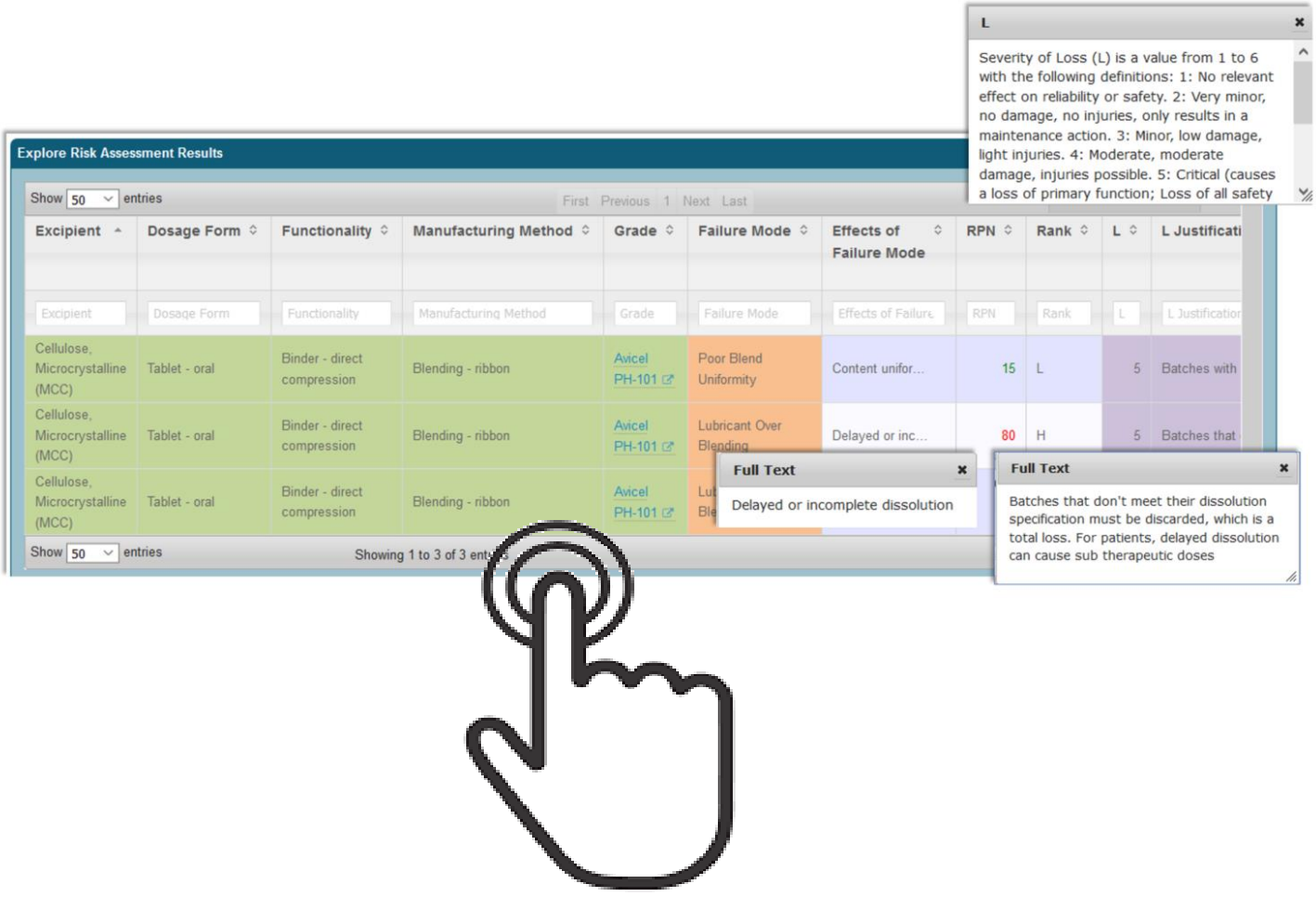
Excipients Risk Analysis Tool

USER GUIDE



Purdue University
Rosen Center for Advanced Computing
September, 2017

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.

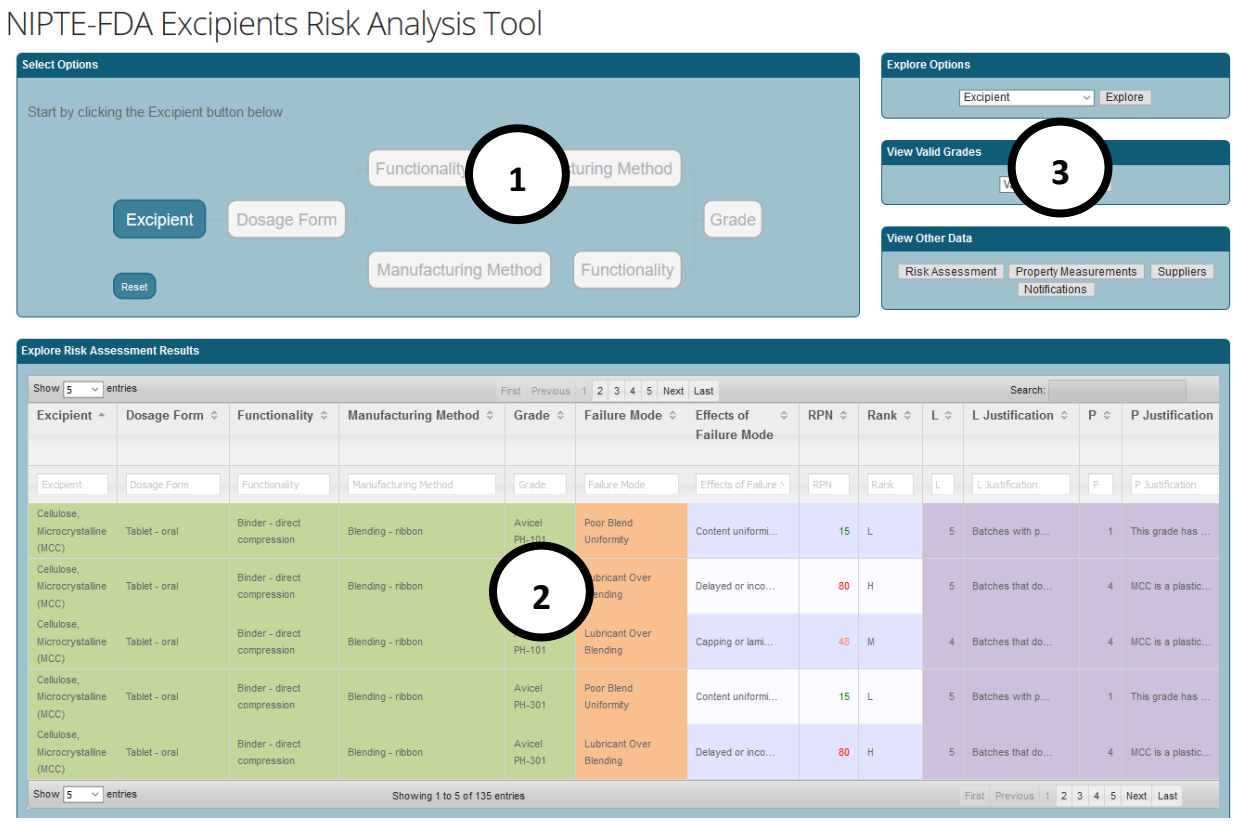
3.0 How to Use the Excipient Risk Analysis Tool

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:

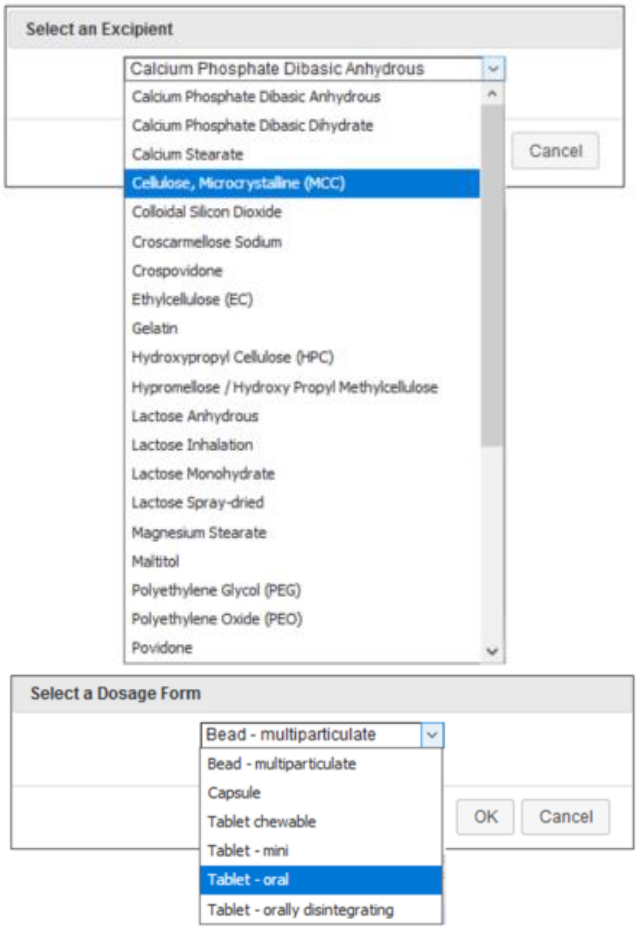
1. Identify the manufacturing process you want to assess by selecting Excipient, Dosage Form, Functionality, Manufacturing Method, and Grade (see area marked “1” below)
2. Review and explore the risk assessment data generated by our knowledge-based rules for the selections you made (see area marked “2” 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.

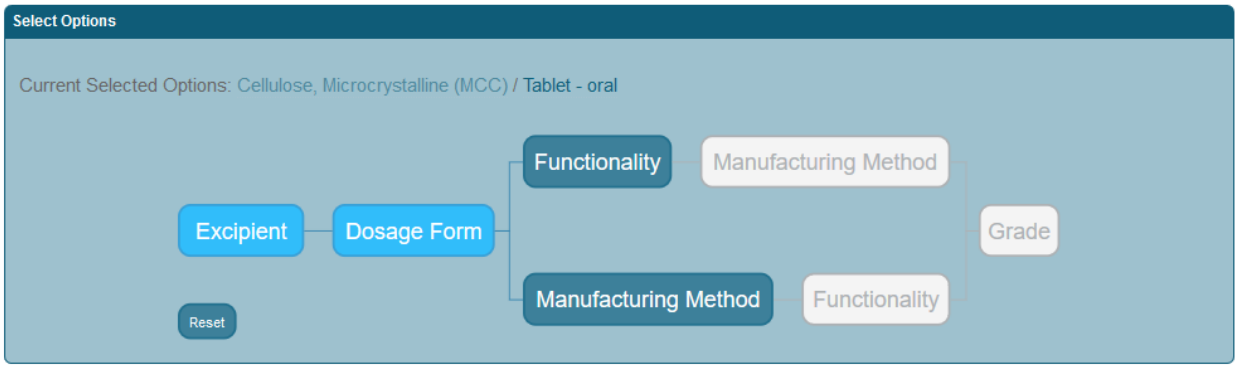


The **Select an Excipient** menu lists all excpients from the risk assessment knowledge base. We select *Cellulose, Microcrystalline (MCC)* from the list and click on OK.

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.

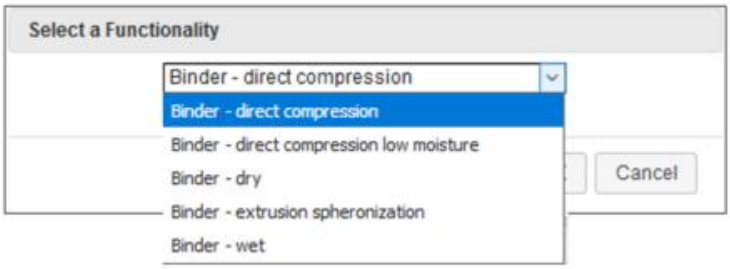
Click on the Dosage Form button to get the menu of possible dosage forms, given that we have already selected MCC. Dosage forms listed in the **Select a Dosage Form** menu are always based on our choice of excipient. Each excipient in the knowledge base is directly linked to the subset of available dosage 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.

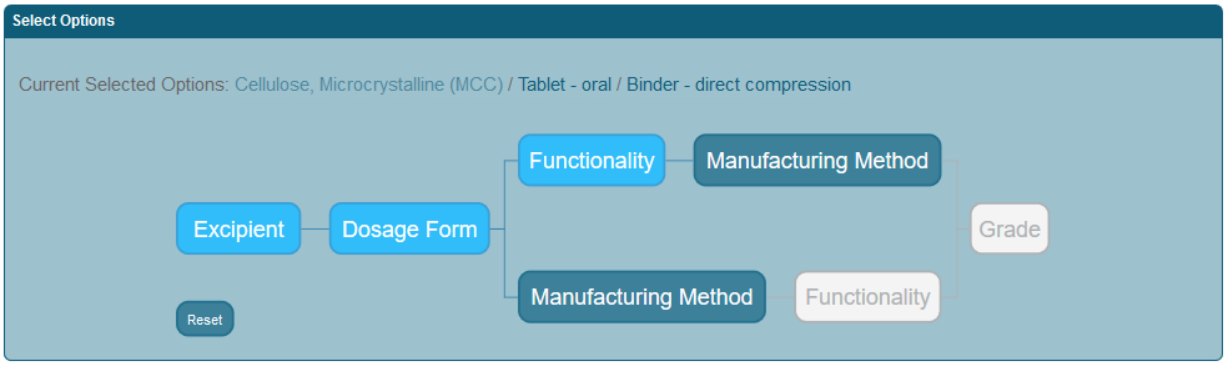


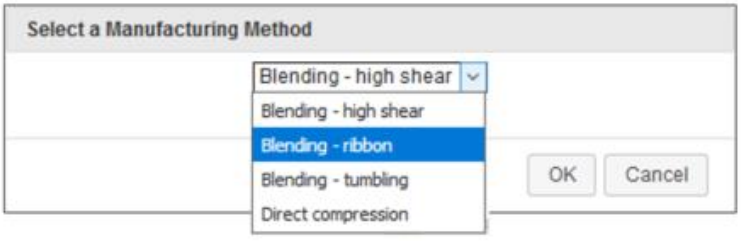
Note that as your selections are made, they are displayed at the top left in the Select Options area following the text **Current Selected Options**. Our choices so far – *Cellulose, Microcrystalline (MCC)* and *Tablet-oral* – are listed there.

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.



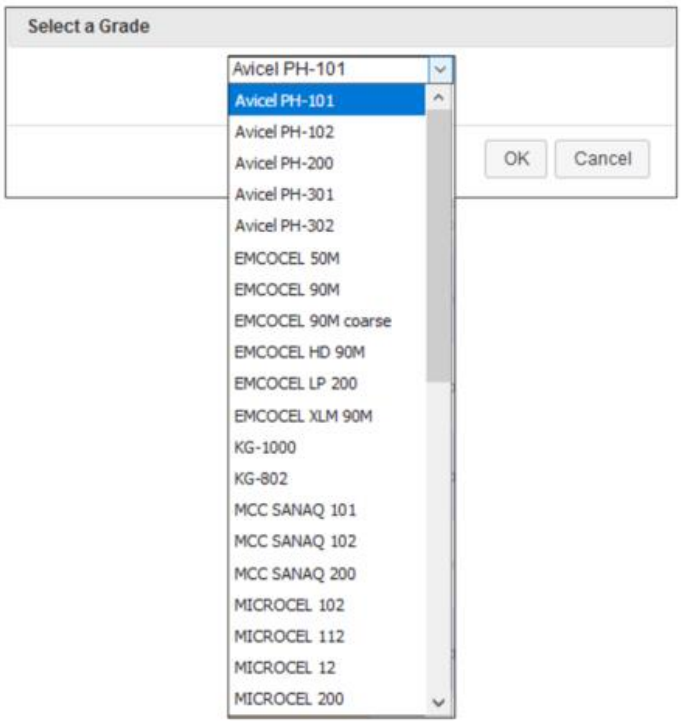
We select *Binder – direct compression* and click on OK. The functionality button turns a bright blue, and manufacturing method can now be selected. We continue to select options using the "top path" for the tool, and click on the Manufacturing Method button.





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 only 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.*



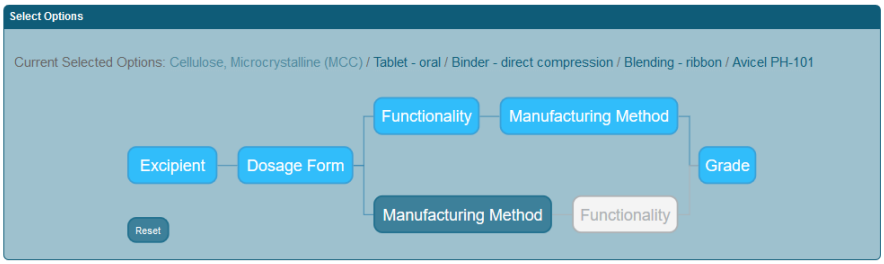
We select *Avicel PH-101* and click on OK.

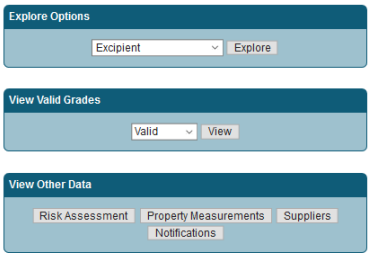
With the final option selected, all five buttons are now bright blue, and our five choices are listed at the top left in the Select Options area.

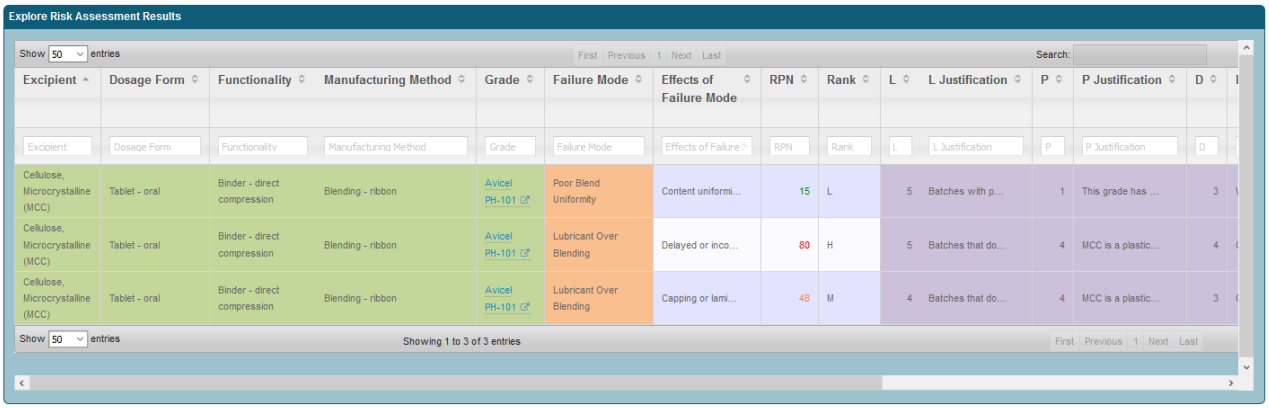
We are ready to review the risk analysis for our choices:

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.

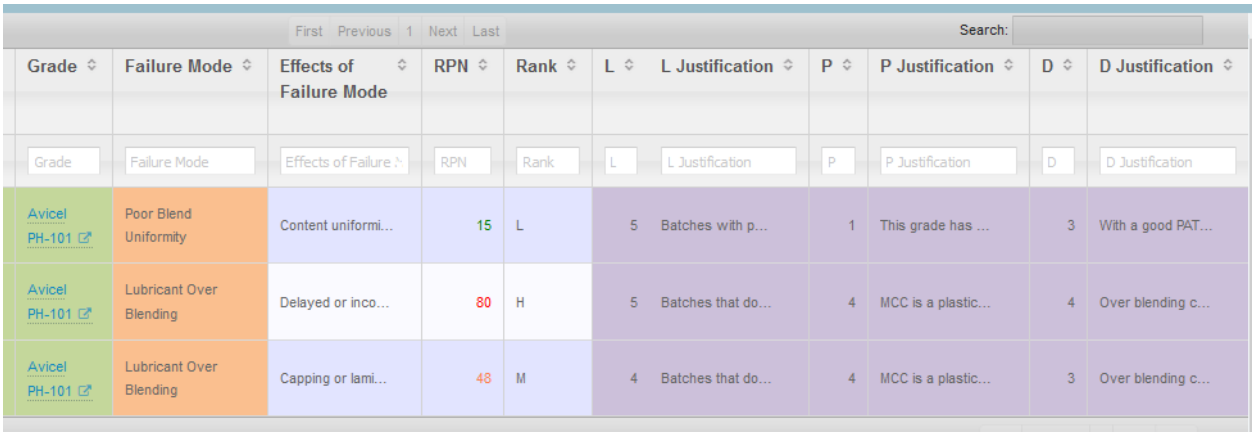




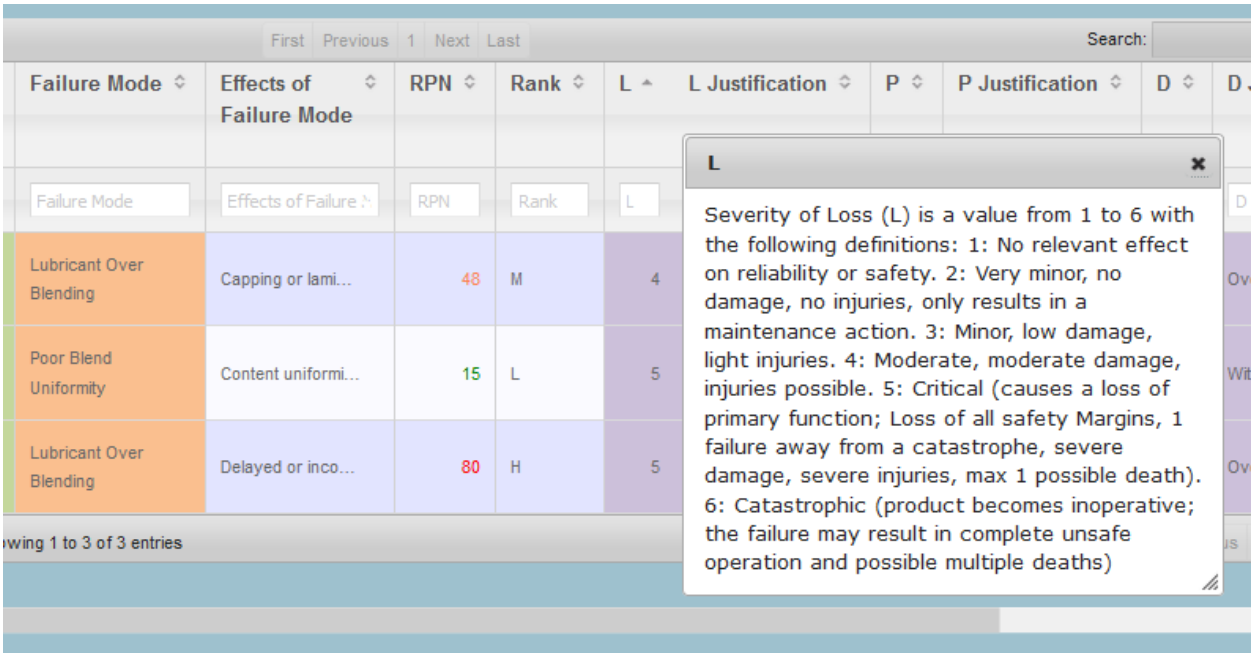


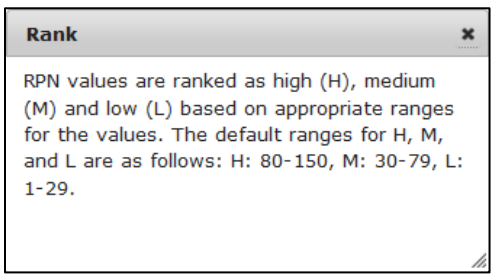
There are three rows describing the risk assessment for the options we have chosen. Note that there are two **Failure Modes**, *Poor Blend Uniformity* (listed in the first row) and *Lubricant Over-blending* (listed in rows two and three). The failure mode Lubricant Over-blending is listed twice because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



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.

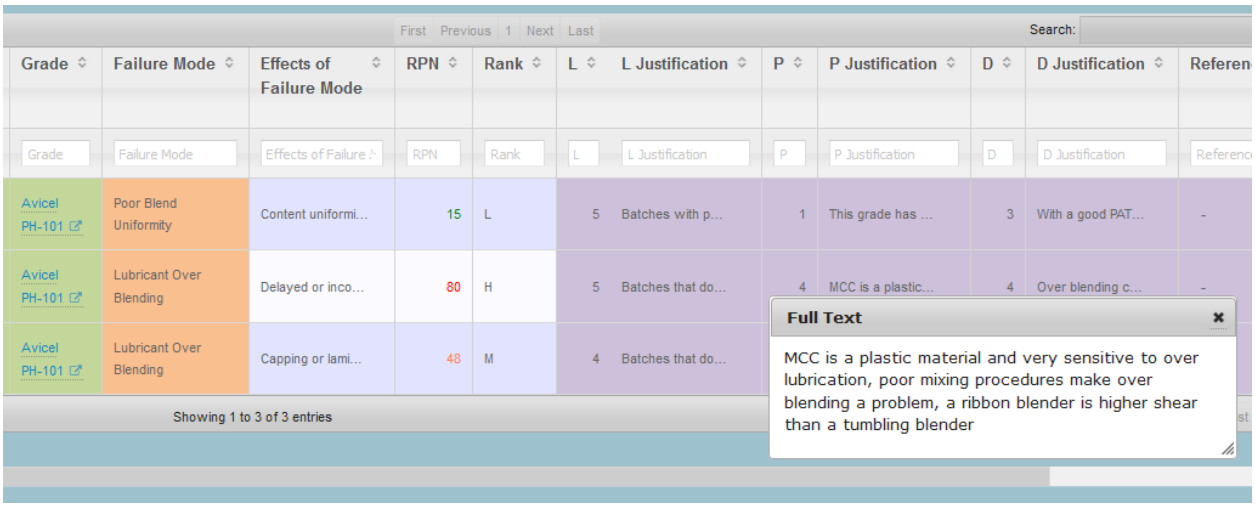




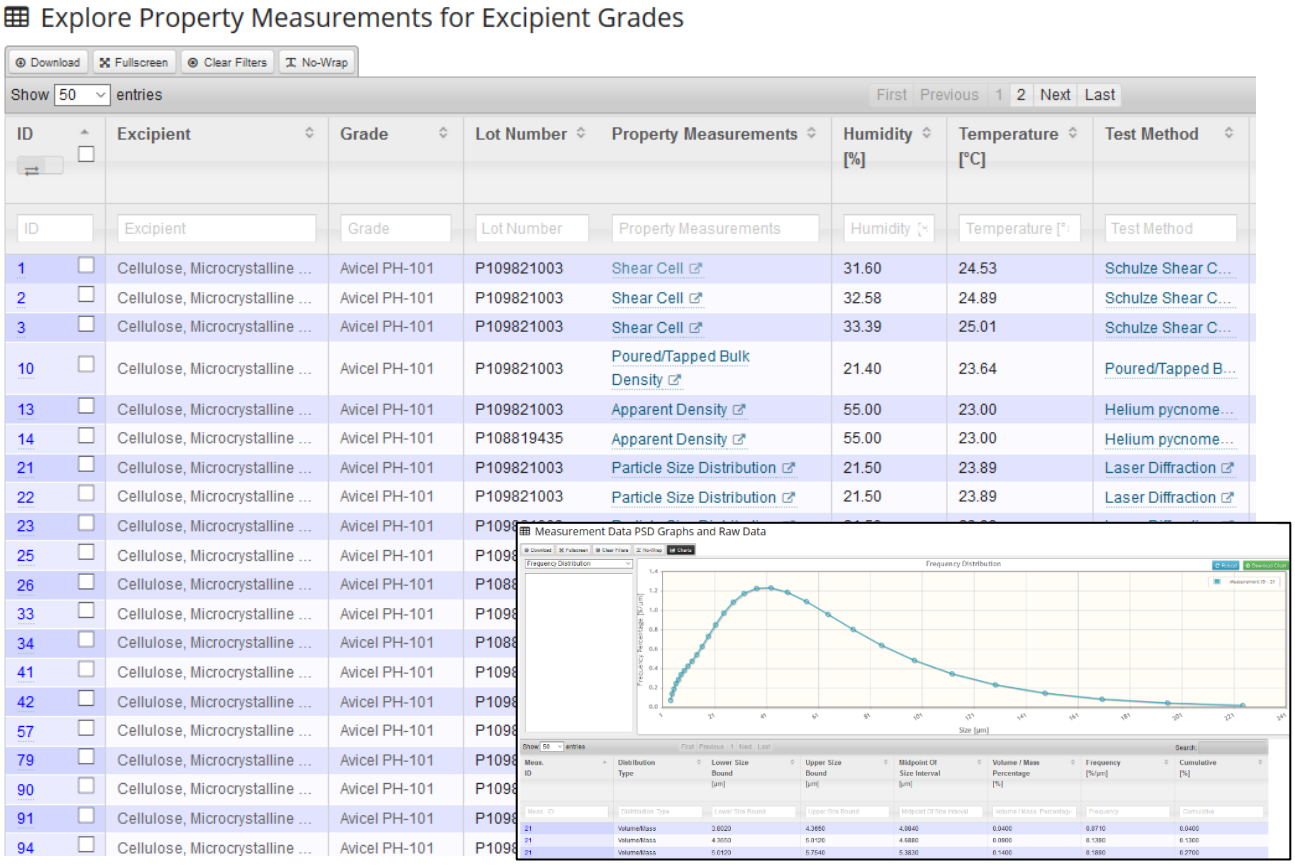
The value in the **RPN** column is equal to L x P x D.

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.

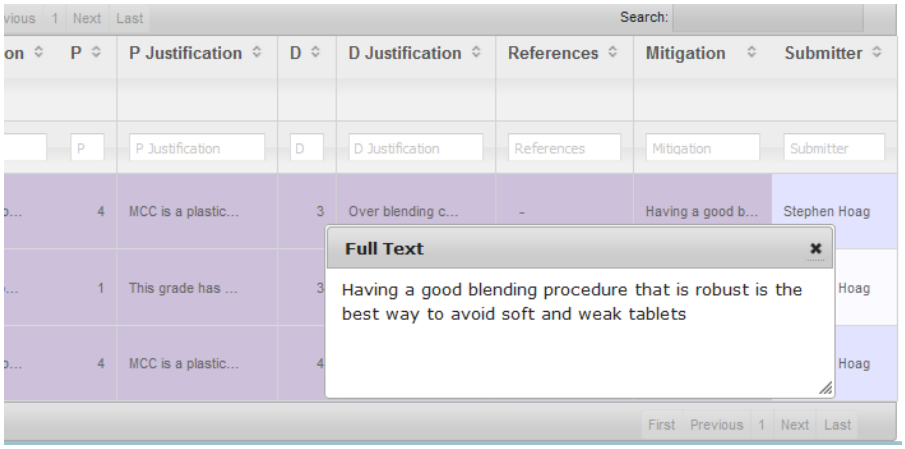
The Failure Mode, L Justification, P Justification, and D Justification columns may have lengthy text descriptions, and the full text can be viewed by clicking on the abbreviated text displayed in the column.



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.

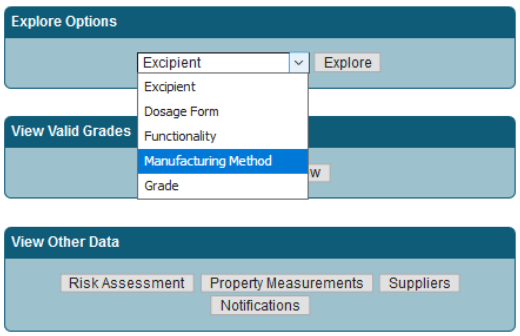
References are links to documents that support and clarify the information on risk assessment, failure modes, effects of failure, RPN data, rankings, justification, and mitigation strategies.

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

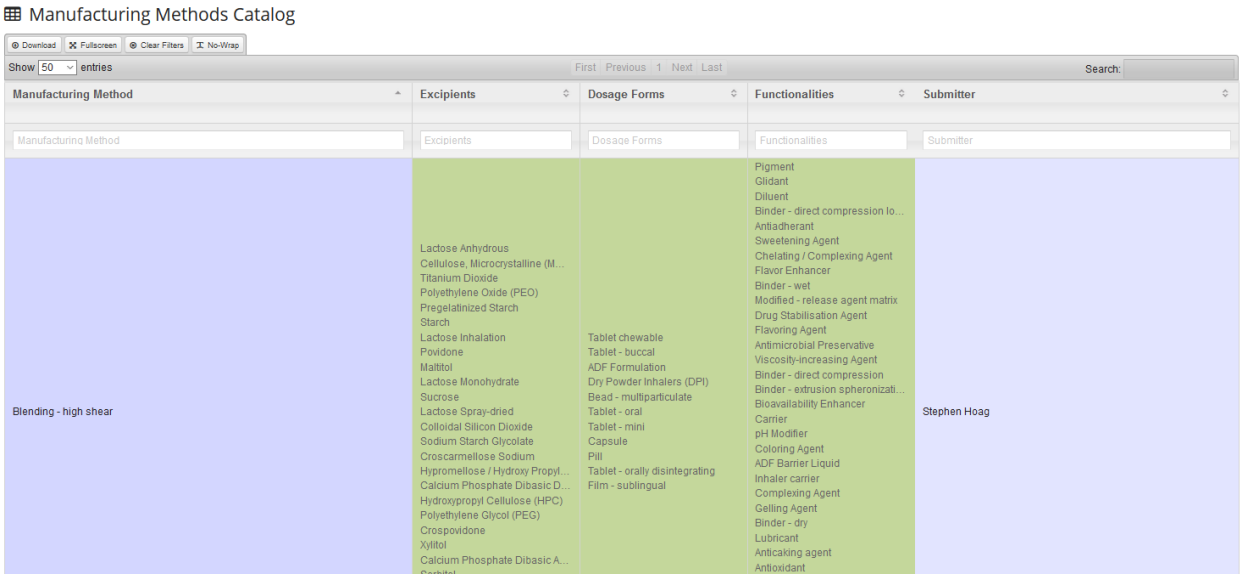
The excipient risk data in the knowledge base includes the following:

# 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



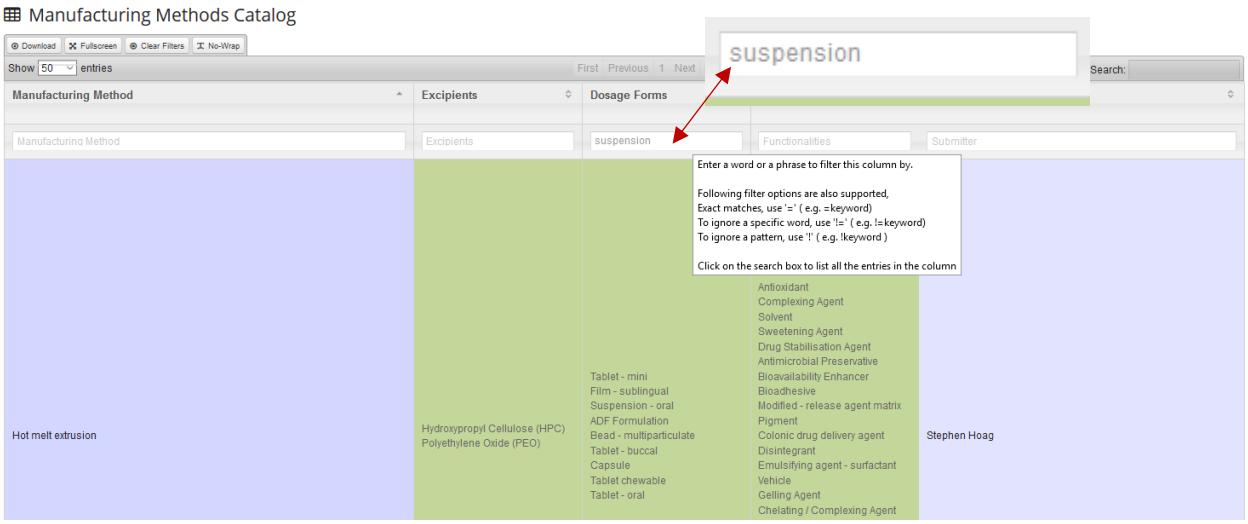
We provide views that enable you to explore *all* data in the knowledge base, including the rules that establish relationships that are valid between excipients, grades, functionality, dosage forms and manufacturing methods. These rules are used by the risk analysis tool for guiding user choices in the 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.



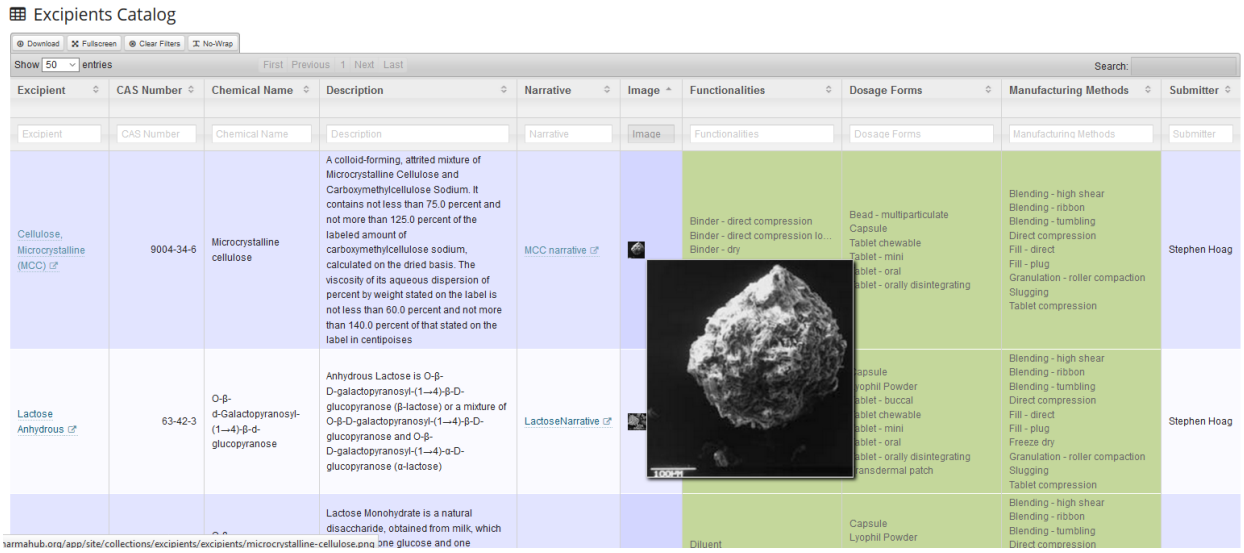
Each manufacturing method in the knowledge base is listed as one row in the tabular view. For every manufacturing method, there are three "rules" columns that show 1) valid choices for excipients, 2) valid choices for dosage forms, and 3) valid choices for functionality. The decision support tool uses 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.

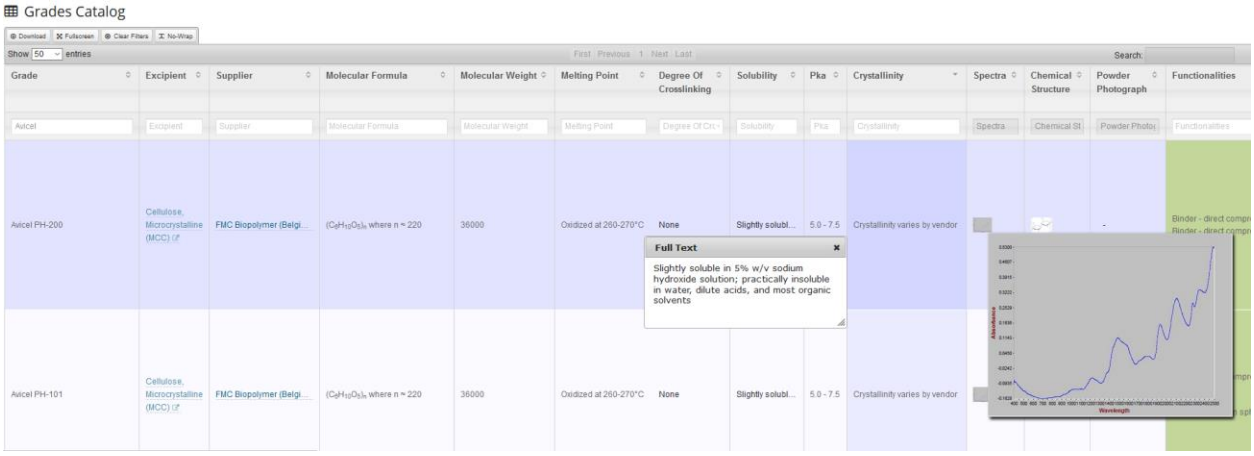


You can also enter search filters for multiple columns to identify combinations that are of interest to you. For example, if you enter *povidone* for excipient, *capsule* for dosage form and *lubricant* for functionality, you will find that 8 methods are valid for manufacturing that combination of options, 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).

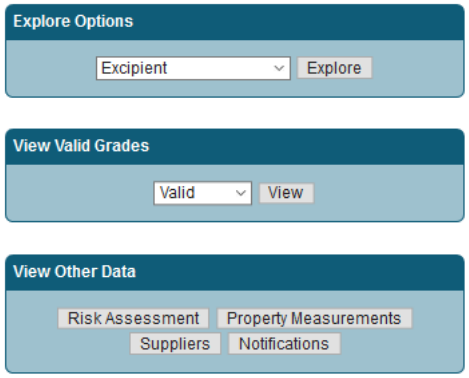


If you choose Excipient in the Explore Options menu, additional information about the excipient is included in the view. Along with the rules for valid choices of functionality, dosage form and manufacturing method, there are additional columns that present the chemical name, CAS number, description, 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

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Show 50 entries — First Previous 1 2 3 4 5 Next Last — Search:

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

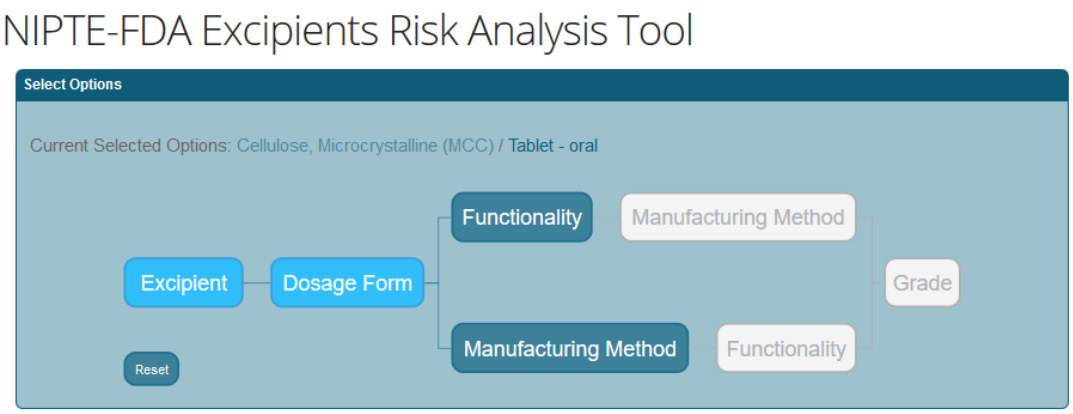
The Risk Assessment and Notifications views in **View Other Data** will be described in a later section.

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.

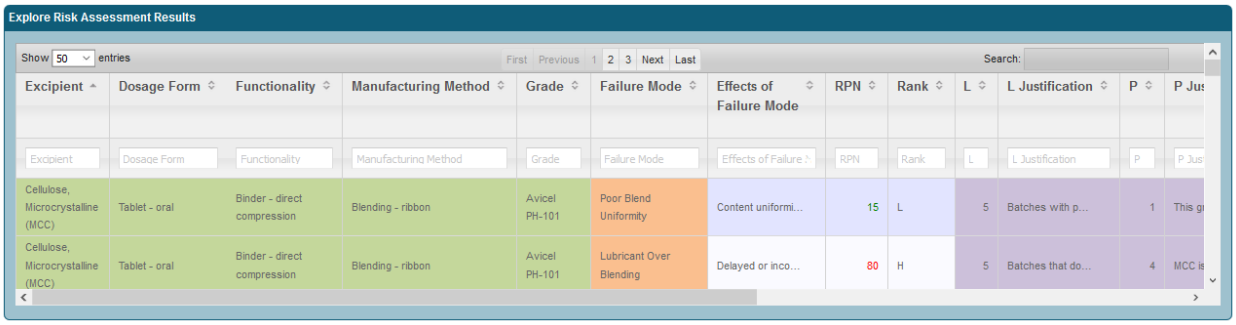
Exploring risk assessment data at each step in the selection process will help you evaluate the risk values assigned to all possible valid "next" choices, before making your next selection. For example, if you have already chosen an excipient and dosage form, you will be able to assess the risk data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

List of Risk Assessments with current selections

Download | Fullscreen | Clear Filters | No-Wrap

Show 50 entries — First Previous 1 2 3 Next Last — Search:

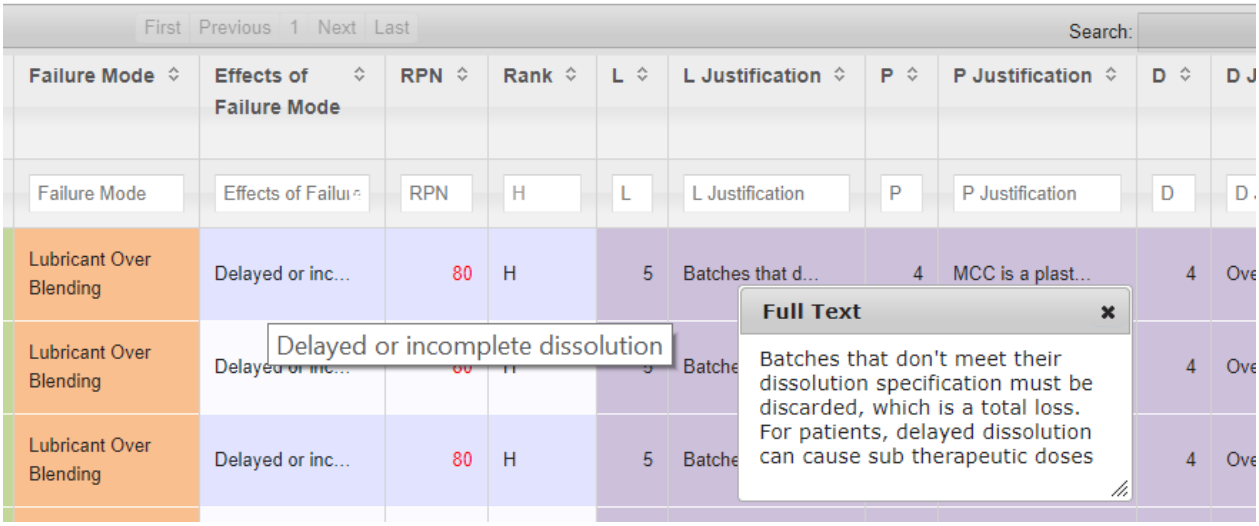
Excipient	Dosage Form	Functionality	Manufacturing Method	Grade	Failure Mode	Effects of Failure Mode	RPN	Rank	L	L Justification	P	P Justification	D	D Justification
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-101	Poor Blend Uniformity	Content unifor...	15	L	5	Batches with p...	1	This grade has...	3	With a good P...
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-101	Lubricant Over Blending	Delayed or inc...	80	H	5	Batches that d...	4	MCC is a plast...	4	Over blending ...
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-101	Lubricant Over Blending	Capping or la...	48	M	4	Batches that d...	4	MCC is a plast...	3	Over blending ...
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-301	Poor Blend Uniformity	Content unifor...	15	L	5	Batches with p...	1	This grade has...	3	With a good P...
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-301	Lubricant Over Blending	Delayed or inc...	80	H	5	Batches that d...	4	MCC is a plast...	4	Over blending ...

Let's review the high-risk entries.

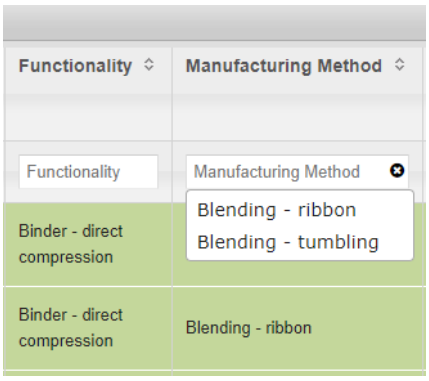
In the Rank column, click on the column search box at the top of the column to see a drop-down menu listing column values. Select H.

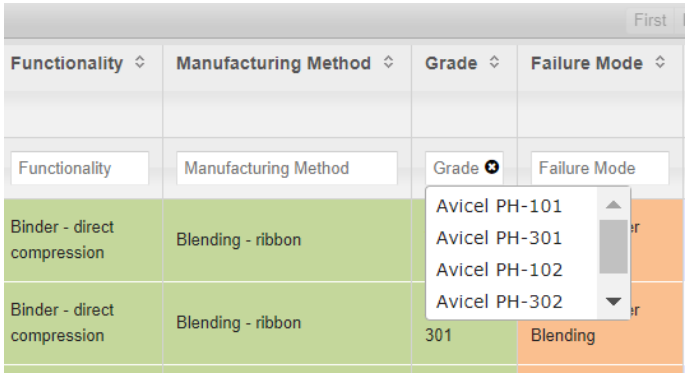
There are 142 results identified as high risk, each with an RPN value of 80. The failure modes for these cases is Lubricant Over Blending, Over Granulation and Under Granulation.

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.

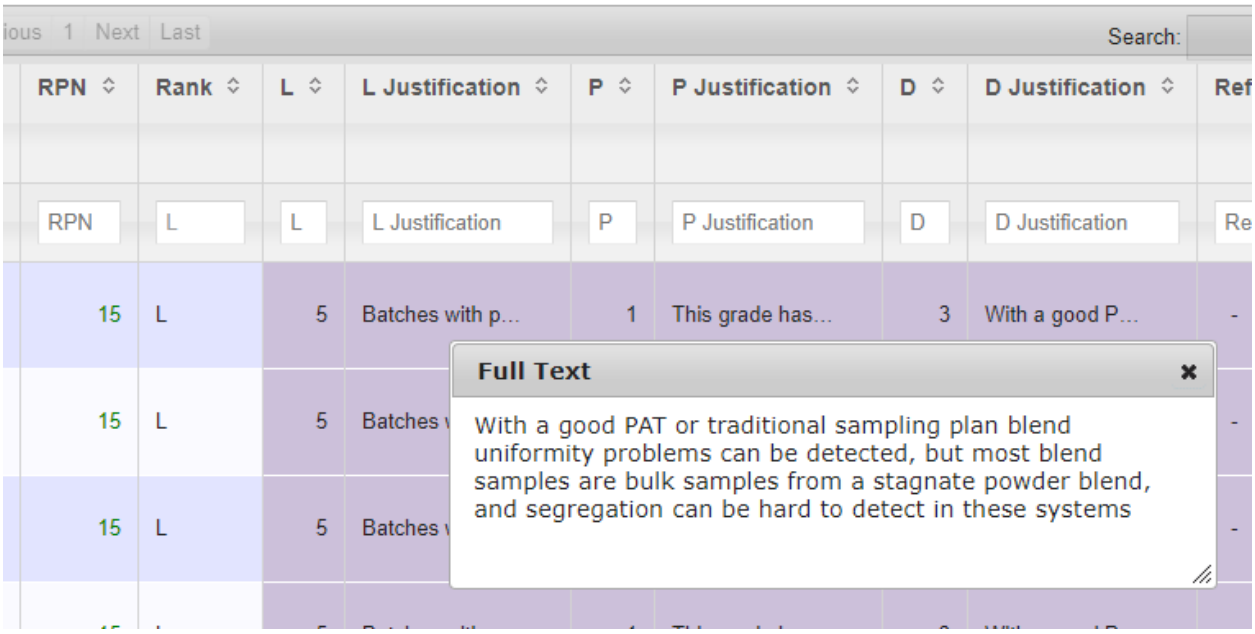


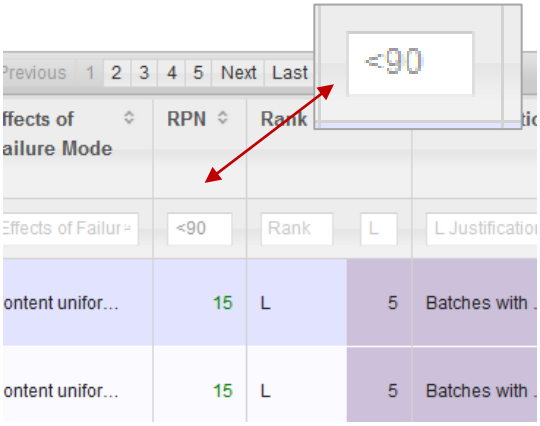
By paging through the results, you can see the Functionalities are *Binder-direct compression, Binder-wet, and Binder-dry*, and the Manufacturing Methods are *Blending-ribbon, Blending-high shear, Blending-tumbling* and *Tablet compression*. Check the Grades column to see which grades appear in the high-risk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





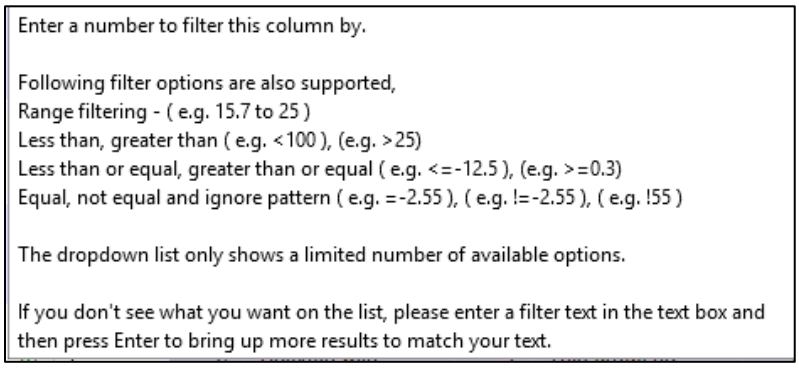
The same process can be followed to review which results are identified as low-risk: there are 71 entries with RPN less than 29. You can check Failure Mode, Effects of Failure Mode, the L, P, D values and their justifications for the low-risk entries.





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.

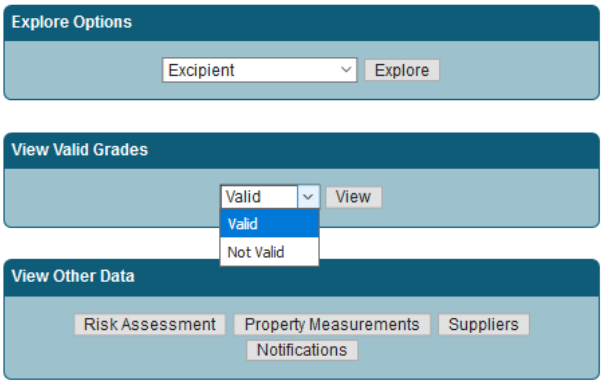


For example, if your value ranges for Ranking are different from the tool's default values (L=1-29, M=30-79, H-80-150), you can easily filter the RPN column for values that match your rankings.

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.



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
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.

List of Valid Grades with current selections

Download | Fullscreen | Clear Filters | No-Wrap

Show 50 entries — First Previous 1 Next Last — Search:

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

Download | Fullscreen | Clear Filters | No-Wrap

Show 50 entries — First Previous 1 Next Last — Search:

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

Download | Fullscreen | Clear Filters | No-Wrap

Show 50 entries — First Previous 1 Next Last — Search:

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

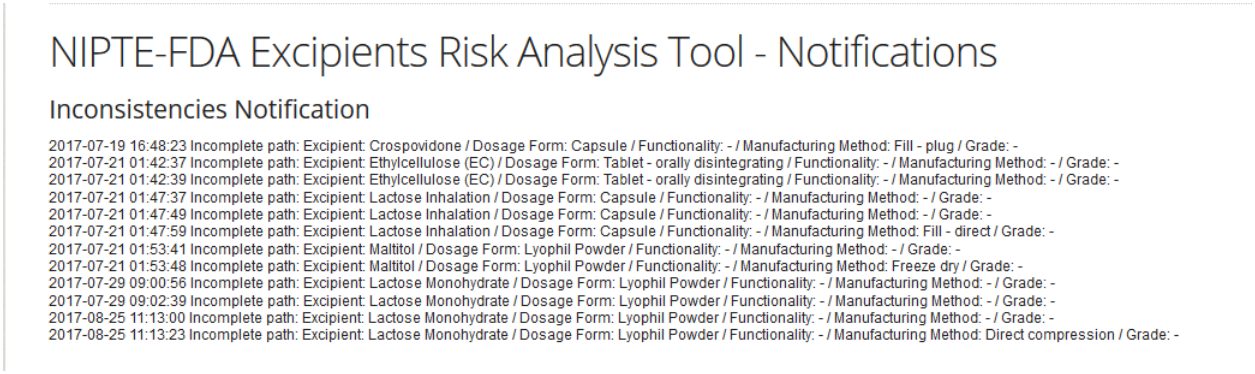
You can scroll down through the grades while looking at the Functionality data, and see that *Binder-dry* is not supported by any of the invalid grades. You could do a filter search on the text *dry*, and the resulting view will be empty, i.e., that text is not found for Functionality in any grade row. 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

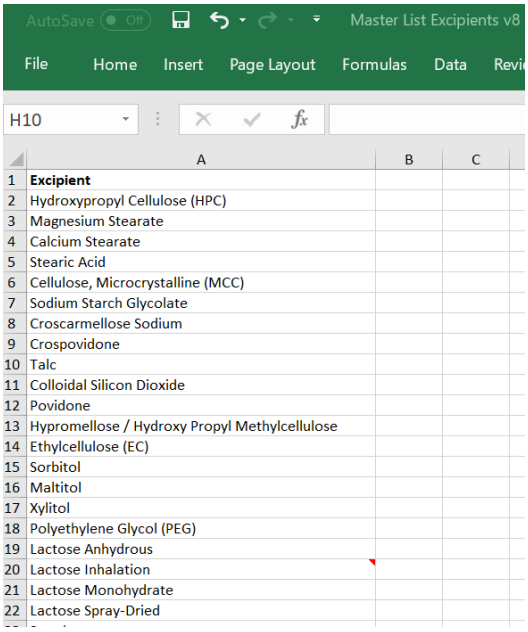
2017-07-19 16:48:23 Incomplete path: Excipient: Crospovidone / Dosage Form: Capsule / Functionality: - / Manufacturing Method: Fill - plug / Grade: -
2017-07-21 01:42:37 Incomplete path: Excipient: Ethylcellulose (EC) / Dosage Form: Tablet - orally disintegrating / Functionality: - / Manufacturing Method: - / 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

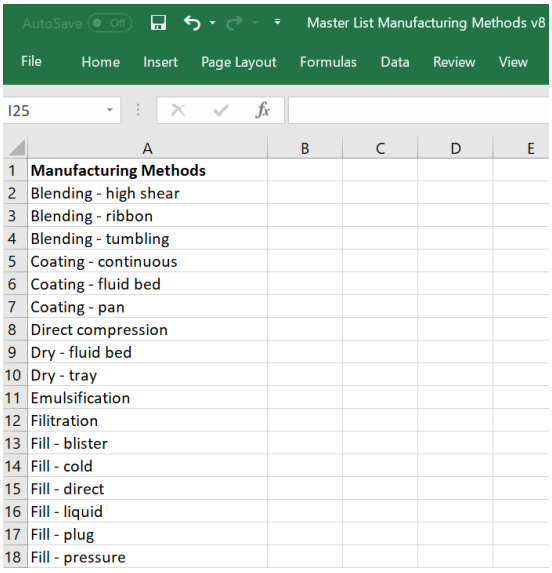
Data entered by users in the risk assessment database is of two types:

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.

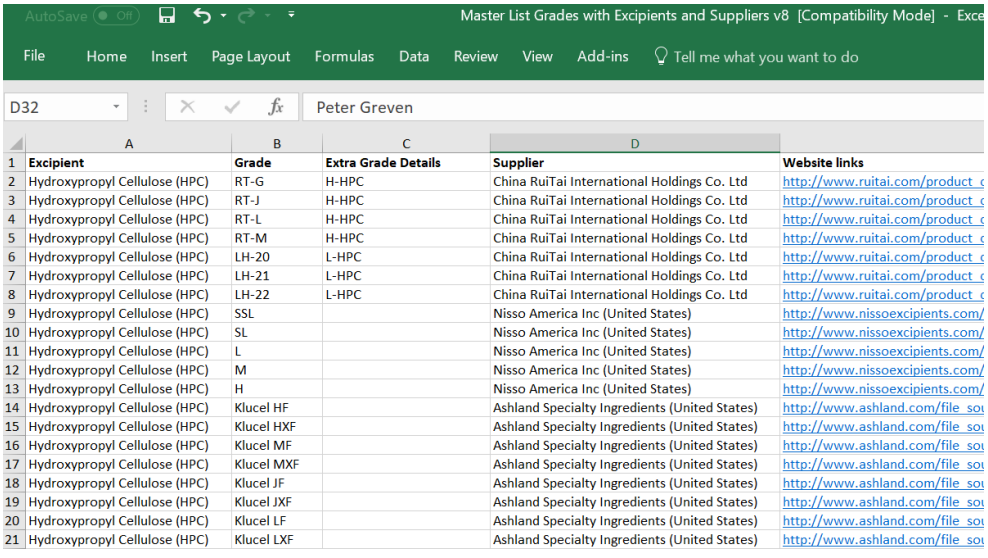
   Examples of partial master lists are shown below.



	A
1	**Excipient**
2	Hydroxypropyl Cellulose (HPC)
3	Magnesium Stearate
4	Calcium Stearate
5	Stearic Acid
6	Cellulose, Microcrystalline (MCC)
7	Sodium Starch Glycolate
8	Croscarmellose Sodium
9	Crospovidone
10	Talc
11	Colloidal Silicon Dioxide
12	Povidone
13	Hypromellose / Hydroxy Propyl Methylcellulose
14	Ethylcellulose (EC)
15	Sorbitol
16	Maltitol
17	Xylitol
18	Polyethylene Glycol (PEG)
19	Lactose Anhydrous
20	Lactose Inhalation
21	Lactose Monohydrate
22	Lactose Spray-Dried



	A
1	**Manufacturing Methods**
2	Blending - high shear
3	Blending - ribbon
4	Blending - tumbling
5	Coating - continuous
6	Coating - fluid bed
7	Coating - pan
8	Direct compression
9	Dry - fluid bed
10	Dry - tray
11	Emulsification
12	Filitration
13	Fill - blister
14	Fill - cold
15	Fill - direct
16	Fill - liquid
17	Fill - plug
18	Fill - pressure

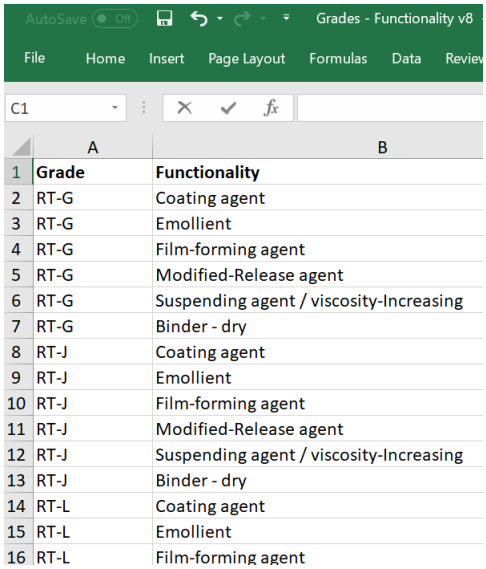


	A	B	C	D
1	**Excipient**	**Grade**	**Extra Grade Details**	**Supplier**	**Website links**
2	Hydroxypropyl Cellulose (HPC)	RT-G	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
3	Hydroxypropyl Cellulose (HPC)	RT-J	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
4	Hydroxypropyl Cellulose (HPC)	RT-L	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
5	Hydroxypropyl Cellulose (HPC)	RT-M	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
6	Hydroxypropyl Cellulose (HPC)	LH-20	L-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
7	Hydroxypropyl Cellulose (HPC)	LH-21	L-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
8	Hydroxypropyl Cellulose (HPC)	LH-22	L-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product_c
9	Hydroxypropyl Cellulose (HPC)	SSL		Nisso America Inc (United States)	http://www.nissoexcipients.com/
10	Hydroxypropyl Cellulose (HPC)	SL		Nisso America Inc (United States)	http://www.nissoexcipients.com/
11	Hydroxypropyl Cellulose (HPC)	L		Nisso America Inc (United States)	http://www.nissoexcipients.com/
12	Hydroxypropyl Cellulose (HPC)	M		Nisso America Inc (United States)	http://www.nissoexcipients.com/
13	Hydroxypropyl Cellulose (HPC)	H		Nisso America Inc (United States)	http://www.nissoexcipients.com/
14	Hydroxypropyl Cellulose (HPC)	Klucel HF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
15	Hydroxypropyl Cellulose (HPC)	Klucel HXF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
16	Hydroxypropyl Cellulose (HPC)	Klucel MF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
17	Hydroxypropyl Cellulose (HPC)	Klucel MXF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
18	Hydroxypropyl Cellulose (HPC)	Klucel JF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
19	Hydroxypropyl Cellulose (HPC)	Klucel JXF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
20	Hydroxypropyl Cellulose (HPC)	Klucel LF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou
21	Hydroxypropyl Cellulose (HPC)	Klucel LXF		Ashland Specialty Ingredients (United States)	http://www.ashland.com/file_sou

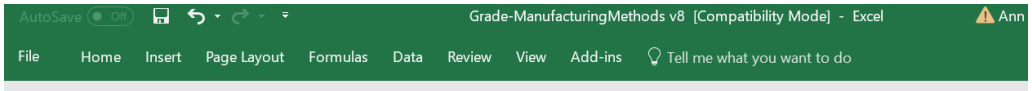
   The Master list spreadsheets are processed and imported to the database.

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.



	A	B
1	**Grade**	**Functionality**
2	RT-G	Coating agent
3	RT-G	Emollient
4	RT-G	Film-forming agent
5	RT-G	Modified-Release agent
6	RT-G	Suspending agent / viscosity-Increasing
7	RT-G	Binder - dry
8	RT-J	Coating agent
9	RT-J	Emollient
10	RT-J	Film-forming agent
11	RT-J	Modified-Release agent
12	RT-J	Suspending agent / viscosity-Increasing
13	RT-J	Binder - dry
14	RT-L	Coating agent
15	RT-L	Emollient
16	RT-L	Film-forming agent



	A	B	C	D	E	F	G	H	I
1	**Excipient**	**Grade**	Blending - high shear	Blending - ribbon	Blending - tumbling	Coating - continuous	Coating - fluid bed	Coating - pan	Direct compression
2	Hydroxypropyl Cellulose (HPC)	RT-G	x	x	x	x	x	x	
3	Hydroxypropyl Cellulose (HPC)	RT-J	x	x	x	x	x	x	
4	Hydroxypropyl Cellulose (HPC)	RT-L	x	x	x	x	x	x	
5	Hydroxypropyl Cellulose (HPC)	RT-M	x	x	x	x	x	x	
6	Hydroxypropyl Cellulose (HPC)	LH-20	x	x	x	x	x	x	
7	Hydroxypropyl Cellulose (HPC)	LH-21	x	x	x	x	x	x	
8	Hydroxypropyl Cellulose (HPC)	LH-22	x	x	x	x	x	x	
9	Hydroxypropyl Cellulose (HPC)	SSL	x	x	x	x	x	x	
10	Hydroxypropyl Cellulose (HPC)	SL	x	x	x	x	x	x	
11	Hydroxypropyl Cellulose (HPC)	L	x	x	x	x	x	x	
12	Hydroxypropyl Cellulose (HPC)	M	x	x	x	x	x	x	

   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 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 Poor Blend Uniformity, Content uniformity problems Under Granulation, Friable granules Under Granulation, High % fines Delayed Dissolution – Low porosity, Poor bioavailability Friability > 1%, Edges chip and weight varies Weight Variation, High variability in the dose Lubricant Over-blending, Capping or lamination and high friability Note that Failure Modes can have more than one Effect Analysis. 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: H: 80-150 M: 30-79 L: 1-29
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)
L Justification	Justification for the L rating.

	Some examples are: 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 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 4: If the granules are too hard they can fail to disintegrate, which can delay dissolution 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: 1: Highly unlikely (Virtually impossible or No known occurrences on similar products). 2: Remote (relatively few failures). 3: Occasional (occasional failures). 4: Reasonably Possible (repeated failures). 5: Frequent (failure is almost inevitable)
P Justification	Justification for the P rating. Some examples are: 5: If don't have good endpoint determination, this can be highly likely 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 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: 1: Certain - fault will be caught on test. 2: Almost certain. 3: High. 4: Moderate. 5: Low. 6: Fault is undetected by Operators or Maintainers.
D Justification	Justification for the D rating. Some examples are: 5: This can be hard to detect as there are no standard release tests for this property 3: Granulation particles size if used as a granulation endpoint can detect this problem 1: Easily detected
Mitigation	Strategies for mitigating the assessed risk. Examples are
Submitter	The person who submitted the data, currently Professor Stephen Hoag

Appendix C: Complete Database Diagram

This appendix shows the tables, column attributes and key linkage for the data representation used for the Excipient Risk Assessment Results.