# Excipients Risk Analysis Tool
# **USER GUIDE**

## 1.0    Introduction

Excipients play a critical role in the manufacturability and clinical performance of dosage forms. When evaluating a proposed product for quality and safety, a reviewer's knowledge of excipient properties, functionalities, and performance is vital for accurate analysis. One of the difficulties in carrying out a review is that there can be a significant number of functional and performance properties that affect the process in different ways, depending on the dosage form type, manufacturing method, and excipient grade. Knowing which of these properties is critical can be difficult to judge. Thus, risk analysis tools that can help reviewers systematically determine which attributes are of paramount concern for a given excipient in a given dosage form for a particular manufacturing process are essential resources in the review process.

To help with a systematic analysis of risks associated with excipient selection, characterization, and use, we developed a decision support tool. The tool couples risk assessment and risk narratives with catalogs of excipients, dosage form types, functionalities, and manufacturing methods. Our tool can be used by the FDA for integrated NDA reviews and efficient knowledge transfer to CGMP inspectors on risk factors to consider during their approval processes. It can also be used by industry during development to provide sound integrated risk analysis that addresses concerns about stability, drug delivery performance, and direct and indirect effects related to impurities and toxicities.

This user guide describes the data and operation of the **Excipient Risk Analysis Tool**, which is publicly available at https://pharmahub.org/excipient-risk-analysis.

## 2.0    Overview

Our Excipient Risk Analysis Tool combines
- an excipient knowledge base, and
- an online, interactive decision support tool

The knowledge base consists of 1) catalogs of excipients, grades, functionality, dosage forms and manufacturing methods, 2) rules that define which choices from each catalog are valid to be used together as part of a manufacturing process, and 3) risk assessment data assigned to the valid combinations.

The decision support tool guides users through the process of selecting valid combinations of excipient, grade, functionality, dosage form and manufacturing method, based on the rules defined in the knowledge base. The tool generates a Failure Mode and Effect Analysis (FMEA) risk analysis report, with risk analysis results available throughout the entire decision support process. As selections are being made by a user, the tool reports on risk associated with selections already made combined with all possible valid "next" selections. When all selections are complete, users can review the final risk analysis report for the completed selection process. Reports present the failure mode and assigned RPN risk levels based on scores for severity of loss, probability of occurrence, and likelihood that a given failure mode can be detected. Users can browse, search, explore and download results in risk assessment reports.

The remainder of this document describes the operation and use of the Excipient Risk Analysis Tool, and includes tips for optimal use of the decision support selection process and risk results exploration.

## 3.0    How to Use the Excipient Risk Analysis Tool

In this section, we describe how the excipient risk analysis tool can help you assess risks associated with excipients used in the manufacturing process. We give step-by-step instructions for using the tool and we include tips on how built-in features can help you better understand and explore analysis results.

In the examples, you will be guided through the decision process, where you will first select an excipient, then choose the dosage form, functionality and manufacturing process, and finally identify a grade. Our knowledge-based selection process ensures that your available options are always valid based on the choices you have already made. Our tool will display risk assessment results throughout the entire selection process. We do this by applying our knowledge-based risk assessment rules to the current state of options selected, whether the selection process is complete or only partially complete. This is a valuable decision support feature of our risk analysis tool, since it can help you understand the risks associated with all possible next selections.

The excipient risk analysis tool is shown below. With this tool, you will be able to:
1.    Identify the manufacturing process you want to assess by selecting Excipient, Dosage Form, Functionality, Manufacturing Method, and Grade (see area marked "1" below)
2.    Review and explore the risk assessment data generated by our knowledge-based rules for the selections you made (see area marked "2" below)
3.    View, search and explore the knowledge base for information about excipients, dosage forms, functionality, manufacturing methods, grades, property measurements, suppliers, and other data used for knowledge-based operation of the tool (see area marked "3" below)

## 3.1　Getting started

Our first example describes a simple scenario for option selection and risk review. We will select the excipient, dosage form, functionality, manufacturing method, and grade – and then review the excipient risk assessment results that are generated and displayed in the analysis view.

Start by clicking the Excipients button in the **Select Options** area to select from a menu of excipient choices. The Excipient button is colored to indicate that this is the only selection button that is available at the start of the selection process.
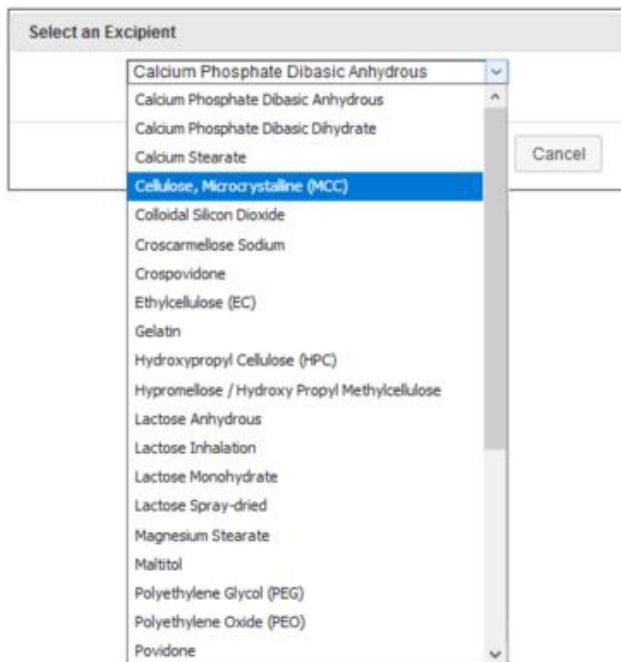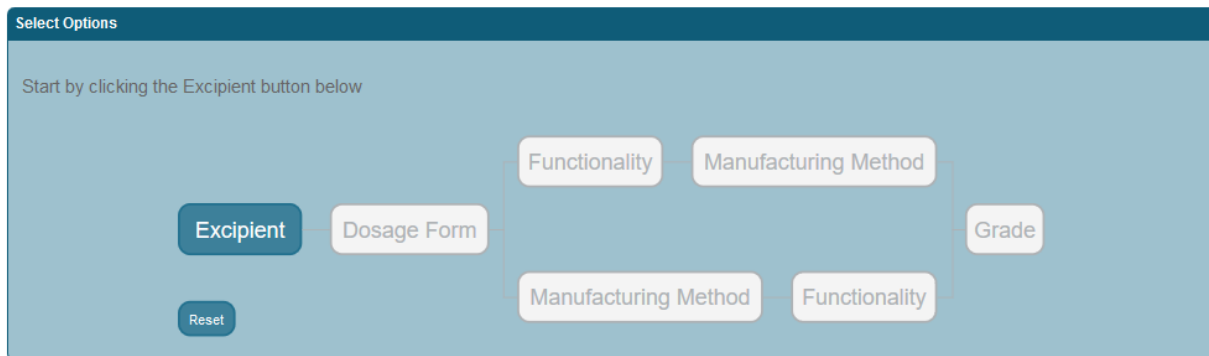


The **Select an Excipient** menu lists all excpients from the risk assessment knowledge base. We select *Cellulose, Microcrystalline (MCC)* from the list and click on OK.

The Excipient button now turns a bright blue to indicate that a choice has been made, and the Dosage Form button is colored to indicate that it is now possible to make a choice for dosage form.
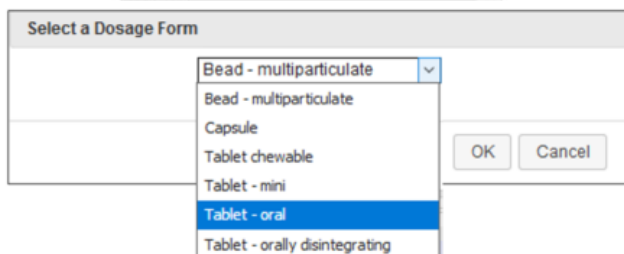
Click on the Dosage Form button to get the menu of possible dosage forms, given that we have already selected MCC. Dosage forms listed in the **Select a Dosage Form** menu are always based on our choice of excipient. Each excipient in the knowledge base is directly linked to the subset of available dosage forms that are valid choices for that excipient. As the risk assessment tool guides you through the decision process, only valid choices are listed on each option menu.

We select *Tablet-oral* and click on OK. The Dosage Form button turns a bright blue to indicate that a choice has been made.
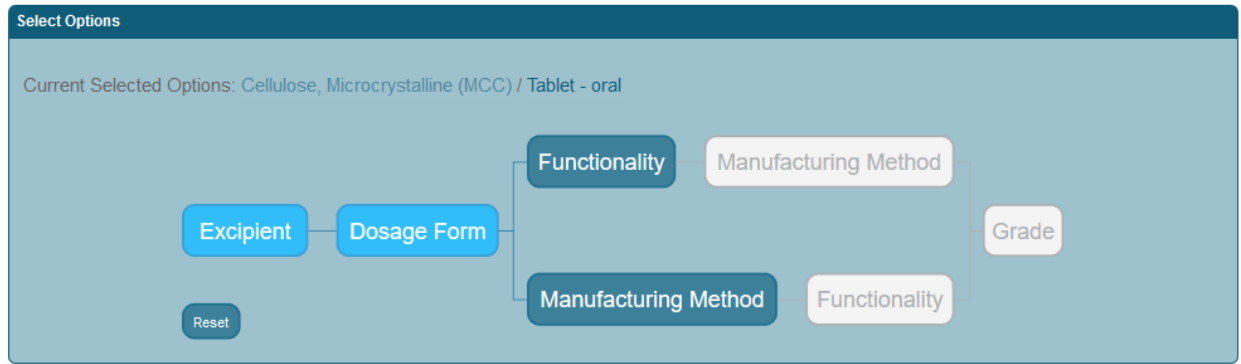
Note that as your selections are made, they are displayed at the top left in the Select Options area following the text **Current Selected Options**. Our choices so far – *Cellulose, Microcrystalline (MCC)* and *Tablet-oral* – are listed there.

It is now possible to choose either Functionality or Manufacturing Method. Note that both buttons are colored, indicating that you may click on either button. Let's follow the "top path" and click on the Functionality button. The menu displays the valid choices for functionality, given that MCC and Tablet-oral are already selected. Note that if you had made different choices for excipient or dosage form, the functionality menu would list the choices that are compatible with the options you selected.
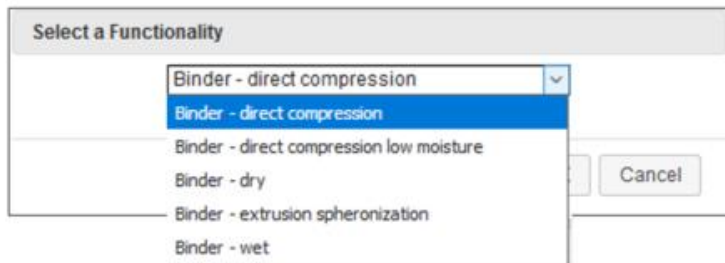


We select *Binder – direct compression* and click on OK. The functionality button turns a bright blue, and manufacturing method can now be selected. We continue to select options using the "top path" for the tool, and click on the Manufacturing Method button.
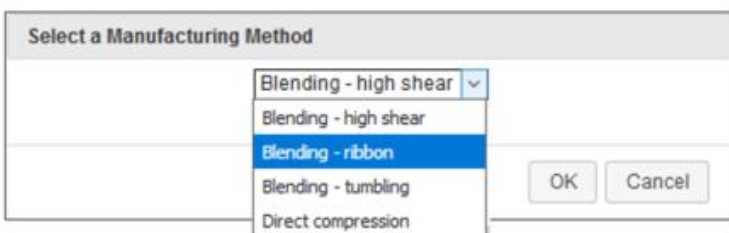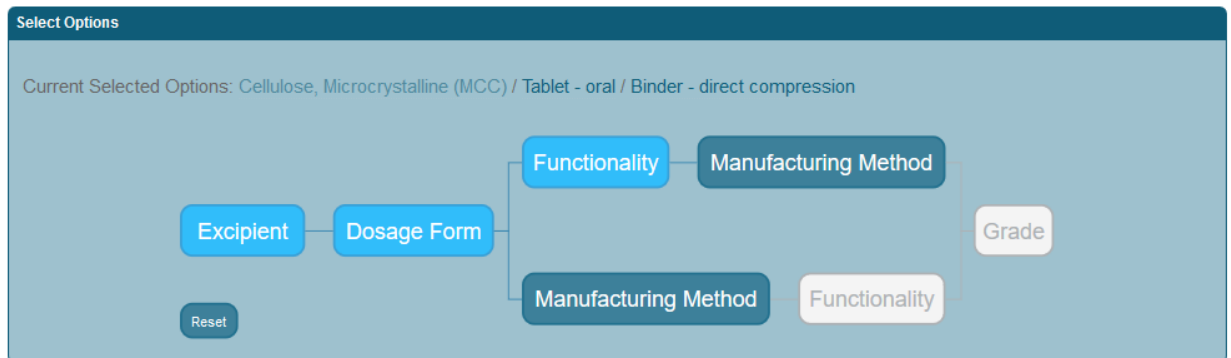




We select *Binding – ribbon* and click on OK. The four option selections we have made are listed in the top left of the Select Options area, and we are now ready to choose the grade. As previously described, the menu

choices for the grade option will list <u>only</u> those grades that are compatible with all four choices made thus far. That is, every grade listed in the menu must be directly connected in the knowledge base to *Cellulose, Microcrystalline (MCC), Tablet-oral, Binder – direct compression* and *Binding – ribbon*.
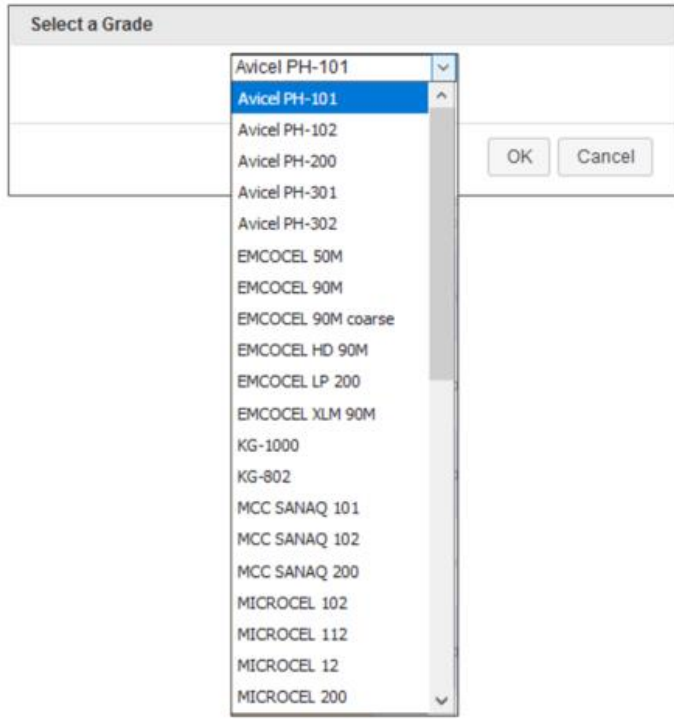
We select *Avicel PH-101* and click on OK.

With the final option selected, all five buttons are now bright blue, and our five choices are listed at the top left in the Select Options area.

We are ready to review the risk analysis for our choices:

Excipient: *Cellulose, Microcrystalline (MCC)*
Dosage Form: *Tablet-oral*
Functionality: *Binder – direct compression*
Manufacturing Method: *Binding – ribbon*
Grade: *Avicel PH-101*

The risk analysis is presented as a tabular, spreadsheet-like display in the **Excipients Risk Assessment Results** area, which is immediately below the **Select Options** area.

**Select Options**

Current Selected Options: Cellulose, Microcrystalline (MCC) / Tablet - oral / Binder - direct compression / Blending - ribbon / Avicel PH-101

**Explore Options**
Excipient | Explore

**View Valid Grades**
Valid | View

**View Other Data**
Risk Assessment | Property Measurements | Suppliers | Notifications

**Explore Risk Assessment Results**

Show 50 entries          First Previous 1 Next Last          Search:

| Excipient | Dosage Form | Functionality | Manufacturing Method | Grade | Failure Mode | Effects of Failure Mode | RPN | Rank | L | L Justification | P | P Justification | D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Excipient | Dosage Form | Functionality | Manufacturing Method | Grade | Failure Mode | Effects of Failure | RPN | Rank | L | L Justification | P | P Justification | D |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Binder - direct compression | Blending - ribbon | Avicel PH-101 | Poor Blend Uniformity | Content uniformi... | 15 | L | 5 | Batches with p... | 1 | This grade has ... | 3 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Binder - direct compression | Blending - ribbon | Avicel PH-101 | Lubricant Over Blending | Delayed or inco... | 80 | H | 5 | Batches that do... | 4 | MCC is a plastic... | 4 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Binder - direct compression | Blending - ribbon | Avicel PH-101 | Lubricant Over Blending | Capping or lami... | 48 | M | 4 | Batches that do... | 4 | MCC is a plastic... | 3 |

Show 50 entries          Showing 1 to 3 of 3 entries          First Previous 1 Next Last

There are three rows describing the risk assessment for the options we have chosen. Note that there are two **Failure Modes**, *Poor Blend Uniformity* (listed in the first row) and *Lubricant Over-blending* (listed in rows two and three). The failure mode Lubricant Over-blending is listed twice because it corresponds to

two different **Effects of Failure Mode**, each with its own (significantly different) **RPN** and **L**, **P**, **D** values. Each Failure Mode with a unique Effects of Failure Mode will be listed in its own row in the risk analysis view.

| Grade ⇕ | Failure Mode ⇕ | Effects of Failure Mode ⇕ | RPN ⇕ | Rank ⇕ | L ⇕ | L Justification ⇕ | P ⇕ | P Justification ⇕ | D ⇕ | D Justification ⇕ |
|---|---|---|---|---|---|---|---|---|---|---|
| Grade | Failure Mode | Effects of Failure | RPN | Rank | L | L Justification | P | P Justification | D | D Justification |
| Avicel PH-101 ☑ | Poor Blend Uniformity | Content uniformi... | 15 | L | 5 | Batches with p... | 1 | This grade has ... | 3 | With a good PAT... |
| Avicel PH-101 ☑ | Lubricant Over Blending | Delayed or inco... | 80 | H | 5 | Batches that do... | 4 | MCC is a plastic... | 4 | Over blending c... |
| Avicel PH-101 ☑ | Lubricant Over Blending | Capping or lami... | 48 | M | 4 | Batches that do... | 4 | MCC is a plastic... | 3 | Over blending c... |

The columns for Severity of Loss (L), Probability of Occurrence (P) and Detectability (D) each have values assigned – the magnitude of each value identifies the level of risk associated with that failure mode for the selected options. You can click on any column name to see an explanation for the data in that column.

| Failure Mode ⇕ | Effects of Failure Mode ⇕ | RPN ⇕ | Rank ⇕ | L ▲ | L Justification ⇕ | P ⇕ | P Justification ⇕ | D ⇕ | D |
|---|---|---|---|---|---|---|---|---|---|
| Failure Mode | Effects of Failure | RPN | Rank | L | | | | | D |
| Lubricant Over Blending | Capping or lami... | 48 | M | 4 | | | | | Ov |
| Poor Blend Uniformity | Content uniformi... | 15 | L | 5 | | | | | Wit |
| Lubricant Over Blending | Delayed or inco... | 80 | H | 5 | | | | | Ov |

**L** ✖

Severity of Loss (L) is a value from 1 to 6 with the following definitions: 1: No relevant effect on reliability or safety. 2: Very minor, no damage, no injuries, only results in a maintenance action. 3: Minor, low damage, light injuries. 4: Moderate, moderate damage, injuries possible. 5: Critical (causes a loss of primary function; Loss of all safety Margins, 1 failure away from a catastrophe, severe damage, severe injuries, max 1 possible death). 6: Catastrophic (product becomes inoperative; the failure may result in complete unsafe operation and possible multiple deaths)

...wing 1 to 3 of 3 entries

**Rank** ✖

RPN values are ranked as high (H), medium (M) and low (L) based on appropriate ranges for the values. The default ranges for H, M, and L are as follows: H: 80-150, M: 30-79, L: 1-29.

The value in the **RPN** column is equal to L x P x D.

An RPN value is ranked as high, medium or low according to pre-set range, and the **Rank** column displays H, M, or L according to this ranking.

The Failure Mode, L Justification, P Justification, and D Justification columns may have lengthy text descriptions, and the full text can be viewed by clicking on the abbreviated text displayed in the column.

Note that the Grade column contains *links* for each grade name – you can click the grade name link to display a view of available property measurements for that grade.



Property measurements and their views are only available for some grades. The measurements and their tabular views have been imported from the published Excipients Property Measurements Database available at https://pharmahub.org/excipientsexplore; that content will not be described in this User Guide.

You can scroll to the right on the risk analysis tabular view to see the rightmost columns for risk analysis: References, Mitigation and Submitter.

References are links to documents that support and clarify the information on risk assessment, failure modes, effects of failure, RPN data, rankings, justification, and mitigation strategies.

Detailed explanations of the meaning and content of all columns included in the excipients risk analysis view are given in Appendix B.

## 3.2 Advanced features for exploring the excipient knowledge base

The excipient risk data in the knowledge base includes the following:

| # Excipients | 30 |
|---|---|
| # Dosage forms | 19 |
| # Functionality categories | 55 |
| # Manufacturing methods | 21 |
| # Grades | 454 |
| Rules that determine all valid relationships between excipients, dosage forms, functionality, manufacturing methods and grades | >500,000 |
| Valid combinations of excipients, dosage forms, functionality, manufacturing methods, and grades that can be selected by the tool for assessing risk | >40,000 |
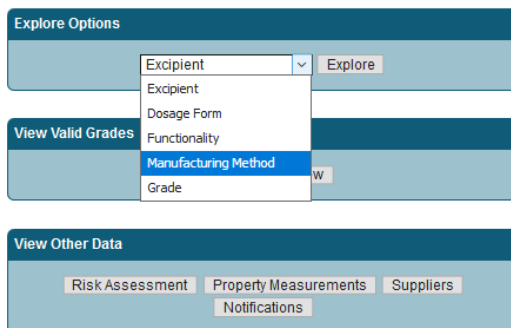


We provide views that enable you to explore *all* data in the knowledge base, including the rules that establish relationships that are valid between excipients, grades, functionality, dosage forms and manufacturing methods. These rules are used by the risk analysis tool for guiding user choices in the decision support process. It is valuable for you to to view, browse, search and explore this data, since it helps you to understand how the tool works and how to interpret the results that are displayed in the risk assessment view.

The **Explore Options** area is to the right of the Select Options area. If you select Manufacturing Methods from the explore menu and click the **Explore** button, a view of the Manufacturing Methods Catalog is displayed.



Each manufacturing method in the knowledge base is listed as one row in the tabular view. For every manufacturing method, there are three "rules" columns that show 1) valid choices for excipients, 2) valid choices for dosage forms, and 3) valid choices for functionality. The decision support tool uses these rules to identify which manufacturing methods should be displayed on the selection menu for the user, given the choices that have already been made for excipient, dosage form and functionality.

Our tabular views offer many features for browsing, searching, and exploring. Column search boxes above each column allow you to type words or phrases for a text search that filters the data in the column. For example, in the Dosage Forms column of the Manufacturing Methods Catalog view, you can type *suspension–oral* or *suspension* or *susp* to locate the two methods (out of 21) that can be used to manufacture this dosage form.

You can also enter search filters for multiple columns to identify combinations that are of interest to you. For example, if you enter *povidone* for excipient, *capsule* for dosage form and *lubricant* for functionality, you will find that 8 methods are valid for manufacturing that combination of options, including *Binding-tumbling* and *Fill-direct*. These selections can then be entered as options in the decision support tool for assessing and viewing the risk.

In a similar way, you can choose Dosage Forms and Functionality from the Explore Options menu, and click the Explore button to search and explore valid combinations corresponding to dosage forms in the knowledge base (valid choices for excipients, functionality, manufacturing methods for each dosage form) and valid combinations corresponding to functionality categories in the knowledge base (valid choices for excipients, dosage forms, manufacturing methods for each functionality).



If you choose Excipient in the Explore Options menu, additional information about the excipient is included in the view. Along with the rules for valid choices of functionality, dosage form and manufacturing method, there are additional columns that present the chemical name, CAS number, description, and image for excipients. In the view, you also can click on the excipient name in the first column. The excipient name is a link that brings up detailed grades information for that excipient. The grades information displayed by the link is from the Grades Catalog, where the excipient column has been filtered for the excipient named in the link.

You can explore the full Grades Catalog by selecting Grade from the Explore Options menu. This view presents the 453 grades that have been entered in the risk assessment database, along with 1) the name of the excipient for that grade, and 2) columns that list valid choices for functionality, dosage form and manufacturing method for that grade. In the Grades Catalog, we also include all property measurements, test methods, chemical structure, spectra, and other data about grades which have been extracted from the published Excipients Property Measurements Database.

Not all grades listed in the Grades Catalog have measurements data. But all grades listed in the Grade Catalog do have columns describing the rules that establish valid relationships for functionality, dosage form and manufacturing method. These rules are used to ensure that the grades available for selection as the final step in the decision flow are valid for the selections users have already made for excipient, functionality, dosage form and manufacturing method. You can explore valid relationships in the Grades Catalog as described above for the manufacturing methods view.
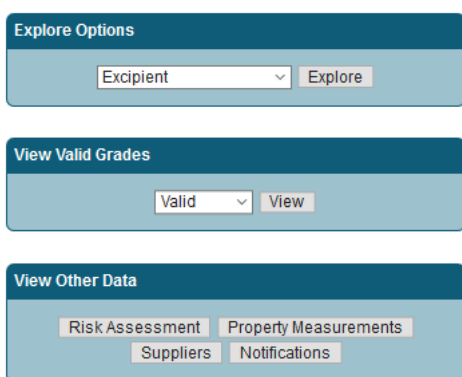


At the bottom of the Explore area, you can also **View Other Data.**

The Property Measurements view offers a sophisticated interface for users to search and explore property measurements by grade, with many property-specific links that generate graphs and provide comparison features.

The Suppliers view lists the suppliers for all grades in the risk assessment knowledge base, along with the supplier product web site.



⊞ List of Suppliers

| Grade | Excipient | Supplier | Supplier Web Site(s) |
|---|---|---|---|
| (Tristar 149) STASMP | Stearic Acid | American International Chemical Inc (United States) | www.aicma |
| (Tristar NF) STTQMP | Stearic Acid | American International Chemical Inc (United States) | www.aicma |
| 1726 VG HyQual | Magnesium Stearate | Mallinckrodt Pharmaceuticals | www2.mallinckrodt |
| 2248 Kosher HyQual | Calcium Stearate | Mallinckrodt Pharmaceuticals | www2.mallinckrodt |
| 2249 Kosher HyQual | Calcium Stearate | Mallinckrodt Pharmaceuticals | www2.mallinckrodt |
| 2257 Kosher HyQual | Magnesium Stearate | Mallinckrodt Pharmaceuticals | www2.mallinckrodt |
| 3-Circles | Shellac | Stroever GmbH & Co. KG (Germany) | www.stroever |
| 3-Stars | Shellac | Excelacs Co. Ltd (Thailand) | www.shellacthailand |
| 400L NF Modified Corn Starch | Starch | Roquette America Inc (United States) | www.roquette |
| 5712 Kosher HyQual | Magnesium Stearate | Mallinckrodt Pharmaceuticals | www2.mallinckrodt |

The Risk Assessment and Notifications views in **View Other Data** will be described in a later section.

## 3.3    Advanced features for exploring risk analysis data

Some advanced features have been added to the risk analysis tool so that users can explore failure mode data throughout the entire decision process – i.e., while users are selecting options for excipient, dosage form, functionality, manufacturing method, and grade, they can review relevant risk data at any step in the decision flow.

Exploring risk assessment data at each step in the selection process will help you evaluate the risk values assigned to all possible valid "next" choices, before making your next selection. For example, if you have already chosen an excipient and dosage form, you will be able to assess the risk data for all possible valid combinations of functionality, manufacturing method, and grade for your choice of excipient and dosage form.

The following example shows how this works. Assume that you have already selected excipient *Cellulose, Microcrystalline (MCC)* and *Tablet—oral.* The state of the decision process is shown below.
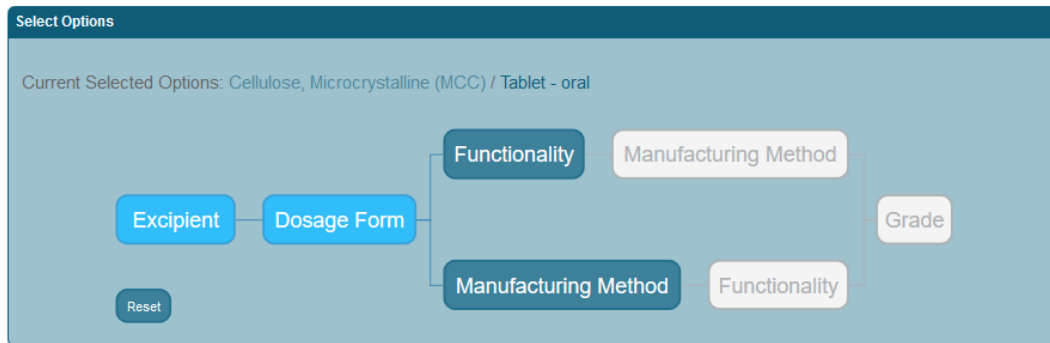


Now look at the view of Excipient Risk Assessment Results. It shows 629 rows (or entries), each with Excipient=Cellulose, Microcrystalline (MCC) and Dosage Form= Tablet—oral. The Functionality, Manufacturing Method and Grade columns show all possible valid combinations with MCC and Tablet-oral selected, according to the knowledge-based rules.

For each valid combination, there will be one or more risk assessment entries that identify failure mode and RPN data. The number of entries for a single valid combination can be greater than one, and is equal to the number of unique "failure mode" + "effects of failure mode" assigned to that combination.



We'd like to explore the risk assessment entries to identify combinations of grades, functionality and manufacturing methods that are high risk (Rank=H) and low risk (Rank=L). We'd also like to see which failure modes occur for different grades of interest and manufacturing methods of interest.

To search and explore the risk data more easily, users should click on the Risk Assessment button in the View Other Data area. This will present the same risk assessment results view, but the view will be

displayed in its own separate browser tab, making it easier to explore large numbers of risk assessment results.



Let's review the high-risk entries.

In the Rank column, click on the column search box at the top of the column to see a drop-down menu listing column values. Select H.

There are 142 results identified as high risk, each with an RPN value of 80. The failure modes for these cases is Lubricant Over Blending, Over Granulation and Under Granulation.

For Over Blending, you can hover over or click on Effects of Failure Mode to see Delayed or incomplete dissolution. Severity of Loss is 5, and you can click on the L Justification to see the full text. You can also review the Probability of Occurrence and Detectability values and their justifications.



By paging through the results, you can see the Functionalities are *Binder-direct compression, Binder-wet, and Binder-dry*, and the Manufacturing Methods are *Blending-ribbon, Blending-high shear, Blending-tumbling* and *Tablet compression*. Check the Grades column to see which grades appear in the high-risk entries.

| Functionality | Manufacturing Method |
|---|---|
| Functionality | Manufacturing Method ✕ |
| | Blending - ribbon |
| | Blending - tumbling |
| Binder - direct compression | |
| Binder - direct compression | Blending - ribbon |

| Functionality | Manufacturing Method | Grade | Failure Mode |
|---|---|---|---|
| Functionality | Manufacturing Method | Grade ✕ | Failure Mode |
| | | Avicel PH-101 | |
| Binder - direct compression | Blending - ribbon | Avicel PH-301 | er |
| | | Avicel PH-102 | |
| Binder - direct compression | Blending - ribbon | Avicel PH-302 | er |
| | | 301 | Blending |

The same process can be followed to review which results are identified as low-risk: there are 71 entries with RPN less than 29. You can check Failure Mode, Effects of Failure Mode, the L, P, D values and their justifications for the low-risk entries.

Search:

| RPN | Rank | L | L Justification | P | P Justification | D | D Justification | Ref |
|---|---|---|---|---|---|---|---|---|
| RPN | L | L | L Justification | P | P Justification | D | D Justification | Re |
| 15 | L | 5 | Batches with p... | 1 | This grade has... | 3 | With a good P... | - |
| 15 | L | 5 | Batches | | | | | - |
| 15 | L | 5 | Batches | | | | | - |

**Full Text** ✕

With a good PAT or traditional sampling plan blend uniformity problems can be detected, but most blend samples are bulk samples from a stagnate powder blend, and segregation can be hard to detect in these systems

<90

| ffects of ailure Mode | RPN | Rank | tic |
|---|---|---|---|
| Effects of Failur | <90 | Rank | L | L Justificatior |
| ontent unifor... | 15 | L | 5 | Batches with .. |
| ontent unifor... | 15 | L | 5 | Batches with .. |

To search columns with numeric data for specific values, you can filter using numeric search features available in the column search boxes.

Numeric data can be searched using arithmetic and range filters. This can be very useful for finding and displaying specific values (using "="), values not equal to a specific value (using "!="), and ranges of values that you are interested in.

Enter a number to filter this column by.

Following filter options are also supported,
Range filtering - ( e.g. 15.7 to 25 )
Less than, greater than ( e.g. <100 ), (e.g. >25)
Less than or equal, greater than or equal ( e.g. <=-12.5 ), (e.g. >=0.3)
Equal, not equal and ignore pattern ( e.g. =-2.55 ), ( e.g. !=-2.55 ), ( e.g. !55 )

The dropdown list only shows a limited number of available options.

If you don't see what you want on the list, please enter a filter text in the text box and then press Enter to bring up more results to match your text.

For example, if your value ranges for Ranking are different from the tool's default values (L=1-29, M=30-79, H-80-150), you can easily filter the RPN column for values that match your rankings.

You can find all RPN values less than 90 (using "<") or search for values in-between 40 and 90 (using "40 to 90").

You can hover over any numeric column to see the numeric search operations.

The text columns also have search features that let you search for exact keywords (using "="), ignore a specific text pattern (using "!") or find a specific text pattern, keyword or phrase (enter the search characters or keyword). Multi-column entries are supported.

**Explore Options**

Excipient ⌄    Explore

**View Valid Grades**

Valid ⌄    View

Valid

Not Valid

**View Other Data**

Risk Assessment    Property Measurements    Suppliers
Notifications

We now describe a feature that allows users to identify the excipient grades that are valid at every step of their selection process. The **View Valid Grades** area is to the right of the **Select Options** area. You can view the grades that are Valid and the grades that are Not Valid for your selected excipient at any point in the decision process.

Before an excipient choice is made, the Valid Grades view lists all grades in the risk assessment database, since they are all valid at this point in the decision process.

Let's choose excipient *Cellulose, Microcrystalline (MCC)* and click on the View button for Valid grades. There are 46 grades entered in the database for this excipient, and when MCC is selected, they are all valid. No MCC grades are invalid at this point in the decision process, so the Not Valid view is empty.

⊞ List of Valid Grades with current selections

⊕ Download   ✕ Fullscreen   ⊕ Clear Filters   ⌶ No-Wrap

Show 50 ⌄ entries                    First  Previous  1  Next  Last                    Search:

| Excipient ⇕ | Grade ⇕ |
|---|---|
| Excipient | Grade |
| Cellulose, Microcrystalline (MCC) | Avicel PH-101 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-102 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-103 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-112 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-113 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-200 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-301 |
| Cellulose, Microcrystalline (MCC) | Avicel PH-302 |
| Cellulose, Microcrystalline (MCC) | EMCOCEL 50M |
| Cellulose, Microcrystalline (MCC) | EMCOCEL 90M |
| Cellulose, Microcrystalline (MCC) | EMCOCEL 90M coarse |

Let's choose *Tablet-oral* for Dosage Form. If you click the View button, you will see that all 46 grades are still Valid. The view shows the choice of excipient (first column) and the choice of dosage form (second column), with a row for each grade that is valid. The view for grades that are Not Valid is still empty.

| Excipient | Dosage Form | Grade |
|---|---|---|
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-101 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-102 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-103 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-112 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-113 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-200 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-301 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | Avicel PH-302 |
| Cellulose, Microcrystalline (MCC) | Tablet - oral | EMCOCEL 50M |

Let's choose *Binder-dry* for Functionality and *Blending-ribbon* for Manufacturing Method. There are now only 35 grades that are still Valid. The view for Valid grades lists the selected excipient, dosage form, Functionality and Manufacturing Method, along with the 35 grades that are still Valid.

⊞ List of Valid Grades with current selections

| Excipient | Dosage Form | Functionality | Manufacturing Method | Grade |
|---|---|---|---|---|
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-101 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-102 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-103 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-112 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-113 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-301 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | Avicel PH-302 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | EMCOCEL 50M |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | EMCOCEL 90M |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | EMCOCEL HD 90M |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | EMCOCEL XLM 90M |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | KG-1000 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | KG-802 |
| Cellulose, Microcrystalline (MCC) | Capsule | Binder - dry | Blending - ribbon | MCC SANAQ 101 |

There are 11 grades that are no longer valid. Was it the selection for Functionality = *Binder-dry* or the selection of Manufacturing Method = *Blending-ribbon* that resulted in a loss of 11 grades on the selection menu?

If you click to view the Not Valid grades, you can see and entry for <u>each grade that is now invalid</u>. For each of the currently invalid grades, we can see what their valid choices are for excipient (MCC), what their valid choices are for dosages forms (from the previous valid view, we know that capsule is valid for all of the grades), and what their valid choices are for functionality and manufacturing methods.

⊞ List of Not Valid Grades with current selections

| Grade | Excipient | Dosage Form | Functionality | Manufacturing Method |
|---|---|---|---|---|
| Avicel PH-200 | Cellulose, Microcrystalline (MCC) | Bead - multiparticulate<br>Capsule<br>Tablet chewable<br>Tablet - mini<br>Tablet - oral<br>Tablet - orally disintegrating | Binder - direct compression low moisture<br>Binder - direct compression | Blending - high shear<br>Blending - ribbon<br>Blending - tumbling<br>Direct compression<br>Fill - direct<br>Fill - plug<br>Granulation - roller compaction<br>Slugging<br>Tablet compression<br>Dry - fluid bed<br>Dry - tray<br>Fill - blister<br>Sieving<br>Sterilization |
| EMCOCEL 90M coarse | Cellulose, Microcrystalline (MCC) | Bead - multiparticulate<br>Capsule<br>Tablet chewable<br>Tablet - mini<br>Tablet - oral<br>Tablet - orally disintegrating | Binder - direct compression | Blending - high shear<br>Blending - ribbon<br>Blending - tumbling<br>Direct compression<br>Fill - direct<br>Fill - plug<br>Granulation - roller compaction<br>Slugging<br>Tablet compression<br>Dry - fluid bed<br>Dry - tray |

You can scroll down through the grades while looking at the Functionality data, and see that *Binder-dry* is not supported by any of the invalid grades. You could do a filter search on the text *dry*, and the resulting view will be empty, i.e., that text is not found for Functionality in any grade row. On the other hand, you can see that the *Bending-ribbon* manufacturing method is supported by all 11 grades. You can filter the column on *ribbon* or just scroll through the rows to verify. Thus the 11 invalid grades are a result of the selection *Binder-dry*.

## 3.4 Final notes about the risk analysis tool

The risk assessment data in this database will continue to be updated. As noted previously, the information and screenshots in this document are based on the content of the risk assessment database when the documentation was written. As new data is added to the database, you will see more selections in the option menus and more risk assessment data in the risk assessment result views.

The data and rules in the knowledge base describing valid relationships for excipients, dosage forms, functionality, manufacturing methods and grades is large and complex. We have built a data validation interface into the excipient risk assessment tool that discovers inconsistences and missing data among the relationship rules entered by users. The notifications are generated as the user makes selections. Our decision support tool applies the rules in the knowledge base during the selection process, and when it encounters inconsistences, the inconsistencies are documented in Notifications. The Notifications listing can be used to identify when data and rules from the database should be checked for accuracy and completeness.

You can view the notifications by clicking on **Notifications** in the **View Other Data** area to the right of Select Options.



### NIPTE-FDA Excipients Risk Analysis Tool - Notifications

#### Inconsistencies Notification

2017-07-19 16:48:23 Incomplete path: Excipient: Crospovidone / Dosage Form: Capsule / Functionality: - / Manufacturing Method: Fill - plug / Grade: -
2017-07-21 01:42:37 Incomplete path: Excipient: Ethylcellulose (EC) / Dosage Form: Tablet - orally disintegrating / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-21 01:42:39 Incomplete path: Excipient: Ethylcellulose (EC) / Dosage Form: Tablet - orally disintegrating / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-21 01:47:37 Incomplete path: Excipient: Lactose Inhalation / Dosage Form: Capsule / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-21 01:47:49 Incomplete path: Excipient: Lactose Inhalation / Dosage Form: Capsule / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-21 01:47:59 Incomplete path: Excipient: Lactose Inhalation / Dosage Form: Capsule / Functionality: - / Manufacturing Method: Fill - direct / Grade: -
2017-07-21 01:53:41 Incomplete path: Excipient: Maltitol / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-21 01:53:48 Incomplete path: Excipient: Maltitol / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: Freeze dry / Grade: -
2017-07-29 09:00:56 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -
2017-07-29 09:02:39 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -
2017-08-25 11:13:00 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -
2017-08-25 11:13:23 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: Direct compression / Grade: -

# Appendix A: Master list spreadsheets and knowledge-based rules defining valid relationships

Data entered by users in the risk assessment database is of two types:

1. **Master Lists** that describe which excipients, grades, functional categories, dosage forms, and manufacturing methods are included in the database and available for selection in the decision support process. The master lists are in the form of spreadsheets, and these spreadsheets can be viewed and downloaded at https://pharmahub.org/excipient-risk-analysis.

   Examples of partial master lists are shown below.







   The Master list spreadsheets are processed and imported to the database.

2. **Knowledge-based Rules** that describe how the excipient, grade, functionality, dosage form, and manufacturing method entries from the master lists are related to each other, i.e., which combinations of relationships are valid. Knowledge-based rules are also in the form of spreadsheets, and these spreadsheets can be viewed and downloaded at https://pharmahub.org/excipient-risk-analysis.

Some examples of the knowledge-based rules spreadsheets are below.





The rules spreadsheets are processed and imported to the database.

# Appendix B: Description of risk data included in the Risk Assessment Results view

This appendix defines the risk variables that are displayed in the Excipient Risk Assessment Results view for each valid combination of excipient, grade, functionality, dosage form and manufacturing method.

| Risk variable | Definition |
| --- | --- |
| Failure Mode<br>Effects of Failure Mode | One of the most common risk assessment methods in the pharmaceutical industry is Failure Mode and Effect Analysis (FMEA). Examples of Failure Mode and their Effects Analysis in the Excipient Risk Analysis Database are<br><br>Poor Blend Uniformity, Content uniformity problems<br>Under Granulation, Friable granules<br>Under Granulation, High % fines<br>Delayed Dissolution – Low porosity, Poor bioavailability<br>Friability > 1%, Edges chip and weight varies<br>Weight Variation, High variability in the dose<br>Lubricant Over-blending, Capping or lamination and high friability<br><br>Note that Failure Modes can have more than one Effect Analysis.<br><br>In addition, the Excipient Risk Analysis Database lists a Failure Mode as "Special Situation" to indicate that an effect is not standard, an example special situation effect is: "This is generally done with multi-particulate beads, to the best of my knowledge no products on the market, an idea in development only" |
| RPN | FEMA failure modes are assigned risk levels based on scores for severity of loss (L), probability of occurrence (P) and likelihood that a given failure mode can be detected (D). The Risk Priority Number RPN = L x P x D |
| Ranking | RPN values are ranked as high (H), medium (M) and low (L) based on appropriate ranges for the values. The default ranges for H, M, and L are:<br>    H: 80-150<br>    M: 30-79<br>    L: 1-29 |
| L | Severity of Loss (L) is a value from 1 to 6 with the following definitions:<br>1: No relevant effect on reliability or safety.<br>2: Very minor, no damage, no injuries, only results in a maintenance action.<br>3: Minor, low damage, light injuries.<br>4: Moderate, moderate damage, injuries possible.<br>5: Critical (causes a loss of primary function; Loss of all safety Margins, 1 failure away from a catastrophe, severe damage, severe injuries, max 1 possible death).<br>6: Catastrophic (product becomes inoperative; the failure may result in complete unsafe operation and possible multiple deaths) |
| L Justification | Justification for the L rating. |

| | |
|---|---|
| | Some examples are:<br>5: If bad enough, the tablets can't be taken, the weight will vary and the patient could end up with a bottle of powder<br>5: Batches that don't meet their dissolution specification must be discarded, which is a total loss. for patients, delayed dissolution can cause sub therapeutic doses<br>4: If the granules are too hard they can fail to disintegrate, which can delay dissolution<br>4: Batches that don't meet their hardness or friability criteria have to be rejected which is a total loss the company, there is little risk to the patient as they generally won't take damaged tablets |
| P | Probability of Occurrence (P) is a value from 1 to 5 with the following definitions:<br>1: Highly unlikely (Virtually impossible or No known occurrences on similar products).<br>2: Remote (relatively few failures).<br>3: Occasional (occasional failures).<br>4: Reasonably Possible (repeated failures).<br>5: Frequent (failure is almost inevitable) |
| P Justification | Justification for the P rating.<br>Some examples are:<br>5: If don't have good endpoint determination, this can be highly likely<br>4: MCC is a plastic material and very sensitive to over lubrication, poor mixing procedures make over blending a problem, a ribbon blender is higher shear than a tumbling blender<br>2: Forms strong tablets, typically is not a problem in direct compression |
| D | Detectability (D) is a value from 1 to 5 with the following definitions:<br>1: Certain - fault will be caught on test.<br>2: Almost certain.<br>3: High.<br>4: Moderate.<br>5: Low. 6: Fault is undetected by Operators or Maintainers. |
| D Justification | Justification for the D rating.<br>Some examples are:<br>5: This can be hard to detect as there are no standard release tests for this property<br>3: Granulation particles size if used as a granulation endpoint can detect this problem<br>1: Easily detected |
| Mitigation | Strategies for mitigating the assessed risk. Examples are |
| Submitter | The person who submitted the data, currently Professor Stephen Hoag |