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A Survey to Understand the Current Practices between Pharmaceutical Companies and Excipient Suppliers in Evaluating the Impact of Excipient Variation on Drug Product Performance

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Introduction

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) is an international association of pharmaceutical and biotechnology companies aiming to advance innovation and quality in the development of pharmaceutical products through scientifically-driven best practices and standards. The ultimate goal is to improve safety and efficacy of medical products for patient benefit.

As part of the IQ Consortium, the Analytical Leadership Group (ALG) formed a working group to improve drug product characterization. As one of three sub-groups under this working group, this sub-team, with primary support from members of the Drug Product Leadership Group (DPLG) and members of IPEC (International Pharmaceutical Excipients Council), has the objective to identify potential improvement opportunities through the understanding of the current practice of evaluating the impact of excipient variation on drug product performance.

The selected approach was to conduct a survey through the IQ Consortium members and IPEC members to understand the current practices between Pharmaceutical Companies and Excipient Suppliers during the development and throughout the lifecycle of a drug product. The survey was designed to understand how Pharmaceutical Companies and Excipient Suppliers interact to conduct studies on the impact of excipient variation on drug product performance. Through the understanding of the current practices and identification of challenges, improvement opportunities could be identified.

Survey Design

Two surveys with similar questions were developed for the two target audiences, Pharmaceutical Companies and Excipient Suppliers. These surveys were designed to provide some preliminary insights into current practices and to identify potential opportunities for improvement. The surveys for Pharmaceutical Companies and Excipient Suppliers consisted of 28 and 14 questions, respectively. The Pharmaceutical-Company survey was distributed to members of the IQ Consortium and the Excipient-Supplier survey was distributed to members of IPEC. The completed surveys were returned to Drinker Biddle & Reath, LLP, where company-specific information was removed from the responses before they were evaluated. The survey questionnaires and responses are presented as received in Appendices A and B.

Survey Findings

Twelve Pharmaceutical Companies and six Excipient Suppliers responded to the survey. The survey results are reported as a percentage of those companies that responded to each individual question. Eight of the Pharmaceutical Companies identified themselves as brand-name manufacturers or brand-name and generic manufacturers. Four companies did not provide a response. All of the Excipient Suppliers indicated that they supply drug release modifier/controller excipients and some included the manufacture of binders, coating agents, wetting agents and suspending agents.

The following summarizes the survey findings:

1. The results of this survey indicate that Pharmaceutical Companies commonly use prior knowledge, risk assessments, actual experimental findings, or some combination of these approaches to determine which excipients or excipient properties to select for assessing the impact of excipient variation on drug product performance. However, Pharmaceutical Companies are less likely to share the findings of excipient impact studies with Excipient Suppliers. (Appendix A. Q2)

2. In general, Pharmaceutical Companies were equally split between one-factor-at-a-time and multivariate DoE approaches to evaluating the potential impact of excipient property variation on drug product performance. One response indicates that if only a single characteristic needs to be evaluated, then a one-factor-at-a-time approach is used. Another response implies that a phase-appropriate approach is used with more limited experiments performed during early clinical phases and more comprehensive studies performed during Phase III clinical studies and beyond. (Appendix A. Q4)

3. It appears that pharmaceutical companies do not routinely evaluate excipient properties outside of the Supplier's specification range because it is difficult to obtain the appropriate samples. One response indicates they may attempt to do this for rate-controlling polymers used in controlled-release dosage forms. (Appendix A. Q5)

4. The impact of excipient variation on drug product performance seems to be studied predominantly at the laboratory scale, followed by some companies conducting studies at pilot and commercial scales. Only one company was evaluating the impact on a continuous process. (Appendix A. Q6)

5. Two thirds of the Pharmaceutical Companies indicate they evaluate excipient material from multiple Suppliers. Among those evaluating multiple sources of excipients, two thirds do so after final drug product formulation selection. Two responders indicated that at least two Excipient Suppliers are qualified for commercial supply. (Appendix A. Q7, Q8)

6. Two thirds of the Pharmaceutical Companies say "no", they generally do not involve the Excipient Supplier in study design or risk assessment. Two implied that they will involve an Excipient Supplier in obtaining samples meeting customized specifications. (Appendix A. Q9) This is consistent with the feedback from the Excipient Suppliers, where half responded that they are infrequently or never contacted. (Appendix B. Q3)

7. Six out of ten Pharmaceutical Companies say "no", they typically do not consider excipient manufacturing process capabilities in drug product performance study design or risk assessments. One respondent indicated they will try to obtain excipients from multiple sites of the same Excipient Supplier. (Appendix A. Q10) Excipient Suppliers are split on whether they are asked about process capability. One respondent commented that this was infrequent until FDA's QbD expectations for generic products were announced. (Appendix B. Q5, Q6)

8. Comments from the Pharmaceutical Companies indicate that the properties of an excipient that are most likely to have an impact on drug product performance depends on the excipient itself, the intended function of the excipient in the drug product, and the type of drug product that the excipient is being used in. From the choices provided, particle size/distribution and moisture content were selected by Pharmaceutical Companies as the most likely attributes to have a large impact on drug product performance. (Appendix A. Q11) The Excipient Suppliers that responded to this survey are most commonly requested to supply material with different viscosities (83%). The next most common request is for samples with different particle size distributions. (Appendix B. Q2)

9. The majority of Pharmaceutical Companies say they begin to consider excipient variability during the selection of excipients prior to the finalization of the commercial formulation. (Appendix A. Q12)

10. Two thirds of Pharmaceutical Companies say "yes", they have found an excipient impact to drug product properties during commercial manufacturing. In addition, 70%

of these companies responded that these impacts may have been identified earlier if a better experimental design was used during development studies at lab/pilot scale. (Appendix A. Q13, Q14) However, it should be noted that this question did not specifically ask if the drug product properties that were impacted were related to drug product performance. Additional research is required in order to understand which drug product properties were impacted.

11. Ninety percent of Pharma responders say excipients for evaluation are obtained by the technical group responsible for the evaluation. (Appendix A. Q15) Suppliers have their manufacturing technical group provide special request material. (Appendix B. Q8)

12. Only one of eleven Pharma Companies indicated that they frequently have technical discussions with Excipient Suppliers prior to and/or during the procurement process. (Appendix A. Q16)

13. Pharma Companies are split almost equally “yes” and “no” on having confidentiality agreements in place for technical discussions. (Appendix A. Q17) Suppliers all indicate they have confidentiality agreements in place but some share standard information without a CDA. (Appendix B. Q4)

14. The top three responses from Pharmaceutical Companies for technical information discussed are excipient production processes/CoA attributes, excipient manufacturing process capability, and the justification of why the excipient and the attribute are selected for study. (Appendix A. Q18) Excipient Suppliers responded that they all (6 of 6) discuss excipient production processes/CoA attributes and nearly all (5 of 6) discuss excipient process capability, while half discuss study design and few (1 of 6) discuss risk assessments in technical discussions. (Appendix B. Q5)

15. Approximately 45% of the Pharmaceutical Companies are either dissatisfied or somewhat dissatisfied with the current procurement process to obtain excipient lots with variation in one or more properties for evaluation. Sometimes it is because the variability is too small, it is not feasible to obtain the material or that the Pharmaceutical Company is not the main buyer, such that incentive is low for Excipient Suppliers. (Appendix A. Q19) Likewise, 50% of the Excipient Suppliers are dissatisfied or somewhat dissatisfied with the process to provide these materials. (Appendix B. Q14) Because both Pharmaceutical Companies and Excipient Suppliers are dissatisfied on this point, there may be an opportunity to improve the current processes for providing and obtaining these materials.

16. The most common ways for Pharmaceutical Companies to obtain appropriate samples for study is through "lot selection" from an Excipient Supplier inventory or by the Pharmaceutical Company manipulating the material in-house. (Appendix A. Q20) Excipient suppliers agree that "lot selection" is the most common approach. (Appendix B. Q9)

17. Pharmaceutical Companies and Excipient Suppliers agree that obtaining samples with properties outside of the range (e.g., at the edges of the compendial specifications) that is typically produced by the excipient manufacturing process is one of the major hurdles to evaluating the effects of excipient variability on drug product performance. For example, it may be cost prohibitive or require long lead times to obtain these samples. In addition, it may not be possible to vary some of the key properties of the excipient without affecting other properties. Suppliers agree that low volume requests are one of the major issues in supplying material for study. One Supplier commented that customers are reluctant to share information on the API and drug product. (Appendix A. Q21 and Appendix B. Q7)

18. Pharmaceutical Companies are less likely to share the findings of excipient impact studies with Excipient Suppliers than to share them. (Appendix A. Q22) Most of the Excipient Suppliers (4 of 6) agree that they are infrequently or never provided with these results. (Appendix B. Q10)

19. Seventy percent of the Pharmaceutical Companies would modify their drug product formulation or manufacturing process if the excipient "as-is" from the Excipient Supplier is not acceptable for product quality. (Appendix A. Q23) Half of the Excipient Suppliers recommend this approach as well. (Appendix B. Q11)

20. Roughly one third of the Pharmaceutical Companies have less than 25% of their excipients from a single source. Another one third of these companies have more than 50% of their excipients from a single source. (Appendix A. Q24)

21. Almost 80% of the Pharmaceutical Companies say that the Excipient Supplier notifies their sourcing group of changes in excipient manufacturing process, product attributes or sourced raw materials. None of the Pharmaceutical Companies are using an online or other monitoring system. (Appendix A. Q25) Excipient Suppliers agree that they notify the sourcing group most often, but that they also notify the Pharmaceutical Company manufacturing group or the contact persons named in the Quality Agreement. (Appendix B. Q12)

22. Regarding Quality Technical Agreements (QTA), most Pharmaceutical Companies include specifics on what process deviations, nonconformances, recalls, changes in raw materials or excipient manufacturing process, etc. that they want to be notified about and what procedure the Excipient Supplier should follow to notify them of these changes. (Appendix A. Q26) Comments indicated that Pharmaceutical Companies rarely have QTAs in place and that some suppliers are not willing to sign them. Some indicate that the Contract Manufacturing site establishes these agreements. One comment indicated that proprietary processes and trade secrets would not be included in a quality agreement. (Appendix A. Q27)

23. New impurities, changes in impurity levels, and new sources of raw materials that are used in the manufacture of excipients were considered important changes by the Pharmaceutical Companies. Fewer companies thought the manufacturing location or process changes that do not impact the CoA requirements were important. (Appendix A. Q28) Two thirds of the Excipient Suppliers indicate that they notify clients regarding new sources of raw materials; however, fewer companies notify their customers about changes in impurities or manufacturing process changes that do not impact the CoA requirements. Others notify regarding stability changes, primary packaging changes etc. Most follow the IPEC Significant Change Guideline (International Pharmaceutical Excipient Council (IPEC) website www.ipec.org). (Appendix B. Q13)

Summary

The results of this survey indicate that Pharmaceutical Companies most commonly use prior knowledge, risk assessments, actual experimental findings, or some combination of these approaches to determine which excipients or excipient properties to select for assessing the impact of excipient variation on drug product performance. However, less than 20% of Pharmaceutical Companies use discussions with Excipient Suppliers when deciding which excipients to evaluate during drug product development. In addition, Pharmaceutical Companies do not commonly share the findings of excipient impact studies with Excipient Suppliers.

It is recognized that it may be more important for Pharmaceutical Companies and Excipient Suppliers to work together in some situations than in others; however, further research is required to determine if Pharmaceutical Companies and Excipient Suppliers are sharing as much technical information with each other as they could so as to leverage each other's technical knowledge and abilities to the fullest extent.

The results of the survey also indicate that sometimes the impact of excipients on drug product properties are being seen at commercial scale that could have been predicted during development. However, it should be noted that this question did not specifically ask if the drug product properties that were impacted were related to drug product performance. Additional research is required in order to understand which drug product properties were impacted.

The majority of Pharmaceutical Companies say they begin to consider excipient variability during the selection of excipients prior to the finalization of the commercial formulation. The timing and scope of these studies could be an opportunity for improvement with additional input from industry experts. Excipient risk assessment starts with risk identification, defined in ICH Q9 as a "systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders." Excipient Suppliers are stakeholders who have the knowledge of variability and unspecified attributes that are critical to successful risk assessments. Their application knowledge can identify potential excipient-related modes of failure that the excipient user may not necessarily be able to identify.

Due to limited responses from pharmaceutical companies (twelve) and excipient suppliers (six) in this survey, the findings are not a statistically significant representation of the industry. However, the identified potential improvement opportunities should be further vetted and verified through additional wider-circulation surveys.

Additional research is required to determine to what extent Pharmaceutical Companies and the Excipient Suppliers are dissatisfied with current practices, when a closer working relationship would be beneficial and if there is willingness by both parties to invest in this effort.

Appendix A - Survey provided to Pharmaceutical Companies with Responses

Survey on "Evaluation of Excipient Variation on Drug Product Performance"

For Pharmaceutical Companies:

Goal of the survey: Design a mutually beneficial best practice between Pharmaceutical Companies and excipient Suppliers to evaluate the impact of excipient variation on drug product performance. The survey is intended to identify gaps and challenges in the current processes with regard to study design, collaboration and procurement both during the development phase and the lifecycle of the drug product.

The survey results are reported as a percent of those Companies that responded to individual questions.

1. Which of the following categories best describes your business? Please choose only one category.

Both Brand-Name and Generics	2 of 8	25%
Brand-Name Pharmaceuticals	6 of 8	75%
Generics	-	
No response	4 of 12	33%

2. How do you determine which excipients to evaluate with regard to their impact on drug product performance? Circle the two most common approaches. If there is other additional information please include in the "Other" category.

Prior knowledge	7 of 11	64%
Risk assessment	7 of 11	64%
Actual experimental findings	7 of 11	64%
Discussion with Suppliers	2 of 11	18%
Other _____	-	

3. What are the excipient characteristics that you select for evaluation with respect to drug product performance impact? Circle the two most common ones. If there is other additional information please include in the "Other" category.

Particle size/distribution	6 of 11	55%
Specific surface area	1 of 11	9%
Processing aid/impurity	3 of 11	27%
Bulk/tap density	0 of 11	0%
Moisture content	4 of 11	36%
Viscosity	2 of 11	18%
Other _____	4 of 11	36%

Comment _____

- All, some or none. What we evaluate depends mostly on the excipients function in the DP. Also the specific process utilized will drive our characterization/control strategy.
- Case by case basis--a result of the detailed product risk assessment. Any one of the other choices could be critically important based on the specific project/product needs.
- Viscosity could be important for control release formulations
- It depends very much on the application and the form of the excipient and the types of product

4. What experimental design approach do you typically use to evaluate excipient property variation on drug product performance? Circle the most common one. If there is other additional information, please include in the "Other" category.

One factor at a time	5 of 9	56%
Multivariate DOE studies	4 of 9	44%
Other _____	4 of 9	36%

- If there is a specific function/property then we may go with a one at a time approach. for example if we know that fines is the only critical factor then we would only look at fines
- In development the approach is a result of hypothesis driven experimentation. In commercial supply the trend is towards one factor at a time.
- N/A as we are only a distributor of the products
- It depends on the stage of development. For Phase I a restricted development program is typically used. For Phase III/commercial, a more comprehensive approach is used (most likely QbD)

5. Do you evaluate excipient properties that are outside the Supplier specification range (for example to determine the edge of drug product performance failure)?

Yes	5 of 11	36%
No	6 of 11	43%
Comment _____	4 of 11	36%

- Not always as sometimes it is difficult to even get material in-side but at the spec limit. We always try to look at edge of failure but this is not very often possible
- Because of limited supply of excipients outside the range, it is not possible to conduct these studies.
- Mostly no, unless clearly identified as a critical quality attribute. In development we do probe varied grades of materials.
- This is not done on a routine basis. However, for controlled-release dosage forms, we might attempt this for the rate controlling polymers.

6. At what process scale do you typically study the impact of excipient variation on drug product performance? Circle all that apply.

Batch Process – Lab scale	9 of 11	82%
Batch process – Pilot scale	6 of 11	55%

Batch process – Commercial scale	3 of 11	27%
Continuous process	1 of 11	9%

7. Do you typically evaluate excipient material from multiple Suppliers?

Yes	7 of 11	64%
No	4 of 11	36%

Comment _____

- Yes, If possible, we will look at least two Suppliers during development. If not possible due to time or API, multiple Suppliers would be evaluated post-submission. Our policy is to have at least two Suppliers qualified at launch or shortly thereafter.
- Yes, we have developed preferred Suppliers for use in development. In commercial supply, this is done all the time for cost reduction, and supply chain flexibility.
- Yes, to meet the needs of our customer base.

8. At what stage in drug product development do you assess multiple sources of excipients? Choose the most common one. If there is other additional information please include in the "Other" category.

Early drug product formulation development	0	
After final drug product formulation selection	7 of 11	64%
Post drug product approval	3 of 11	27%
None	1 of 11	9%

Other _____

- If not possible during development then would be post approval

9. Do you typically involve the Supplier in excipient variability study design or risk assessments?

Yes	4 of 11	36%

No	7 of 11	64%

Comment _____

- Yes but limited and depends on Supplier and/or excipient. At a minimum we would involve Supplier in obtaining "special" specs
- no, Depends on Supplier interest, data availability, and ability to provide variable materials
- No, Not done systematically across all projects, though has been done for isolated cases.
- No, unless there is an issue in meeting customer specifications.
- Yes, If necessary

10. Do you typically consider excipient manufacturing process capabilities in drug product performance study design or risk assessments?

Yes	4 of 10	40%
No	6 of 10	60%

Comment _____

- No response, Sorry but I do not understand the question
- Yes, we try to obtain excipients from multiple sites of the same Supplier.

11. In your experience, which excipient properties demonstrate a large impact on drug product performance? Circle the two most common ones. If there is other additional information please include in the “Other” category.

Particle size/distribution	6 of 11	55%
Specific surface area	3 of 11	27%
Processing aid/impurity	0 of 11	
Bulk/tap density	0 of 11	
Moisture content	4 of 11	36%

Viscosity	1 of 11	9%
Other _____	6 of 11	

Comment _____

- varies a lot depending on the excipient and its functionality in the DP
- Depends on the product
- N/A
- Specific surface could be representative by particle size/distribution
- Depends on the type of product, the excipient and its function.

12. When do you begin to consider the impact of excipient variability on drug product performance? Circle the most common one. If there is other additional information please include in the "Other" category.

Early formulation development	1 of 10	10%
During selection of excipient prior to the finalization of the commercial formulation	7 of 10	70%
After selection of commercial formulation	2 of 10	20%
Post approval	0 of 10	0%
Other _____		

13. During commercial manufacturing of a drug product have you found an excipient to impact either the drug product properties in a manner that was not seen in the development phase of the drug?

Yes	7 of 11	64%
No	4 of 11	36%

14. If yes, could this impact have been predicted by a better design of experiments at the lab or pilot scale or does this impact show up only at the commercial scale?

Lab or Pilot Scale	5 of 7	71%
Commercial Scale only	2 of 7	29%

15. Which group is responsible to obtain excipient lots with variation in one or more attributes for drug product performance impact evaluation? Circle the most common one. If there is other additional information please include in the "Other" category.

Procurement group	1 of 9	11%
Technical group responsible for the evaluation	8 of 9	89%

Other _____

- Tech group is responsible but we do need to often involve the procurement group for support
- Procurement approaches us at the direction of the R&D group for samples.
- Depends on the project

16. How often does a technical discussion occur between your company and the excipient vendor prior to and/or during the procurement process?

Never				Always
1	2	3	4	5

Comment _____

Never	0 of 11	0%
Infrequently	3 of 11	27%
Neither frequently or infrequently	7 of 11	64%

Frequently	1 of 11	9%
Always	0 of 11	0%

- Dependent on excipient and familiarity with Suppliers

17. Is a confidentiality agreement in place for the technical discussion?

Yes	6 of 11	55%
No	5 of 11	45%

Comment _____

- Depends on timing and type of information exchange
- Some vendors have requested a CDA

18. What type of technical information is typically discussed? Circle all that apply. If there is other additional information please include in the "Other" category.

The justification of why this excipient and its attribute are selected for the evaluation	6 of 11	55%
Risk Assessment	2 of 11	18%
Study design: scope, excipient range etc.	4 of 11	36%
Excipient production process(es)/CoA	9 of 11	82%
Excipient manufacturing process capability	8 of 11	73%

Other _____

19. How satisfied are you with the current procurement process to obtain excipient lots with variation in one or more properties for your evaluation?

Not Satisfied				Satisfied
1	2	3	4	5

Comment_____

Dissatisfied	2 of 11	18%
Somewhat dissatisfied	3 of 11	27%
Neither	4 of 11	36%
Somewhat satisfied	2 of 11	18%
Satisfied	0 of 11	0%

- It is very difficult to get lots with meaningful variability. Often the variability in properties of interest in less than 1%.
- Not always feasible to obtain within ranges
- For vendors where Pharma is not the main buyer, it can be difficult to get them to accommodate our needs. Gelatin is a good example. Pharma is probably less than 5% of their business so we have very little influence

20. If you were able to obtain excipient lots with variation in one or more properties from a Supplier, how was this achieved? Circle all that apply. If there is other additional information please include in the "Other" category.

The Supplier selected lots in inventory that met the requested requirements

9 of 11 82%

The Supplier varied the manufacturing process to produce lots with a systematic variation in the desired property

5 of 11 45%

The Supplier manipulated the material post manufacture to create the desired variation (for example sieving for particle size)

3 of 11 27%

Your company manipulated the material from excipient Supplier to create the desired variation (for example sieving for particle size)

7 of 11 64%

Other _____

- We have and continue to lot select products for some customers

21. List some of the major issues that you faced with respect to obtaining excipient lots with variation in one or more properties for drug product performance evaluation. Circle all that apply. If there is other additional information please include in the "Other" category.

Requesting excipient material with properties in a narrow range or at extremes of property range (material not available from the standard manufacturing process)

	7 of 11	64%
Cost prohibitive	3 of 11	27%

Not feasible to obtain excipient material when specifying a combination of 2 or more attributes (for example, attributes are not independent)

	5 of 11	45%
Long lead time	7 of 11	64%

Other _____

- Some of our Suppliers can make arrangements for "special" above normal production of lot select excipients. There are two issues: how much are you willing to pay for the special treatment and becomes where the product goes as they cannot hold onto it when it becomes available due to the down turn in the economy the ability to predict order patterns of our customers is difficult to impossible.
- Supplier did not see the potential for large commercial volumes

22. How frequently have you shared the findings of studies focused on excipient variation impact on drug product performance with excipient vendors?

Never				Always
1	2	3	4	5

Comment _____

Never	3 of 11	27%
Neither frequently or infrequently	3 of 11	27%
Infrequently	3 of 11	27%
Frequently	2 of 11	18%

- Never, N/A to our business
- Infrequently only if there is a major issue.

23. If the excipient “as is” from the Supplier is not acceptable, what is your typical action plan? Circle the most common one. If there is other additional information please include in the “Other” category.

Negotiate with vendor to obtain excipient with the required properties (upgrade the specification to meet fitness for purpose)

3 of 10 30%

Modify the drug product formulation and/or manufacturing process

7 of 10 70%

Other _____

24. Approximately what percentage of your excipients is from a single source?

<25%	4 of 11	36%
25%-50%	3 of 11	27%
50%-75%	3 of 11	27%
>75%	1 of 11	9%

Comment: _____

- We always strive to have at least two Suppliers for all excipients at the time of launch

25. Which group is notified by excipient Supplier of changes in excipient manufacturing process, sourced raw materials or excipient product attributes? Choose one. If there is other additional information please include in the "Other" category.

Supplier notifies Sourcing Group 7 of 9 78%

Supplier notifies Manufacturing Group 1 of 9 11%

Using an on-line or other access system for monitoring of Supplier excipient properties none

No notification. 1 of 9 11%

Other _____

- Our Suppliers notify our sales group, we in turn have a Management of Change (MOC) by way of a Supplier mailbox at our corporate office. We in turn inform all of our customers that purchased the product in the past 24 months...
- Formulation Group (dedicated excipients group)

26. What elements do you currently include in a Quality Technical Agreement with excipient Suppliers to ensure the quality of excipients you receive on a regular basis? Circle all that apply. If there is other additional information please include in the "Other" category.

Access to real time excipient manufacturing process data and process capabilities 1 of 10 10%

Specifics on what changes in excipient process triggers a notification (for example sourced raw material, excipient product attributes)

7 of 10 70%

Description on the procedure for notification when important excipient changes occur 6 of 10 60%

Other _____

- Rarely have QTAs with excipient Suppliers. This is handled by the CMO.

- Don't know
- Many Suppliers will not sign this type of agreement, as many will not sign quality agreements either.
- Process deviations, nonconformances, CAPAs and recalls

27. Is any specific element not included in the Quality Technical Agreement due to disagreement between Pharmaceutical Company and Supplier?

Comment _____

- None that come to mind although reaching a final agreement always takes some negotiation. Mostly due to IP and duration of non-disclosure agreement
- See above. Not relevant.
- No
- Don't know
- Not that I am aware of.
- Some proprietary processes that are a matter of "know how" and not part of a patent; for example, trade secrets.

28. Which changes do you consider to be important changes in excipient manufacturing or properties? Circle all that apply. If there is other additional information please include in the “Other” category.

New sourced raw material	9 of 11	82%
New or changed excipient impurity levels	10 of 11	91%
Excipient manufacturing process changes that do not impact the CoA requirements	7 of 11	64%

Other: _____

- This depends on the excipient. For example, lactose if they changed cows (source or raw material) this would not be important. However for gelatin,

switching from bovine to porcine this would be significant. In special cases with gelatin sourcing from different regions can have an impact (say South American versus European cows. This is for two reasons: 1 is the fact that the hides are sufficiently different based on feeding that a different process is required to obtain gelatin, 2 regulatory issues (BSE, foot/mouth) different country regulations have different perspectives on "risky" regions and can conflict

- Manufacturing location
- Out of trend and outside the control lots from SPC trending

Appendix B - Survey provided to Excipient Suppliers with Responses

Survey on "Evaluation of Excipient Variation on Drug Product Performance"

For Excipient Supplier:

Goal of the survey: Design a mutually beneficial best practice between Pharmaceutics Companies and excipient Suppliers to evaluate the impact of excipient variation on drug product performance. The survey is intended to identify gaps and challenges in the current processes with regard to study design, collaboration and procurement both during the development phase and the lifecycle of the drug product.

The survey results are reported as a percent of those companies that responded to individual questions.

Which of the following categories best describes your business? Please choose only one category.

Excipient Supplier	2 of 6	33%
No response	4 of 6	66%

1. What type of Pharmaceutical excipient do you supply?
Circle all that apply. If there is other additional information please include in the "Other" category.

Filler	2 of 6	33%
Binder	3 of 6	50%
Disintegrant	1 of 6	17%
Lubricant/Glidant	2 of 6	33%
Drug release modifier/controller	6 of 6	100%
pH modifier/Buffering Agent	1 of 6	17%

Colorant/Dye	1 of 6	17%
Taste masker/Flavoring Agent	2 of 6	33%
Coating Agent	3 of 6	50%
Wetting/Solubilzing/Emulsifying Agent	3 of 6	50%
Suspending and/or Viscosity-increasing Agent	3 of 6	50%
Solvent	2 of 6	33%
Other _____		

- adhesion

2. What are the typical excipient attribute variation(s) that you are requested to provide? Circle the two most common. If there is additional information please include in the "Other" category.

Particle size/distribution	3 of 6	50%
Specific surface area	0 of 6	
Processing aid/impurity	0 of 6	
Bulk/tap density	0 of 6	
Moisture content	1 of 6	17%
Viscosity	5 of 6	83%
Other _____	3 of 6	50%

- Copolymer composition (assay)
- volatile content or non-volatile content (NVC) adhesion

- We supply synthetic excipients. Customers ask for material at the edge of the pharmacopeia specifications. We recognize that many users do not really understand the type of function.

3. How often do Pharmaceutical Companies consult with you about the excipient variation impact on drug product performance study design or risk assessments?

	Never			Always
	1	2	3	4	5

Comment _____

Never	1 of 6	17%
Infrequently	2 of 6	33%
Neither frequently or infrequently	2 of 6	33%
Frequently	1 of 6	17%

- They start very late in their development process. Sometimes they seem to rather observe patent issues than performance issues and request something from the polymers at the edges of their functionality

4. Is a Confidential Agreement in place for technical discussions?

Yes	5 of 5	100%
No		

Comment _____

- Approximately 33 % of the time
- Standard information is available without CDA

5. What type of technical information is discussed? Circle all that apply. If there is other additional information please include in the “Other” category.

The justification of why this excipient and its attribute variation are selected for the evaluation

Risk Assessment	1 of 6	17%
Study design: scope, excipient range etc.	3 of 6	50%
Excipient production process (es)/CoA	6 of 6	100%
Excipient process capability	5 of 6	83%

Other _____

- Customers ask for material at the edge of pharmacopeia specifications. The chemical production processes however are set up to provide consistent material. We try to guide users to the formulation processes.
- Process capability requests were infrequent until FDA announced that generics need to include QbD in submissions starting 2013

6. Are you typically asked by Pharmaceutical Companies to provide excipient manufacturing process capabilities for evaluation of excipient variation impact on drug product performance?

	Never				Always
	1	2	3	4	5

Comment _____

Never	0 of 6	
Infrequently	2 of 6	33%
Neither frequently or infrequently	2 of 6	33%
Frequently	2 of 6	33%
Always	0 of 6	

- Again, this was infrequent until FDAs QbD expectations were announced

7. What are the major excipient supply issues in regard to providing excipient variation for the evaluation of excipient impact on drug product performance? Circle all that apply. If there is other additional information please include in the "Other" category.

Producing excipient with properties narrower than specification range

4 of 6 67%

Producing excipient with properties outside the specification range (excipient material is not available from the standard manufacturing process)

5 of 6 83%

Low volume requests for excipient property variations

5 of 6 83%

Cost prohibitive 3 of 6 50%

Time consuming 4 of 6 67%

Not feasible to obtain excipient material when specifying a combination of 2 or more attributes (for example attributes are not independent)

3 of 6 50%

Other _____

- Sometimes we also need to understand the customer's application and API because those impact the performance of our polymers. Customers are reluctant to share.

8. Which group in your company is responsible to provide excipient lots with variation in one or more attributes for drug product impact evaluation? Circle the most common one. If there is other additional information please include in the "Other" category.

Sales group 0 of 6

Technical group responsible for manufacturing 4 of 6 67%

Other _____ 2 of 6 33%

- R&D
- We do not supply such material. We supply of shelf standard material. We offer technical service and ideas, for example mixtures of the materials could cover questions on variability. We offer such ideas.

9. If you were able to provide excipient lots with variation in one or more properties, how was this achieved? Circle all that apply. If there is other additional information please include in the "Other" category.

Lots were selected from inventory that met the requested requirements

3 of 6 50%

The excipient manufacturing process was varied to produce lots with a systematic variation in the desired property

1 of 6 17%

The excipient material was manipulated post manufacture to create the desired variation (for example sieving for particle size)

1 of 6 17%

Other _____

- We have difficulty supplying outside normal process, plants to big to make changes for samples

10. How frequently have you been informed of the findings from Pharmaceutical Companies with regard to excipient variation impact on the drug product performance?

Never Always

1 2 3 4 5

Comment _____

Never 1 of 6 17%

Infrequently	3 of 6	50%
Neither frequently or infrequently	1 of 6	17%
Frequently	1 of 6	17%

11. If the excipient property variation is not acceptable to the Pharmaceutical Company, what is your typical recommendation? Circle the most common one. If there is other additional information please include in the “Other” category.

Recommend an alternate excipient grade or product for re-evaluation

1 of 6 17%

Recommend that the Pharmaceutical Company modify the drug product formulation and/or manufacturing process

3 of 6 50%

Select specific lots meeting the narrower specification

1 of 6 17%

Modify process to meet narrower specification

1 of 6 17%

Other _____

- Unfortunately customers only show up at phase III. They have done their submission, formulation cannot be adjusted but FDA asks for data. We would recommend doing QBD early in formulation process.

12. What group do you notify of changes in the excipient manufacturing process, sourced raw materials or excipient product attributes? Circle all that apply. If there is other additional information please include in the “Other” category.

Notify Pharmaceutical sourcing group 5 of 6 83%

Notify Pharmaceutical manufacturing group	4 of 6	67%
On-line or other monitoring system	0 of 6	
No notification	0 of 6	

Other _____

- When quality agreements in place we inform contact persons named in the quality agreement. When no quality agreement is in place we choose our standard contact

13. What changes trigger the notification to the Pharmaceutical Company that uses your products? Circle all that apply. If there is other additional information please include in the "Other" category.

New sourced raw material	4 of 6	67%
New or changed excipient impurity levels	2 of 6	33%
Excipient manufacturing process changes that do not impact the CoA requirements	2 of 6	33%

Other: _____

- Changes in stability or use life, changes in primary packaging, changes in specifications/specification limits, etc.
- We evaluate change according to IPEC Americas significant change guide. Level 3 changes are informed.
- We follow IPEC Significant Change guidelines

14. How satisfied are you with the current process to provide excipient lots with variation in one or more properties to a Pharmaceutical Company?

	Not Satisfied				Satisfied		
	1	2	3	4	5		
Dissatisfied						2 of 6	33%

Somewhat dissatisfied	1 of 6	17%
Neither dissatisfied nor satisfied	1 of 6	17%
Somewhat satisfied	1 of 6	17%
Satisfied	1 of 6	17%

Comment_____

- Neither, we have worked at this very hard.
- Satisfied, we make a product to specification and material outside specification is not available in most cases.