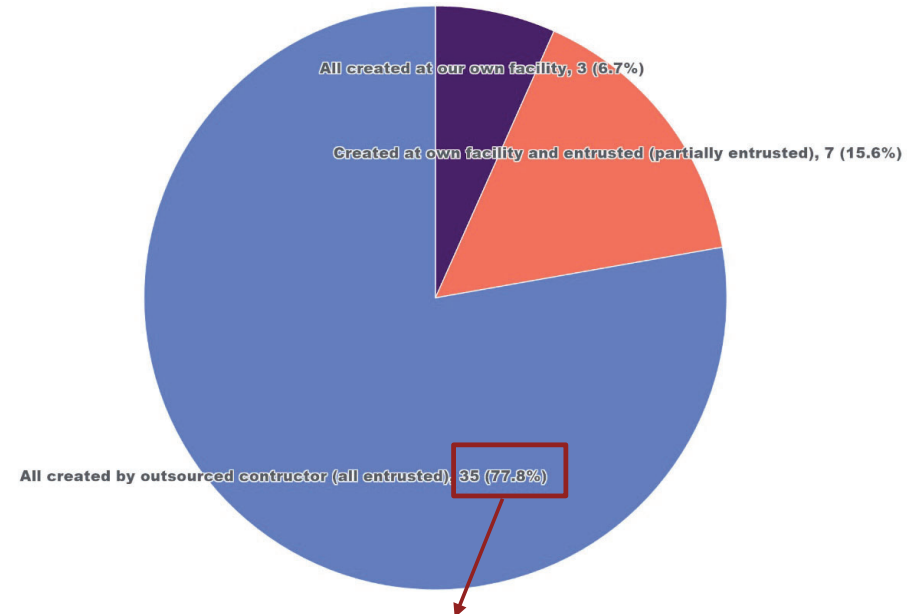
- Total: 45 member companies in JSQA GLP Division
- Details

Position in creating SEND data packages



32/45 companies (71.1% of all members answered) were submitter and entruster of SEND.

SEND data creation status of participating member companies



35/45 companies (77.8% of all members answered) entrust all of SEND data package creation.

# The contents of questionnaire

1. Are there procedures to refer to for creating SEND data packages?
2. How does your facility manage the storage specifications for creation of SEND data packages?
3. How does your facility do about the SEND data creation where there is no convention in Implementation Guide and Controlled Terminology?
4. Does your facility manage the version of SEND data packages to be submitted to the authorities?
5. Where is the storage management department in your facility for SEND data packages to be submitted to the authorities?
6. Are there procedures for storing and managing SEND data packages to be submitted to the authorities?
7. Are there any education and/or training systems for personnel contributed to SEND data creation?
8. Does your facility assure quality of SEND data packages by QC, QA, third party review, etc.?
9. Who assure the quality of SEND data packages by QC, QA, and third-party reviews, etc.?
10. What level is QA contributed to assuring the reliability of SEND data packages to?

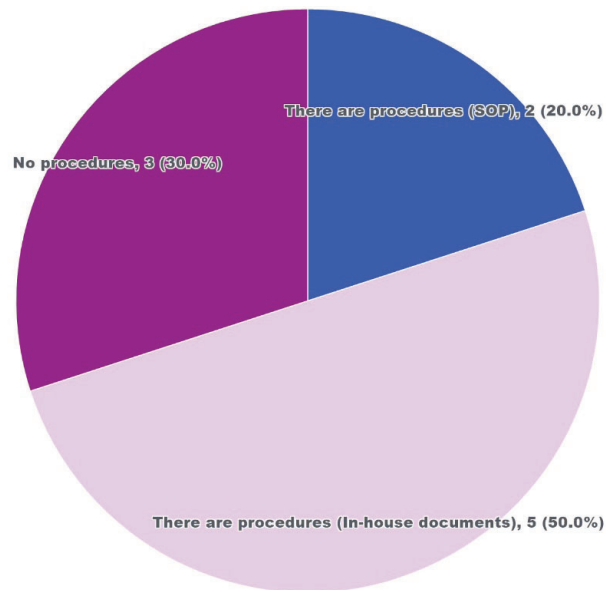
11. Are there any procedures for QC?
12. What are the audit items in SEND data packages?
13. What are the items for review in SEND data packages?
14. How long does it take usually for QC or QA?
15. Does your facility create a document stating the quality assurance for SEND data packages?
16. How many people in your facility can conduct QC or QA of SEND data packages?
17. Are there any education programs for newly assigned personnel for QC or QA of SEND data packages?
18. Who confirms the SEND data packages received from the outsourced contractor?
19. What are the confirmation items in the SEND data packages?
20. Have your facility ever found any problems that need to be corrected in the created SEND data packages?
21. If possible, please give a concrete example of the problem.
22. Please feel free to describe any possible issues regarding assuring reliability for the SEND data packages.
23. Please feel free to write any questionnaire your facility would like to ask about the assuring reliability for the SEND data packages.

## Notice:

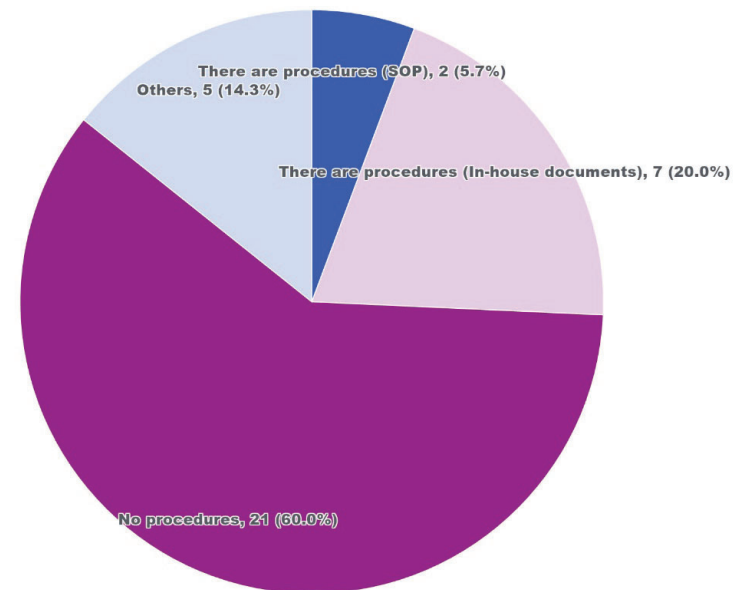
"No Answer" and "Not applicable" were subtracted the results of each questionnaire.  
Multiple answer is allowed in some questions.

# Are there procedures to refer to for creating SEND data packages?

As facilities create SEND data packages at their own facility



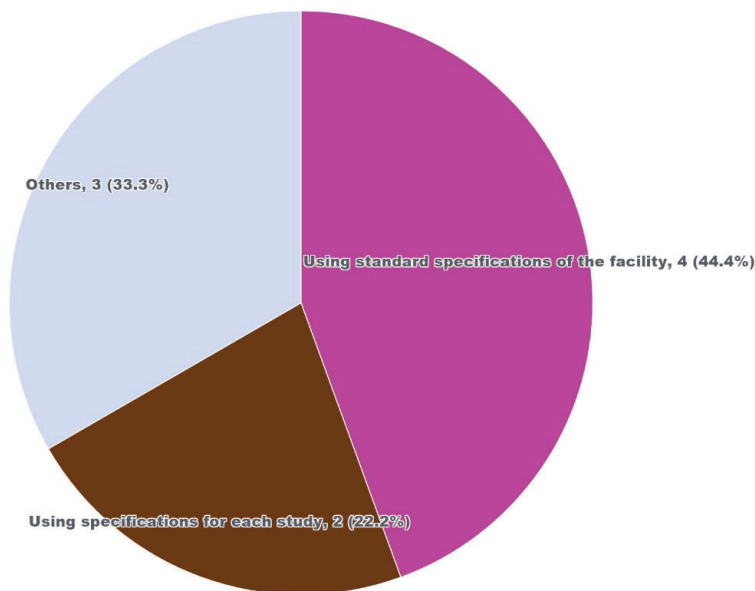
As facilities entrust creating SEND data packages



**Facilities that create SEND data packages tend to have a higher rate of possession of SOP or procedures.**

## How does your facility manage the storage specifications for creation of SEND data packages?

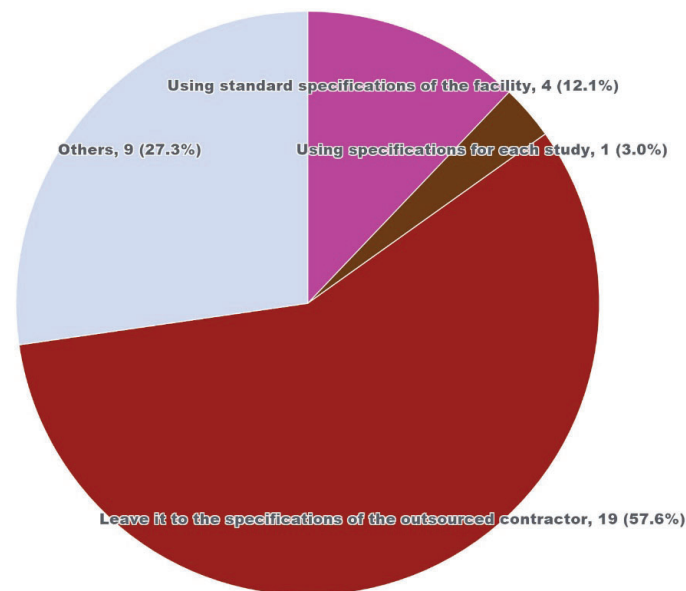
As facilities create SEND data packages at their own facility



### Comments in "Others" :

- There are approximate standard specifications, but we will watch the latest information and update the specifications as needed.

As facilities entrust creating SEND data packages



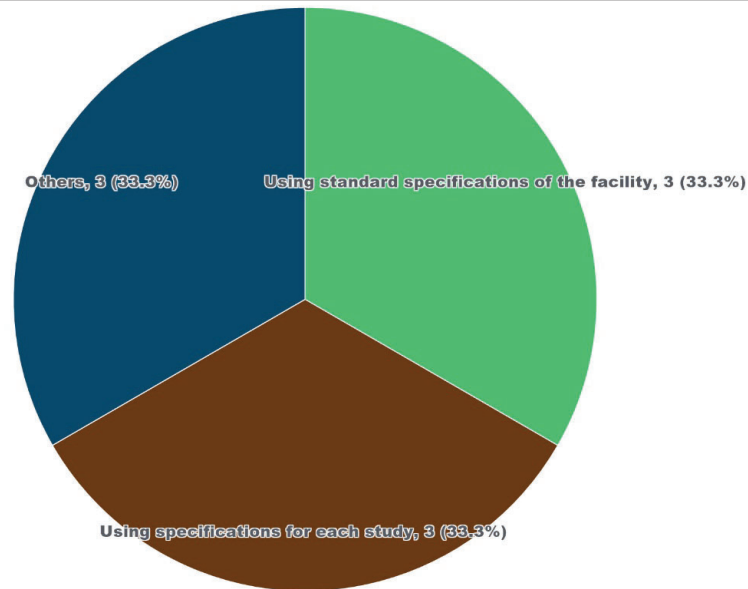
### Comments in "Others" :

- We are creating standard specifications between the outsourced contractor and us, but we will update them as needed based on the latest information.
- We set the standard specifications of our facility, but the parts that cannot be handled due to the specifications of the outsourced contractor are rely on the outsourced contractor's.
- Specifications for each study are specified based on the standard specifications of the outsourced contractor.

**In most cases, the entruster leaves the storage specifications policy to the outsourced contractor.**

## How does your facility do about the SEND data creation where there is no convention in Implementation Guide and Controlled Terminology?

As facilities create SEND data packages at their own facility

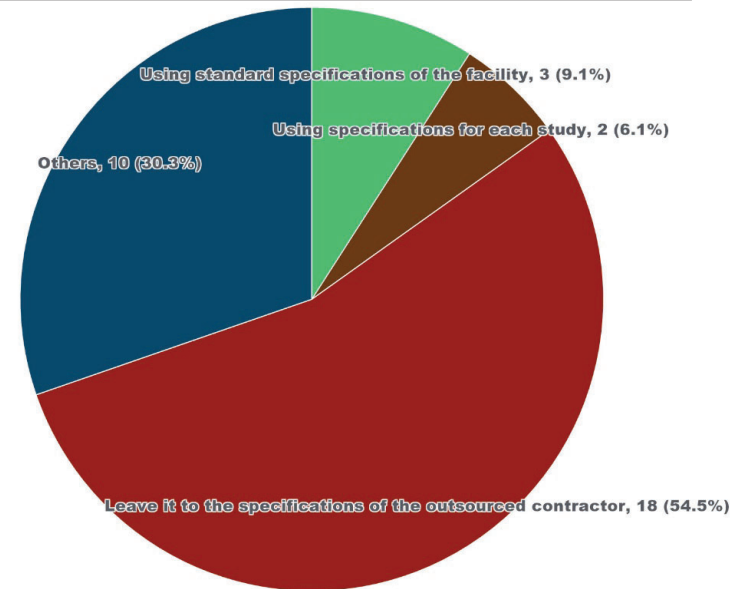


### Comments in "Others" :

- There are approximate standard specifications, but we will watch the latest information and update the specifications as needed.

**The entruster side is often leave it to outsourced contractor side.**

As facilities entrust creating SEND data packages



### Comments in "Others" :

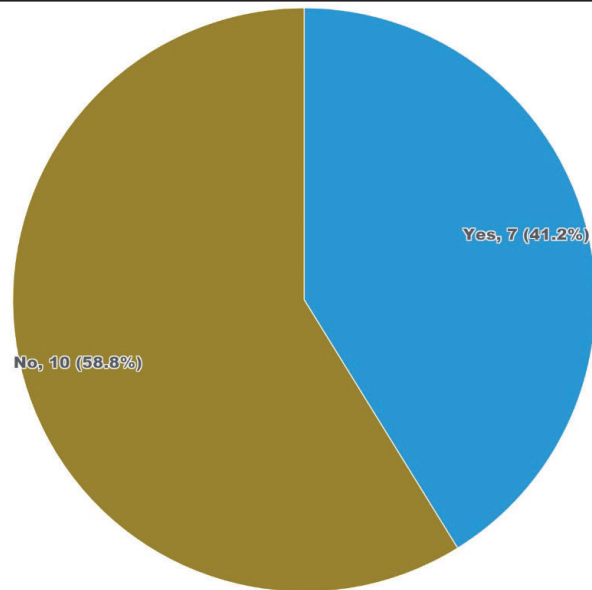
- There are approximate standard specifications, but we will watch the latest information and update the specifications as needed.
- We leave it to the specifications of the outsourced contractor, but we will discuss it for each study.
- Decide in consultation with the outsourced contractor.
- We refer standard specifications. If there is no specification in the standard specifications, it is specified in the specifications for each study.



## Manage the version of SEND data packages and the department of SEND storage

Does your facility manage the version of SEND data packages to be submitted to the authorities?

Remaining facilities after deducting "Not applicable" or "No answer"



It did not depend on the position of SEND creation.

Among the answers yes or no, the number of yes was ...

- 3 out of 7 facilities who creates SEND data packages.
- 4 out of 10 facilities who does not create SEND data packages.

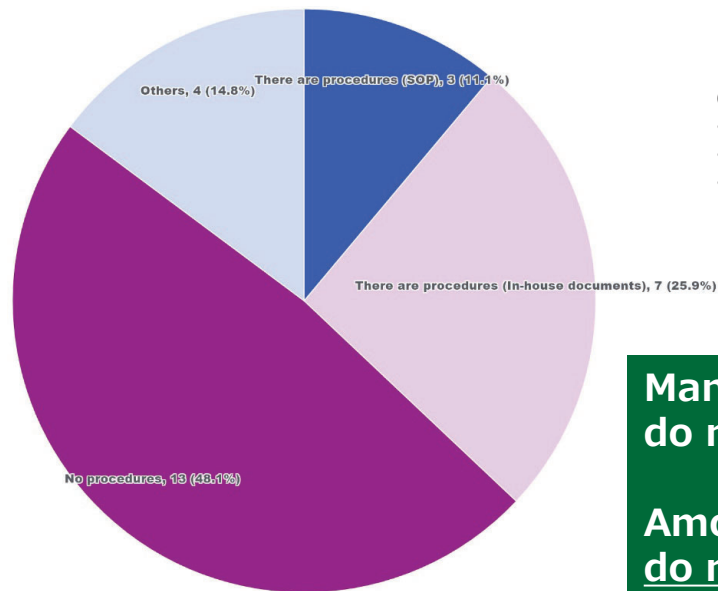
Where is the storage management department in your facility for SEND data packages to be submitted to the authorities?

- Safety Research Division
- Safety Metabolism Laboratory
- Pharmaceutical affairs department
- Department in charge of application
- Department in charge of study entrust
- Information system department
- Department in charge of SEND
- Overseas Subsidiary Pharmaceutical Affairs Division
- Outsourced contractor

**Most cases: Safety research or application division.**

# Are there procedures for storing and managing SEND data packages to be submitted to the authorities?

Remaining facilities after deducting "Not applicable" or "No answer"



## Comments in "Others" :

- Follow paper materials.
- There is no SEND procedures. Treated the same as other electronic documents.
- Follow outsourced contractors.

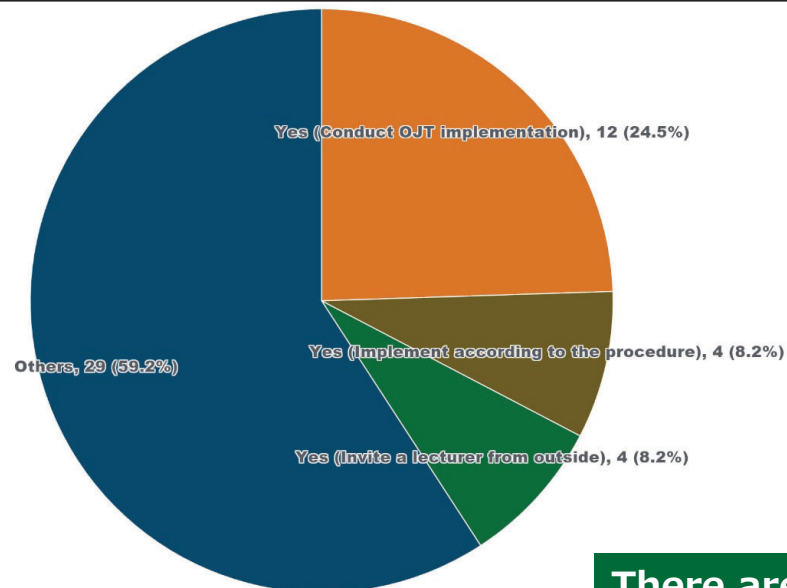
Many facilities do not have procedures, but the entruster (they do not create SEND) side is a little remarkable.

Among answering with or without Procedure, the number who do not have procedure was ...

- 2 out of 6 entrusters and/or outsourced contractors who creates SEND data packages.
- 11 out of 17 entrusters who do not create SEND data packages.

# Are there any education and/or training systems for personnel contributed to SEND data creation?

Remaining facilities after deducting "Not applicable" or "No answer"



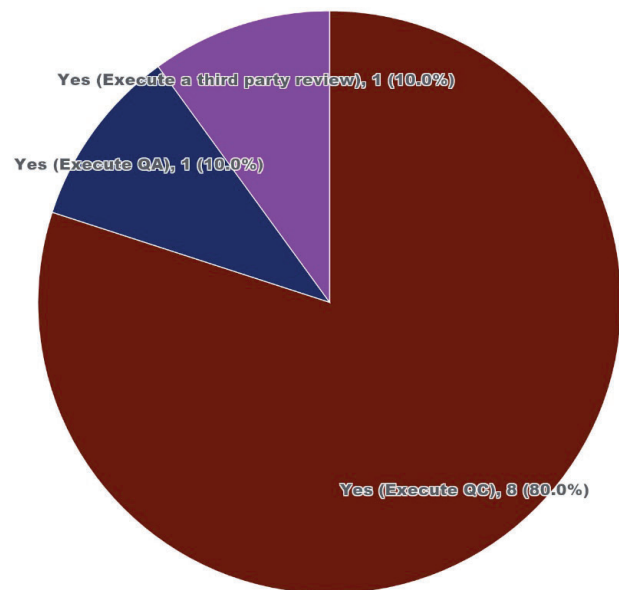
## Comments in "Others" :

- Self-help efforts of the person in charge
- Technology transfer from entrusters or training at an educational institution designated by entrusters.
- There is no regulation of the staff involved.
- It is in the stage of considering introduction.
- Information sharing through in-house training.
- Creating educational materials.
- There are no educational regulations. We provide education as appropriate.
- None (multiple answers)

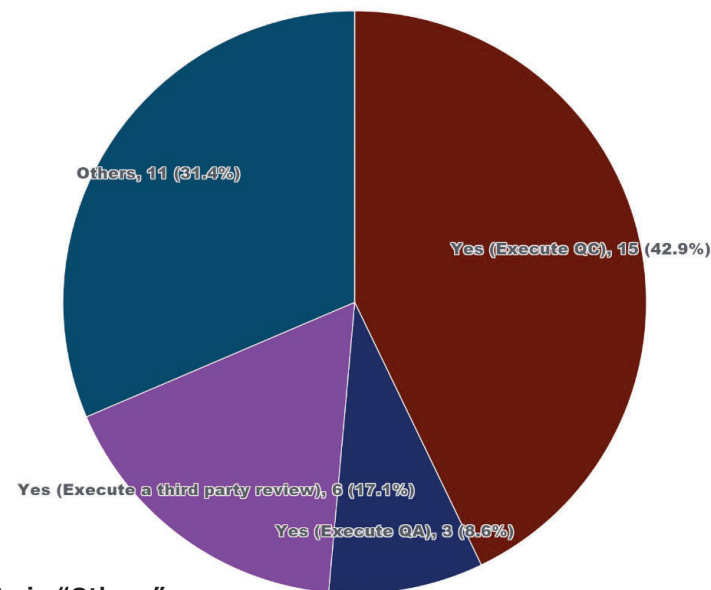
**There are some kind of educational systems at the facilities who creates SEND data packages (8 out of 10 facilities).**

# Does your facility assure quality of SEND data packages by QC, QA, third party review, etc.?

As facilities create SEND data packages at their own facility



As facilities entrust creating SEND data packages



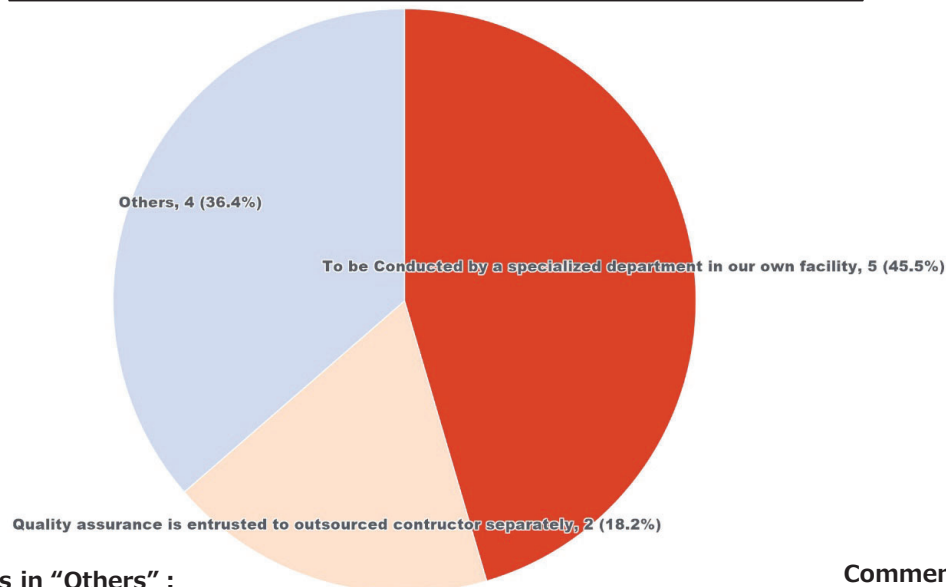
## Comments in "Others" :

- We do not perform QC in detail, but we carry out rough data specification confirmation.
- I have no experience in implementing it, but I plan to implement some kind of quality assurance, and I am thinking of entrusting it.
- I don't know because I only act as an intermediary between the CRO and the partner.

**QC is carried out at most facilities create SEND data packages.**

# Who assure the quality of SEND data packages by QC, QA, and third-party reviews, etc.?

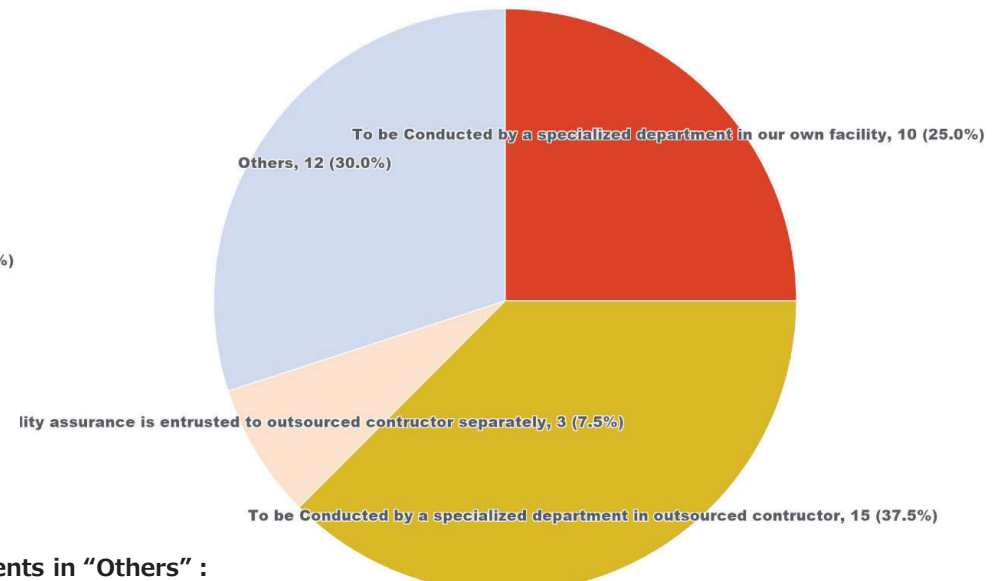
As facilities create SEND data packages at their own facility



## Comments in "Others" :

- QC is conducted by the person in charge in own facility (not a professional staff, but a person who also serves as another business).
- A QC manager is assigned and implemented in the SEND creating department.
- Self-check by the person in charge.

As facilities entrust creating SEND data packages



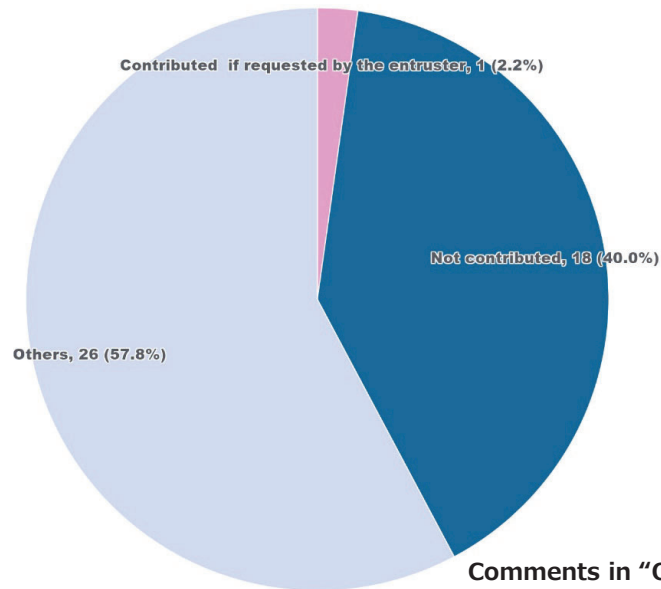
## Comments in "Others" :

- Entrust if it is not possible to perform it in-house.
- The QC of the SEND datasets created by outsourced contractor is carried out by the safety department.
- By an entrust officer.
- Safety group member of own facility.

**QC, QA or third-party review was conducted internally in own facilities who create SEND data packages. It is not conducted and left it to outsourced contractor in the facilities not create SEND data packages.**

## What level is QA contributed to assuring the reliability of SEND data packages to?

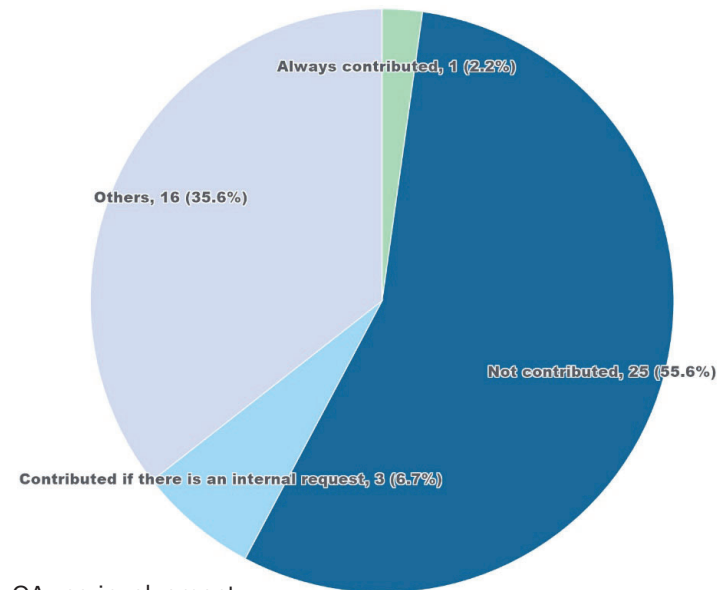
As facilities create SEND data packages at their own facility



### Comments in "Others" :

- If the question means our company's QA, no involvement.
- If it means the QA of the outsourced contractors, it depends on the policy of the other facility.
- Investigate outsourced contractors when selecting facilities.

As facilities entrust creating SEND data packages

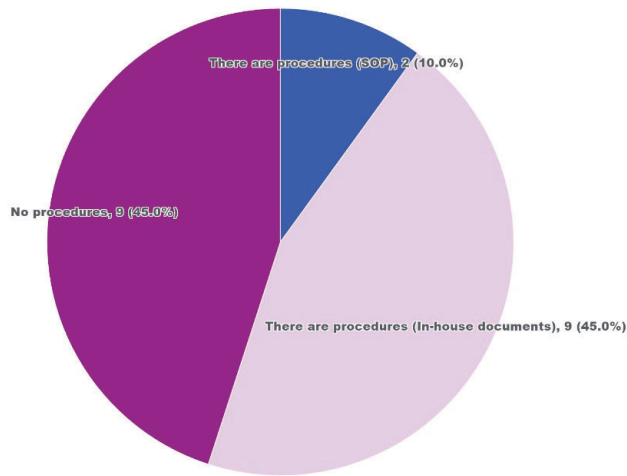


**There are few facilities where QA is contributed to SEND.**

# Regarding QC, QA and third-party review

## Are there any procedures for QC?

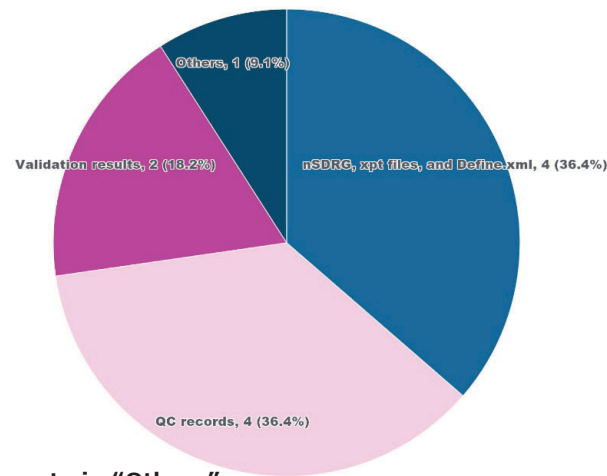
Facilities who conduct QC



Approximately half have procedures.

## What are the audit items in SEND data packages?

Facilities who conduct QA



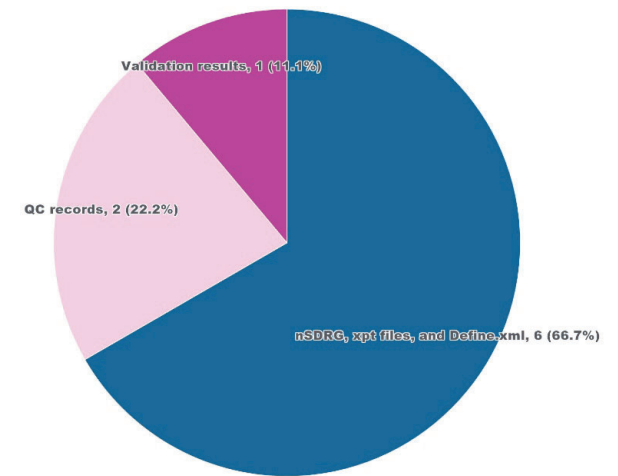
### Comments in "Others" :

- We must audit nSDRG, and others are on a case-by-case basis.

When QA is contributed to SEND, QC records are of particular interest.

## What are the items for review in SEND data packages?

Facilities who answered they conduct third-party reviews

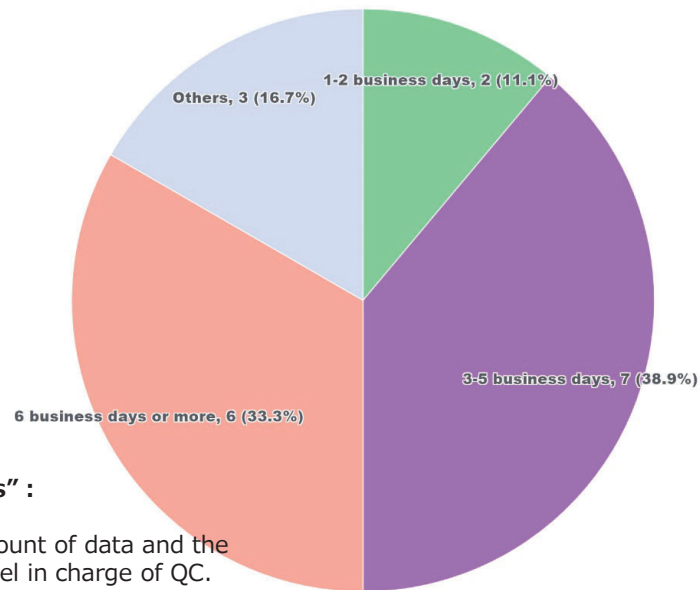


Basically, the whole content tends to be confirmed as a SEND data packages.

# Regarding QC and QA

How long does it take usually for QC or QA?

Facilities who conduct QC or QA



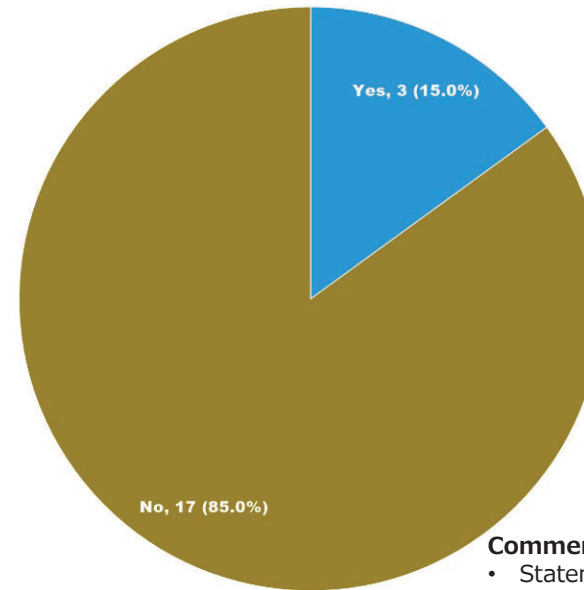
**Comments in "Others" :**

- About 2 weeks
- Depends on the amount of data and the schedule of personnel in charge of QC.
- We adjust at the time of contract with the outsourced contractor.

**Most facilities' answers were 3-5 business days or more.**

Does your facility create a document stating the quality assurance for SEND data packages?

Facilities who conduct QC or QA



**Comments in "Other" :**

- Statements are prepared at the request of the entruster.

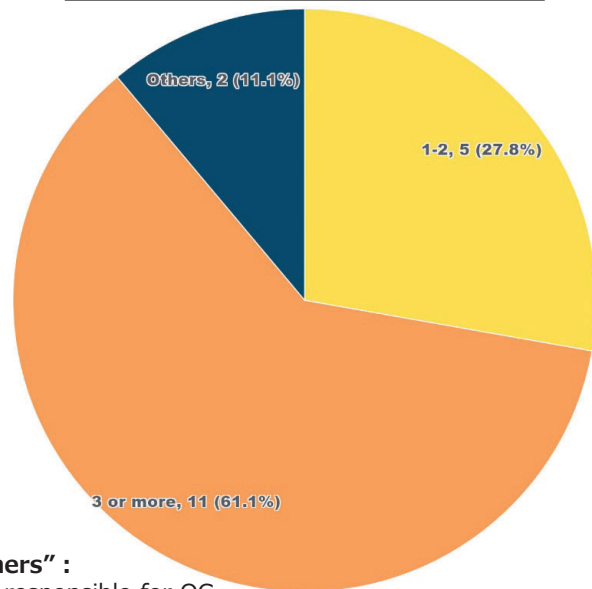
**Most facilities do not prepare statements.**



## Regarding QC and QA (Continued)

How many people in your facility can conduct QC or QA of SEND data packages?

Facilities who conduct QC or QA



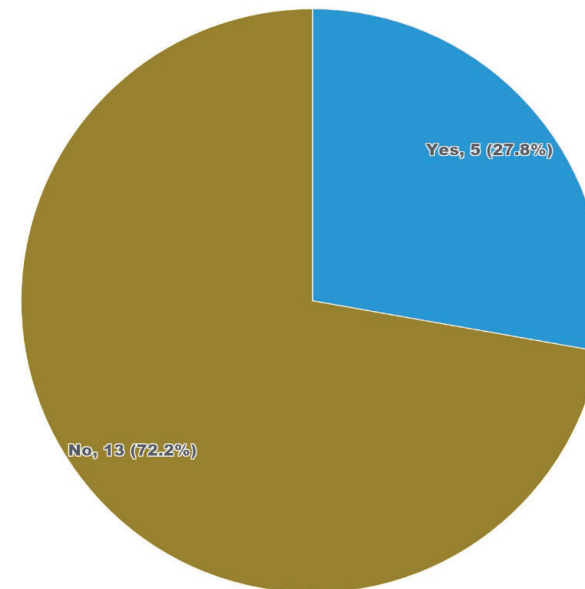
Comments in "Others" :

- Study monitor is responsible for QC.

**Facilities that carry out QA or QC tend to have multiple persons (3 or more) in charge.**

Are there any education programs for newly assigned personnel for QC or QA of SEND data packages?

Facilities who conduct QC or QA

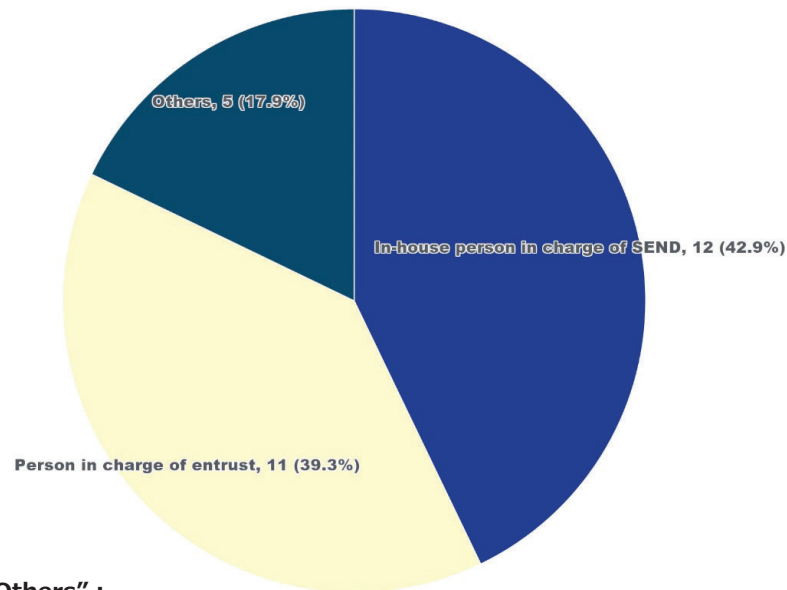


**Few facilities have education system.**

# Regarding facilities who entrust creating SEND

## Who confirms the SEND data packages received from the outsourced contractor?

As facilities entrust creating SEND data packages

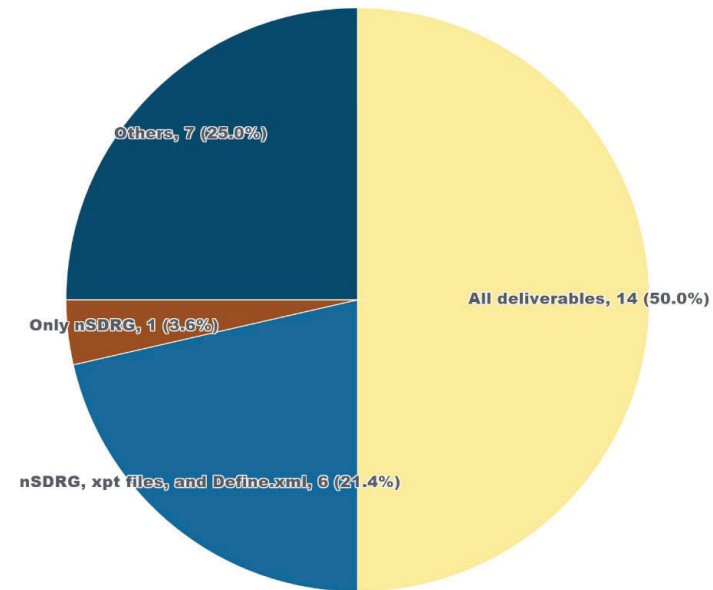


### Comments in "Others" :

- Define and nSDRG are confirmed by the entrust staff and the in-house SEND staff.
- Member of the safety group confirm xpt files. Final confirmation is conducted by SEND staff.
- QA and entrust staff.

## What are the confirmation items in the SEND data packages?

As facilities entrust creating SEND data packages



### Comments in "Others" :

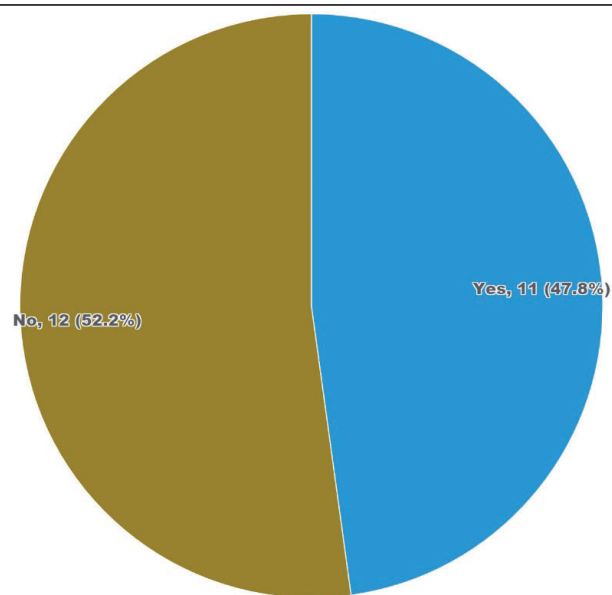
- All deliverables including nSDRG, various xpt files, and Define.
- Only items specified by CRO.

**At the entruster side, the entrust staff or person in charge of SEND may confirm it.**

**Basically, whole deliverables is confirmed.**

## Have your facility ever found any problems that need to be corrected in the created SEND data packages?

As facilities entrust creating SEND data packages



### Examples of the problem.

- Acceptance/rejection of domain variables, specifications of stored values, description of nSDRG, depth of definition.xml settings, etc.
- The medium name was incorrect. Lack of data. Error of the administration route.
- We asked for a fix for contractor, but it wasn't fixed.
- Insufficient explanation for warning.
- Difference from the specifications of the outsourced contractor, CT is not used, typing error or omission of entry in nSDRG and Define.
- Mismatch between SEND data package and final report (it was concluded error in the final report).
- Non-compliance with various regulations.
- Non-compliance with agreed specifications.
- Incorrect group configuration in nSDRGa and Pinnacle 21 error counts bug.
- Inappropriate explanation of baseline date.

# Comments for ensuring SEND

## **Regarding QC**

- We are wondering how much we should be involved (QC, QA) or whether we can be involved as a sponsor if we entrust everything,.
- How range should be QC?
- We carry out 100% QC for parts that are not mechanically QC, but to be honest, the burden required for QC is so large.
- It seems to be expected by entruster and within the company to play a QC role as a facility of outsourced contractor, but I feel that dealing with it will be an issue.
- The issues are whether it is enough only to evaluate the assurance system in the outsourced contractor, how much the entruster should reconfirm the received SEND data packages, and what tasks entruster and outsourced contractor should collaborate with, etc.
- The number of data is too large in the xpt files, so 100% check is difficult. Therefore, there is no choice but to extract and confirm only a part.
- The issue is how to build an in-house check system.

## **Regarding Education**

- There is no point in checking quality unless person in charge is familiar with SEND.
- If the person in charge who does not understand well confirms SEND and tell what to do, it will be very stressful for the SEND package creator.
- Sometimes feel that the QC person's understanding of SEND knowledge is insufficient, and it feels that the lack of education for the QC staff is an issue compared to the SEND dataset creator.
- Needs the education for those who check data even on the outsourced contractor side, implementation and operation of tools for creating SEND data packages, effective method for confirmation.
- It is difficult to train members who can confirm the consistency of the description in nSDRG and Define. The burden is so heavy because the person in charge of SEND data package creation have to also in charge of the final confirmation.
- Education method and scope for entruster, QC staff and QA staff.

## **Regarding QA**

- QA contribution is necessary since the SEND data package is not a GLP-regulated document. The things we should ensure is not a reliability, but a quality.
- Whether QA should contribute to SEND, which is not applicable to GLP. How and how much QA should do if necessary?
- If the SEND data is linked to the recording and output of the study results, QA may contribute to assure the reliability of the system itself. QA won't contribute SEND when it is made by transcribing the data from the final report.

## **Others**

- Explanations of extended terms for histopathological findings are not unified by institution.
- Regarding SEND materials, we have not even seen whether there are any submissions to the Japanese authorities or requests for revisions from the authorities. We don't think it's a good idea to spend money and effort on SEND materials for items that you don't know whether to apply in the future, while you can't see what the SEND materials should be in Japan.
- It is difficult to understand guidance and regulations regarding SEND. We don't know the appropriateness of the created data, and there are some parts that are left to the CRO. In addition, for outsourced studies, since SEND data is created directly from the system, the outsourcer cannot confirm from the raw data, and some items are left to the CRO. (In addition, since the CRO also prepares QC and statements, there is no choice but to trust the CRO for items that cannot be confirmed by the contractor.)

# Summary and Conclusion

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## Summary

- In this questionnaire, it was confirmed that there is a big difference in the situation between the facilities that SEND data package can make by themselves and the facilities that entrust the creation.
- There are relatively large number of personnel in charge for SEND in the facilities they can make SEND data package. QC is also carried out there and procedure have been prepared, and there are also some educational systems.
- For facilities that outsource the creation of SEND data packages, QC is often outsourced and often lacks or is planning procedures and education systems.
- Many facilities have not been involved in SEND at all in this questionnaire, and some facilities thought they can not actively prepare for SEND because PMDA's response to SEND was not decided yet.
- The SEND creator side regards the gap in knowledge level regarding SEND with the entrust side as an issue.
- In contrast, the facilities entrust do not know what and how to do regarding for assuring SEND data package, so it seemed that they were often left all to outsourced contractors.
- At all facilities, QA tended not to be involved in SEND, and there seemed to be little awareness of the need for QA involvement since SEND data package is not GLP-regulated document.
- Our opinion is that what and how to be involved in QA for quality assurance of SEND data packages depends on company policy and personnel.

## Conclusion

- In non-clinical facilities, quality assurance has long been carried out under GLP. However, most facilities do not have established non-GLP quality assurance such as SEND, and quality management systems vary from facility to facility.
  - In order to ensure the quality of SEND data packages, it is necessary not only to confirm the consistency with various guidelines such as SENDIG, TCG and TRC, but also to confirm the consistency of the data based on scientific knowledge with the final report and control terms. It is not sufficient only to confirm SEND data packages using computer system.
  - Therefore, it is essential to have QC by a person in charge who is familiar with SEND using validation and check tools provided by SEND specialist groups.
  - However, a huge amount of education and experience is required in order to become familiar with SEND, and it takes a lot of labor and time to train the person in charge.
  - In order to ensure sustainable quality, it is considered that the procedure of know-how and the system to manage education are issues.
  - We would like to propose the implementation of ISO9001, an international standard of quality management system (QMS), to all entruster and outsourced contractor facilities of related to SEND to ensure the quality of electronic application data including SEND data packages.
-