Quality Practices: Meeting and Exceeding Regulatory Expectations

CPhI North America
Insight Briefing

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Advancing Development & Manufacturing Pharmaceutical Technology PharmTech.com

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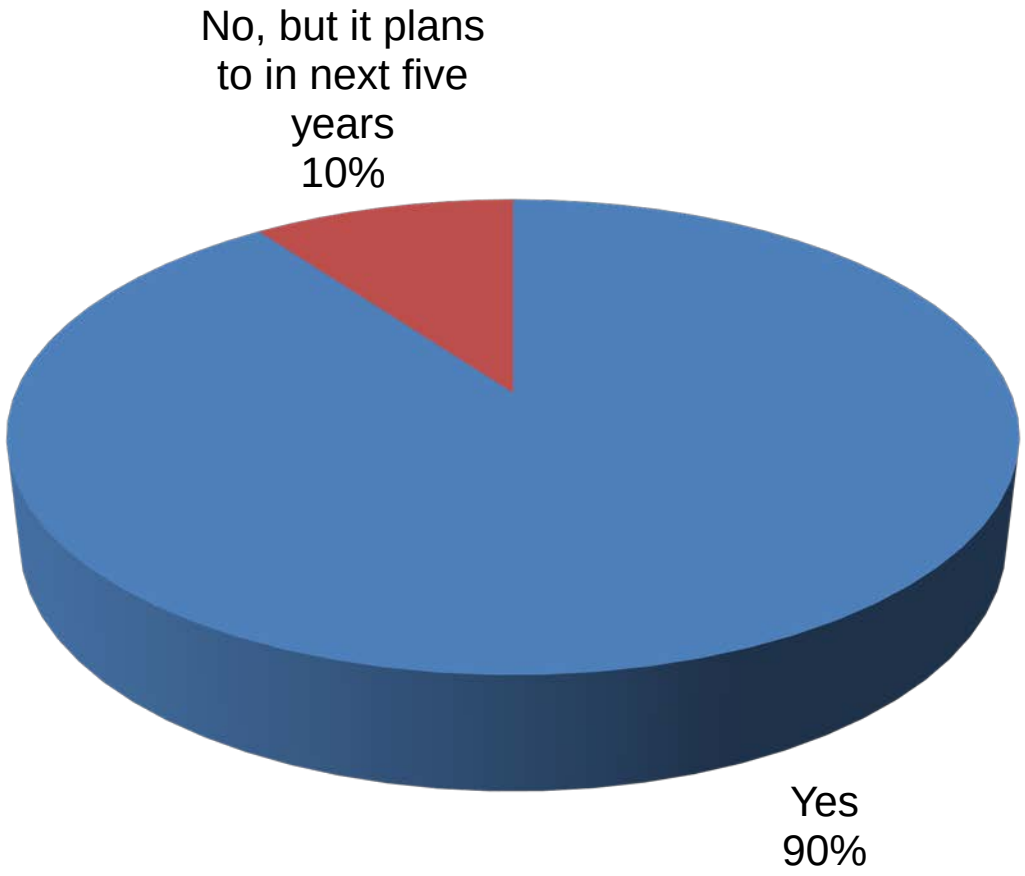
Goals of Survey

- Assess quality practices in the US bio/pharma market.
- Understand “quality culture” in bio/pharma and contract service sectors.
- Measure perceptions about FDA’s role in ensuring quality of drug products.
- Identify best practices and areas for improvement.

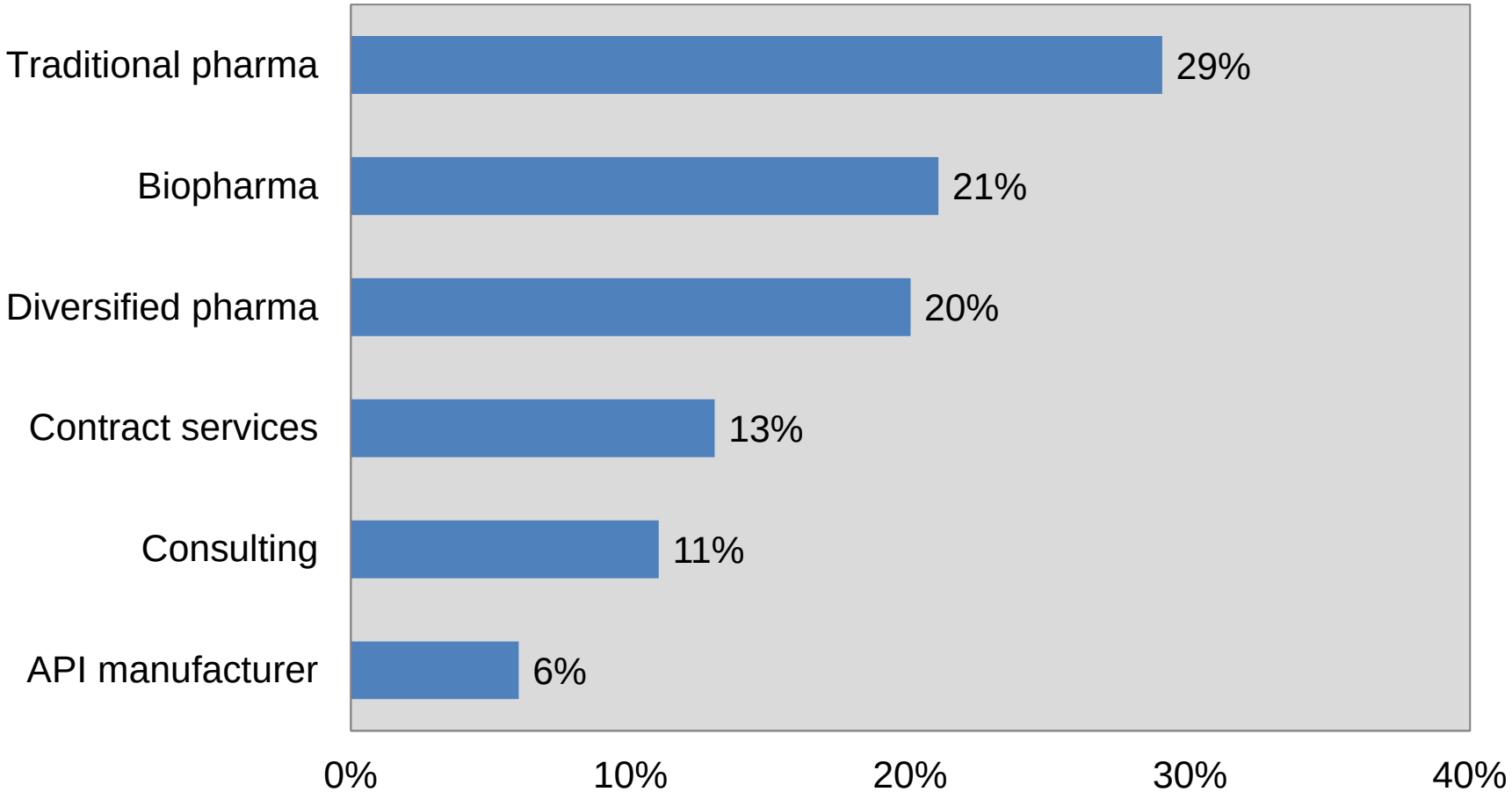
About this Survey

- US-based readers of *Pharmaceutical Technology* and *BioPharm International*
    - Bio/pharmaceutical development and manufacturing companies
    - Contract service providers
    - API manufacturers
    - Consultants involved in drug development or manufacturing
- Develop or manufacture drugs for the US market
- Confidential online survey conducted February–April 2017
- 116 qualified results

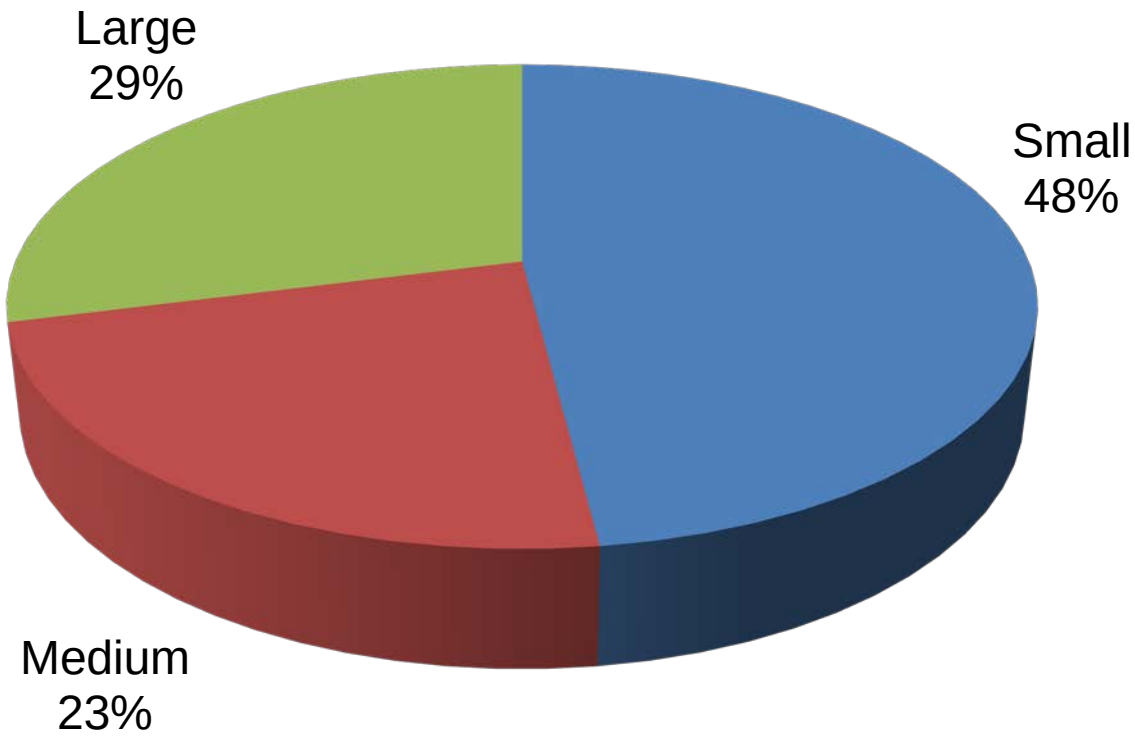
Does Your Company Develop or Manufacture Drugs for the US Market?



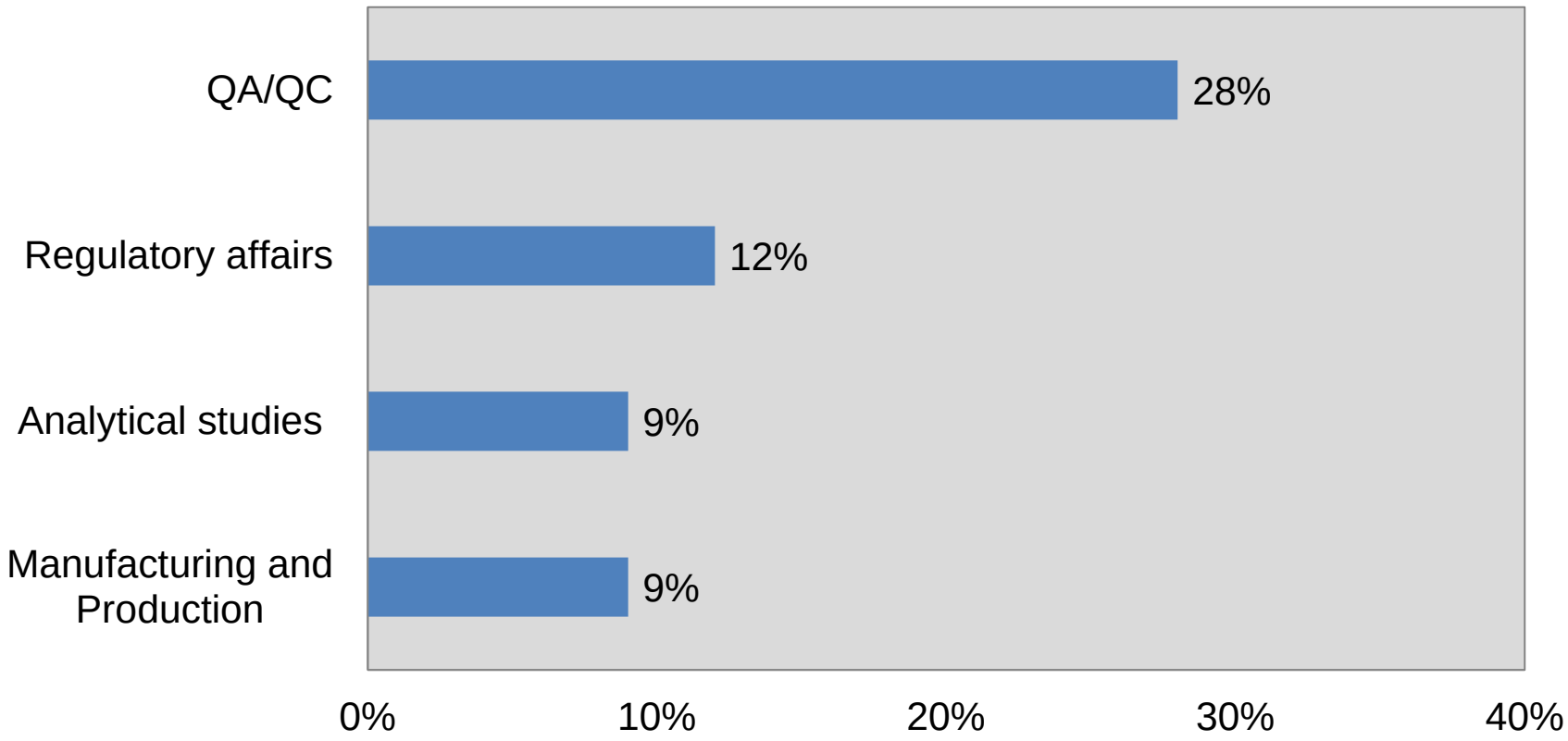
Type of Organization



Organization Size

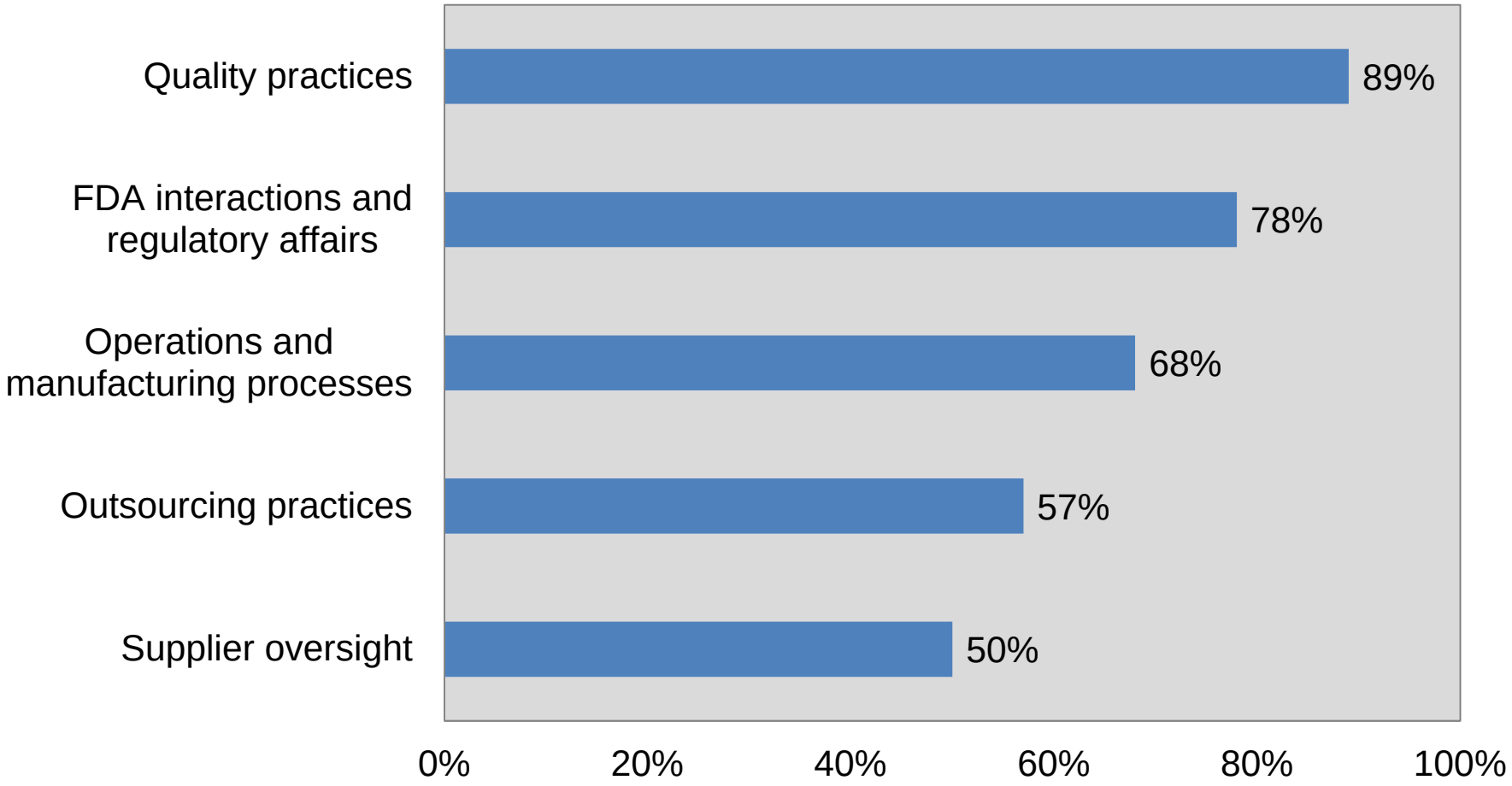


Primary Responsibility



Other responses cited by 6% or fewer respondents: CMC, R&D, corporate management, process development, and scale-up.

Quality-Related Areas of Expertise



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Quality Practices in Organization

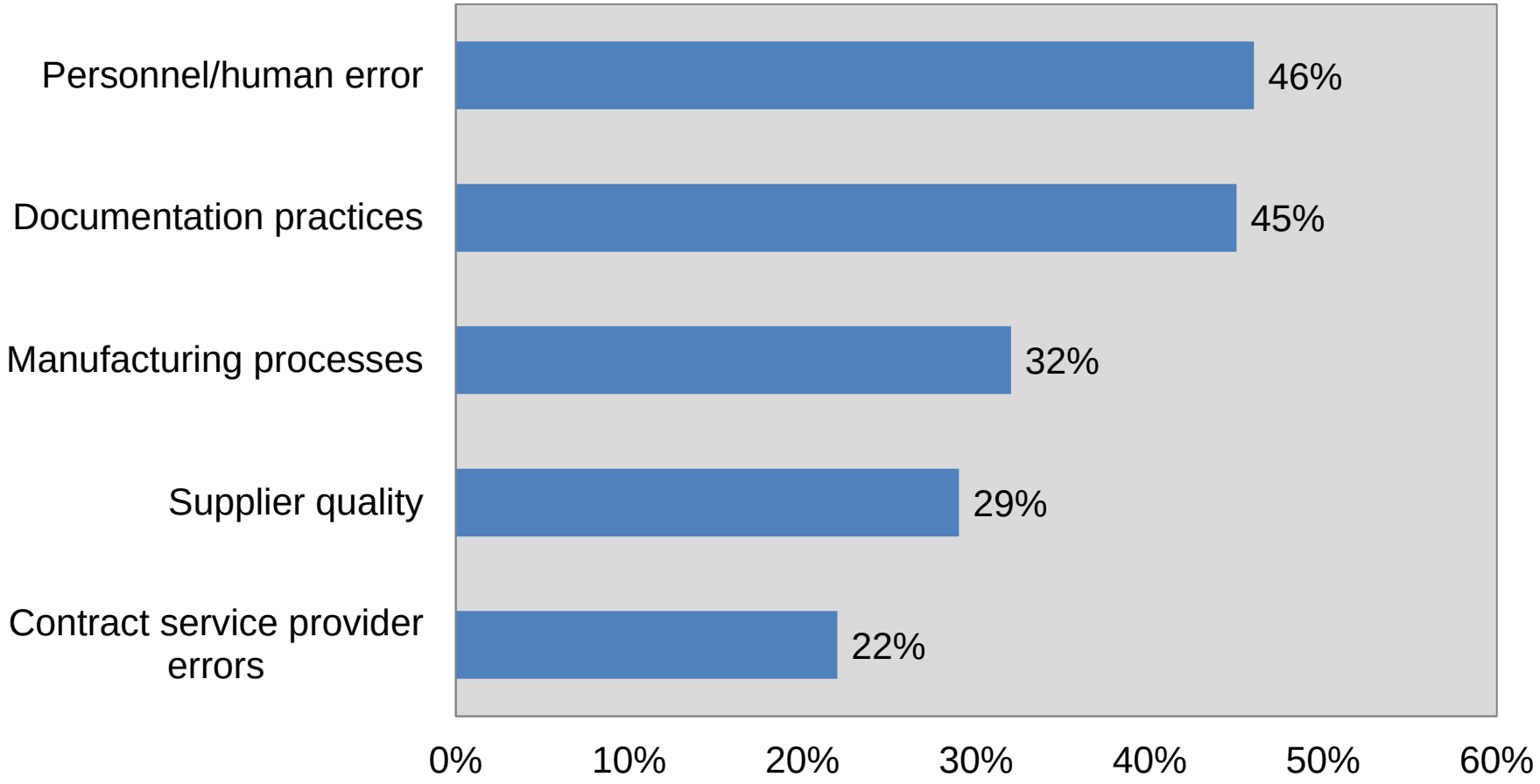
Industry Quality Concerns

- FDA warning letters more than doubled from 23 in 2012 to 58 in 2016.
  - Adulterated APIs and finished drug products
- Average of 700 Form 483s per year (2012–2016)
- 434 drug recalls in 2012
- 1224 drug recalls in 2016, down from 2028 in 2015

Adverse Events

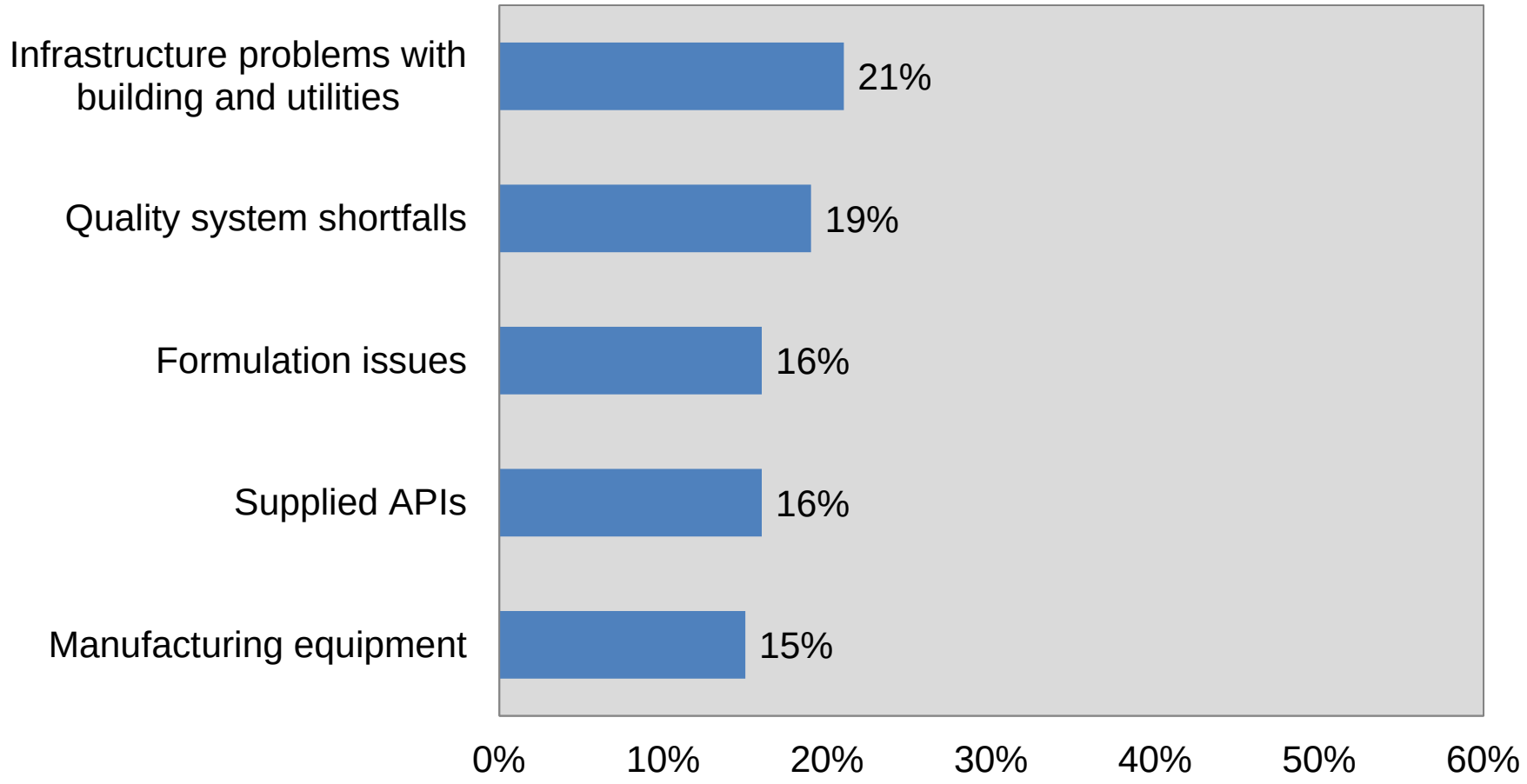
- 30% of survey respondents experienced an adverse quality or regulatory event in the past five years.

Source of Quality Problems: Top Responses



Up to 5 responses allowed

Source of Quality Problems: Next 5 Responses



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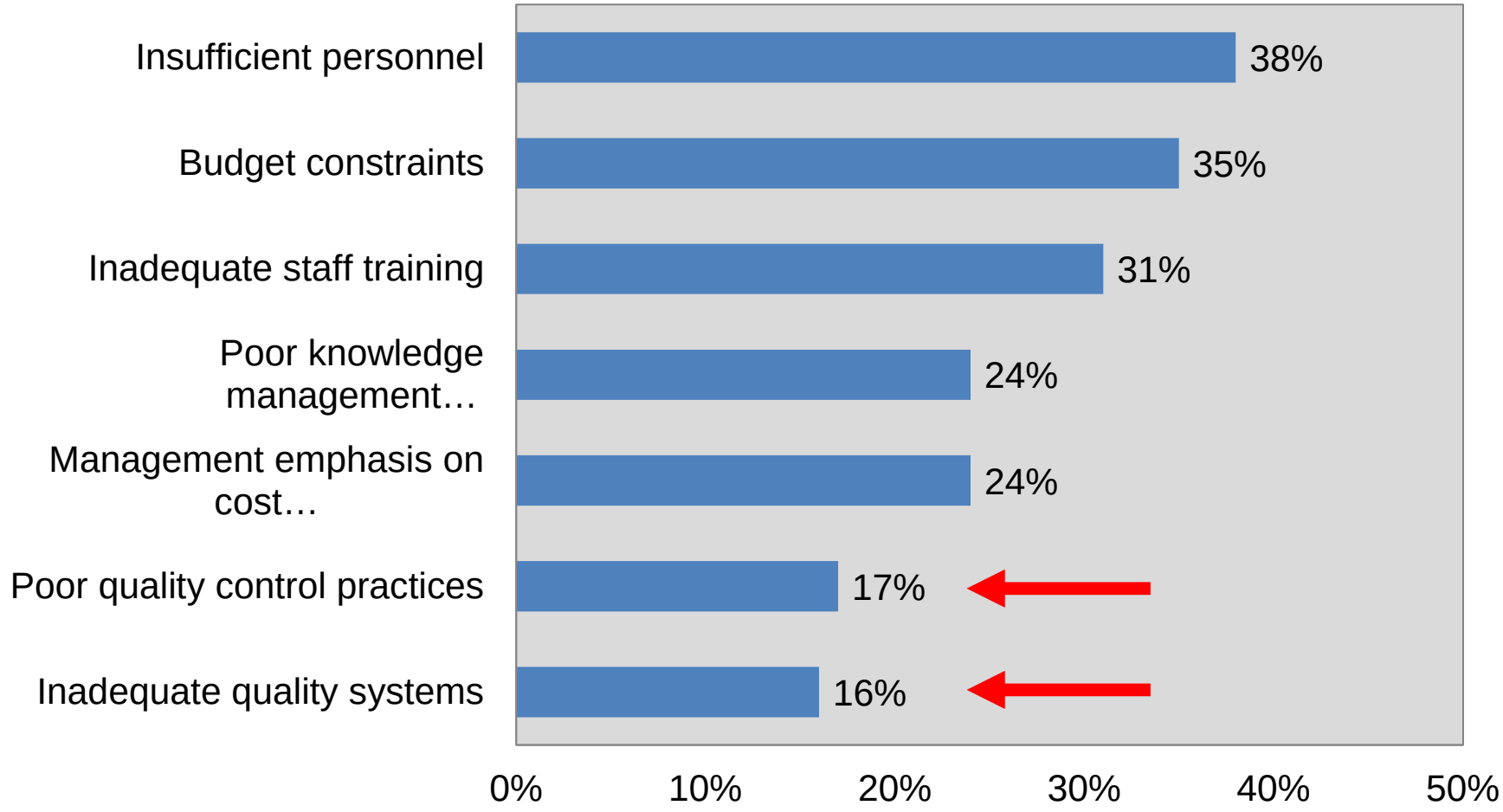
Factors Contributing to Quality Problems: Top Responses



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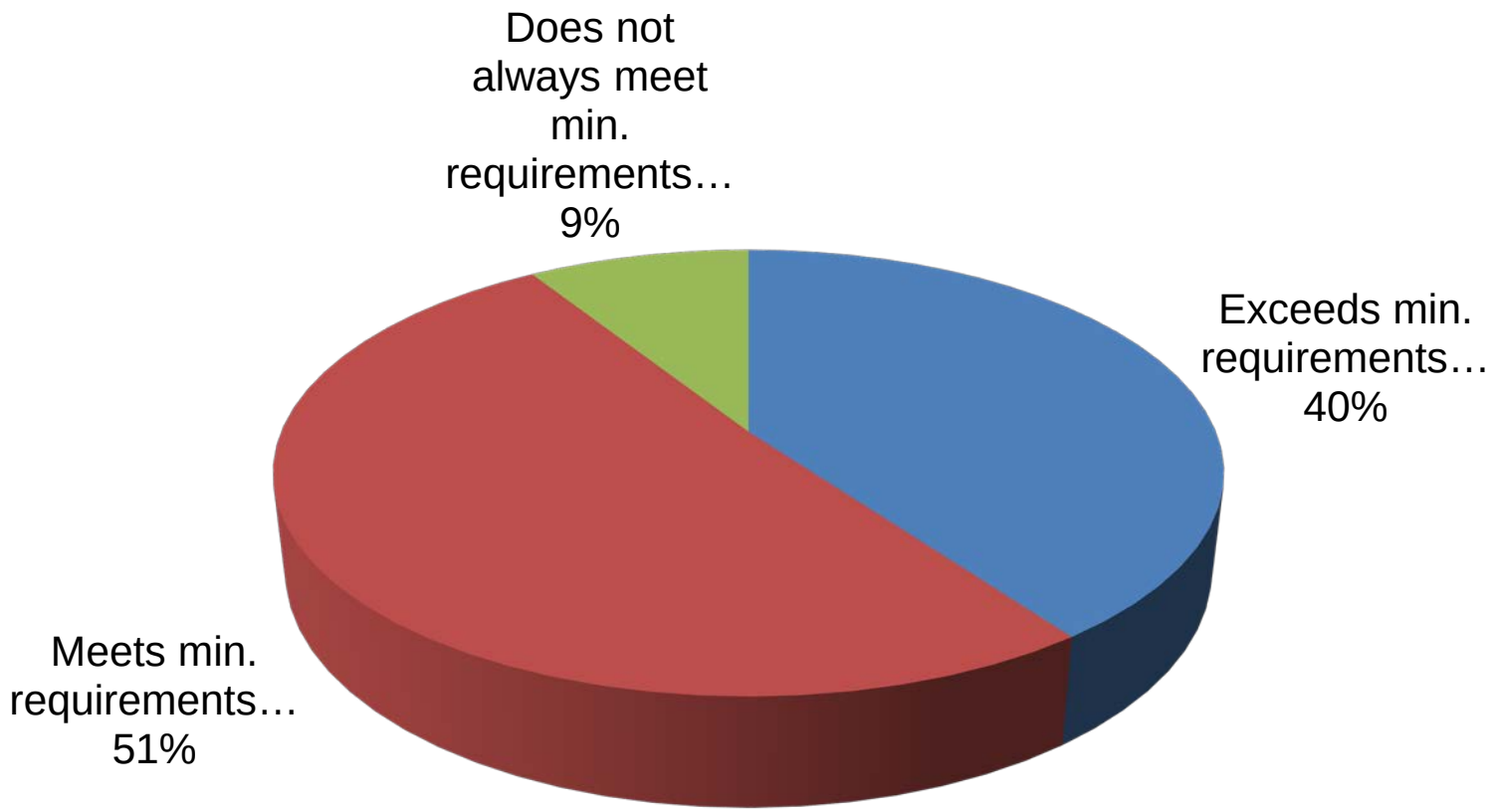
FDA Quality Observations

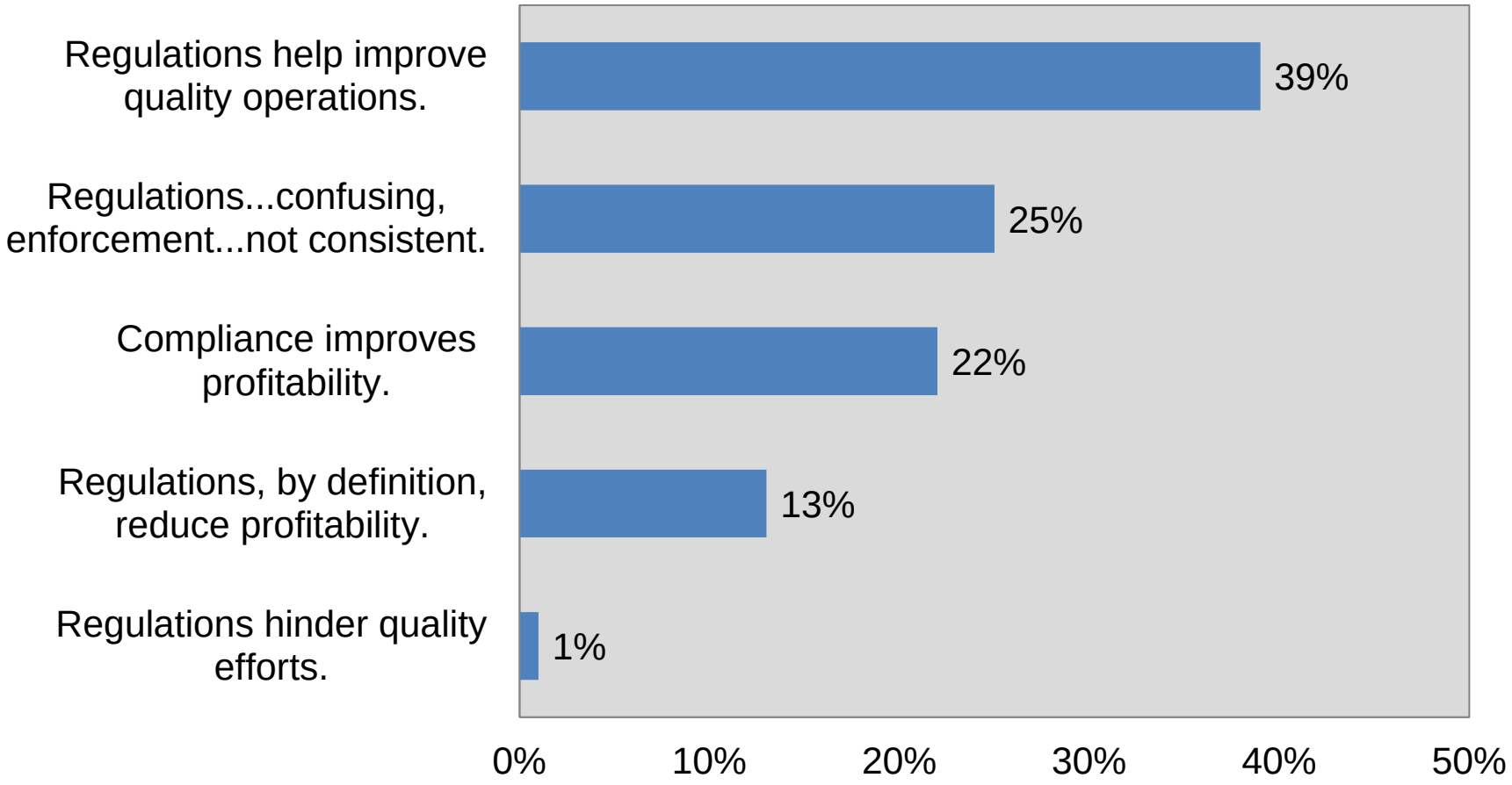
- Quality control procedures not in writing or fully followed
- Lack of investigations of batch discrepancies, failures
- Lack of scientifically sound laboratory controls
- No written procedures for production and process controls
- Procedures for sterile drug products not in writing or fully followed

Top 5 Form 483 observations, 2012–2016

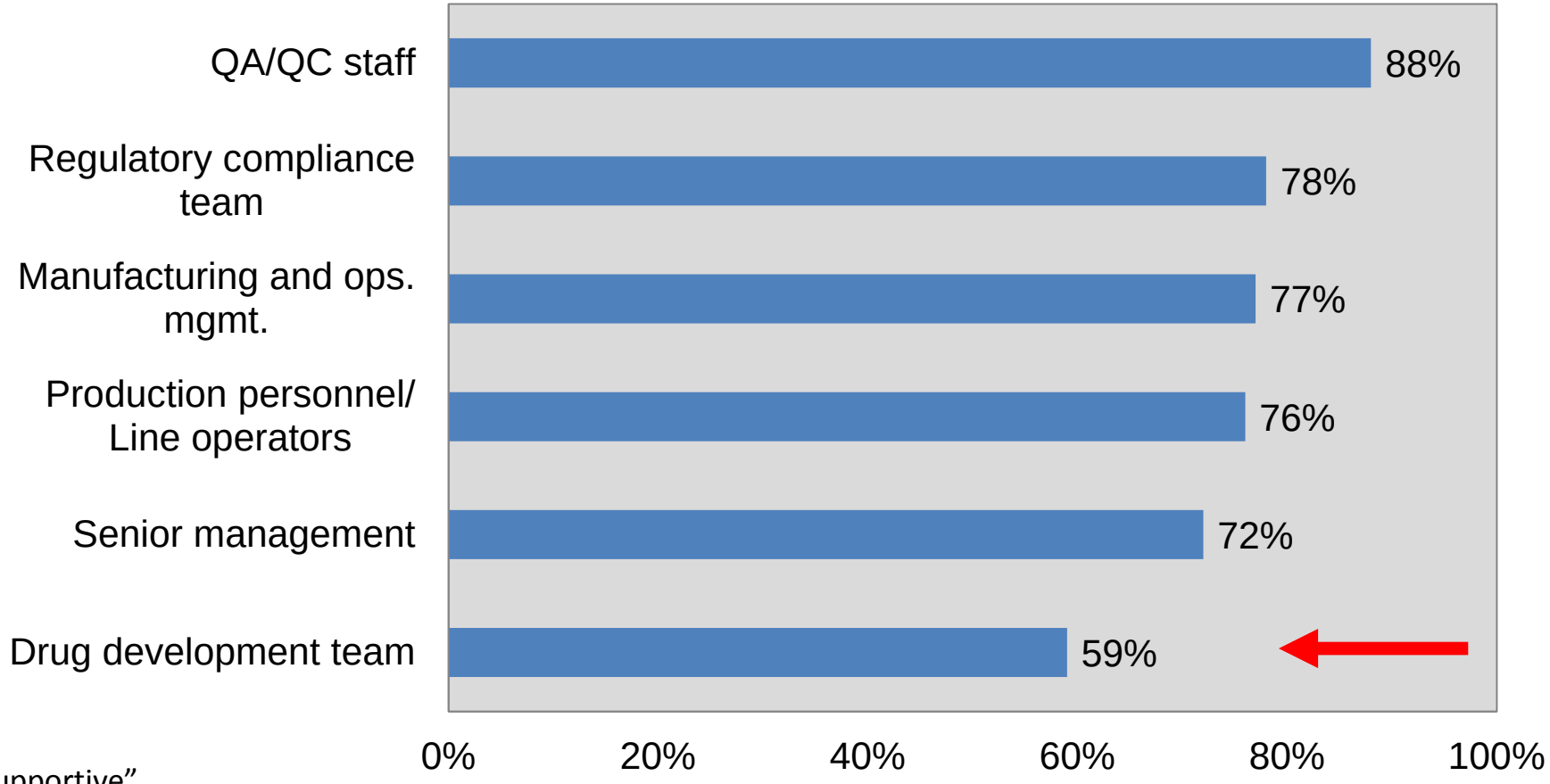
Company's Quality Management Practices



Company's Quality Philosophy

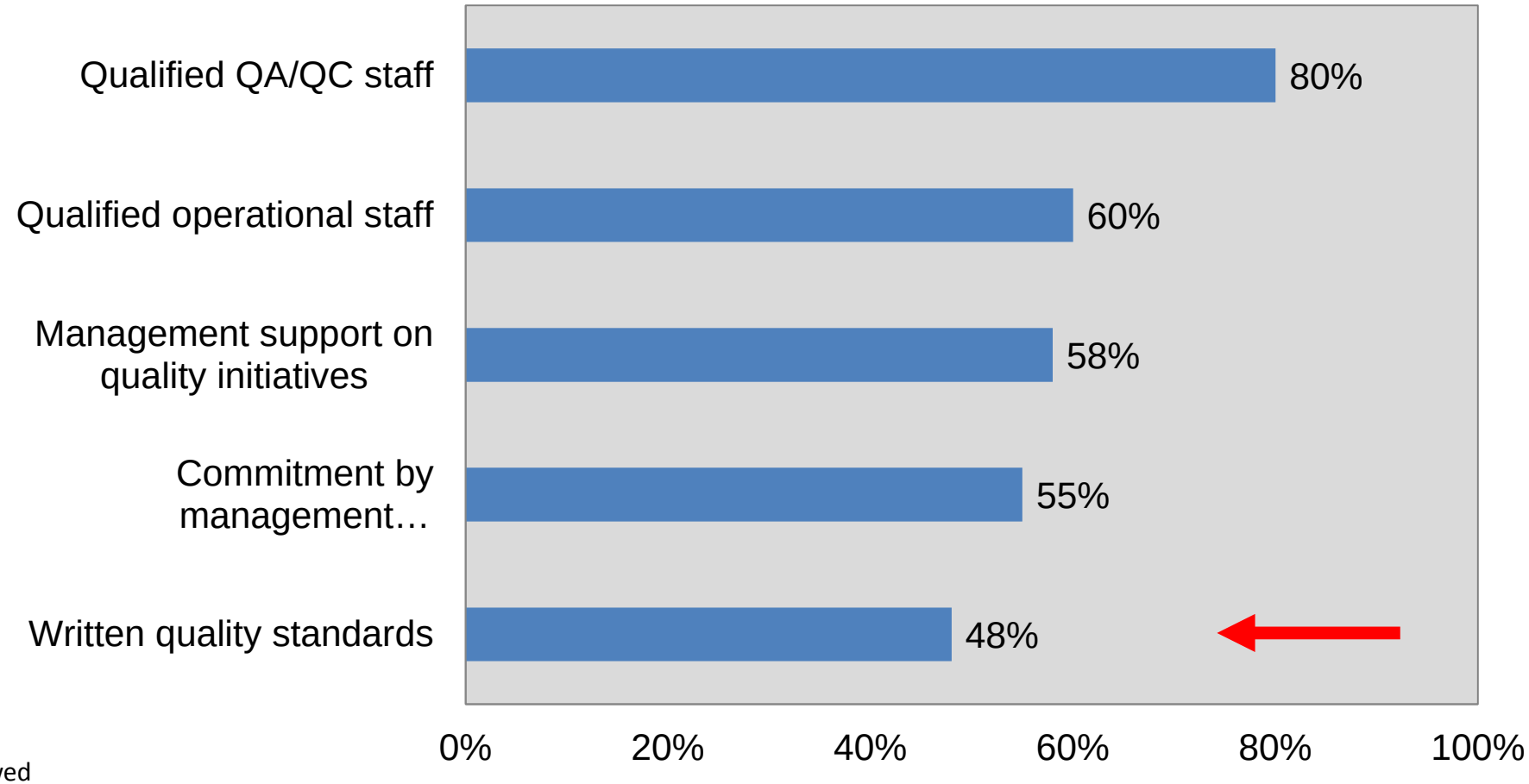


Who Supports GMP Practices and a Quality Culture?



"Supportive or very supportive"

Most Important Resources Needed: Top Responses



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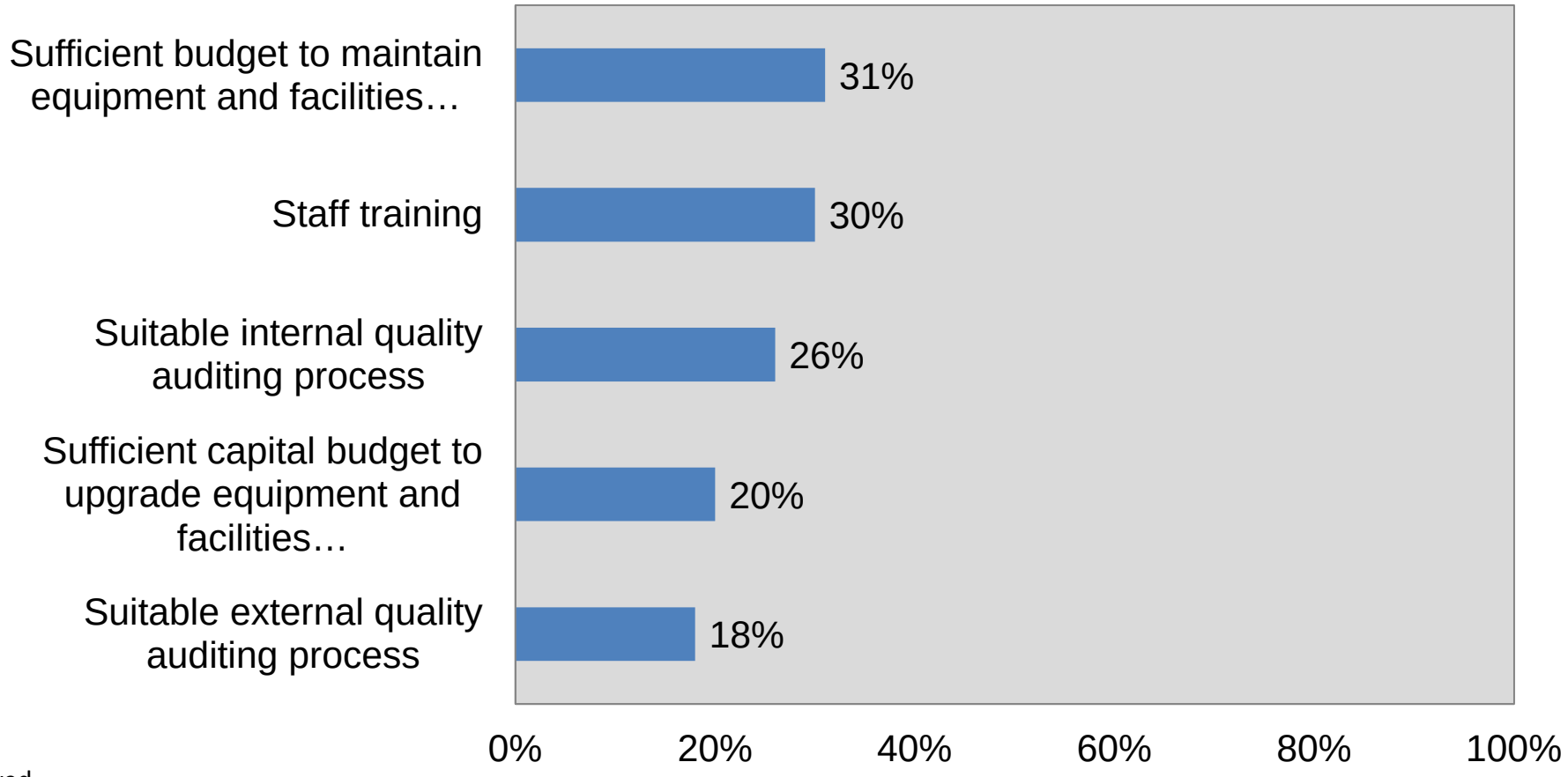
Most Important Resources Needed: Next 5 Responses



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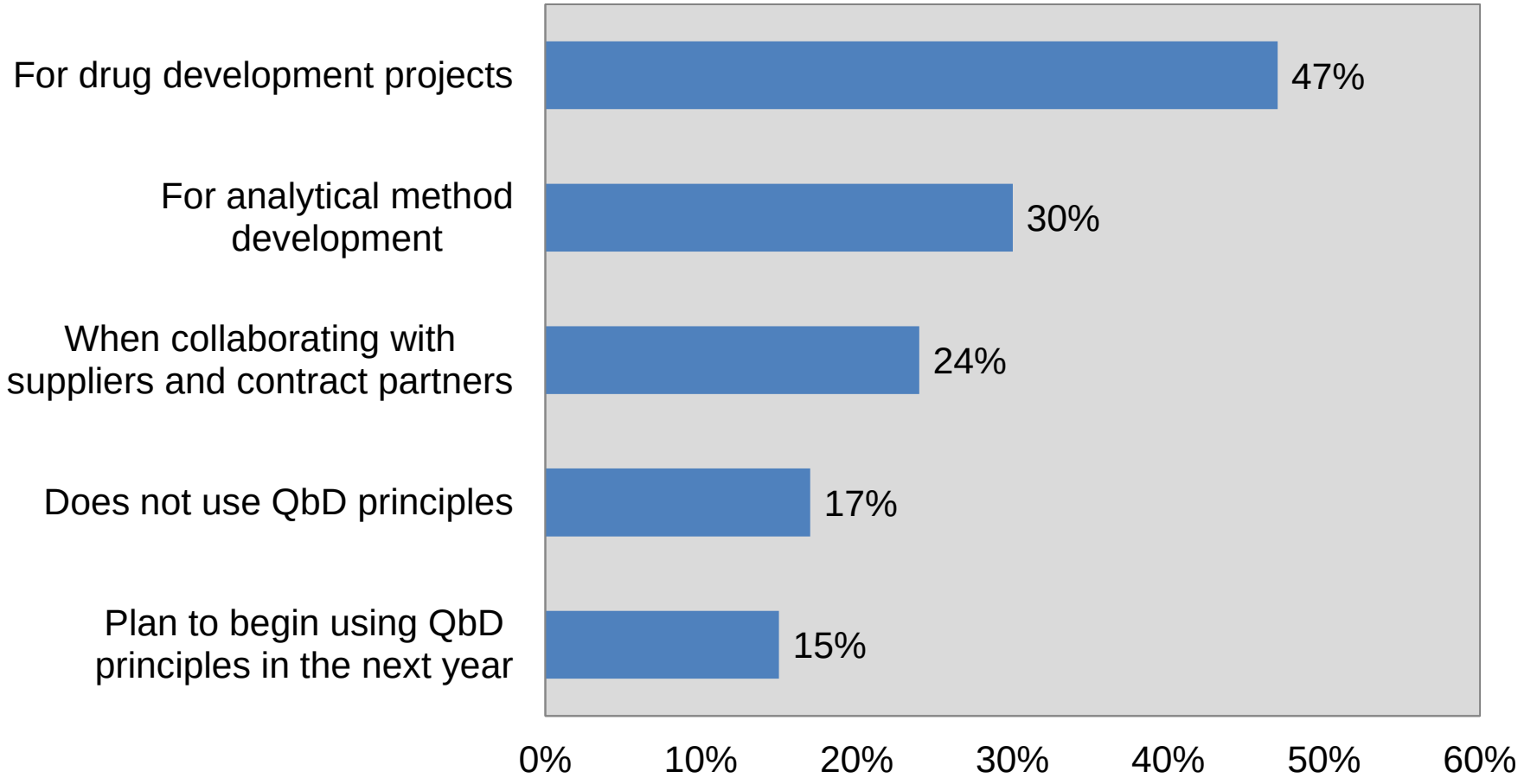
Applications of Quality by Design



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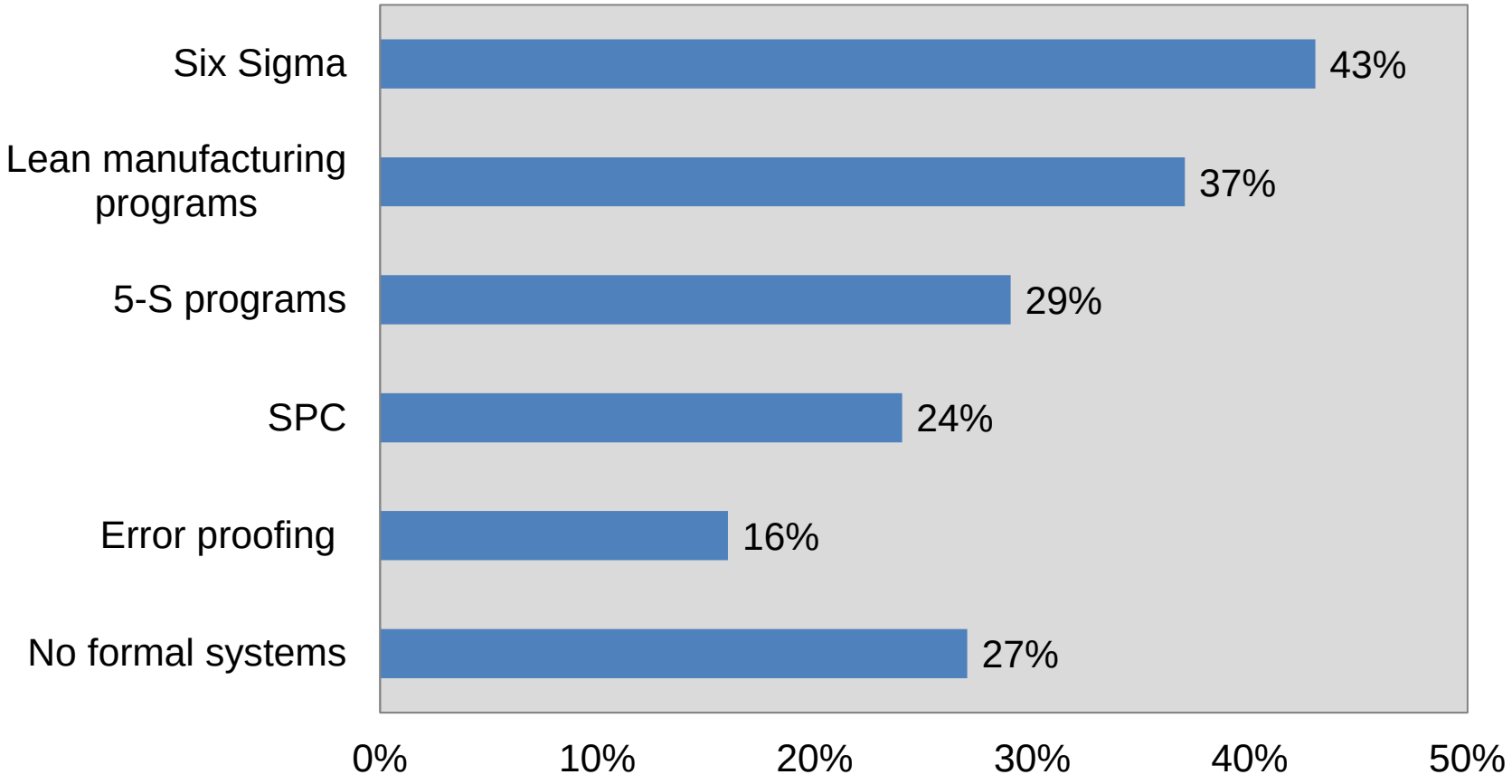
Formal Quality Systems Used



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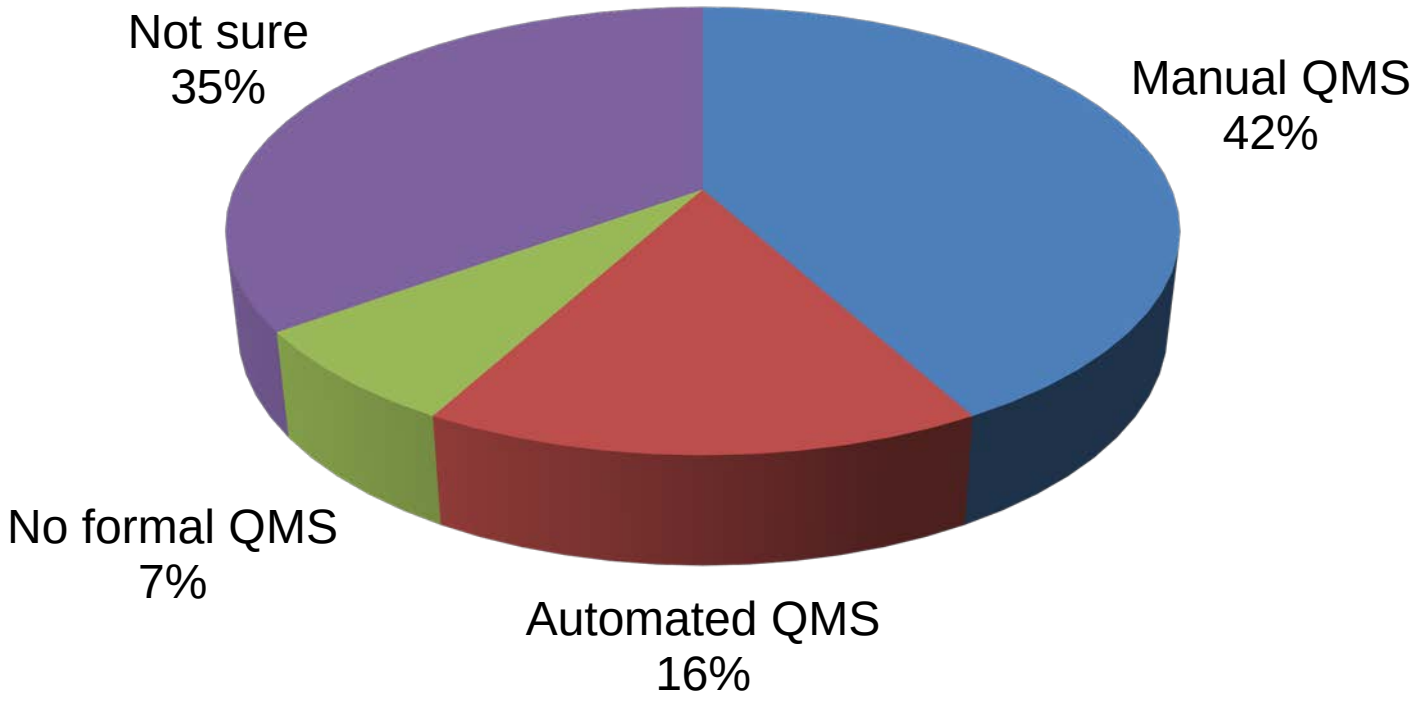
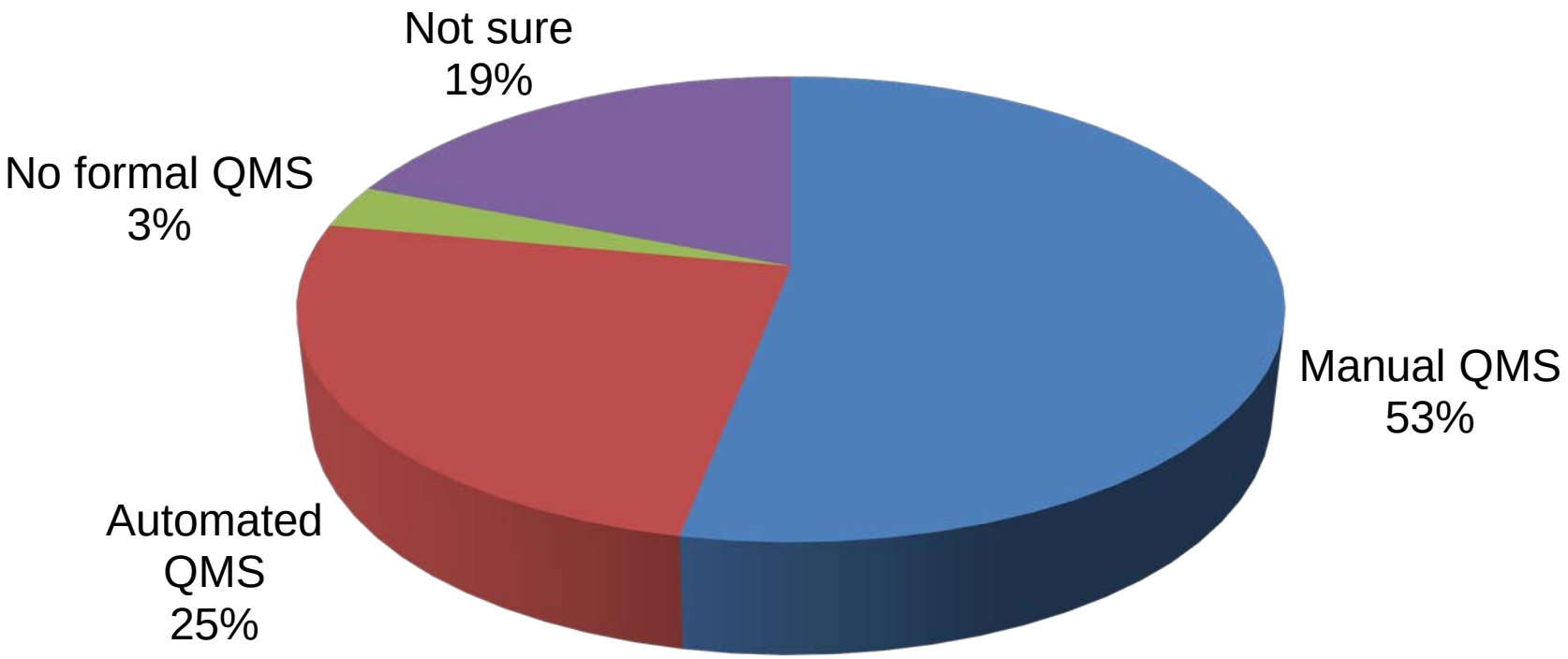
Other responses: Error proofing, ISO 9000, ISO 14001

Quality Management Systems Used Within Organization



Quality Management Systems Used With Outside Suppliers



Quality Practices: Summary

Best Practices

- Effective, trained quality staff
- Meet or exceed minimum quality requirements

Areas for Improvement

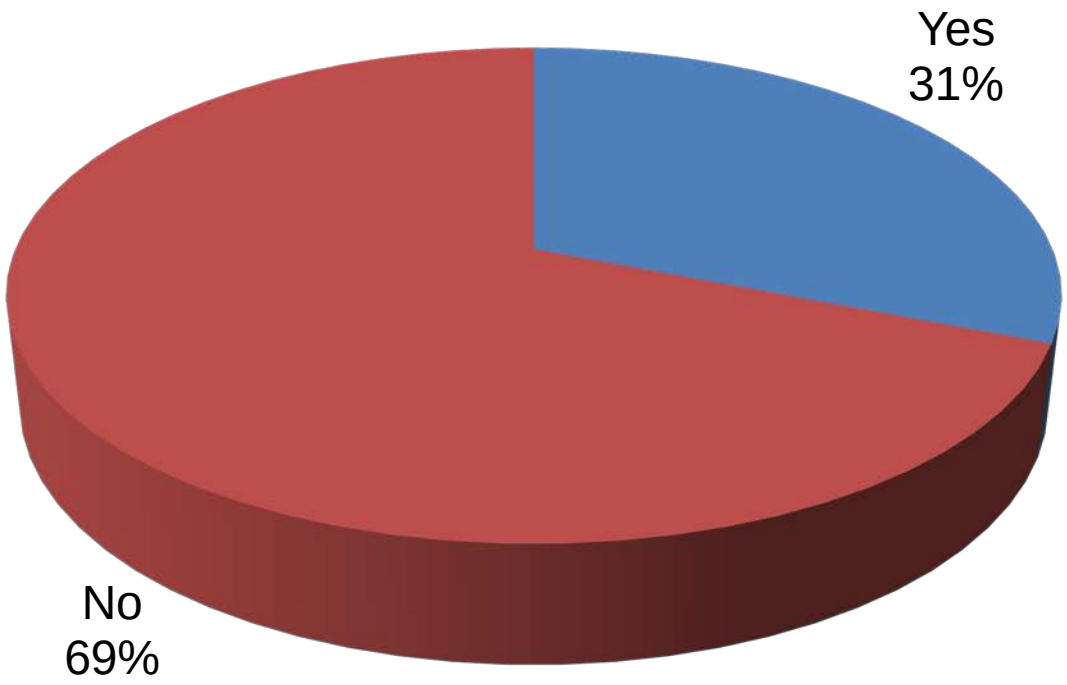
- Place more emphasis on written procedures.
- Consider formal QMS.
- Conduct critical evaluation of quality systems.
- Secure more quality support from drug development team.

Operations and Manufacturing Processes

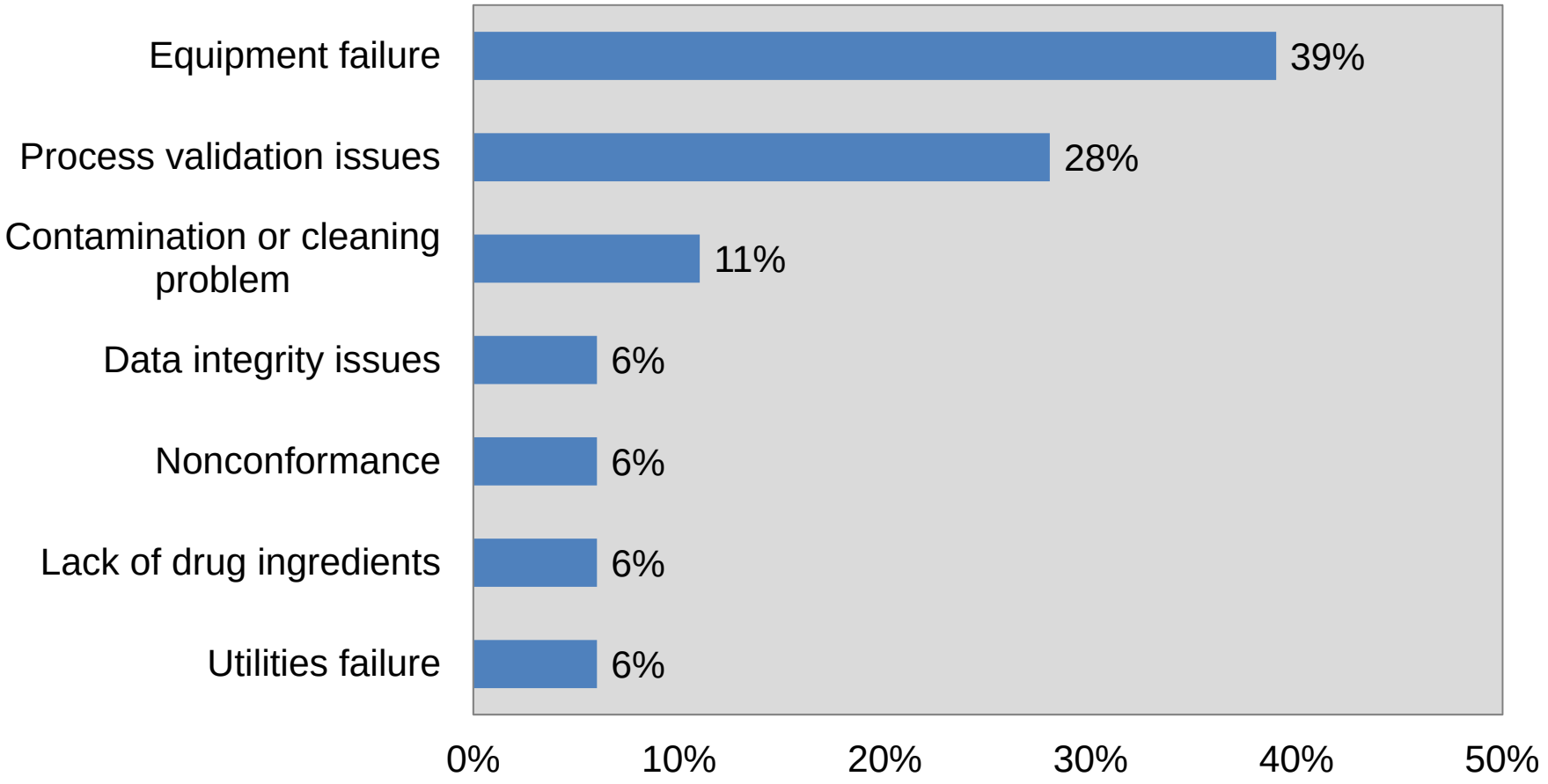
Operations/Manufacturing

- No systematic approach to equipment maintenance
- General lack of formal equipment maintenance programs
- No formal use of metrics to measure equipment performance
- Focus on preventive maintenance
- No predictive maintenance
- Inadequate use of trend analysis to connect process or product problems with equipment performance
- Analytical test method development is a weak spot in quality control operations.

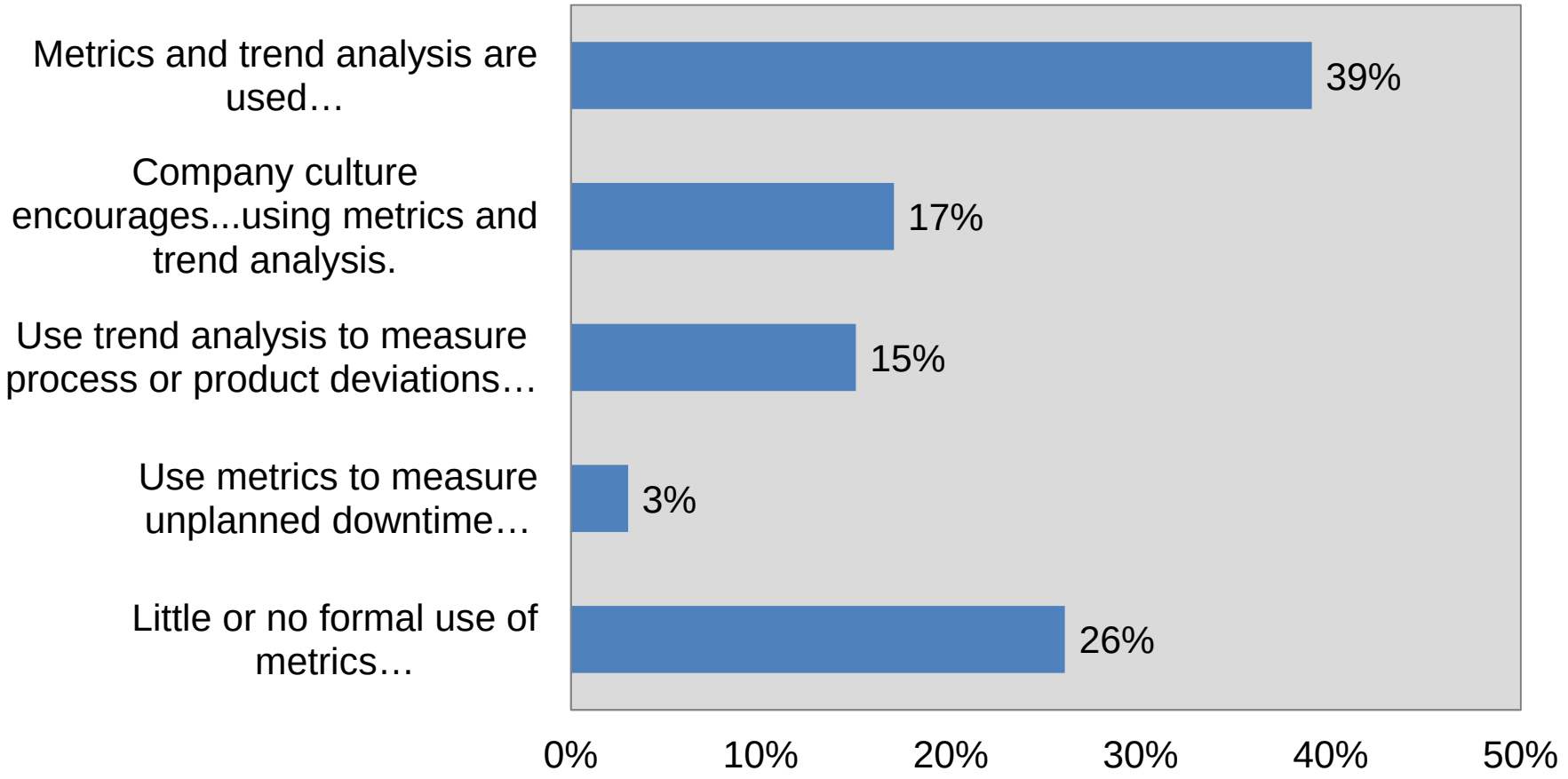
Experienced Any Significant Production or Process Failures in Past Five Years?



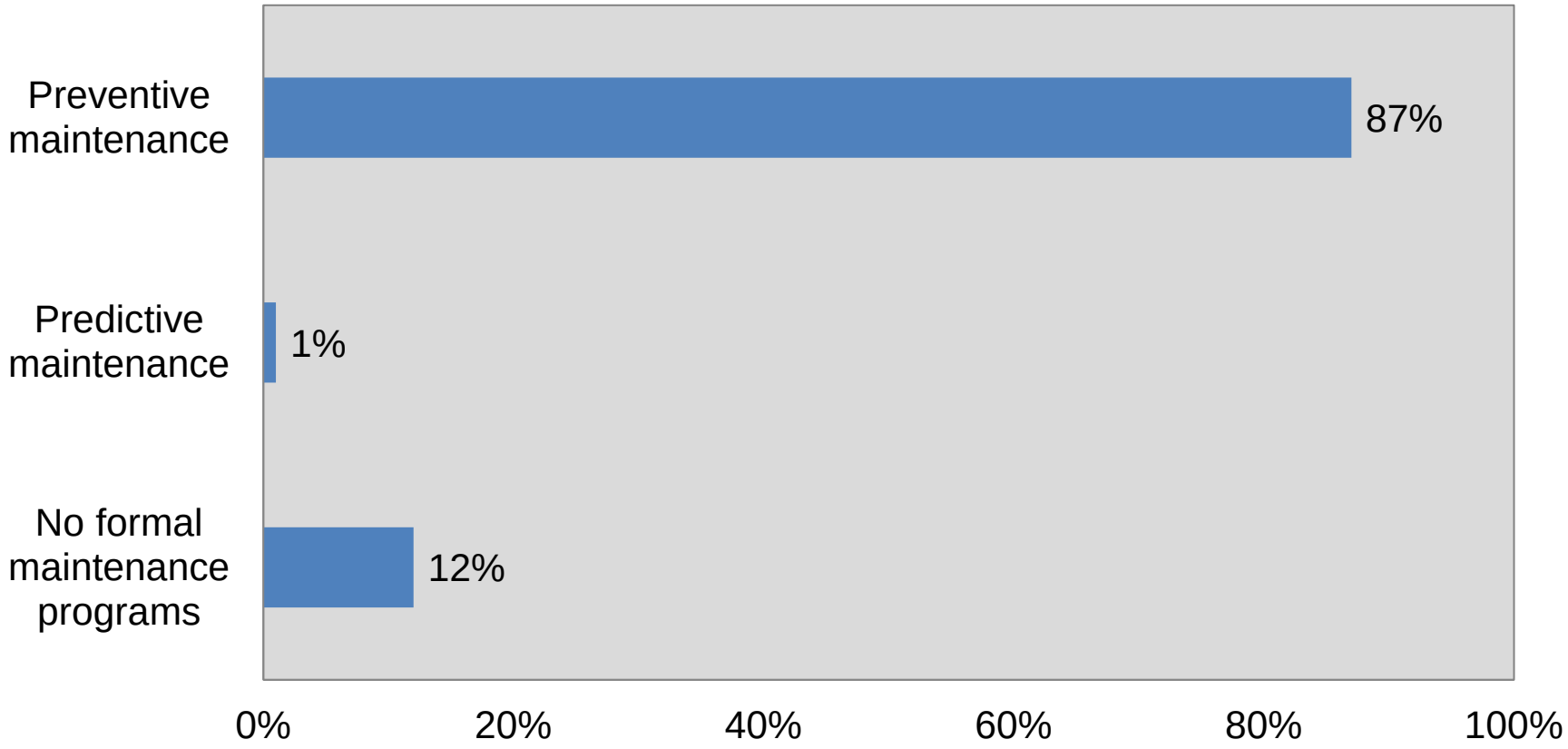
Root Causes of Product or Process Failures Encountered in Past Five Years



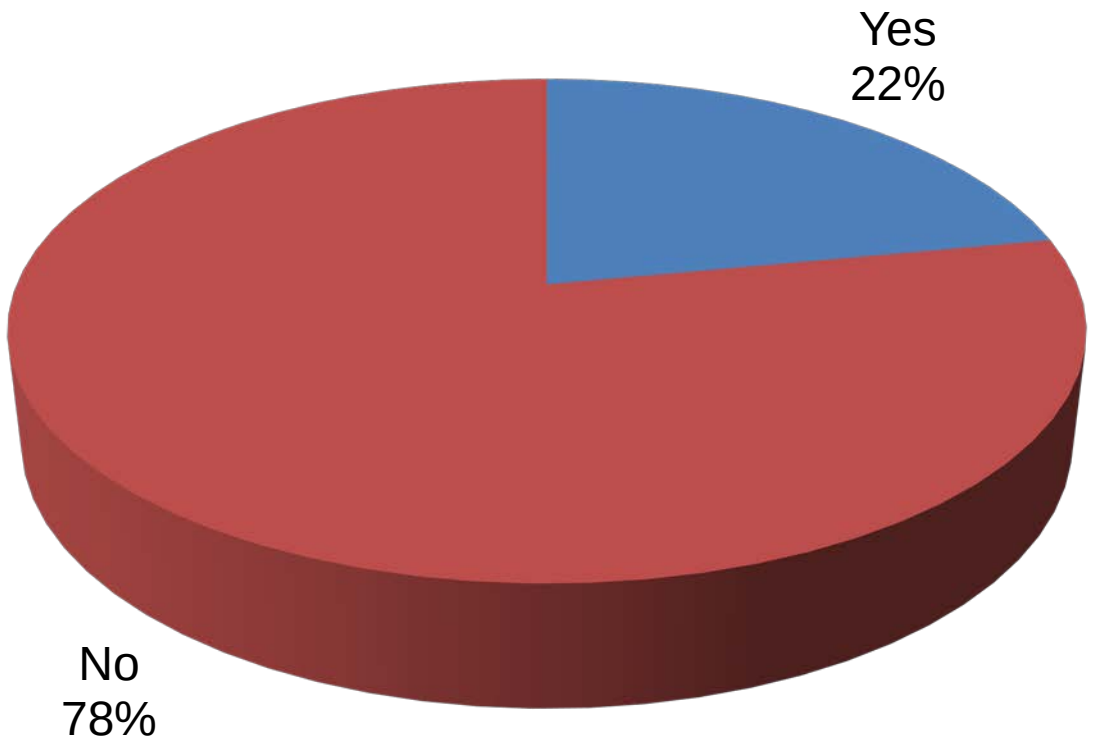
Use of Metrics to Measure Equipment Performance



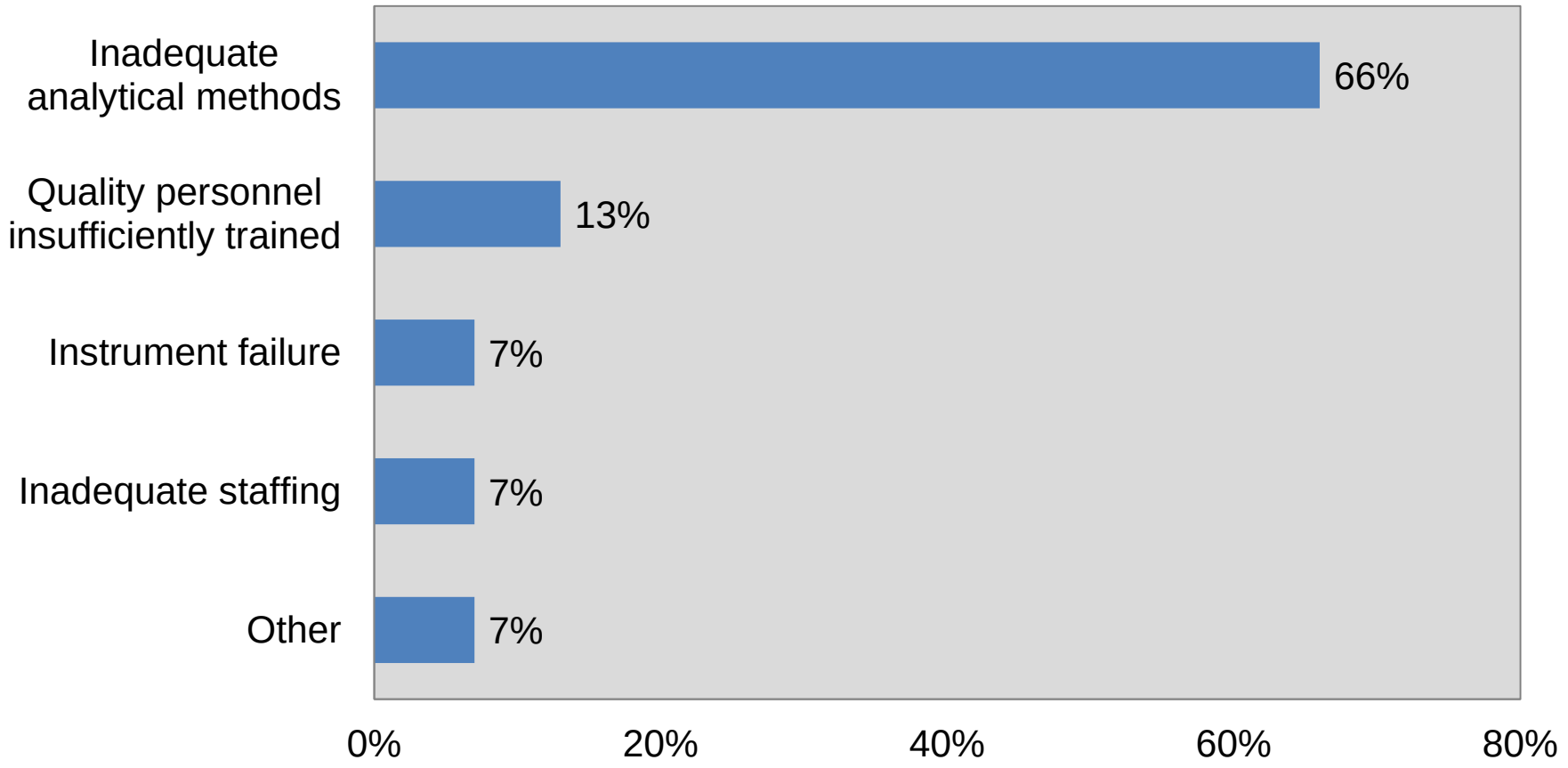
Types of Maintenance Programs in Place



Experienced Any Significant Problems in QC Department in Past Five Years?



Root Causes of Significant QC Problems in Past Five Years



Operations/Manufacturing Summary

Best Practices

- Preventive maintenance is good

Areas for Improvement

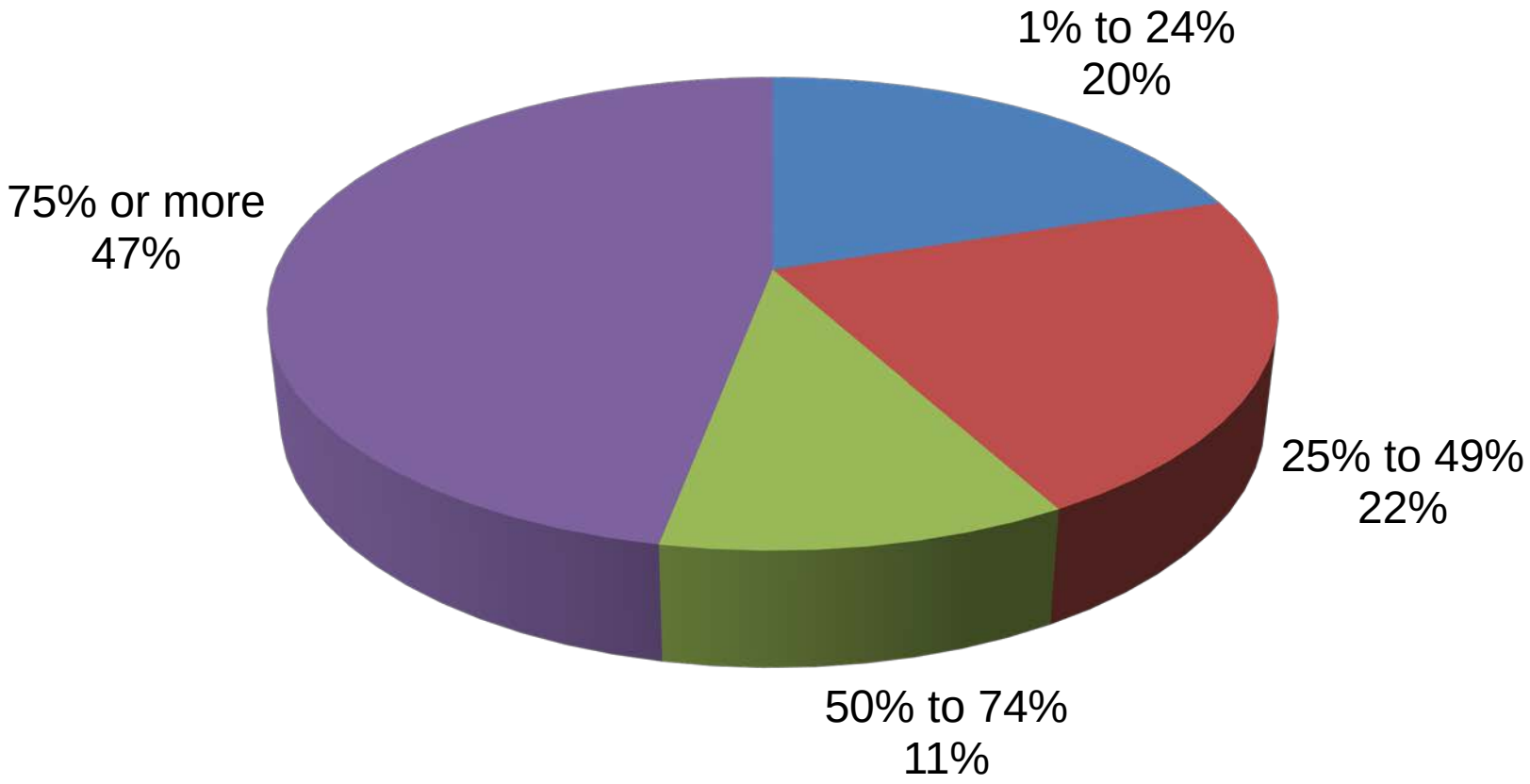
- Need for a systematic and formal approach to equipment maintenance and performance metrics
- More attention to process validation and to cleaning
- More emphasis needed on analytical test method development to prevent downtime
- Use trending analysis to connect plant issues to equipment problems.

Outsourcing and Supplier Oversight

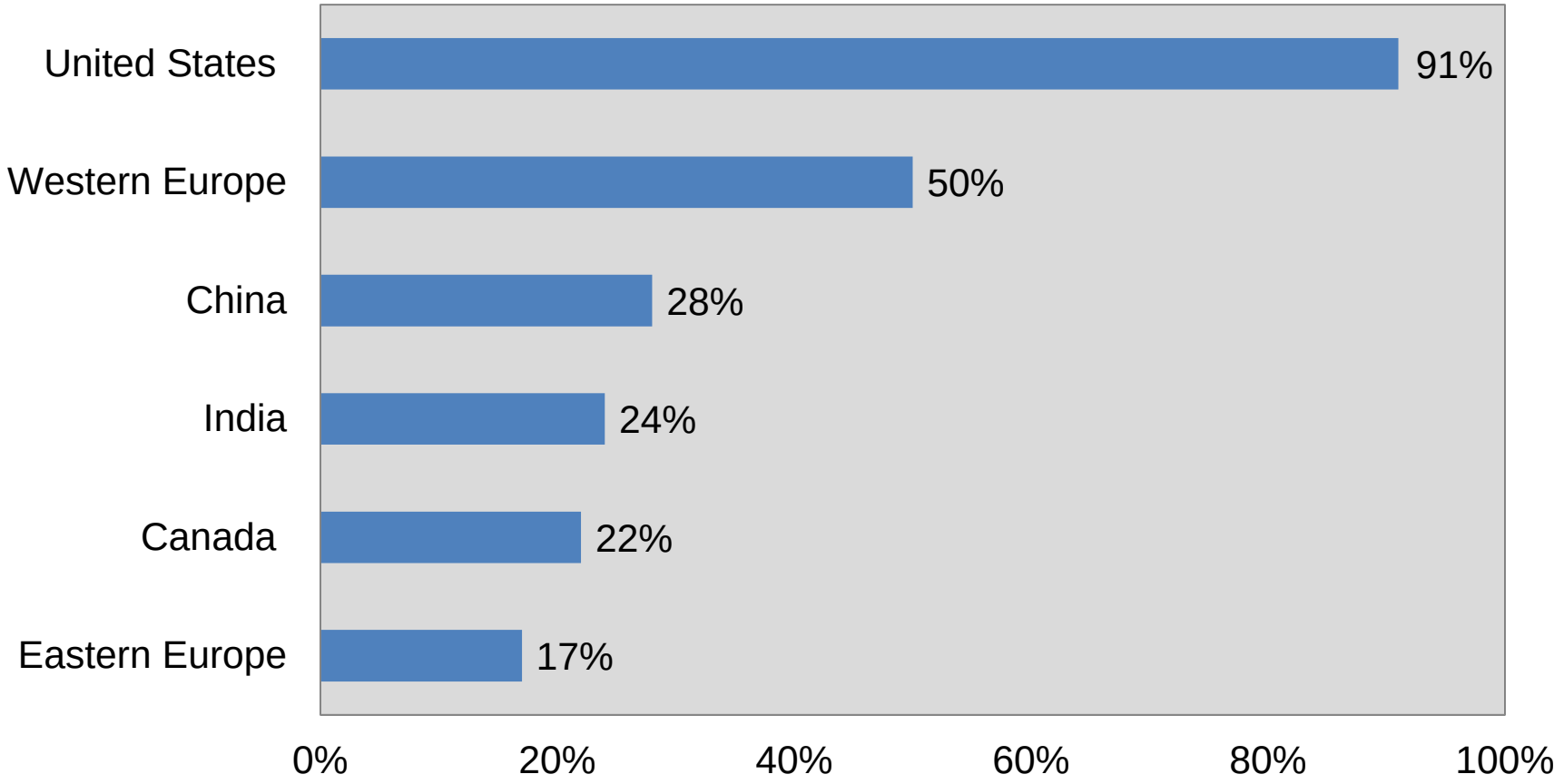
Outsourcing/Supplier Oversight

- 58% of respondent companies outsource at least half of development and manufacturing tasks.
- Most contract partners are based in the US and Western Europe.
- Most sponsors have experienced problems with a contract partner that led to product quality issues.
- Communication can be a challenge, including the clear delineation of responsibilities.

Percentage of Company's Drug Development or Manufacturing That is Outsourced

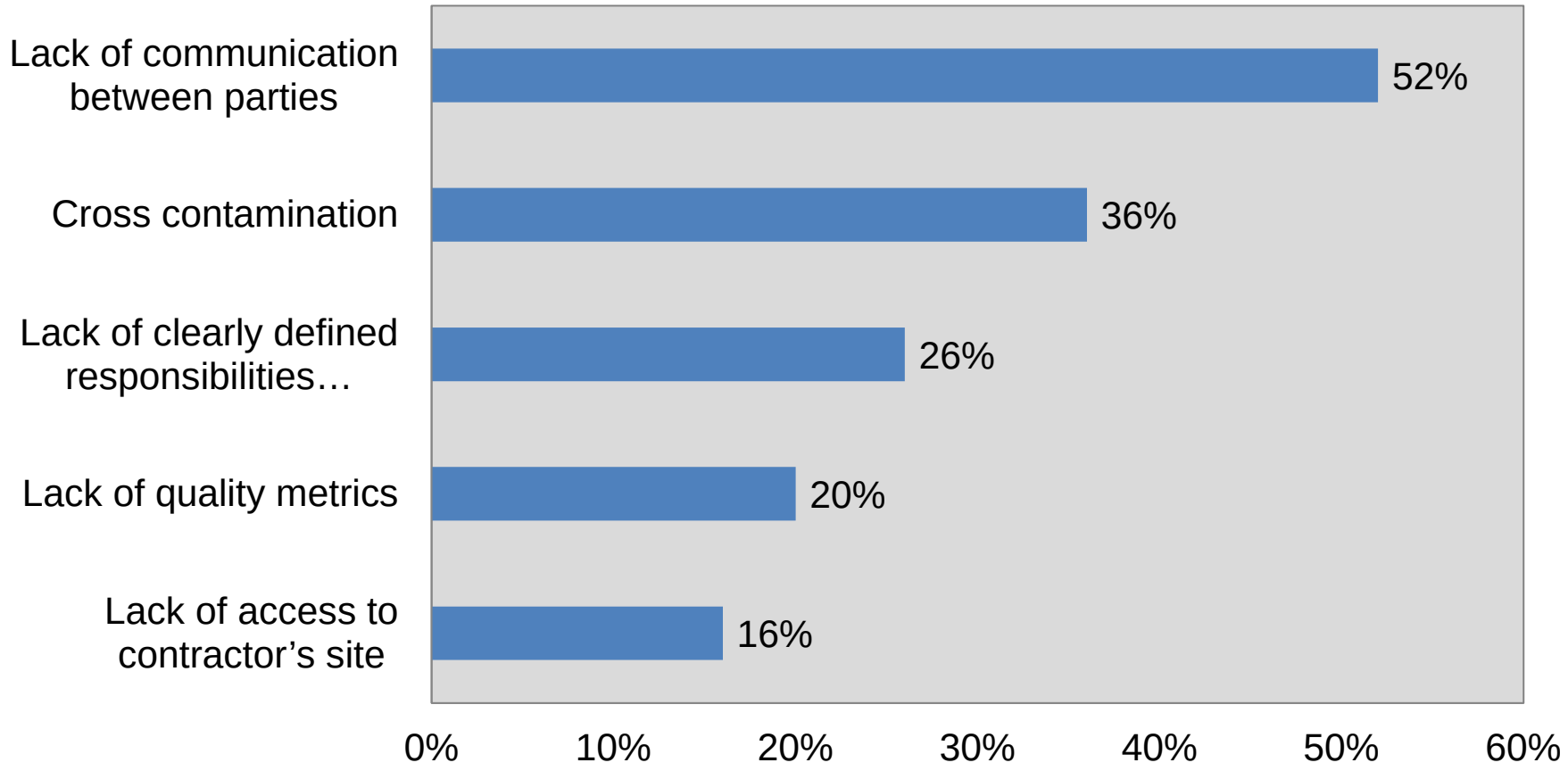


Geographic Locations of Contract Service Providers: Top Responses



Multiple responses allowed

Problems Encountered When Working with Contract Service Providers



Multiple responses allowed

Supplier Oversight

- 71% of respondents have quality agreements with all suppliers/contractors.
- 9% use third-party certifications.

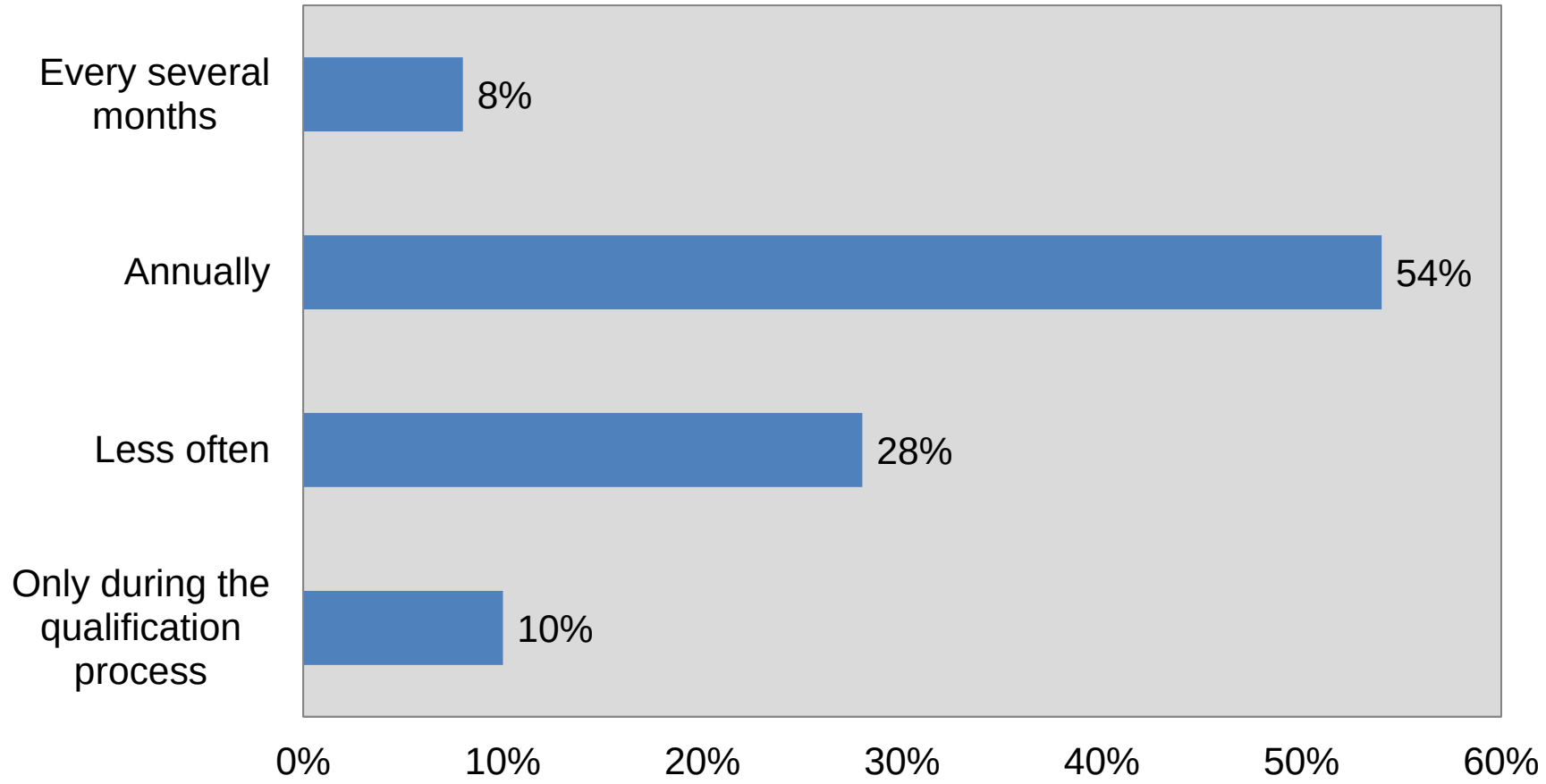
Other responses:

- Conduct audits/inspections themselves
- Conduct mock audits with overseas suppliers
- Use third-parties to conduct audits/inspections
- Have a comprehensive supply-chain risk assessment program

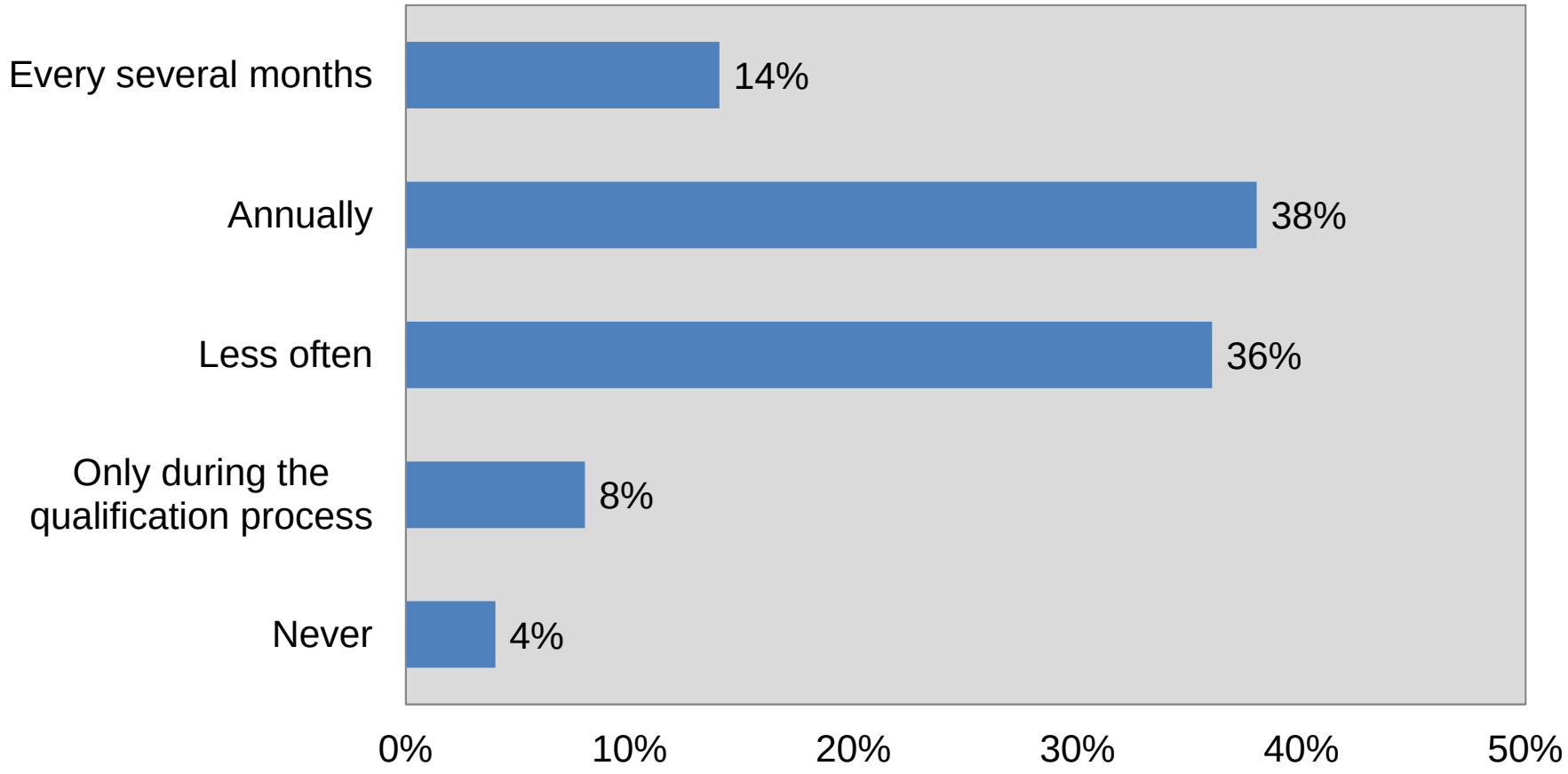
Supplier Oversight

- Communication with contract partners
  - Weekly: 60%
  - Monthly: 20%
  - Daily: 6%

Supplier Facility Audits: Onshore



Supplier Facility Audits: Offshore



Outsourcing/Supplier Oversight Summary

Best Practices

- Quality agreements are in place.
- Most companies are performing onshore audits at least annually.

Areas for Improvement

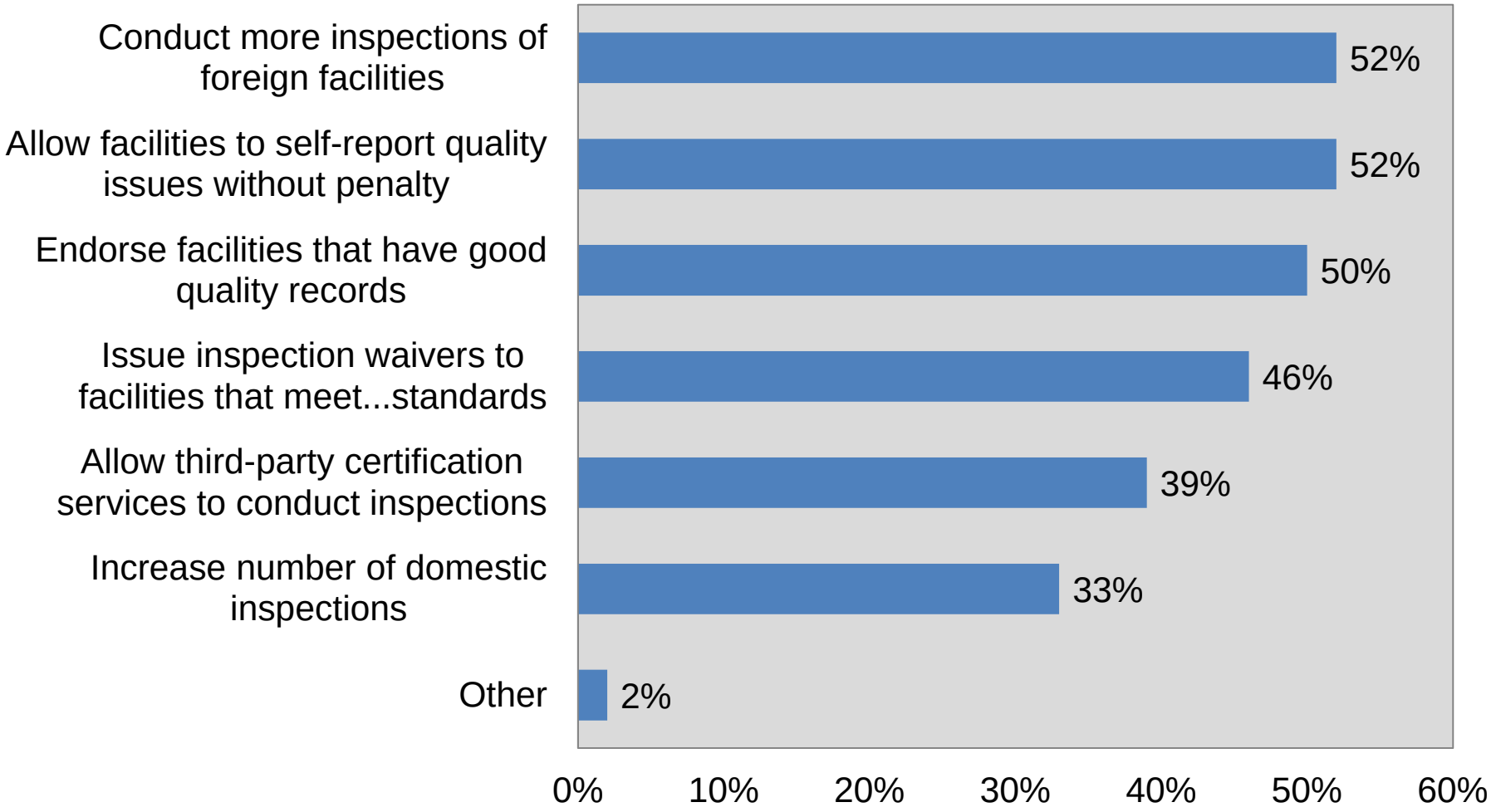
- More audits are needed, particularly offshore.
- Better, more frequent, communications would help prevent misunderstandings.
- Greater clarity is needed in defining responsibilities for both sponsor and service provider.

Working with Regulatory Authorities

FDA's Role in Quality Efforts

- Believe that FDA could improve drug quality by inspecting more offshore facilities
- Favor the use of self-reporting and inspection waivers to facilities that meet predefined quality metrics
- Are communicating more frequently with FDA
- Refer to guidance documents, rather than inspection reports, to improve compliance and quality practices
- Rate guidance on data integrity and quality agreements as useful, followed by quality metrics guidance

How Can FDA Improve Drug Quality?



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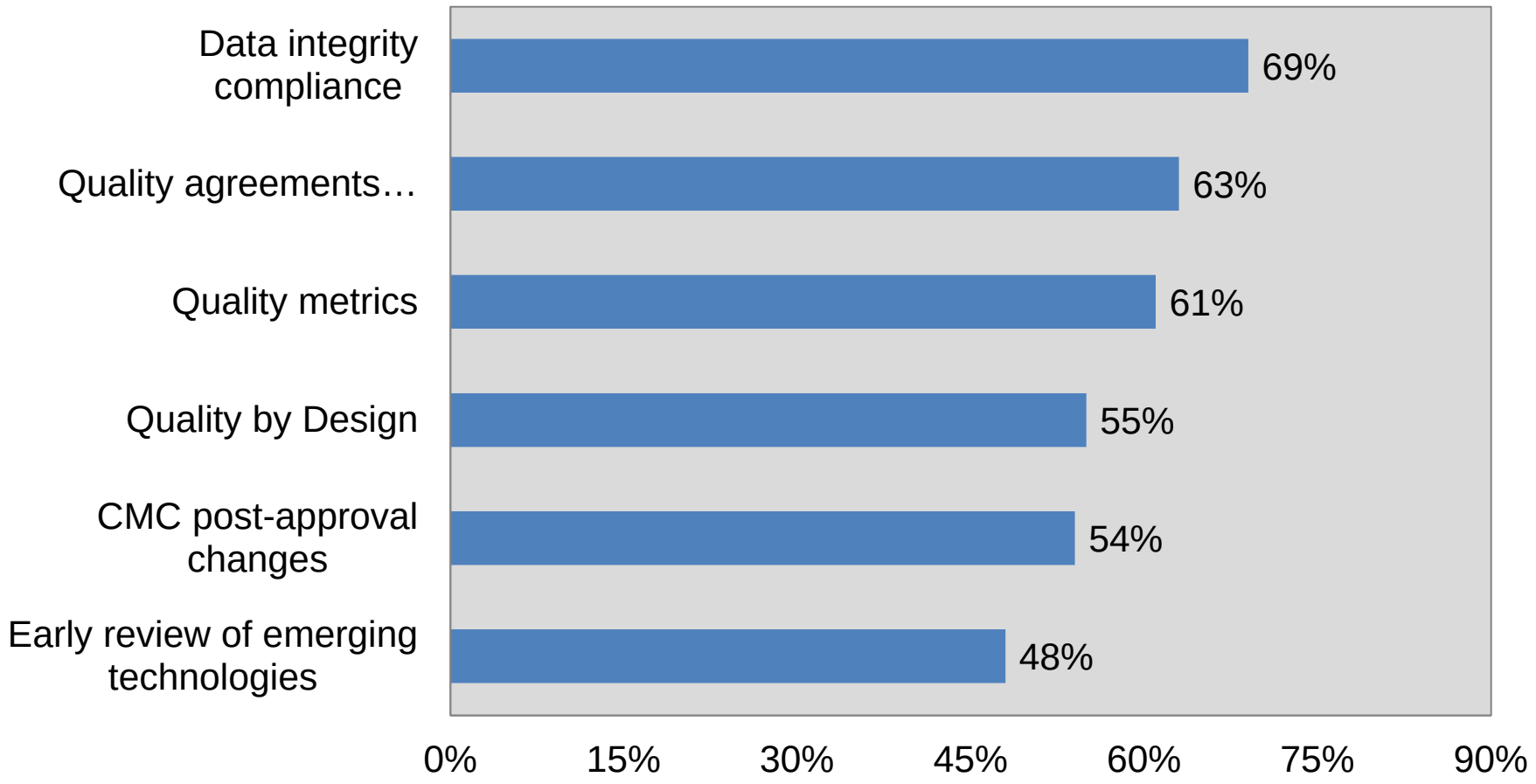
Usefulness of FDA Guidance and Initiatives



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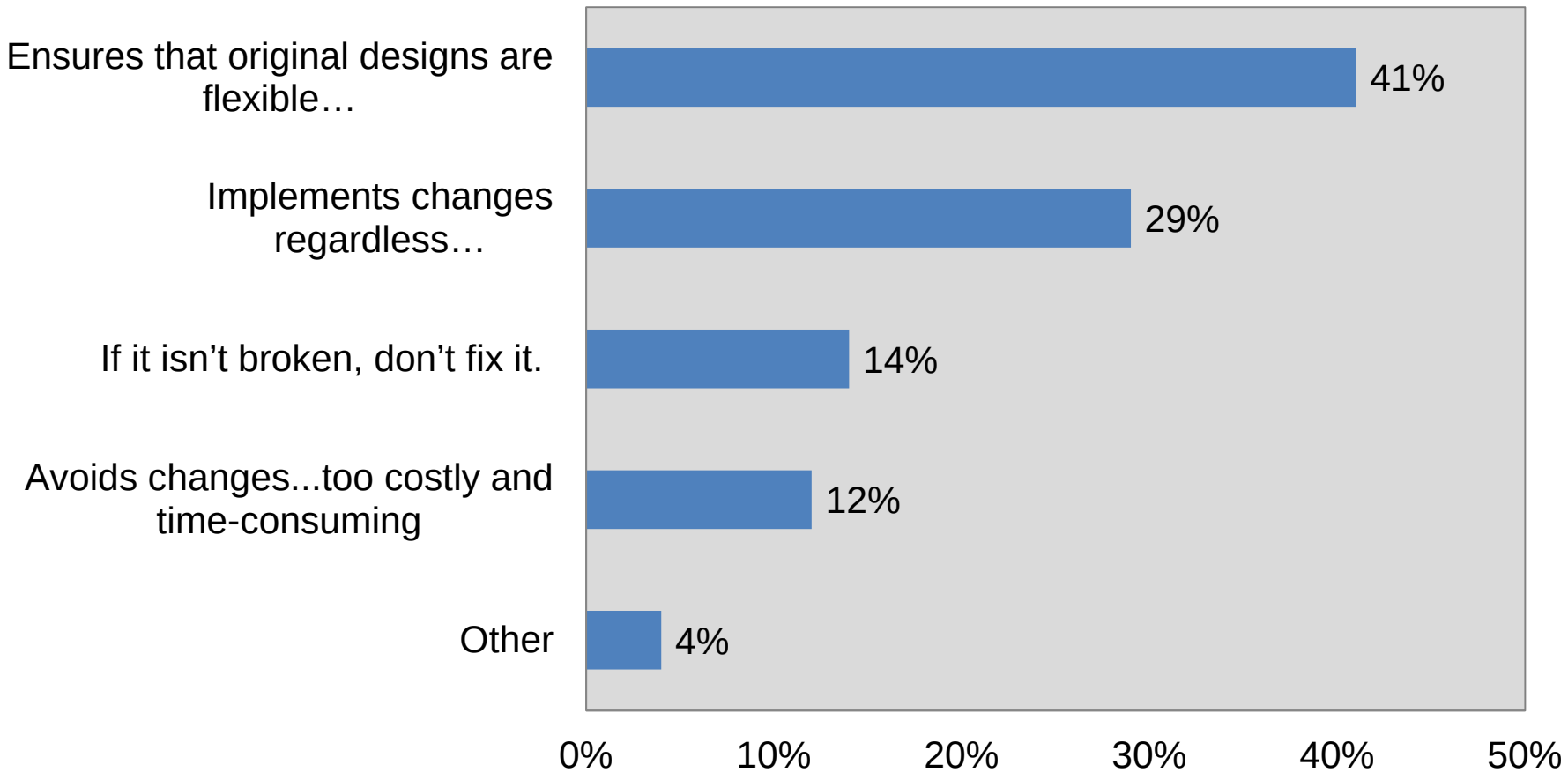
Post-Approval Changes: Company Attitudes



Working with Regulatory Authorities

Best Practices

- Communication and face-to-face meetings with FDA staff
- Regular consultation of guidance documents

Areas for Improvement

- Use inspection reports to improve operations.
- Sponsors should employ stricter auditing of offshore suppliers and contract partners.
  (Don’t wait for FDA to do it.)
- Greater use of trending and formal approaches to equipment and maintenance, and root cause analysis.

General Observations

- Importance placed on quality staff members (people focus vs. process or procedural focus)
- Lack of emphasis on written quality standards
- Lack of formal or automated QMS
- Lack of formal maintenance programs
- Inadequate communication with, and limited supervision, of suppliers especially offshore
  - However, expectation is that FDA should audit more suppliers

Recommendations

- Greater use of inspection reports and not just guidance documents
- Need for metrics and systematic, holistic practices for maintenance, equipment OOS, and quality issues
- Management and development team support of quality systems, practices, and GMPs
- Consider automation, software, etc., to facilitate quality efforts.
- Thorough evaluation of existing quality systems and efforts by internal and external quality experts

Thank you

Additional survey details will be published by

Pharmaceutical Technology and *BioPharm International*

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