BioPhorum DEVELOPMENT GROUP

CONNECT
COLLABORATE
ACCELERATE ™

Leveraging Prior Knowledge (PK) for marketing approval filings in accelerated settings

BioPhorum Development Group (BPDG)

CMC Considerations for Expedited Development Subteam

Representative: Athena Nagi, Merck

BioPhorum Development Group (BPDG) – Mission and Scope

To CONNECT process development biopharmaceutical organizations, provide an effective environment for the community to COLLABORATE on shared issues and ACCELERATE improvement across the biopharmaceutical development arena.

Ultimately, to support the industry in its quest for better & faster process development

Background and logistics

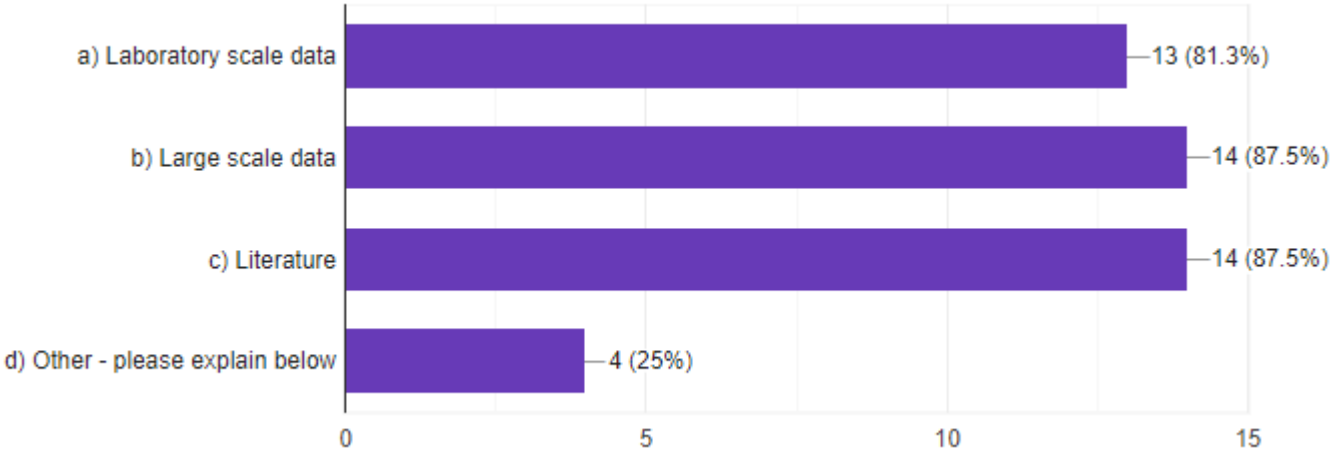
- Objective of Survey: To understand how member companies are defining and using Prior Knowledge (PK) to support marketing approval (eg BLA) filings in accelerated settings
- The survey was conducted July – October 2019
- 23 companies were invited to participate
- 16 companies provided responses to the survey
- The survey, consists of 11 key questions and was designed by the BPDG CMC Considerations for Expedited Development Point Share team.
- Thanks to Tim Iskra (Pfizer), Nick Abu- Absi (AbbVie) and Latonia Harris (Janssen) for leading the survey design
- The survey was co-ordinated and responses collated by Nadia Turner, BioPhorum Facilitator
- The responses are blinded

Prior Knowledge – summary of survey results

- Companies classify and use Prior Knowledge in different ways, in different contexts

- "It depends": responses influenced by the multiple types and uses of PK
  - Usage of Large scale studies, Lab scale studies, and Literature
  - Area of application: viral clearance as an example where PK has been embraced
- Companies are in different stages of their "Prior Knowledge journey"
  - Evolution and formalization within the company
  - Opportunities connected with overall Knowledge Management efforts
- The value of Prior Knowledge is often calculated with a forward-looking view
  - Streamlined approach to experimental work

1. i) What kind of data do you consider to be PK for a marketing authorisation filing? Check all that apply
16 responses



ii) If you checked "other" in question 1(i) please provide details here:

6 responses

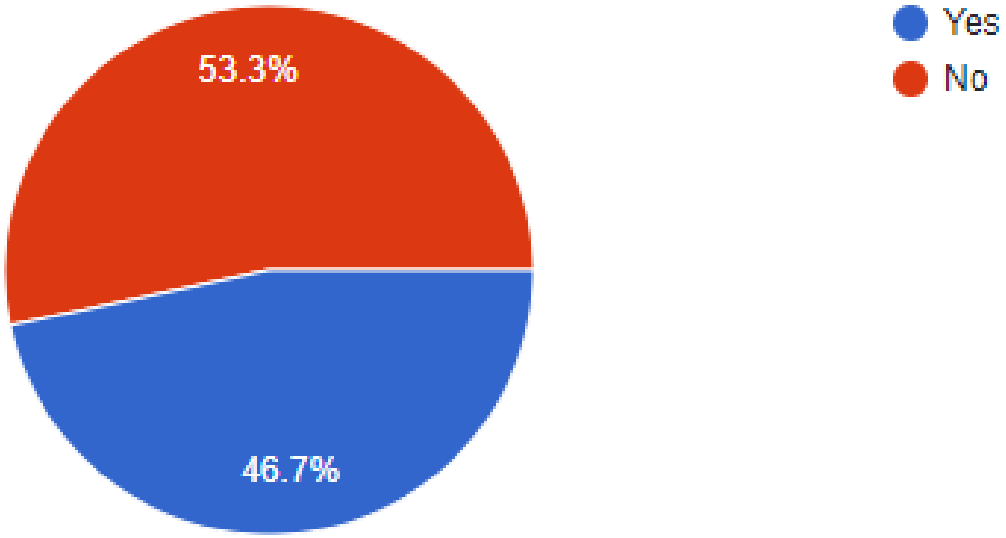
clarify that the large scale data is across multiple products
No experience of using PK for MA yet, however in theory all 3 options could be considered depending on the situation
All three are applicable, depending on context. Literature can be used as PK for certain product quality attributes. On the process side, large scale information is certainly helpful, but one may rely on appropriate small scale models. Large scale studies would be important as part of MA filing for lyo products (esp from engineering batches). Matrix/bracketing strategies for liquid DP manufacturing - such as mixing studies prior to vial fill. May not cover all parameters, or cover with proxy solution rather than product. (for response 2 - answered Yes, but have possibilities for No with appropriate small scale model)
cross-project platform Knowledge; under evaluation: modeling data
Knowledge from similar molecules and/or platforms (process and analytical)
prior validation data (for same unit operation step but different product)

Prior Knowledge is context dependent

- There will be different structure and requirements depending on the nature of the Prior Knowledge
  - Lab Scale Data
  - Large Scale Data
  - Literature

- As a follow-up, the group will work to identify the specific applications and understand what feedback has been received by HAs, with data set examples if possible. These details can define guidelines/parameters to govern PK use.

2. Is large scale data considered a required part of the PK package for a marketing authorisation filing? Yes/No
15 responses



Response likely influenced by individual definition of PK and requirement

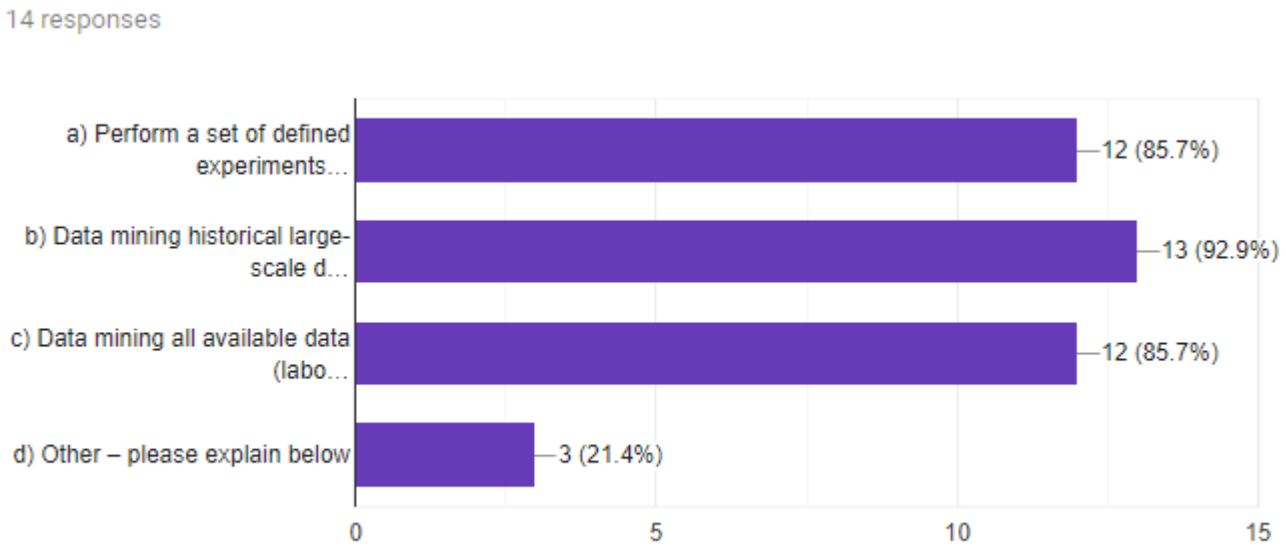
3 i) How do you obtain PK for a marketing authorisation filing ? Check all that apply

a) Perform a set of defined experiments (such as a DOE) with intended purpose to eliminate the need for future experiments (example: modular viral package)

b) Data mining historical large-scale data

c) Data mining all available data (laboratory, pilot, and large scale)

d) Other – please explain below



Teams use a variety of approaches employing all relevant data

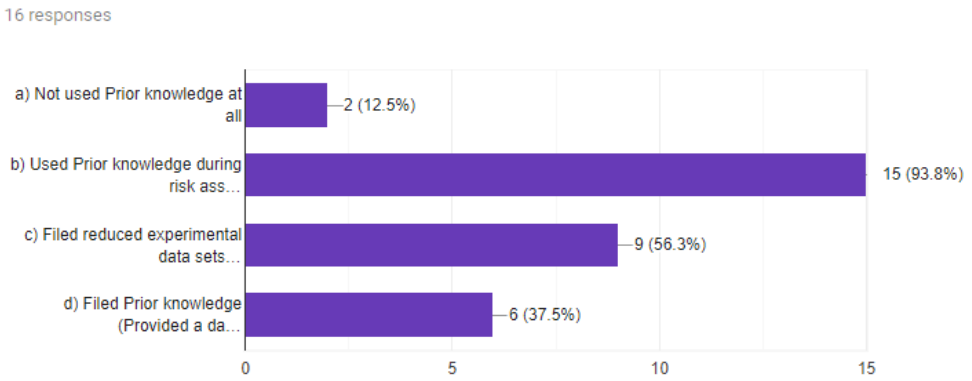
4 i) How have you used PK data for a marketing authorisation filing?
ii) How have you used PK data for an IND filing?

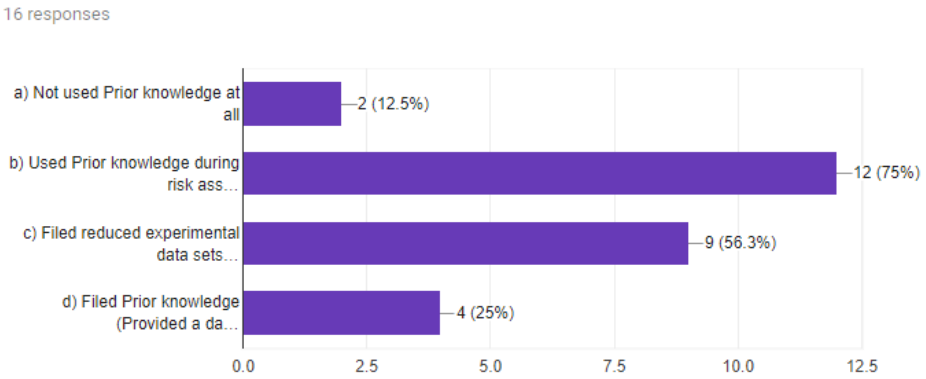
a) Not used Prior knowledge at all

b) Used Prior knowledge during risk assessments as a guide/support decisions as well as eliminate potential areas of study

c) Filed reduced experimental data sets and claimed prior knowledge was used to eliminate the need, but did not file actual data set.

d) Filed Prior knowledge (Provided a data package with filing)





Similar responses for MA and IND filings; follow-up will examine which PK supported which filing sections

5 i) What form is the majority of your PK in? Check all that apply

a. Scientist/SME knowledge…a.k.a in their memories

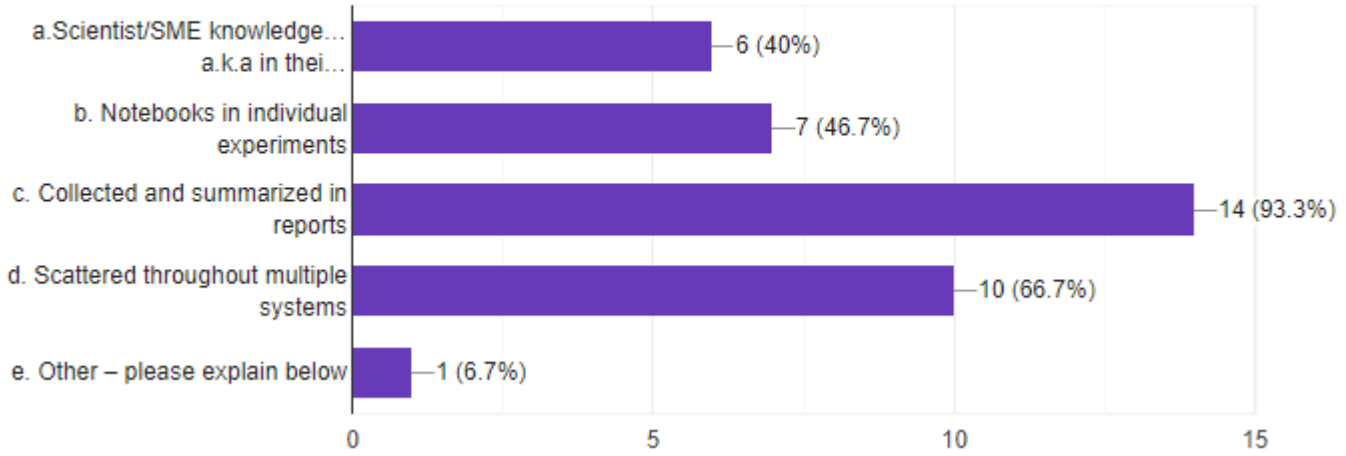
b. Notebooks in individual experiments

c. Collected and summarized in reports

d. Scattered throughout multiple systems

e. Other – please explain below

15 responses



Yes if required. For example if there is not enough data for developing the criticality of parameters, they can be determined by risk assessments with prior knowledge

dependent on stage of development (A early, C for late stage, D overall)

Internal databases

Some risk from less formal knowledge capture
Connections with Knowledge Management in Development Point Share

Free Response…

- Responders recognize the power of a well-designed small-scale model
- Companies are aspiring to establish business practices and standards around PK, with ad hoc or functional area-dependent approaches currently in place rather than formal standards (11/14 responders)
- One critical component of PK use is justifying (and documenting) its applicability for your product
  - Risk assessments
  - Statistical analyses
  - Justification of use of platform methods and processes
  - Knowing where PK is applicable, and where it is not
  - *Documentation in technical reports*

Perceived and Potential Benefits of PK

- Reduction in number of experiments – translating into a reduction in cost, time, and resources
- More targeted and efficient effort
- Reducing levels of risk across the program
- Consolidation of knowledge across programs: avoid spending to confirm what is already known
- Deeper understanding of process and product
- Greater confidence in process and methods
- Better to deal with accelerated timelines: certain steps off critical path

An overarching challenge to realizing these benefits is how to structure PK and make it more accessible for decision making

Next Steps and Opportunities

- The group will continue to define structure and examples of PK uses (lab scale, large scale, literature)
- Work to refine PK application for expedited product development
  - Success stories and business cases
- Consider development of Business Practices and Standards around PK uses

Participating companies

Company	Company
AbbVie	Janssen
Alexion	Kyowa Kirin Co., Ltd
Bayer	Lonza
Biogen	Merck
BMS	Merck KGaA Darmstadt Germany
Boehringer Ingelheim	Pfizer
Eisai Inc	Regeneron
GC Pharma	Roche/Genentech
GSK	Samsung Biologics
ImmunoGen	UCB

The content in this presentation represents the collated view of the companies listed here who contributed to and/or commented on the survey. The views are not attributable to any individual company.

Team members

Company	Team member	Company	Team member
AbbVie	Nick Abu Absi, Julie Fokema, Dan Sayut	**Janssen**	Santosh Thakkar, Ping Hu, Latonia Harris
Alexion	Saranya Sivanandam	**Kyowa Kirin Co., Ltd**	Hirofumi Kawai, Satoru Kamoda, Naoyuki Hanada, Yuya Kinoshita
Bayer	Markus Eser, Klaus Kaiser	**Lonza**	Imtiaz Alam, Jon Cook, Mark Davies, Suzanne Aldington
Biogen	Tia Estey, Valerie Tsang, Amy Morrison	**Merck**	Athena Nagi, Henry Lin
BMS	Angela Lewandowski, Duncan McVey, Girish Pendse, Ji Zheng	**Merck KGaA Darmstadt Germany**	Philippe Dupraz, Andrea Ruggiero, Kevin O'Mahony
Boehringer Ingelheim	Joey Studts, Jochen Schaub	**Pfizer**	Jaclyn Moxham, Tim Iskra
Eisai Inc	Andrew Taylor, Lisa Kahn, Wolfgang Ebel	**Regeneron**	Zachary Longino
GC Pharma	Denis Feshin, Jun sic Kim	**Roche/Genentech**	Josefine Persson, Florian Schelter, Michael Adler
GSK	Saroj Ramdas, Aston Liu, Wayne Kelley	**Samsung Biologics**	Hyejee Jang, Minsun Shin
ImmunoGen	Daniel Milano	**UCB**	Alex Clinch, Nadine Kochanowski
		BioPhorum	Nadia Turner

Anti-Trust Compliance Statement v4.0

It is the clear policy of BioPhorum that Biophorum and its members will comply with all relevant anti-trust laws in all relevant jurisdictions.

All BioPhorum meetings and activities shall be conducted to strictly abide by all applicable antitrust laws. Meetings attended by BioPhorum members are not to be used to discuss prices, promotions, refusals to deal, boycotts, terms and conditions of sale, market assignments, confidential business plans or other subjects that could restrain competition.

Anti-trust violations may be alleged on the basis of the mere appearance of unlawful activity. For example, discussion of a sensitive topic, such as price, followed by parallel action by those involved or present at the discussion, may be sufficient to infer price-fixing activity and thus lead to investigations by the relevant authorities.

Criminal prosecution by federal or state authorities is a very real possibility for violations of the antitrust laws. Imprisonment, fines or treble damages may ensue. BioPhorum, its members and guests must conduct themselves in a manner that avoids even the perception or slightest suspicion that antitrust laws are being violated. Whenever uncertainty exists as to the legality of conduct, obtain legal advice. If, during any meeting, you are uncomfortable with or questions arise regarding the direction of a discussion, stop the discussion, excuse yourself and then promptly consult with counsel.

The antitrust laws do not prohibit all meetings and discussions between competitors, especially when the purpose is to strengthen competition and improve the working and efficiency of the marketplace. It is in this spirit that the BioPhorum conducts its meetings and conferences.

Supplier interactions policy v3.0

The BioPhorum Operations Group facilitates a cross industry collaboration process for Biopharmaceutical developers and manufacturers with the aim of accelerating the rate at which the biopharma industry attains a mature and lean state benefitting patients and stakeholders alike. Collaboration modes include best practice sharing, benchmarking, joint-solution development to common challenges, definition of standards requirements and formation of collective perspectives to mutual opportunities and regulatory guidelines.

Biopharmaceutical developers and manufacturers recognize the legally enforceable duties they have including the responsibility to control the quality of materials from their suppliers. From time to time BioPhorum-facilitated collaboration requires, and benefits from, supplier interaction.

Suppliers are providers of supply chain materials such as chemicals, glass, components, excipients, and media. They are also providers of process equipment such as single use systems, engineering parts and consumables. BioPhorum-facilitated supplier interactions may involve: harmonizing manufacturer requirements and communicating these to suppliers; seeking feedback on proposed standards; gaining opinions and ideas related to business process improvement; use of problem solving tools; and gaining support for new ways of working.

The ultimate goal of the BioPhorum collaboration is to strengthen competition, assure product quality and protect patient supply.

The purpose of this document is to set out the principles and policies that BioPhorum follows to ensure that BioPhorum - facilitated supplier interactions are conducted in the correct and appropriate way to meet all legal and business compliance requirements.

Underlying Principles and Policies

Competition Laws: All supplier interactions will comply with anti trust and competition laws and have regard to BioPhorum's anti-trust compliance statement

Member responsibilities: Individual biopharma companies are responsible for defining their requirements of suppliers.

Innovation and commercial interests: All supplier interactions will recognise and respect the need for suppliers to innovate and pursue their own commercial interests.

Intellectual Property: All supplier interactions will respect suppliers' intellectual property rights.

Confidentiality / Non Disclosure: All supplier interactions will take into account, respect and encourage compliance with confidentiality and non-disclosure agreements.

Equal Treatment: All suppliers will be treated equally

Communication: These principles, policies and procedures will be communicated to BioPhorum members and suppliers whenever supplier interactions are planned or are taking place.

BioPhorum responsibilities

- It is the responsibility of BioPhorum Directors to ensure that these principles and policies are upheld and procedures are in place to support them.
- BioPhorum will educate and train its staff so they understand and follow these principles and policies and are able to communicate them when needed.
- BioPhorum documentation will reference or directly include relevant parts of the Supplier Interaction Policy.
- BioPhorum will establish and maintain records to demonstrate compliance with these principles and policies.

Code of Conduct – BioPhorum information sharing v3.0

Introduction

The BioPhorum Operations Group is a cross industry collaboration with the aim of sharing best practice in the area of Operational Excellence.

Participation in BioPhorum is restricted to authorized member company representatives as described in the Principles of Membership Agreement.

While sharing information is central to the process of this collaboration, it is important to understand what information is appropriate to share. Our companies have a great deal of confidential information and intellectual property that should not be shared within BioPhorum .

This document seeks to guide the reader so that the individuals and companies involved follow the correct code of conduct and problems are avoided.

It is the clear and stated intention of BioPhorum that the Group and its activities are conducted at all times in full compliance with relevant competition/anti-trust rules.

Responsibilities

It is the responsibility of every person who participates in a BioPhorum event or sharing activity to make sure they are aware of what information is appropriate to share. Furthermore, all participants are responsible for vetting any information to be shared via their company's public disclosure review processes and that all information shared is free of any "Confidential" stamps or markings.

The key contact (L2) for each member company should ensure confidentiality and that IP issues are highlighted to their colleagues and all applicable company policies regarding external collaboration and public disclosure are adhered to.

The BioPhorum facilitators are responsible for reminding all participants of their obligations with respect to information sharing.

Sharing information

The following list is representative of the types of disclosures commonly allowed by corporate policies. BioPhorum participants should review their company policies to ensure they are in compliance prior to any disclosures. Information in the following areas is typically allowed:

- Operational excellence best practice models
- Management approaches and philosophies
- Organizing and planning ways of working
- Non-product or process specific generic operating procedures
- Information in the public domain
- Information provided by suppliers which would ordinarily be shared with customers
- Non-product or process specific generic engineering or technical information relating to process equipment
- General learning and 'context' conclusions from QA and Regulatory activity

Sharing information from the following areas is typically prohibited by corporate policies

- Product related information
- Product related process data which constitutes intellectual property
- Specific audit or regulatory inspection findings or observations
- Product specific analytical methods
- Specific cost numbers where a market advantage may result or a supplier might be disadvantaged
- Information that is marked as confidential by the member company or a supplier
- Price information of any type
- Proprietary information including intellectual property and patented processes and equipment

BioPhorum event participants should direct all questions regarding information disclosure to their L2 BioPhorum representatives or corporate legal departments.

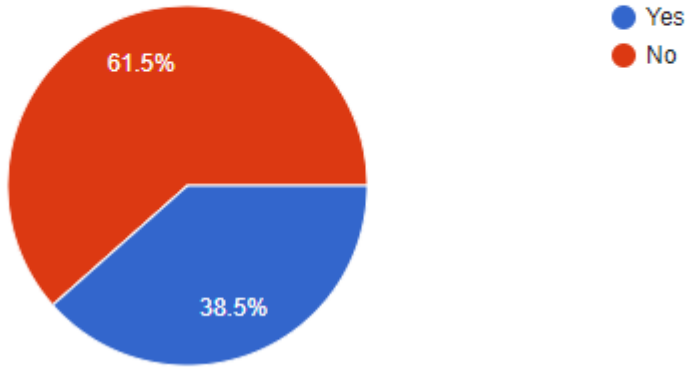
3 ii) If you checked "other" in question 3(i) please provide details here:

5 responses

A, B, and C are all important for appropriate filing storyboarding, and will help for a smooth dossier preparation. for a) experience with modular viral package. For b - using ranges of experience (manufacturing and clinical) for select CQAs. For c - data mining can also include literature and other products. Lots of discussion on approach: can leverage literature and not do the experiment, or one can recognize a gap/difference in the literature and address the gaps. No formal company requirement for PK package.
cross-project platform Knowledge; under evaluation: modeling data
Prior knowledge comes in our opinion from platform data, other molecules development, or literature.
Data from similar molecules
look at applicable data from previous filings. We do not see data from experiment performed for the project as PK, this is actual product specific data. PK is non product specific data.

3 iii) If you checked (a) in question 3 (i), is this your company requirement of the PK package? Yes/No

13 responses



6. Should PK be considered at Small Scale and verified at Large Scale? Yes/No, please explain. 15 responses – 7/14 yes; 5/14 no; 3 –" it depends"

Yes - trouble shooting; providing the reference information for developing the reports
Yes. PK should be considered at Small Scale and verified at Large Scale. For example, a set point of operational parameters for manufacturing process is determined based on PK. The appropriateness of the set point is verified during process characterization studies and PPQ runs.
No. If you perform large scale verification runs then this is not really PK, but rather a validated process step.
It depends. Small scale is good if linked to first principles; large scale may be needed to verify if based only on empirical data
Depends - if the small scale model is solid, large scale should not be needed. Need to be able to explain validated scale down models, and include a scale-dep vs independent parameter table. An understanding of what may be different is critical for justification.
No. It depends on criticality of inputs and outputs under consideration and how well qualified your small scale systems are.
No, when Scale down model (SDM) is qualified
PK is Independent from scale and both can be used
Yes, if the platform approach is used
I would think no - large scale verifies findings from small scale
Small scale data can serve as PK of Large scale scale batches
Yes. Small scale DOE studies are easier to design and perform.
Yes
Yes, if the small scale is a good representation of large scale.
If you use PK you should already have knowledge fro prior experiments (projects) that show the small scale experiments are relevant to use.

7. What are the perceived/potential benefits of leveraging PK?
16 responses

Preparation of the required documentation
To reduce the number of experiments.
The perceived benefits are related to Money/time/resources. There should be a reduction in all three of these.
Resource and time savings
PK can be used to fill in gaps in data which would typically delay submission of an accelerated product if the company had to wait to generate product-specific data
Cost/time/resource savings - fewer experiments, more targeted efforts. Without a full mechanistic understanding, may still have additional work (when empirical is not sufficient)
Reduction in number of experiments. Sate time, resources, and materials.
Reduced effort, time saving, lower risk,
reduce Experiments (also via consideration in risk assessments), provide additional evidence (e.g. in case available informatoin lacks some clarity)
reduction of repeating experiments, reduce time, resource and cost
Faster filing
Consolidate knowledge from prior projects to avoid spending resources in confirming elements already demonstrated. Use scientifically proven principles to justify choices made during development. Opportunity to show HAs the know how of the Company.
Leverage platform knowledge, speed up development and reduce cost.
reduce the total experimental numbers and experimental design
Reduced experiment burden, increased confidence in process/methods
Deeper and better understanding of a unit operation or specific topic, e.g. buffer stability.

8. Does your company have defined business practices for establishing PK? Yes/No, please explain
14 responses – majority responded “No”

No
Not yet
No, not yet. It will be developed as the relevant group (CDMOs) are expanding the work scope and accumulated experiences.
No. This has been more independently between various departments.
No, but moving towards this with business process mapping and product history files
No as have not yet used PK for submission purposes
Not an overarching defined business practice; select pieces are embedded into practices in different functional areas. Use of Platforms (processes, methods, specifications). It is always a challenge to determine when one can use the general case vs specifics. How many molecules "prove it"? How many examples/batches? It is not always an absolute number, but diversity / variability that is more important.
No.
Yes, electronic lab journals, large sale campaign reports, development reports
No, various approaches
N/A
No. The practice of leveraging prior knowledge still varies from project-to-project.
Yes, via project CMC process
Yes, we have a functional rep that owns our PK and the strategy for how to use and develop the PK.

9. Does your company have defined standards for what data is required to leverage PK ? Yes/No, please explain
12 responses – majority no or not yet

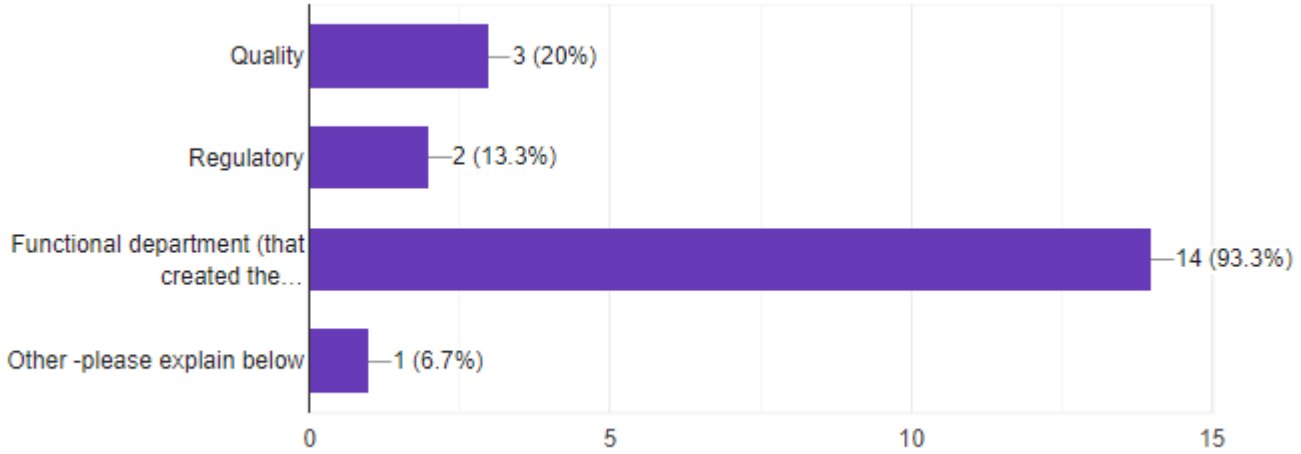
No
Not yet
Yes. My company provides SOP and technical documents to provide internal knowledge (development and manufacturing experiences) and external knowledge (established scientific principles)
No. Upon review this scientific basis is evaluated and checked, but there are no company standards in place that need to be met between the various departments.
No, scientific rationale is used case by case
No as have not yet used PK for submission purposes
General knowledge management is in the building stage - descriptors, tagging, etc. Trying to look at a wide range and individual categories / data mining to see what knowledge is applicable where - then set up an experiment. Some challenge with examining an attribute vs an assay (and often there is comingling of information - gaps in an assay, or not comparable over time)
No.
No, but can be defined
N/A
No.
Needs to be traceable, defend-able data that is summarized in one doaument

10. How do you document and justify that the PK applies to your product?
15 responses

In my case I performed: FMEA; QRA (gap analysis, hazard analysis); safety evaluation
We use PK for antibodies, including biosimilar. We document and justify considering the subtype, MoA and reference product (biosimilar) of antibodies.
Documented in internal reports that demonstrate why the prior knowledge applies. This is not a formal process and in some cases this type of information can be captured in risk assessments.
Technical reports and risk assessments
Document via risk assessment, reports from different functional areas (working toward a more integrated approach). Some justification elements discussed in responses to questions 6-8.
Technical reports and risk assessments.
Risk assessments, statistical analysis
Justifications and reference to documented PK
summary report with data and justification
Product characteristics compared on relevant dimensions to PK
On reports of platform development projects and based on the scientific PK & justification that the general conclusion applies to the type of product.
Captured in product or process development reports.
similar molecule
Development reports and associated justifications
This is done for each project in the risk ranking and filtering procedure.

11 i) Who owns the PK in your company? Check all that apply
15 responses

- Quality
- Regulatory
- Functional department (that created the prior knowledge)
- Other -please explain below



11 ii) If you checked "other" in question 11 i) please provide details here:

2 responses

Considerable discussions on where PK should reside - how to maintain, distribute, cadence of updates. There are tradeoffs of publication (what to publish/disclose)

Not yet defined