Use of R in Japan's Pharma Industry

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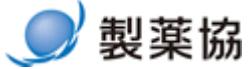
Task Force 5,
Data Science Expert Committee,
Drug Evaluation Committee,
Japan Pharmaceutical Manufacturers Association

Disclaimer
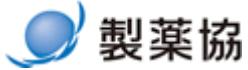
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Agenda

- **General background – JPMA Task force**

- **Open-Source Software Usage Questionnaire Report**

- **Conclusion**

- **QA session**

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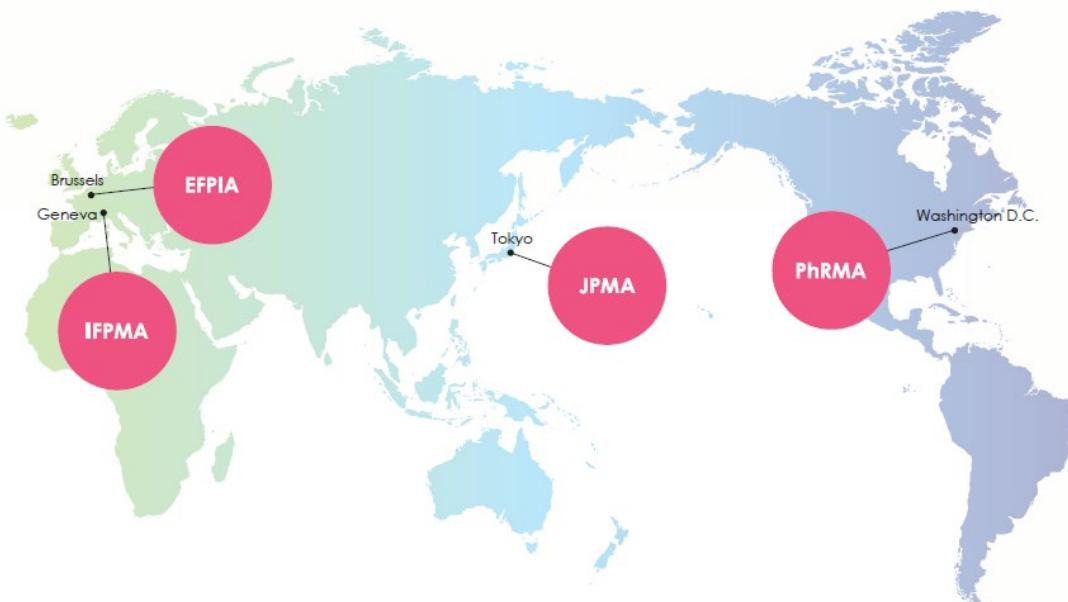
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Introduction of JPMA

JPMA (Japan Pharmaceutical Manufacturers Association)

https://www.jpma.or.jp/english/about/about/

List of Committees

- Code Compliance Committee
- Pharmaceutical Industry Policy Committee
- Distribution Improvement Committee
- Drug Evaluation Committee
- Quality & Technology Committee
- Biopharmaceutical Committee
- Regulatory Affairs Committee
- Intellectual Property Committee
- R&D Committee
- International Affairs Committee
- Public Affairs Committee
- Patient Cooperation Committee

List of Specialized Organizations

- Office of Pharmaceutical Industry Research (OPIR)
- Review Board of Ethical Drug Product Information Brochure
- ICH Project
- APAC Project
- Consumer Consultation Review Committee
- Environmental Issue Committee

JPMA's Logo Mark

JPMA's 5 Messages

1. Contributing to global healthcare through the development of new drugs
2. Driving Japanese economy as a leading industry
3. Creating innovative, highly effective new drugs
4. Becoming a business association with excellent R&D capabilities
5. Contributing to patient-centered healthcare

Thoughts behind the logo

Symbolizing the five messages, it expresses the way we continue to move forward with the world.
The five arcs are continuous around the sphere, and their ascending shape evokes the image of "leap" or "growth."
The color blue is used as a base color to evoke a sense of "progress," "internationality," "high technological capabilities," and "freshness."

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Task force "Open-Source Software (OSS)" in JPMA

Members   : 10 persons (2023)
Establishment   : since 2022

Background of Start-up
- **Many pharmaceutical companies were interested in OSS(R, Python)**
- **Consider the use of OSS**
   (Use for Regulatory submission, Validation, Internal Operation, etc..)

Requirement of use of specific software in PMDA

Technical Conformance Guide on Electronic Study Data Submissions

4.1.6 Submission of programs

4.1.6.1 Programs to be submitted

With respect to the programs related to electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted for the analyses performed to obtain the important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration shown in 4.1.1.3. The main purposes of requesting the submission of these programs are to understand the process by which the variables for the analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment. Also, although the programs to be submitted are not limited to specific software or versions, information on the environment in which the programs were created or run (operation system and software used and their versions) must be provided together in the reviewer's guide. If programs with macros had been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient.

[2022]
- Release the document:
  "Utilization and Considerations for Open Source Software"

- Release the survey report:
  "Open Source Software Usage Questionnaire Report"

[2023-]
- Sharing Internal Case Study in Each company (On going)

Utilization and Considerations for Open Source Software

1. OPEN SOURCE SOFTWARE

    1.1 Open source software licenses

    1.2 Software for statistical analysis "R"

    1.3 R-related activities in the pharmaceutical industry
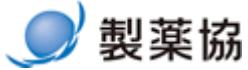
2. Challenges in using OSS for approval applications

    2.1 Management of operational tasks

    2.2 Versioning of R

    2.3 Version control of R packages

        2.3.1 When operating with a fixed version of the R package

        2.3.2 When operating R packages with multiple versions

    2.4 R package management

    2.5 Management system

        2.5.1 R package management system

3. R education and training

    3.1 R Training Cases

    3.2 Curriculum for R training

    3.3 R Learning Resources

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Open Source Software Usage Questionnaire Report

➢ **Purpose**
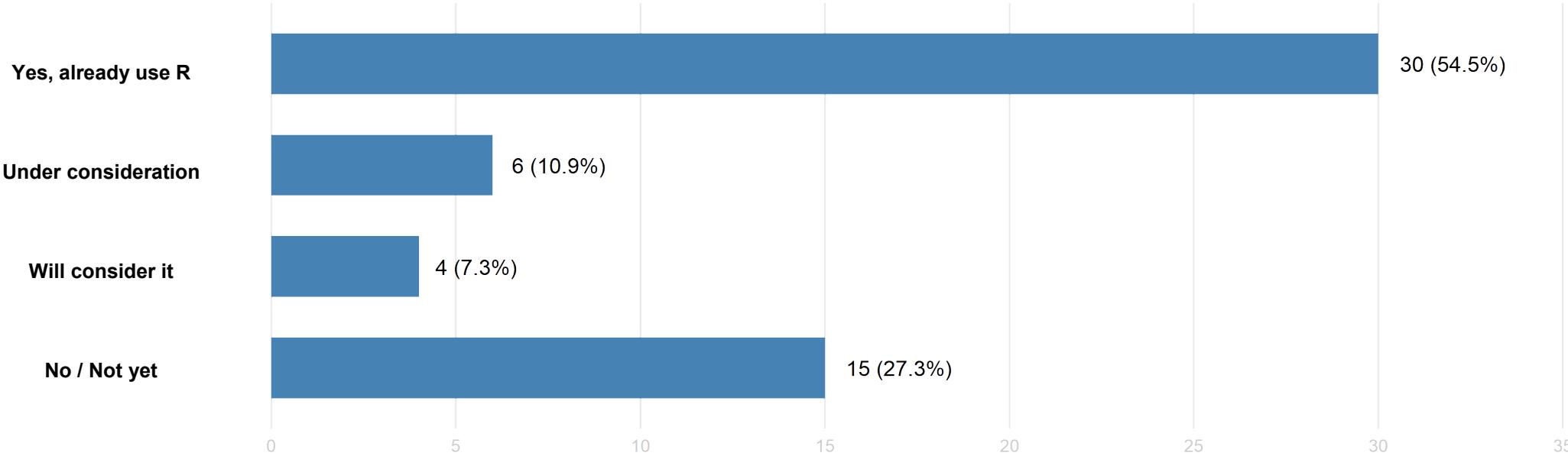
  ■ **To understand the use condition of Open Source Software in clinical development in pharmaceutical companies**

Open Source Software Usage Questionnaire Report
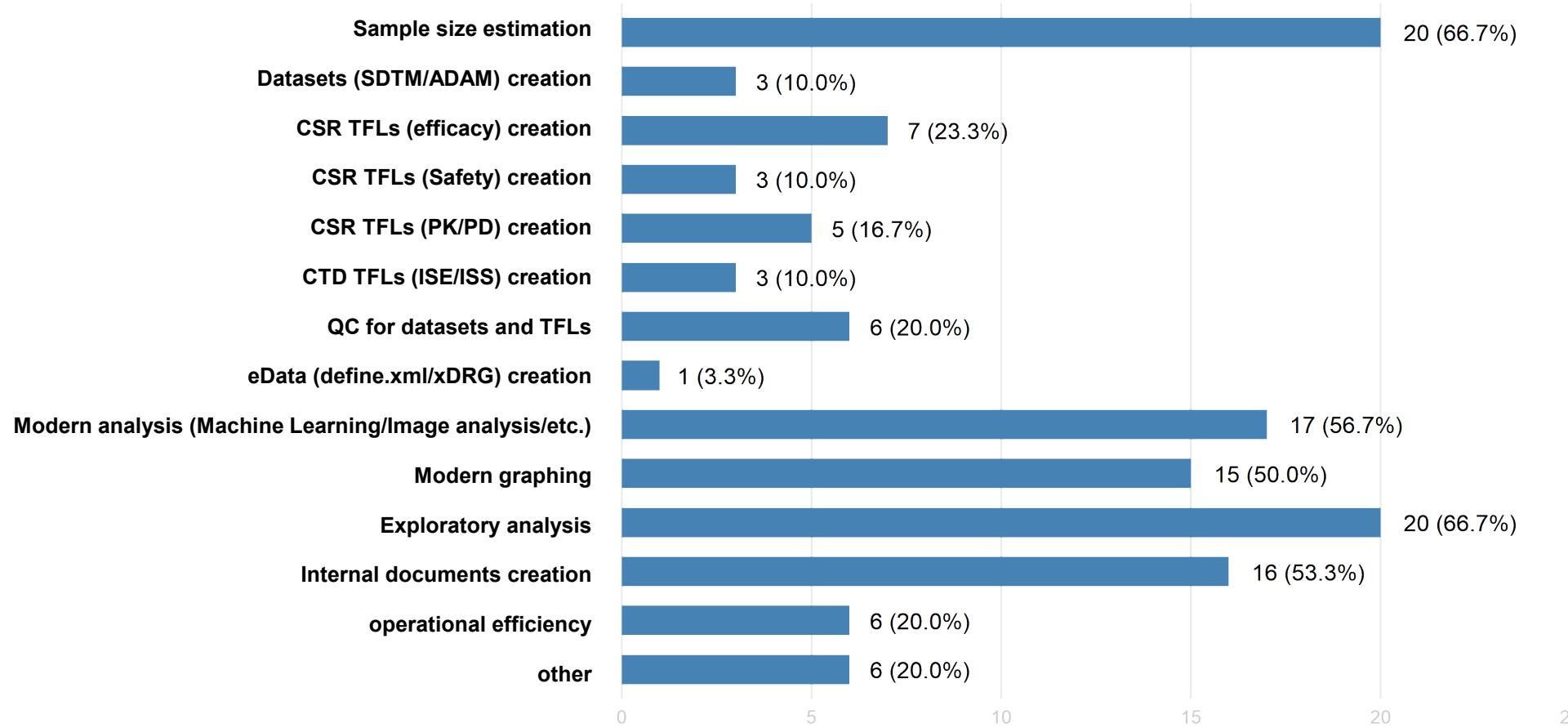
➢ **Survey period**
 - ■ **Thursday, October 27, 2022 to Friday, November 25**

➢ **Survey subject**
  - ■ **Companies registered to the Data Science Expert Committee**
    - ✓ **Japanese companies and Foreign capital companies**


➢ **Survey result**
  - ■ **Responses were received from 55 of 64 companies registered with the Data Science Expert Committee.**

Which steps do you use R?
(Multiple choices allowed) (N=30)

Step	Count (%)
Sample size estimation	20 (66.7%)
Datasets (SDTM/ADAM) creation	3 (10.0%)
CSR TFLs (efficacy) creation	7 (23.3%)
CSR TFLs (Safety) creation	3 (10.0%)
CSR TFLs (PK/PD) creation	5 (16.7%)
CTD TFLs (ISE/ISS) creation	3 (10.0%)
QC for datasets and TFLs	6 (20.0%)
eData (define.xml/xDRG) creation	1 (3.3%)
Modern analysis (Machine Learning/Image analysis/etc.)	17 (56.7%)
Modern graphing	15 (50.0%)
Exploratory analysis	20 (66.7%)
Internal documents creation	16 (53.3%)
operational efficiency	6 (20.0%)
other	6 (20.0%)

In 30 companies that have already use R. It is often used for sample size estimation, exploratory analysis, modern analysis, and preparation of documents for internal use.

There was little use experience of R for preparation and QC of clinical study datasets and TFLs, and preparation of eData related materials.
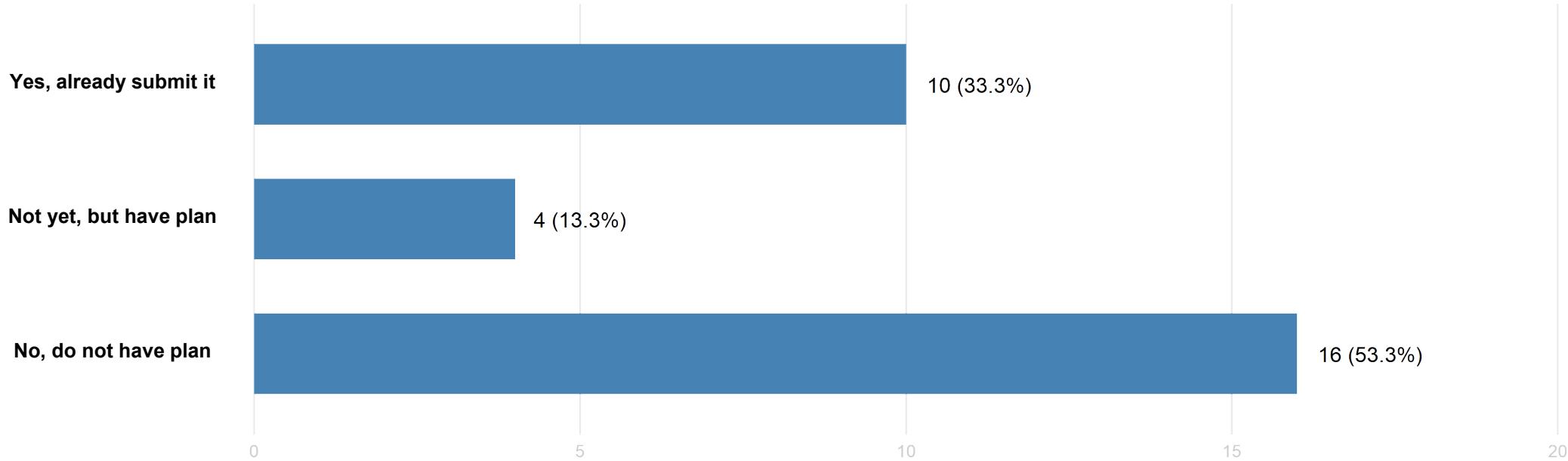
Have you experienced or plan to submit documents written in R to regulatory authorities? (N=30)

About half of the companies have submitted documents written in R to the regulatory authorities. On the other hand, about 40% of the companies do not plan to submit it.

R is already used by many companies, but it is often used for purposes other than preparing documents to be submitted to regulatory authorities.
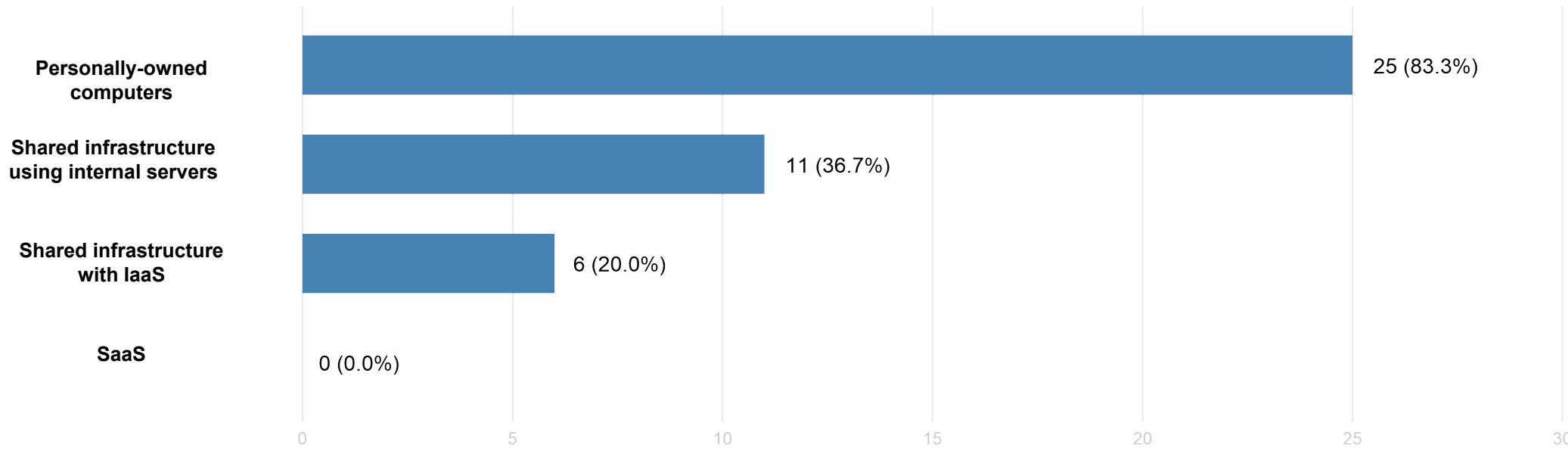
Have you submitted experiences or plan to submit the program in R to regulatory authorities? (N=30)

Over half of the companies have no experience of submitting the program in R to the regulatory authorities or no plan to submit it. On the other hand, about 30% of the companies have submitted such programs before.
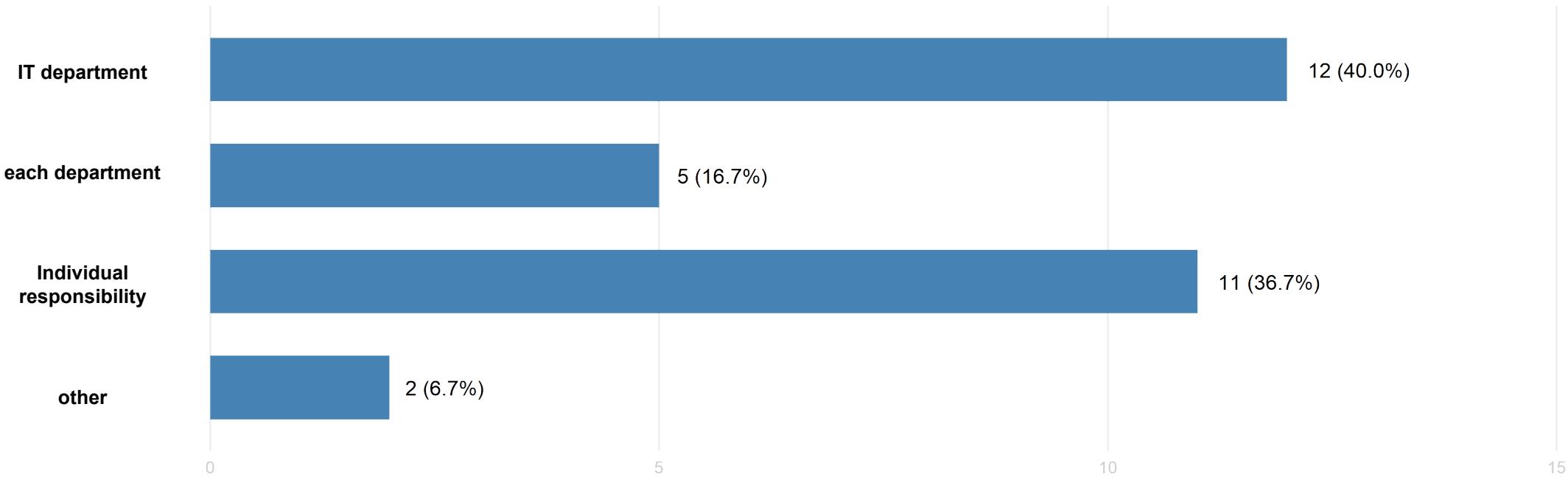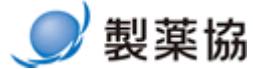
Some companies use of R for purposes other than preparing documents to be submitted to regulatory authorities. It is also possible that R is used for documents for which the regulatory authorities does not require programs.

# What environment you use R. (Multiple choices allowed) (N=30)

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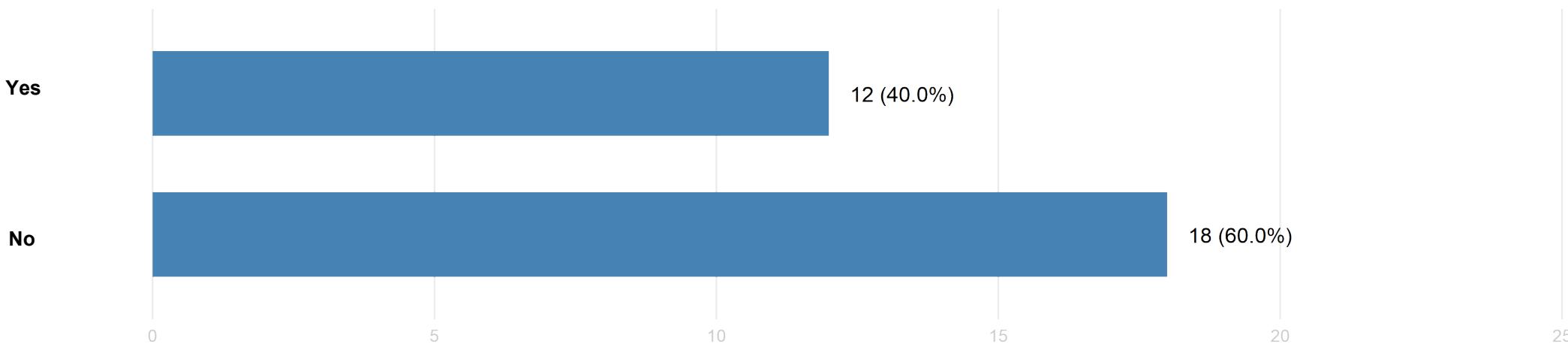
Many companies that have already started using R were using it in the following order: personally-owned computers, shared infrastructure using internal servers, and shared infrastructure with IaaS.

Who mangage the environment for using R? (N=30)

Many companies indicated that their internal IT departments or individuals manage the environment for using R.
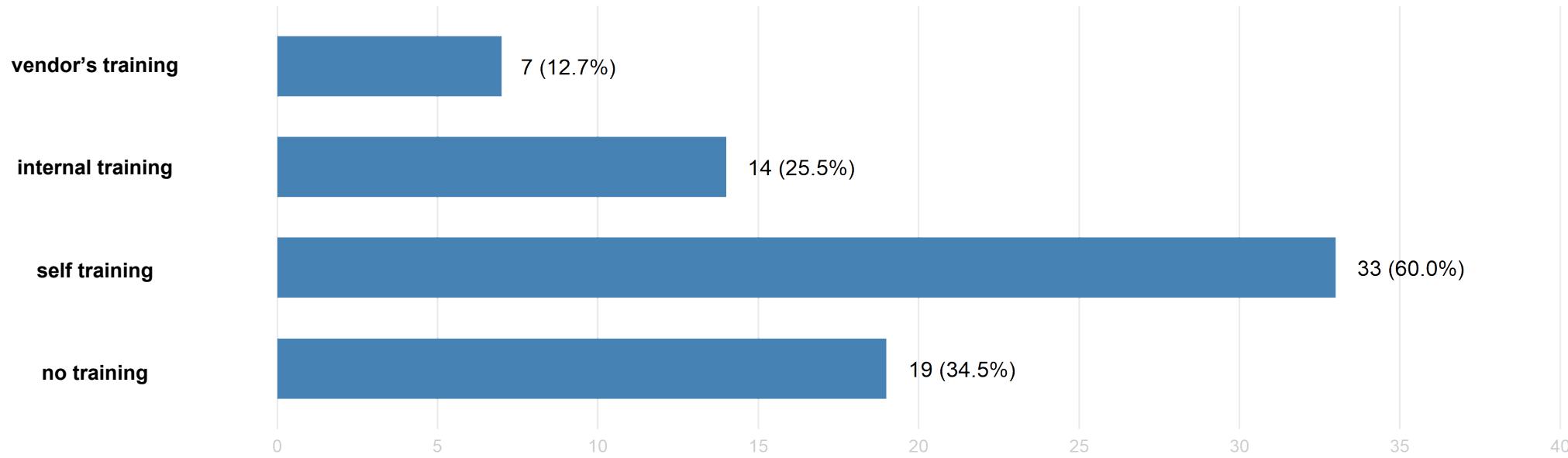
Do you manage R libraries? (N=30)

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Fourty percent of company answered that they manage libraries and 60% answered that they do not.
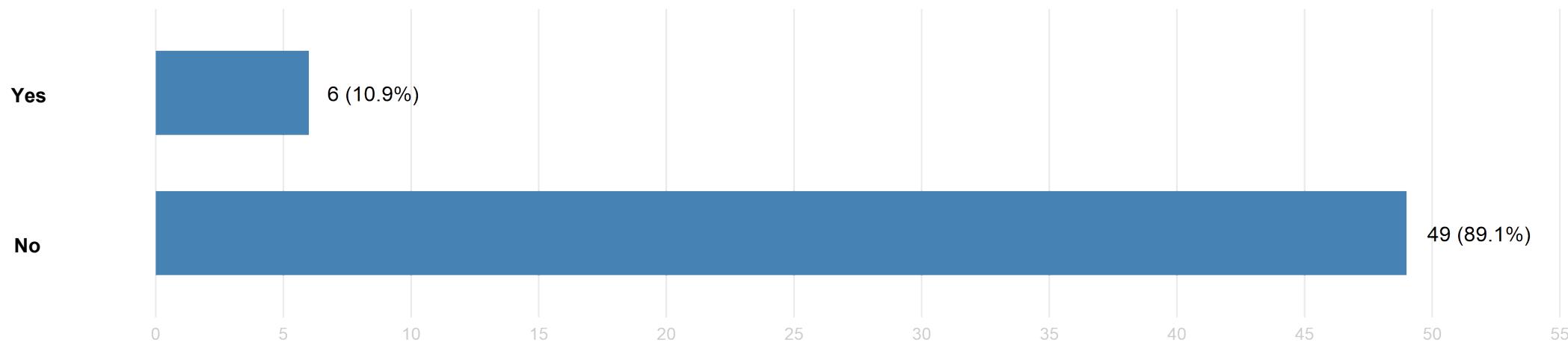
Many companies mentioned the reliability for libraries as the challenge (in the following questions), suggesting that many companies are still considering handling libraries.

How to train/learn R in your company (Multiple choices allowed) (N=55)

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Most common (60%) answer is that they learn R by themselves.
**On the other hands, R training/learning is not conducted by 30% of the companies.**
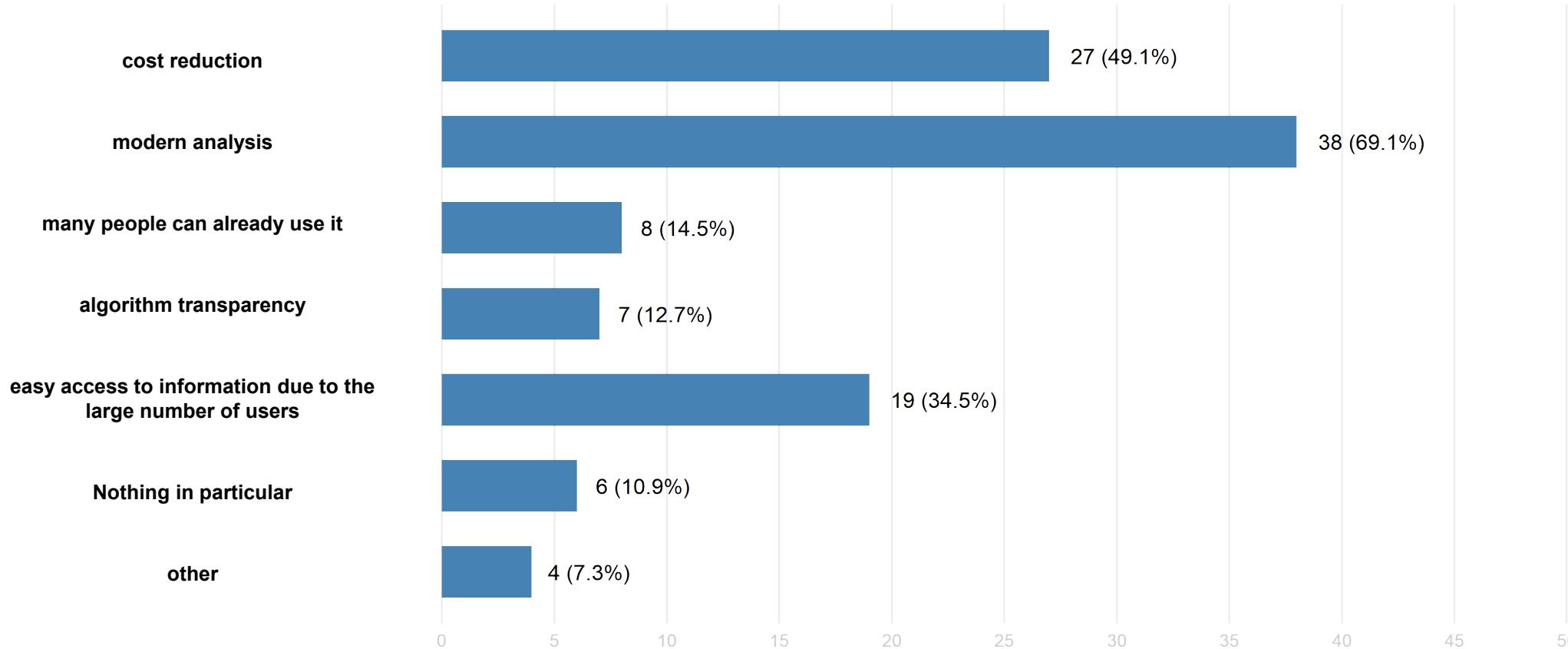
Have you ever outsourced analysis using R? (N=55)

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Yes	6 (10.9%)
No	49 (89.1%)

About 90% of the companies answered that they have no experience of outsourcing using R.

In the response to the following question, there is an opinion that there are few CROs can do an analysis using R. At least in Japan, there seems to be few opportunities to outsource R analysis.
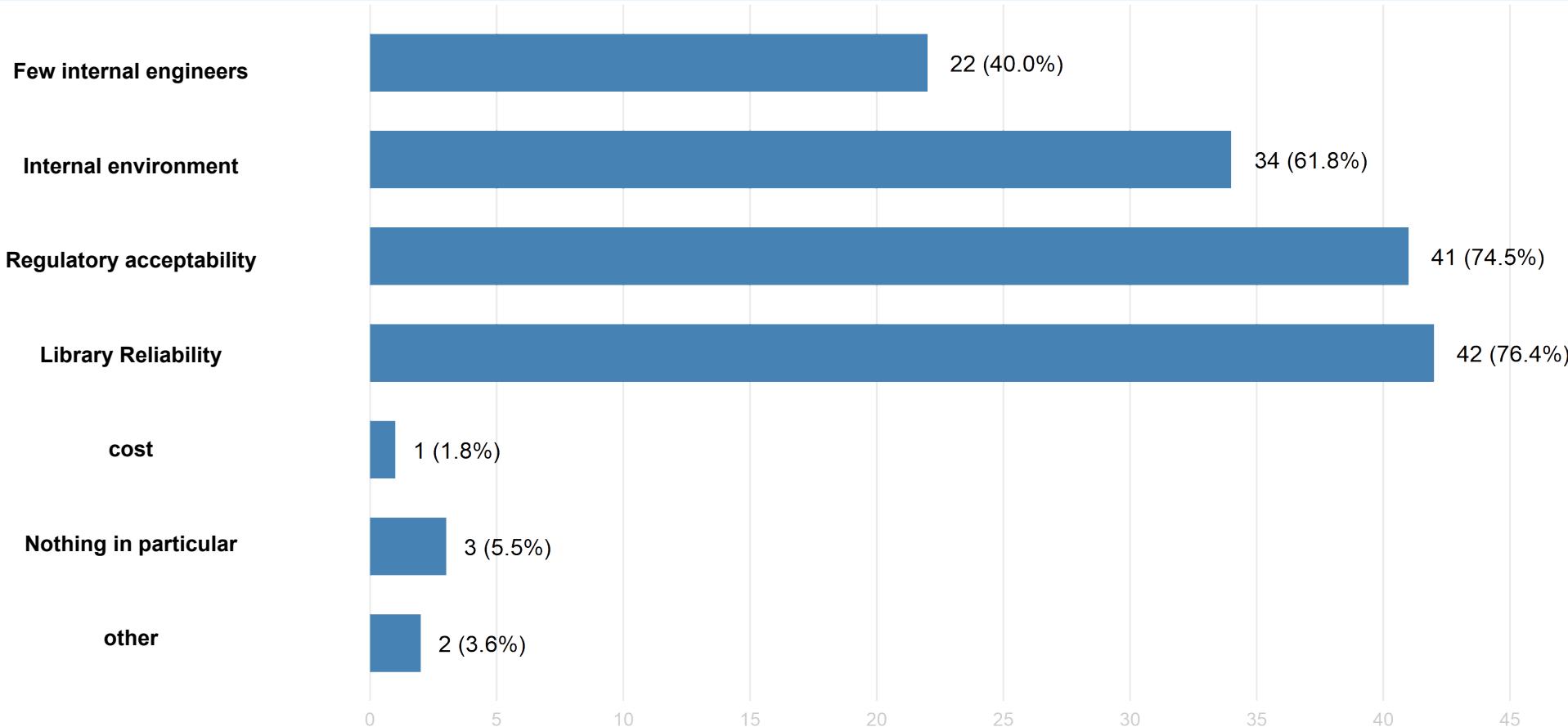
What are the expected effects of introducing R into your company? (Multiple choices allowed) (N=55)

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Category	Value
cost reduction	27 (49.1%)
modern analysis	38 (69.1%)
many people can already use it	8 (14.5%)
algorithm transparency	7 (12.7%)
easy access to information due to the large number of users	19 (34.5%)
Nothing in particular	6 (10.9%)
other	4 (7.3%)

About 70% of the companies answered that they expected for modern analysis. About 50% of the companies answered that they expected for cost reduction.

On the other hand, few companies answered that they expected transparency of algorithms, which is a characteristic of open source.
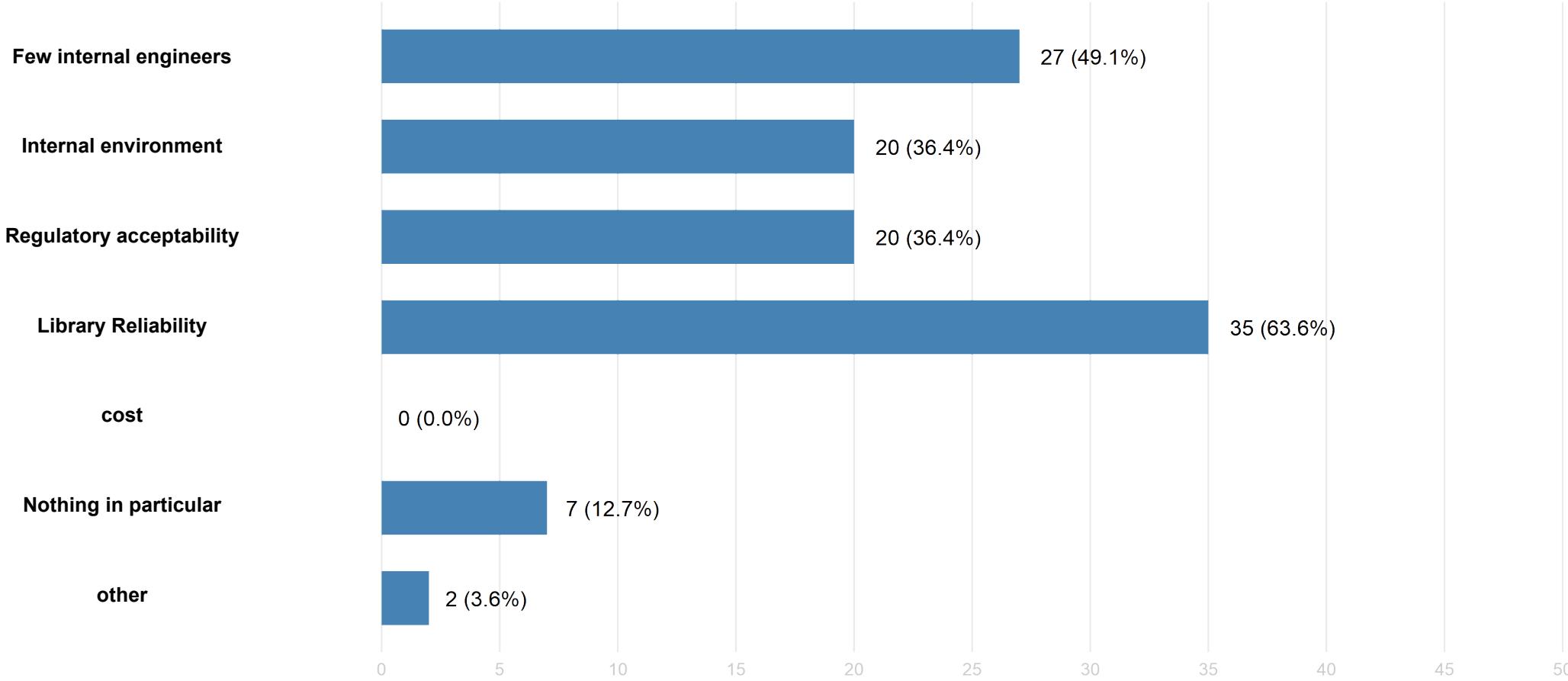
What are the concerns about R when use for NDA? (Multiple choices allowed) (N=55)

Category	Value
Few internal engineers	22 (40.0%)
Internal environment	34 (61.8%)
Regulatory acceptability	41 (74.5%)
Library Reliability	42 (76.4%)
cost	1 (1.8%)
Nothing in particular	3 (5.5%)
other	2 (3.6%)

The reliability of the library is the biggest concern because everyone can release the package.
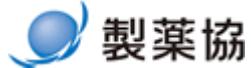
In addition, although there is no message from regulatory authorities such as PMDA to allow specific software, there seems to be a concern about the acceptability of R by regulatory authorities because there is still limited experience and information on the use of R.
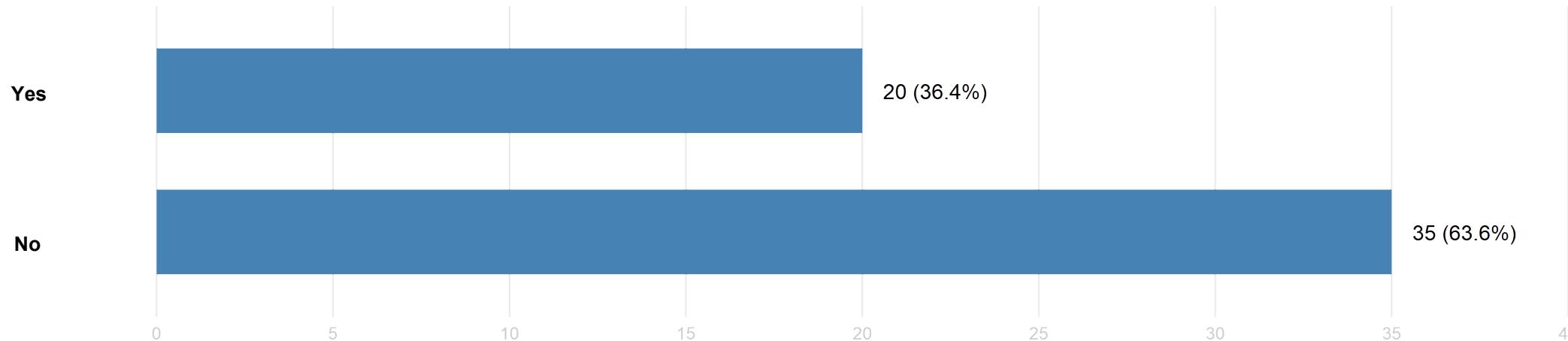
which departments in your company use R. (comments)

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Clinical development, data science, statistical analysis, and pharmacology department mainly use R, but other departments also use it.
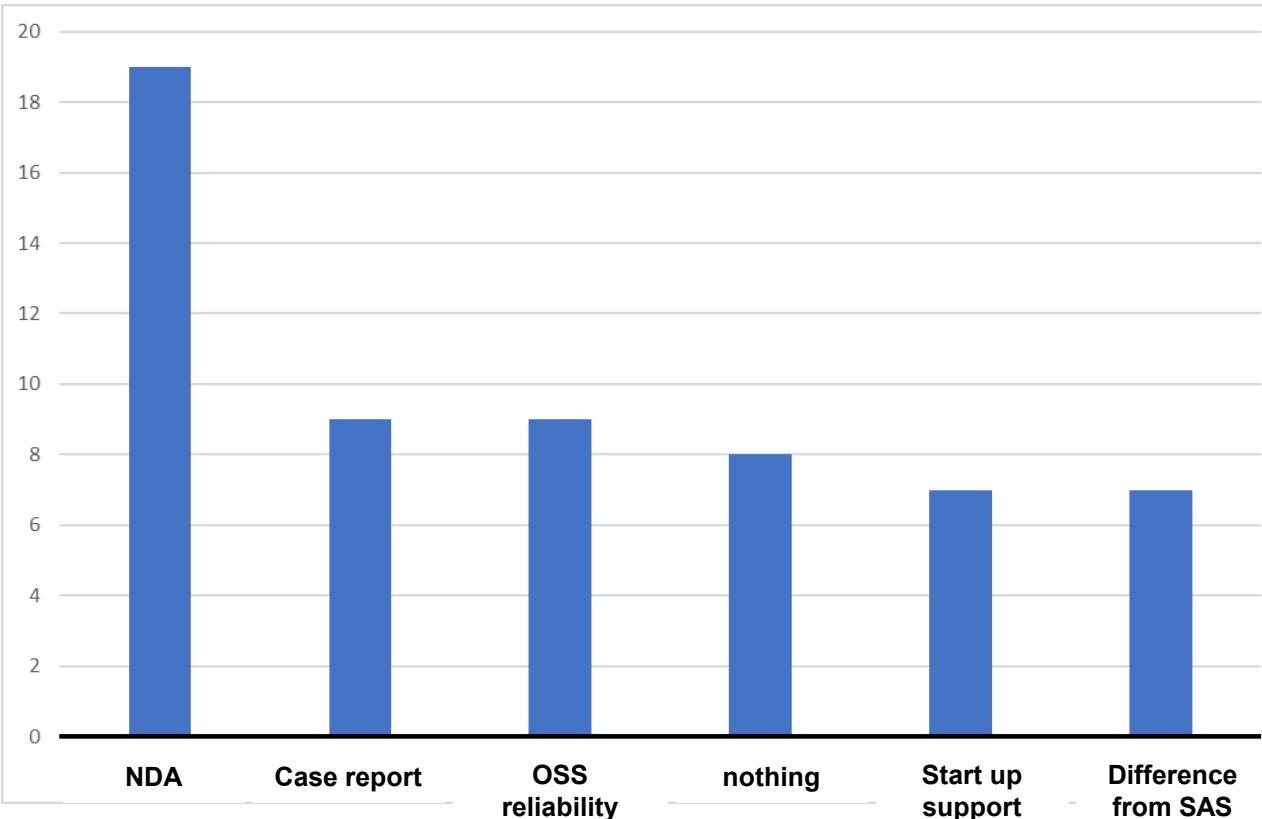
Since the questionnaire was conducted by the Data Science Expert Committee of the Japan Pharmaceutical Manufacturers Association (JPMA), many responses may come from the Clinical Development Division. In fact, there is a possibility that R is already used across the company.
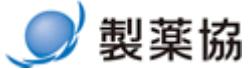
What do you expect from the JPMA Task Force in the future regarding the use of open sources such as R/Python? (comments)

Classification	Description
Use for Regulatory submission (NDA)	Acceptability of OSS by regulatory authorities, quality control at the regulatory submission
Case report	Introduce examples of utilization of what OSS can do, sample programs, etc.
OSS reliability	Validation of OSS, list of reliable packages, etc.
Difference from SAS	Differences from SAS, things that cannot be done without OSS, etc.
Start up support	Training, Approach and preparation for using R, etc.
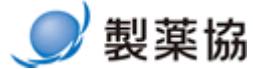
Comments are categorized into "Use for Regulatory submission (NDA)", "case report", "OSS reliability", "Difference from SAS", "Nothing" and "Start up support".
There were particularly high expectations regarding the use of OSS in regulatory submissions.

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Conclusion

OSS, especially R, is already widely used in many Japanese pharmaceutical companies.

On the other hand, many concerns remain, such as the reliability of the package and limited experience for regulatory authority acceptance.

JPMA plans to continue its activities to ensure that OSS is widely used in the Japanese pharmaceutical industry.

QA Session