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Lessons Learned

Smart Specification Setting for Dry Powder Inhalation Carriers

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ABSTRACT

The specifications of excipients are important to pharmaceutical manufacturers to ensure that the final product can be manufactured robustly over the entire lifecycle of a drug product. Particle size specifications are key for dry powder inhalation excipients and they should be agreed between users and suppliers. The current paper evaluates two development strategies to set particle size specifications. It is shown that the application of quality-by-design principles to specification setting could result in broader specifications, while it guarantees that efficacy, safety and manufacturing of the medication is not affected. A multitude of reasons exist to keep specifications broader than the production capability range, including improved risk-mitigation and potentially reduced regulatory challenges during and after registration.

Introduction

Dry powder formulations are generally produced by mixing micronized drug particles with larger carrier particles. Lactose monohydrate is by far the largest commercially utilized excipient as a carrier.[1] Lactose characteristics, such as particle size distribution, highly affect the aerosol performance of a powder.[2] Mixing coarse with fine lactose, in combination with influencing other properties, provides formulators a means to optimize the aerodynamic behaviour of a final DPI blend. Studies have shown that the inclusion of fine particles can significantly increase in the respirable fraction of the drug.[3] Control on the particle size of lactose, and especially the fines content is therefore crucial.[4]

All production processes however, including the production processes for inhalation grade lactose monohydrate, have some inevitable degree of variation.[5] Production processes can shift amongst others due to equipment getting older, variation in conditions, human intervention and variability of starting materials. The occurrence of variations does not mean that a process is out of control. It refers to the fact that not all batches are exactly the same and that the impact of variations on the final dosage form should be understood. Formulators should ask themselves which ranges of variation are acceptable for their formulation, to maintain efficacy and safety of the final product. Additionally, the impact of variation (e.g. lactose variability) can be minimized and controlled. Such evaluation should include the entire scope of potential variations and their effect on the full set of critical to quality attributes.

One way to control the particle size of the lactose carrier is the application of pre-set particle size distribution specifications. A specification refers to a defined test method with specified acceptance criteria. Most commercially available inhalation lactose grades are supplied with pre-defined specifications. For unique, customized grades of lactose however, specifications should be agreed upon by the supplier and the user. Specifications are proposed and justified by the applicant during registration of a drug product, and they need to be approved by the competent authorities. For changes in the registered specification, applicants must assess the effects of the change through appropriate studies.

For suppliers, particle size specifications indicate which level of variation is acceptable by the users and should therefore be in line with the capability of the production process. For the users, particle size specifications ensure that commercial products can be manufactured robustly over the entire lifecycle of a product. Manufacturing processes should be developed in such a way that starting material

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variation does not impact the performance outside the acceptable limits.

This paper evaluates two extreme strategies for the agreement of specifications between suppliers and users. The first strategy considered is based on evaluation of the production capabilities of a supplier only. The second strategy focuses on understanding the effect of variability on the final performance, in line with Quality by Design (QbD) principles.

Experimental

Two different lactose specification setting strategies were evaluated for a formulation with 1% w/w salbutamol sulfate. This simplified case study is performed to showcase how specifications could be derived during the development trajectory, assuming early development studies have been completed. The quality attribute for functionality was the cumulative deposition on stages 2 to 4 of a Next Generation Impactor, with a target deposition of 30-40% w/w of the total recovered dose. Assumed was that the evaluated variation in particle size does not change the mixing or filling optimization.

Lactose blends with different particle size distributions were created by blending Lactohale® 206 and Lactohale® 220 for 8 min at 96 rpm in a Turbula blender (Willy A. Bachofen AG, Basel, Switzerland). The resulting lactose blends were blended for 10 min at 96 rpm with 1% w/w of salbutamol sulfate (University of Groningen, Groningen, Netherlands) with a median particle size (x50) of 1.39 μm to test the functionality. Size 3 HPMC capsules (Quali-V®-I, Qualicaps, Madrid, Spain) were filled manually with 20 +/- 2 mg of blend at standard laboratory conditions. Next Generation Impactor (NGI, Copley Scientific ltd, Colwick, UK) measurements were performed on ten capsules in duplicate with a RS01 model 7 device with high resistance (Berry Global Healthcare, IN, US). The flowrate was set to 60 L/min, corresponding to a pressure drop of 4 kPa.

Results and Discussion

Strategy 1: The Capability Approach

The first strategy considered for specification setting is based on evaluation of the production capabilities of a supplier. In this case, formulators typically do not actively assess the capabilities of a supplier, but they identify a lactose grade that is suitable for their formulation and process. This lactose grade, like any grade, will be available with a certain variability that originates from the production capability of the supplier. For commercially available standard grades, the potential variability is already captured in the provided particle size specifications. When a customized lactose grade is used however, it might be the first time that these specific ranges are selected. Specifications therefore still need to be discussed and aligned between the user and the supplier.

This approach starts with exploratory and screening development work to identify which particle size distribution(s) results in the desired performance. When a suitable lactose particle size distribution is identified, multiple batches of this specific lactose particle size distribution will be ordered and tested in the formulation. The variation in the particle size distribution of the lactose batches that will be tested is assumed to be representative for the variability that can be expected over longer time periods and is a measure for the production capability of the supplier. For the user, testing these batches helps to determine if the developed formulation and process are robust and able to cope with the expected variability.

The example below is focused on lactose blends with 7% w/w of lactose fines (fraction <4.5 μm). Exploratory studies confirmed that a lactose blend with this fines content resulted in approximately 35% w/w deposition on stages 2-4. Therefore, three batches with a target fraction <4.5 μm of 7% w/w were ordered from the supplier. Batches were produced by the supplier based upon different batches of starting material to capture the natural variability, resulting in fines concentrations <4.5 μm of 6.8 – 7.1% w/w. Note that this illustration considers three batches to evaluate the variability, while typically at least six batches are recommended to get statistically relevant data.

Fig. 1 shows the NGI profiles of the three blends with a target fraction <4.5 μm of 7.0% w/w. The cumulative deposition of salbutamol sulfate on the stages 2-4 of these samples were 34.8% w/w, 31.5% w/w and 33.1% w/w. All batches therefore performed well within the set acceptance criteria of 30-40% w/w deposition on stages 2-4.

Blends with a target fraction <4.5 μm of 7.0% w/w performed well within the pre-set acceptance criterium. A specification of 6.8 - 7.1% w/w <4.5 μm might therefore look desirable from user perspective. With the inevitable degree of variation in production processes however, this narrow target would result in high risks for the supply security. Business continuity with secured supply over the entire

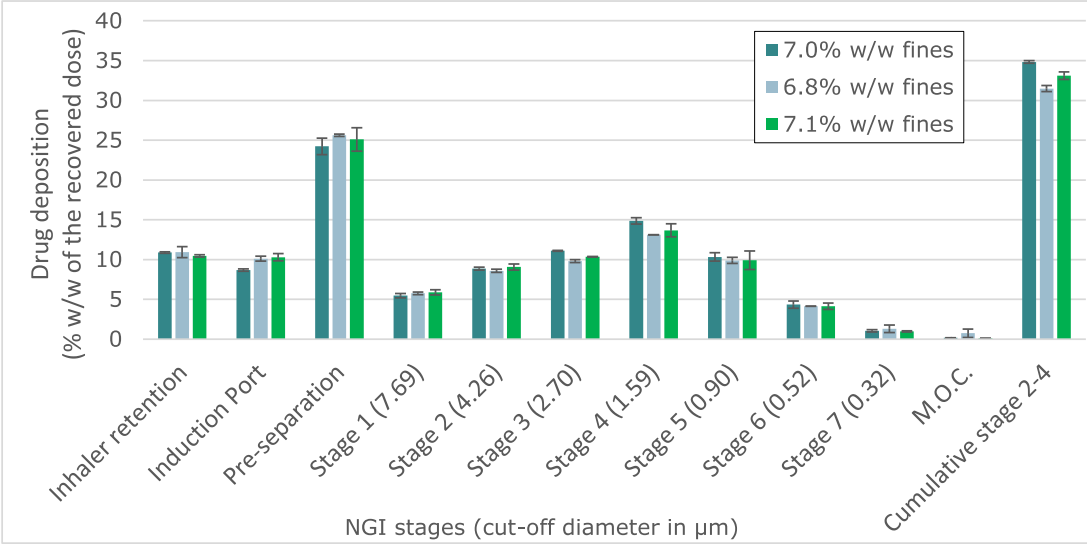

Figure 1. Next Generation Impactor profiles of 1% w/w salbutamol sulfate blended with three blends with a target lactose fines fraction <4.5 μm of 7.0% w/w. Error bars represent the standard deviation of a duplicate measurement. The total deposition on stages 2 till 4 is 31-35% w/w of the recovered dose and therefore well within the set acceptance criterium of 30-40% w/w.

Table 1
Particle size values and deposition on stages 2-4 for three evaluated blends with 7% w/w fines. The theoretical production capability is calculated as the average ± 3 standard deviations, corresponding to the 99.7% confidence interval.

	fraction <4.5 μm (% w/w)	x10 (μm)	x50 (μm)	x90 (μm)	Deposition on stage 2-4 (% w/w of the recovered dose)
7% w/w fines - Batch 1	7.0	7.7	64	140	34.8
7% w/w fines - Batch 2	6.8	6.5	58	138	31.5
7% w/w fines - Batch 3	7.1	6.7	50	139	33.1
Production capability	6.5 – 7.5	5.8 – 7.1	35 – 69	135 – 142	

lifecycle of the formulation can be only guaranteed when the production capability of the supplier is taken into account as well. In this case, the production capability of the supplier to produce a fraction <4.5 μm of 7.0% w/w was calculated as the 99.7% confidence interval (average ± 3 standard deviations) of previously produced batches, as indicated in Table 1. This resulted in a specification proposal for the fines fraction <4.5 μm of 6.5 – 7.5% w/w.

Specifications as proposed in Table 1 were acceptable for both users and suppliers. For suppliers, the specifications are in line with the production capability. For users, the robustness of the developed DPI formulation and process was confirmed by testing three batches.

The proposed specifications derived with this approach do have some risks, which could become a challenge during and after registration. During initial registration, questions might arise on confirmation of the final product quality when lactose batches are used that are on the edge of the specification. The extremes of the specification typically have not been tested with this approach and additional testing could be requested by regulatory agencies. This regulatory hassle does result in delays and additional costs for testing, especially when stability testing needs to be repeated.

Furthermore, the narrow ranges submitted provide limited freedom in case of unforeseen other variations that may occur, which again can be a risk for business continuity. Examples of unforeseen variations that might require broader specifications based on an in-depth understanding of acceptable ranges, are related to alternative sourcing, changes in the Active Pharmaceutical Ingredient (API), changes in the formulation process or processing equipment, and changes in measurement equipment.

Alternative Sourcing

Many people's health and wellness depend largely on the availability of medical treatment. It is the responsibility of pharmaceutical companies to ensure that their medication is constantly available to the market. A strong supply chain and reliable partners are critical for this, which has become even more clear during the COVID-19 pandemic. To mitigate the risk of unavailable starting materials, pharmaceutical companies should only work with trusted partners with a reliable supply chain. Additionally, starting material specifications in registrations are recommended to be kept as broad as possible. Key is that the registered specifications ensure product quality (meet final product specifications), whilst at the same time allow for maximum flexibility. This flexibility may become especially relevant in case a certain starting material is not available, and a new grade or supplier should be considered. Extensive reformulation work is typically required to allow for the change to a different starting material, but the regulatory burden can be minimized when excipient specifications remain within the registered range. Changing or adding a new grade or supplier is typically accepted by the regulatory agencies via an annual report, but only "if the excipient specification remains unchanged".[6] With very narrow specifications that are derived from the production capability of a specific product from a specific supplier, the chance that the specification can remain unchanged is very low. Specifications that span a wider range than the production capability in contrast, allow more narrow targeting without a change in specification.

Changes in the API

The impact of variability of active pharmaceutical ingredients (APIs) is not always thoroughly considered during the development of a formulation, due to the low quantities of API that are typically available. Nevertheless, changes in the physical properties of an API during the life cycle of a formulation can be expected, due to minor changes in for example the synthesis, milling, production scale or packaging.[7] APIs could vary in crystal structure, water content, particle size, or surface properties; resulting in slightly different behaviour in a final formulation. To keep the performance within the acceptable ranges, a slight modification in the particle size distribution of the lactose grade might be desired. However, with the tight (registered) specifications, there is no option to implement this solution on the short term with a minimal effort related to the registration. Re-alignment with the supplier, followed by regulatory hassle to adjust the registration might be required.

Unforeseen Changes in The Formulation Process or Processing Equipment

Imagine that a specific commercial formulation has been produced with the same equipment for decades. The process that was developed and validated takes into account that the blending step results in a minor increase in fines content of the lactose of 1% w/w. Suddenly however, the blender breaks (or has reached the end of life) and has to be replaced with a new, state-of-the-art, model. The new blender has a more controlled set-up and process, which is beneficial for achieving a good content uniformity. A challenge of this new blender however is that only 0.2% w/w additional lactose fines are created during the mixing process. The proposed solution by the formulators to deal with this difference is to use a lactose grade with 0.8% w/w more fines. This proposal was shown to be successful. Just like in the previous example however, tight specifications do not allow to implement such a solution on the short term with a minimal effort related to registration.

Potential Changes in Measurement Equipment

The particle size distribution of lactose is commonly determined by laser diffraction methodologies. However, inevitable offsets are present between different laboratories and different equipment. These offsets can be become a challenge in the circumstance that analytical equipment breaks or needs replacement. When measurement equipment has to be replaced, material with the optimal particle size distribution might suddenly be measured and reported with a slight offset. When narrow specifications are in place, this could even result in out of specification measurements. As a consequence, adjustments in the specification and the registration might be required, even though the product has not been changed and the risk is neglectable.

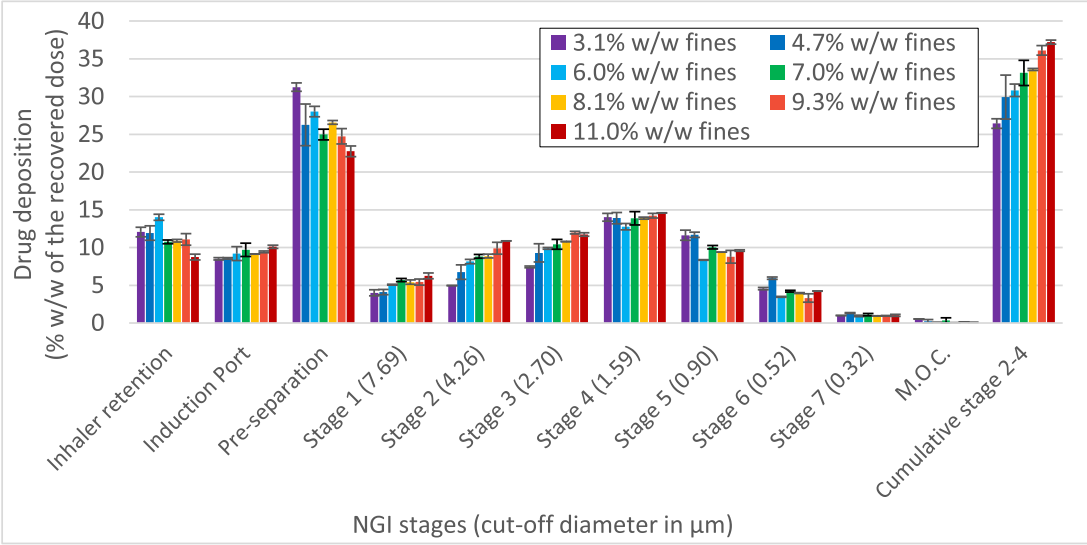

Figure 2. Next Generation Impactor profiles of blends of lactose with a target fines content fraction <4.5 μm of 3.0-11.0% w/w. Error bars for the 7.0% w/w fines represent the standard deviation over the three tested batches. The other error bars represent the standard deviation of a duplicate measurement. The total deposition on stages 2 till 4 varies between 26-37% w/w of the recovered dose.

Strategy 2: the Quality-by-design Approach

The second strategy considered for specification setting is based on quality-by-design (QbD) studies. In this case, formulators typically evaluate the design space to determine which particle size parameters are most critical, and which ranges result in acceptable performance. This range is typically broader than the production capability of the supplier, allowing to request for a 'target range' within the specification when required.

In the QbD example below, lactose blends with 3-11% w/w of lactose fines (fraction <4.5μm) were investigated. Exploratory studies had demonstrated that 33% w/w cumulative deposition on the stages 2-4 was achieved when a blend with a fraction <4.5 μm of 7% w/w was used. Six QbD batches around this target range were therefore ordered with a target fraction <4.5 μm of 3, 4.5, 6, 8, 9.5 and 11% w/w. Fig. 2 shows the NGI profiles of the QbD blends with a fraction <4.5 μm between 3.0 and 11.0% w/w. Note that in this example all QbD batches are produced with the same batch of starting material, while inclusion of natural variability between batches would be desirable.

Table 2 shows the particle size distribution parameters fraction <4.5 μm, x10, x50, x90 and the total deposition on stages 2-4 for the evaluated blends. The measured deposition on stage 2-4 of blends with a fraction <4.5 μm between 6.0 till 11.0% w/w were all within the pre-set acceptance criterium.

Fig. 3 shows the correlation between particle size parameters and the cumulative deposition on stages 2-4. A strong linear correlation was observed between the size fraction <4.5 μm and the cumulative deposition on stages 2-4. Based upon the correlation line, all batches with a fraction <4.5 μm of 5.1 till 12.4 % w/w would result in deposition on stages 2-4 within the set acceptance criterium of 30-40% w/w.

The correlation graphs in Fig. 3 show, in line with previous research, that the size fraction <4.5 μm is the key driver for the deposition on stages 2-4.[3] Control on this parameter is therefore most critical. Consequently it is recommended to add a small additional safety margin when considering the fraction <4.5 μm specification. The target deposition on stages 2-4 for setting this specific parameter is reduced with 2.5% w/w on both sides, to allow for potential variability or interaction effects of other variables. The used range of 2.5% w/w was derived from the standard deviation observed for batches with a target of 7.0% w/w fines. All batches with a fraction <4.5 μm of 6.9 till 10.6% w/w would result in deposition on stages 2-4 within the range of 32.5-37.5% w/w. Based upon the provided evaluation,

Table 2
Particle size values and deposition on stages 2-4 for evaluated blends. Batches with 6.0-11.0% w/w fines provided deposition on stages 2-4 within the set acceptance criterium of 35-45% w/w. The theoretical production capability with a target of 7% w/w fines is also provided as a reference.

Target amount of fines	fraction <4.5 μm (% w/w)	x10 (μm)	x50 (μm)	x90 (μm)	Deposition on stage 2-4 (% w/w of the recovered dose)
3.0% w/w fines	3.1	18	79	146	26
4.5% w/w fines	4.7	10	72	144	30
6.0% w/w fines	6.0	7.7	64	140	31
7.0% w/w fines	7.0	6.5	58	138	33
8.0% w/w fines	8.1	5.6	48	133	34
9.5% w/w fines	9.3	4.9	39	125	36
11.0% w/w fines	11.0	4.1	28	116	37
Production capability	6.5 – 7.5	5.8 – 7.1	35 – 69	135 – 142	

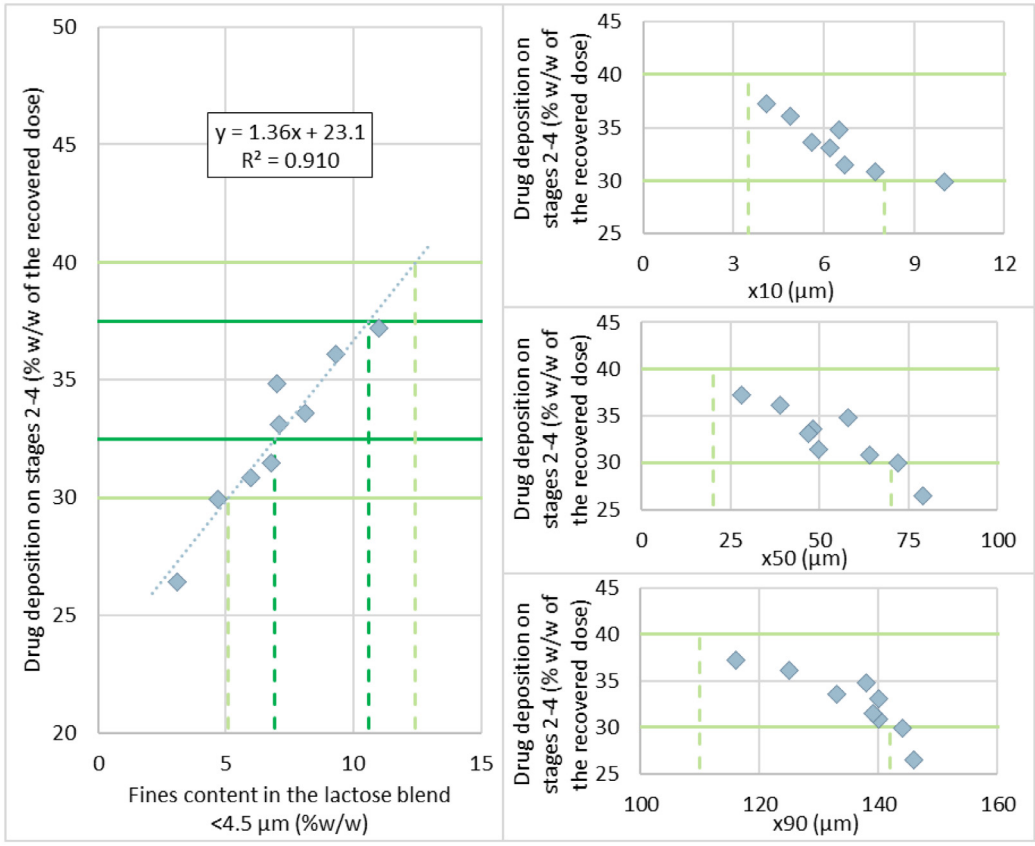

Figure 3. Correlation between particle size parameters of the lactose blend and the salbutamol sulfate deposition on stages 2-4. A strong linear correlation was observed for the fines content in the lactose blend (fraction <4.5 μm) and the deposition on stages 2-4. Light green lines correspond to the acceptance criterium of 30-40% w/w deposition on stages 2-4. Dark green lines correspond to the acceptance criterium of 32.5-37.5% w/w deposition on stages 2-4, which includes an additional safety margin as used for the fines content specification proposal.

particle size specifications as indicated in Table 3 could be justified – with a request to the supplier to target as close as possible to a fraction <4.5 μm of 8.8% w/w. No challenges are foreseen for the supplier to produce with this precision, as a bandwidth of 3.7% w/w is proposed, while the production capability indicates a bandwidth of 1% w/w for the target fraction of <4.5 μm.

Business Continuity

Similar to specification setting based upon the suppliers capability (strategy 1), QbD specification setting (strategy 2) leads to a product that meets the performance requirements and the production capability of the supplier to produce this lactose grade. The proposed ranges from strategy 2 are however wider and experimentally validated, resulting in reduced risks for business continuity.

Formulators that work with specifications that are set from QbD studies typically have reduced risks for failure in product quality as a result of starting material variability. This is due to the available performance data from batches at the edge of the specification, which confirmed that these batches resulted in acceptable performance. The reduced risks in this case are also acknowledged by regulatory agencies, resulting in less complexity during regulatory filing, reducing the time to market.

Also in the case of unforeseen circumstances after registration, broader ranges allow for more (regulatory) flexibility. For example during the qualification of a second source of starting material, extensive reformulation studies are usually required. This can be a challenging job for formulators, which might come along with additional work and costs for the update of regulatory filings. In this situation, the regulatory burden can be minimized when specification remains within the same range as originally was filed, as changing to a new grade or supplier can then be communicated via an annual report.[6] Also when unforeseen changes in API, processing equipment or measurement equipment occur, broader specifications can help to prevent unnecessary work. Small shifts in acceptable particle size limits can be discussed and aligned with the supplier, especially in case this shift is minor compared

Table 3
QbD acceptance range for the particle size parameters of the evaluated blends. Batches with 6.0-11.0% w/w fines provided deposition on stages 2-4 within the set acceptance criteria of 35-45% w/w of the recovered dose. The theoretical production capability with a target of 7% w/w fines is also provided as a reference.

	fraction <4.5 μm (%)	x10 (μm)	x50 (μm)	x90 (μm)
QbD acceptance range (30-40% w/w of the recovered dose on stages 2-4)	5.1 – 12.4	3.5 – 8	20 – 70	110 – 142
Proposed specifications (target)	**6.9 – 10.6 (8.8)**	**3.5 – 8**	**20 – 70**	**110 – 142**
Production capability (target 7% w/w)	6.5 – 7.5	5.8 – 7.1	35 – 69	135 – 142

to the production capability of the supplier and the registered specification range. No regulatory hassle is expected in this case, as the limits of the new agreement between supplier and user are within the originally registered specification limits.

Conclusion

Any inhalation grade of lactose and active pharmaceutical ingredient (API) is produced with some inevitable degree of variation in its particle size distribution. This variation can have a large impact on the inhalation performance of carrier-based DPI formulations, for example regarding the fine particle fraction that is generated during inhalation performance testing. Control of the particle size is thus crucial to product performance and quality, and can be achieved by agreement of particle size specifications between users and suppliers. Users should indicate which level of variation is acceptable to guarantee efficacy and safety of the medication. In parallel, specifications should be aligned with the production capabilities of the supplier to secure supply and guarantee business continuity.

This paper evaluated the two extreme strategies for the agreement of specifications between suppliers and users. The first strategy considered is based on evaluation of the production capabilities of the supplier only. This strategy typically results in narrow specifications, which could be a challenge during and after registration and jeopardize business continuity. The second strategy focuses on understanding the effect of variability on the final performance, in line with Quality by Design (QbD) principles. It is shown that this strategy could result in specifications that span a wider range than the production capability of a supplier, allowing for re-alignment on more narrow acceptable ranges without a change in specification. Pharmaceutical manufacturers become more resilient by having broader specifications agreed with their suppliers, by mitigating risks for unforeseen circumstances and reducing the regulatory burden during and after registration.

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