# Initial risk assessment matrix related to the impact of raw material attributes on product quality attributes

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| --- | --- | --- | --- | --- | --- | --- |
| Raw material attributes  | Product data Or data on similar products or Literature data  | Particle size distribution | Crystal structure | Jet milling yield | EHS | Comments and mitigation plan |
| Particle size of unmilled material | Large particle size could induce blow back of jet mill.The unmilled material contains very large lumps.  | High impact and high probability of occurrence. High risk having score of 90 | Low impact and low probability of occurrence. Low risk having score of 2 | High impact and high probability of occurrence. High risk having score of 90. | High impact and high probability of occurrence. High risk having score of 90. | De-lumping would be requiredIt necessitates to evaluate oscillating sieving mill versus conical-Sieve-mill |
| Hardness of not jetmilled material | Hard material requires high energy to break.The API is an organic material exhibiting hardness that could be managed by jet mill performances. No issue was observed during early stage development | High impact and low probability of occurrence. Medium risk having score of 18. | Low impact and low probability of occurrence. Low risk having score of 2. | Low impact and low probability of occurrence. Low risk having score of 2. | Low impact and low probability of occurrence. Low risk having score of 2. | Conduct parametric study to define the relationship between the particle size or the surface specific area and the specific energy |
| Bulk density and Flow properties of un-jet milled material | Impact on feeding of jet mill.The API exhibits a very low bulk density and poor flow property | High impact and high probability of occurrence. High risk having score of 90 | High impact and medium probability of occurrence. High risk having score of 54 | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Evaluation of gravimetric feeder versus volumetric one. Design of sealed process allowing efficient recovery |
| Crystal structure of un-jet milled material  | Crystal structure of jet milled material may be impacted either by jet milling specific energy or by grinding gas humidity.The API presents 2 crystalline forms. Polymorphic transition could occur during milling. Stability of particle size during storage may be impacted  | Low impact and low probability of occurrence. Low risk having score of 2 | High impact and high probability of occurrence. High risk having score of 54 | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Monitoring of crystal structure as a function of the applied specific energy. |
| Surface charge of un-jet milled material | Impacts solid flow rate and build-up inside the mill.Resistivity of API powder is about 3.105 Ω.m indicating that the API is prone to electrostatic charge accumulation. | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 54 | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Evaluation of gravimetric feeder versus volumetric one. Design of sealedsealed process allowing containment and efficient recovery |
| Morphology of un-jet milled material | Impacts solid flow rate and build-up inside the mill.The API is a needle shaped material that could increase the inter-particle friction and therefore the flowability. | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 54 | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Evaluation of gravimetric feeder versus volumetric one. Design of sealed process containment and efficient recovery |
| Stickiness of un-jet milled material | Impacts solid flow rate and therefore the applied specific energy.The API exhibits high tendency to adhesiveness to stainless steel and some polymers.Likely build-up inside the mill. | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 54 | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Selection of adequate jet mill having material that can lower adhesiveness of API.Evaluation of gravimetric feeder versus volumetric one.  |
| Abrasiveness of un-jet milled material | Impacts particle size distribution and wearing of jet milled material.The API is an organic material exhibiting hardness that could be managed by jet mill performances. No issue was observed during early stage development. | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | No action plan |
| Residual solvent of un-jet milled material | Can induce build-up inside the mill.The API contains organic solvent which is compliant with the official limits according to ICH residual solvents requirements by USP and Ph. Eur. | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | No action plan |

# Initial risk assessment matrix related to the impact of operating parameters on product quality attributes

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| --- | --- | --- | --- | --- | --- | --- |
| Operating parameters | Product data or data on similar products or Literature data  | Particle sized distribution | Crystal structure | Jet milling yield | EHS | Comment and / or mitigation plan |
| Grinding gas humidity | Impacts crystal structure if hydrate or anhydrous API is processed.The API in our case is not in the form of hydrate or anhydrous | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | Low impact and low probability of occurrence. High risk having score of 2 | No action plan |
| Grinding gas type | Gas with low molecular mass will induce high specific energy of jet milling.The API is classified as class 2 as per dust explosion classification.High oxygen rate can induce explosion.To avoid any incident operators (anoxia) must protected with clothing a hood and having breathable air mask | High impact and low probability of occurrence. Medium risk having score of 18. | High impact and medium probability of occurrence. High risk having score of 54. | Low impact and low probability of occurrence. High risk having score of 2. | High impact and high probability of occurrence. High risk having score of 54 | Conduct Safety, Hazards and Risk Evaluation.Design a process with explosion barrier or use clothing with hood having breathable air for operators if Nitrogen blanketing is used |
| Grinding gas pressure | Higher is the pressure, higher is the jet milling specific energy.The behavior of the API to the applied specific energy is not known | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Low impact and low probability of occurrence. low risk having score of 2 | Low impact and low probability of occurrence. low risk having score of 2 | Conduct parametric study to design the space where the API could be obtained with targeted particle size but without polymorphic change |
| Injection gas pressure | Need to be slightly higher than grinding pressure to avoid blow back | Low impact and low probability of occurrence. low risk having score of 2 | Low impact and low probability of occurrence. low risk having score of 2 | High impact and low probability of occurrence. Medium risk having score of 18. | High impact and low probability of occurrence. Medium risk having score of 18. | Fix the injection pressure at 1 bar higher than the grinding pressure. Design sealed jet milling system with pressure balancing |
| Solid feeding rate | Higher is the feeding rate, lower is the jet milling specific energy.The API exhibit poor flow property and tendency to stick | High impact and high probability of occurrence. High risk having score of 90 | High impact and medium probability of occurrence. High risk having score of 54 | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Evaluation of gravimetric feeder versus volumetric one.  |
| Grinding gas temperature | Higher is the temperature, higher is the jet milling specific energy. The sound velocity is proportional to square of temperature.Jet milling will be used at ambient temperature  | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Operate jet milling at ambient temperature if amorphization is not observed |

# Initial risk assessment matrix related to the impact of geometrical parameters of equipment on product quality attributes

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| --- | --- | --- | --- | --- | --- | --- |
| Geometrical parameters of equipment | Product data Or data on similar products or Literature data  | Particle sized distribution | Crystal structure | Jet milling yield | EHS | Comment and / or mitigation plan |
| Jet mill type | Define the jet milling specific energy level.In general, the loop jet mill and the opposite jet mill are softer than the spiral jet mill and can result in slightly higher intermediate particle size distributions than those obtained with spiral . In our case, the target particle size is 2.6-4.4 µm | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18. | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Conduct parametric study to design the space where the API could be obtained with target particle size but without polymorphism. The jet mill will be defined accordingly.Based on target particle size use a spiral jet mill as first intention |
| Size of jet mill | Impacts only the capacity of jet milling if the scale-up rules are applied.Small batch size if processed using large mill, so yield could be impacted  | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18. | High impact and low probability of occurrence. Medium risk having score of 18. | High impact and low probability of occurrence. Medium risk having score of 18. | Define scale-up rule, and select the mill size according the batch size to be processed |
| Grinding nozzles type | Define the jet milling specific energy level as it impact the gas velocityConvergent-divergent nozzles will induce higher velocity than convergent and straight nozzles.The behaviour of the API at the applied specific energy is not known | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18. | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Characterizations of aerodynamic behavior of nozzles to be used. Select the grinding nozzles to be used according to the specific energy level to be applied |
| Grinding nozzles number | The jet milling specific energy level is proportional to grinding nozzles number.The behaviour of the API at the applied specific energy is not known | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18. | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Define number of nozzles according to the required specific energy of milling |
| Grinding nozzles diameter | The jet milling specific energy level is proportional to grinding nozzles number.The behavior of the API at the applied specific energy is not known | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18. | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | Define number of nozzles according the required specific energy of millingCharacterization of aerodynamic behavior of nozzles to be used |
| Grinding nozzles angle | Impact on the notional circle diameter and therefore the build-up inside the mill if the spiral jet mill is usedOptimal grinding nozzle angle can ensure proper functioning of the jet mill | Low impact and low probability of occurrence. Low risk having score of 2 | Low impact and low probability of occurrence. Low risk having score of 2 | High impact and low probability of occurrence. Low risk having score of 18 | High impact and low probability of occurrence. Low risk having score of 18 | If spiral jet mill is used, use an optimal grinding nozzle angle |
| Classifier gap | The spiral jet mill is used, impact on particle size distribution and the nominal solid flow rate and therefore the blowback.Optimal classifier gap can ensure proper functioning of jet mill | High impact and low probability of occurrence. Low risk having score of 18 | High impact and low probability of occurrence. Low risk having score of 18 | High impact and low probability of occurrence. Low risk having score of 18 | High impact and low probability of occurrence. Low risk having score of 18 | If spiral jet mill is used, use an optimal classifier gap that can ensure proper feeding  |
| Jet mill material | Impact the build-up inside jet mill and in API transport pipe.The API exhibits high tendency to adhere to stainless steel and to some polymers | High impact and high probability of occurrence. High risk having score of 90 | High impact and low probability of occurrence. Medium risk having score of 18 | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Characterization of API adhesiveness depending to the jet mill material to be used |
| Micronized product recovery | Impacts particle size and yield.The recovery efficiency is much higher when filter sleeve is used in comparison to the cartridge filters and cyclone | High impact and high probability of occurrence. High risk having score of 90 | Low impact and low probability of occurrence. Low risk having score of 2 | High impact and high probability of occurrence. High risk having score of 90 | High impact and high probability of occurrence. High risk having score of 90 | Evaluation of filter sleeve versus cartridge filters. Cyclone will not be considered as it leads to two fractions of milled API which are to be then blended  |