GLOBAL EXPERIENCE & SURVEY RESULTS

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BIOGEN

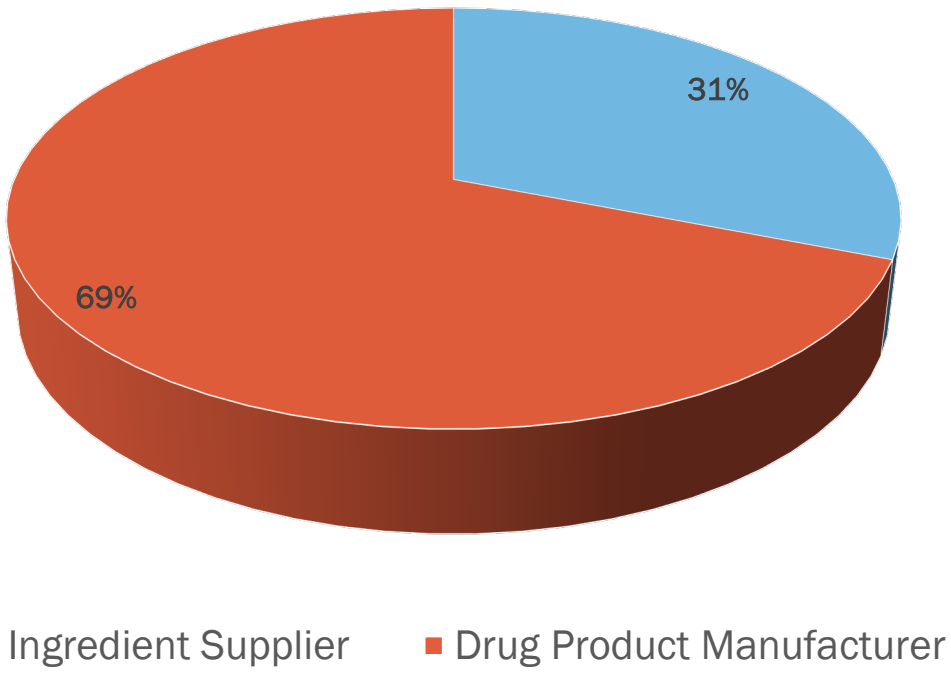
GLOBAL EXPERIENCE

GLOBAL IMPLEMENTATION – A LONG WAY TO GO

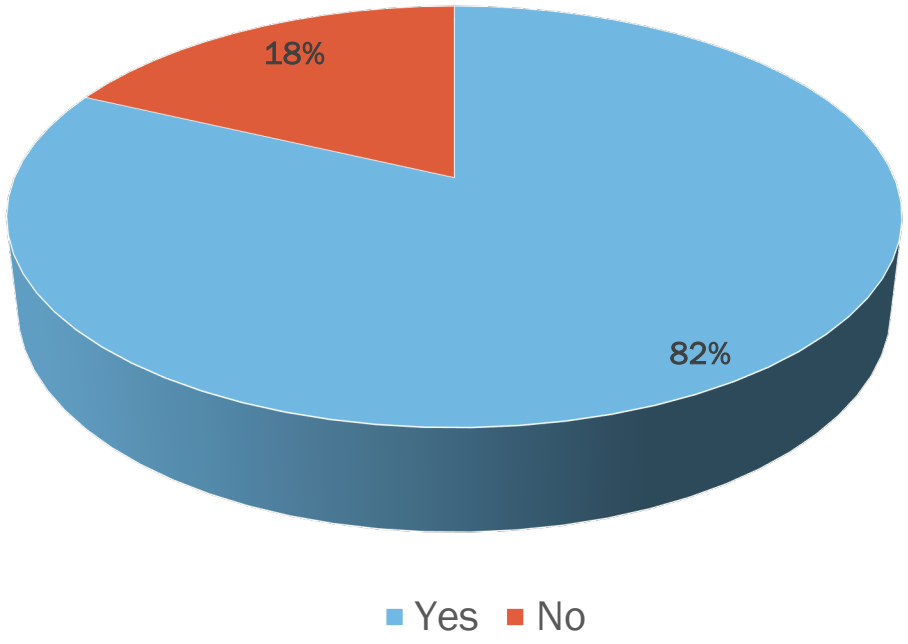
- Diversity of implementation for both new and existing products
  - Some still reference Heavy Metals
  - Some are filing Q3D
- Ensure Affiliates /Packaging Facilities are aware of the Risk Assessment and Elemental Impurity Profile

PQRI SURVEY RESULTS:
STATE OF IMPLEMENTATION OF ICH Q3D

WHO PARTICIPATED



ENQUIRIES FROM HEALTH AUTHORITIES OVER PAST 2 YEARS



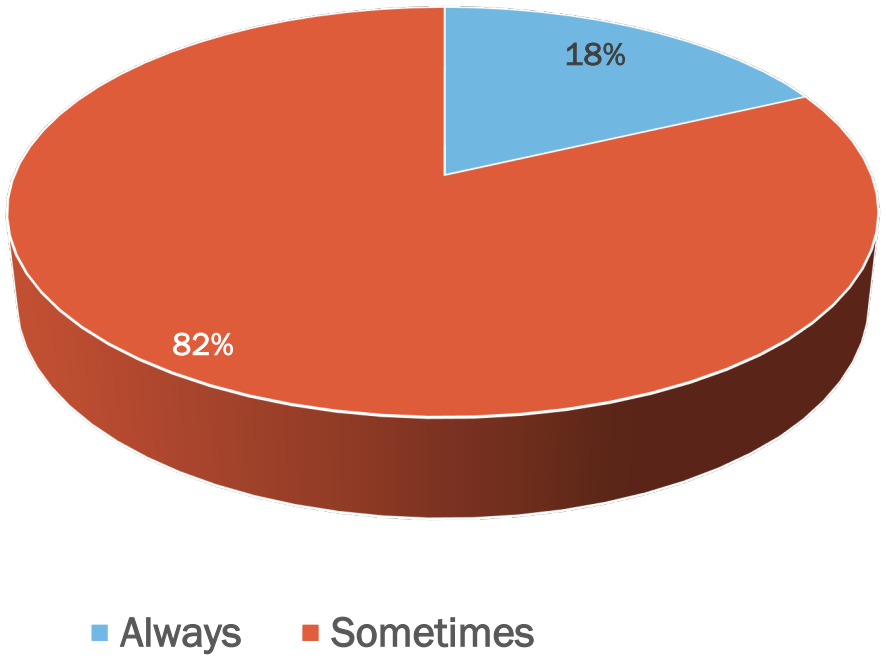
Requests are evolving over time with agency experience

Regulatory Questions, Feedback, Request for additional information

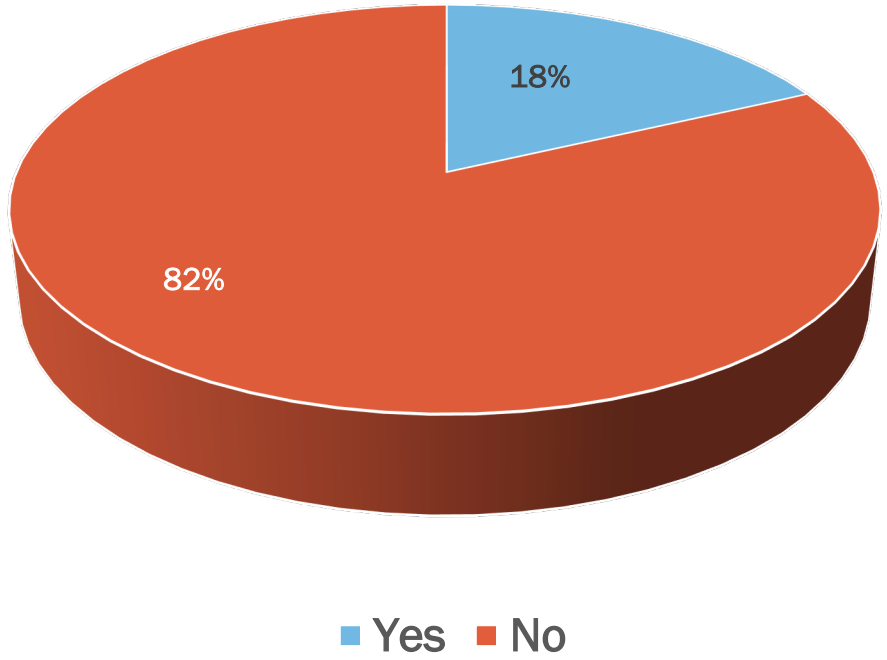
CONCERNS REGARDING ENQUIRIES

- Numerous questions around analytical method performance
- Requests for the risk assessment option to be declared on DP specifications and CofAs
- Requests for supplier statements/ methods used / validation data / vendor CofAs
  - NOTE: Suppliers are not obligated to provide this information
- Agency requesting control of EI for ingredients with the Drug Product option was requested
  - In direct conflict with ICH guidance – justification was finally accepted
- Agency expectation for routine testing of drug products
  - When class 1 metal theoretically exceeded 30% threshold based on worst case use of limit value test
  - Finished product testing confirmed that class 1 metal was well below 30%

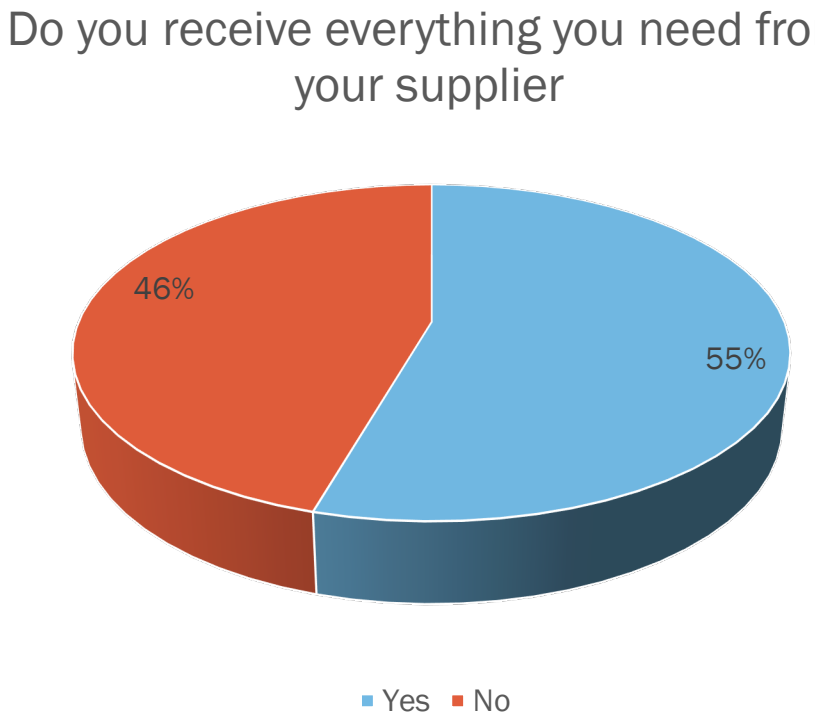
SUPPORT FROM SUPPLIERS



Received support when needed



Change in level or quality of support



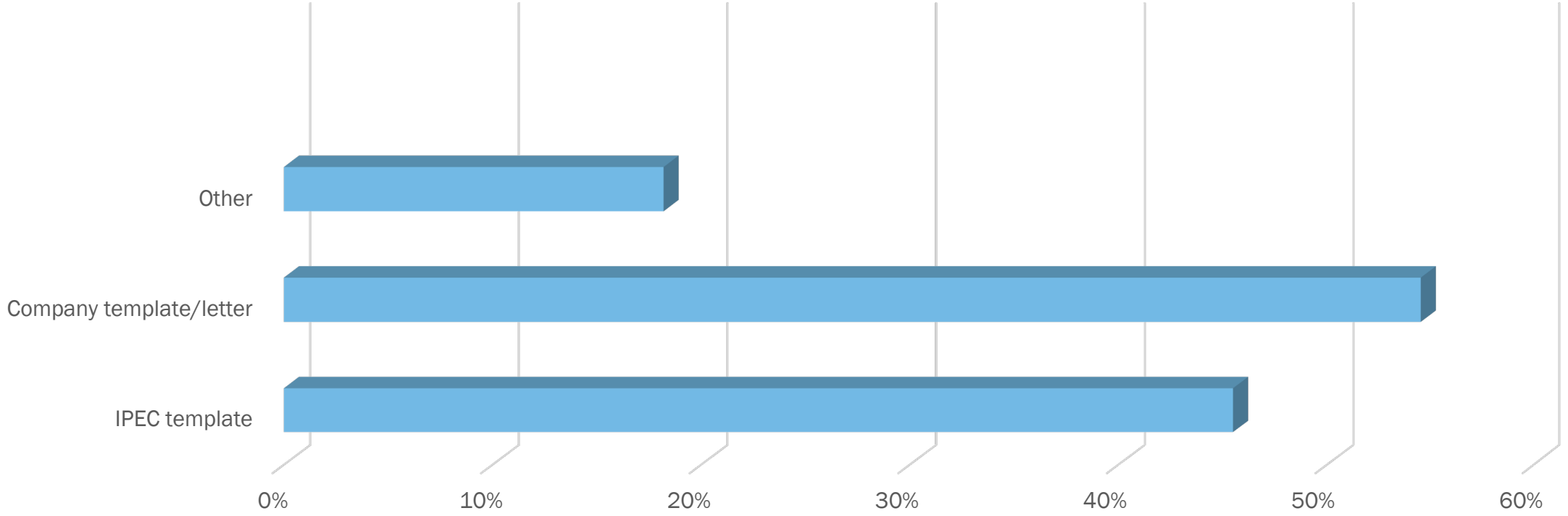
- If not, how do you complete risk assessment
  - Followup with supplier
  - Use available information in literature
  - Other sources of information
    - Empower reports
    - Lhasa Database
  - Finished product screening

PRODUCT TESTING

- 46 % of companies test in all cases
  - 3 batches or more based on PDE/Threshold
  - All DP tested to support risk assessment
  - Screening of excipients
- 55% only when not enough information

INFORMATION GATHERING

Additional outreach sometimes needed (91%)



RISK ASSESSMENTS AND MITIGATION

Overall

- Drug Product near or exceeds Q3D Limit: (1-5%)
  - Control strategy
  - Depends on the dosage (ie daily vs monthly)
  - Testing of drug product
- Drug Product is near or exceeds 30% control threshold: (1-10%)
- Drug product is well below 30% control threshold: (95-100%)

Components

- Component exceeds 30%
  - Control strategy
  - Testing
  - Work with supplier
  - Analyse drug product
  - Search for another supplier

OPTIONS

- Data was variable across use of different Options
- Option 1 and 3 most commonly used
- Option 2a/2b slightly less common

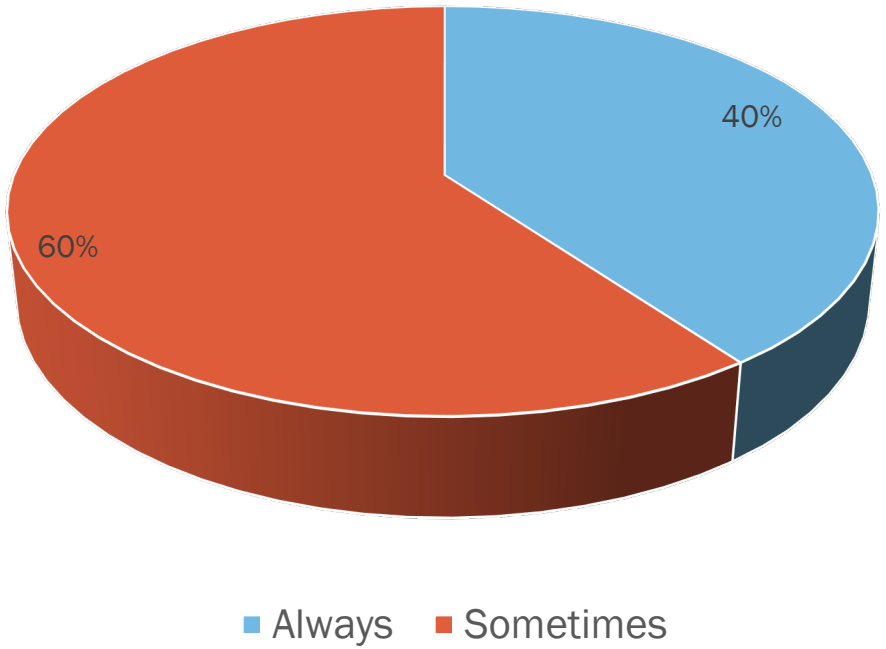
TESTING

75% of participants increased internal capacity for testing

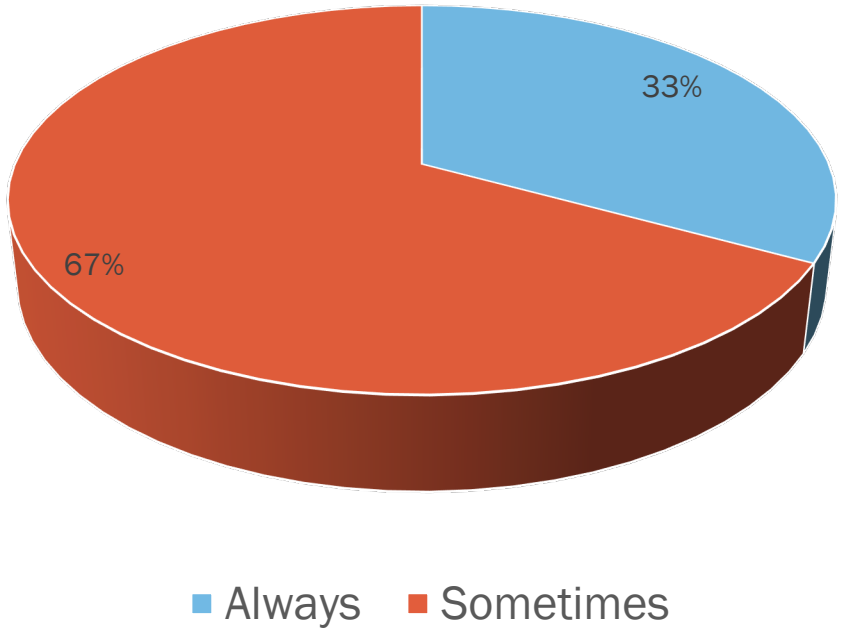
75% of participants are using additional contract laboratories

SUPPLIER VIEWPOINTS

Has the nature of requests from drug companies been appropriate



How often do manufacturers conduct an adequate risk assessment to justify ingredient specification



Companies (still learning) often treat Option 1 levels as specifications, which is not the intent of Option 1

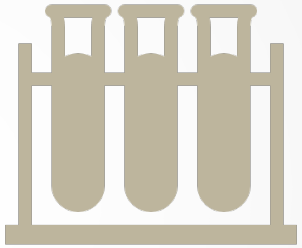
SUPPLIERS FEEDBACK

Sharing of Information

Use IPEC template

Use same format, but provide in Product Regulatory Datasheet

Test reports



Testing

33% of participants expanded internal testing capability

67% of participants added additional contract laboratory testing

Companies performed testing in preparation for Q3D to understand the levels

KEY MESSAGES

- Risk of EI in drug products is low
  - Excipient suppliers and drug product manufacturers should partner to ensure this message is clear to regulators
- Levels in ICH /USP are NOT limits
- Option 1 is not the only option
- Responsibility for Q3D compliance and Risk Assessments lies with pharmaceutical manufacturers, not the suppliers