# 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 <u>https://pharmahub.org/excipient-risk-analysis</u>.

# 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)



# NIPTE-FDA Excipients Risk Analysis Tool

plore Risk Assessment Results												
Show 5 v er	tries			First Previous	1 2 3 4 5 Next	Last				Search:		
Excipient *	Dosage Form ≎	Functionality \$	Manufacturing Method 🗘	Grade ≎	Failure Mode ≎	Effects of ⇒ Failure Mode	RPN ≎	Rank ≎	L ¢	L Justification \$	Р \$	P Justification
Excipient	Dosage Form	Functionality	Manufacturing Method	Grade	Failure Mode	Effects of Failure N	RPN	Rank		L Justification		P Justification
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
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	2	ubricant Over ending	Delayed or inco	80	н	5	Batches that do	4	MCC is a plastic
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - nibbon	PH-101	Lubricant Over Blending	Capping or lami	48	м	4	Batches that do	4	MCC is a plastic
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-301	Poor Blend Uniformity	Content uniformi	15	L	5	Batches with p	1	This grade has
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-301	Lubricant Over Blending	Delayed or inco	80	н	5	Batches that do	4	MCC is a plastic
Show 5 ~ er	tries		Showing 1 to 5 of 135 er	ntries						First Previous 1 2	3 4 5	Next Last

#### 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.

Select Options	
Start by clicking the Excipient button below	
	Functionality Manufacturing Method
Excipient - Dosage Form -	Grade
Reset	Manufacturing Method Functionality

# NIPTE-FDA Excinients Risk Analysis Tool



Tablet chewable

Tablet - orally disintegrating

Tablet - mini

Tablet - oral

The Select an Excipient menu lists all excients 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 Tabletoral 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.

Binder - direct compression	~	
Binder - direct compression		
Binder - direct compression low moisture	1	
Binder - dry	-	Cancel
 Binder - extrusion spheronization	-	
Binder - wet		

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.

Select Options	
Current Selected Options: Cellulose, Microcrystalline (MCC) / Tablet - oral / Binder - direct compression	
Functionality Manufacturing Method	7
Excipient — Dosage Form –	Grade
Reset Manufacturing Method Functionality	

Blending - high shear 🗸		
Blending - high shear		
Blending - ribbon		
Blending - tumbling	OK	Cancel
 Direct compression		

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.* 

Select a Grade			We select Avicel PH-101 and click on OK.
	Avicel PH-101	×.	Martha de a fracta a de actual a de fra
	Avicel PH-101	^	with the final option selected, all five
	Avicel PH-102		buttons are now bright blue, and our five
	Avicel PH-200	OK Cancel	choices are listed at the top left in the Select
	Avicel PH-301		Options area.
	Avicel PH-302		
	EMCOCEL 50M		We are ready to review the risk analysis for
	EMCOCEL 90M		we are ready to review the risk analysis for
	EMCOCEL 90M coarse		our choices:
	EMCOCEL HD 90M		
	EMCOCEL LP 200	-	Excipient: Cellulose, Microcrystalline (MCC)
	EMCOCEL XLM 90M		Dosage Form: Tablet-oral
	KG-1000		Functionality: Binder – direct compression
	KG-802		Manufacturing Method: <i>Binding – ribbon</i>
	MCC SANAQ 101		Grade: Avicel PH-101
	MCC SANAQ 102		Grade. Ancentri-101
	MCC SANAQ 200		
	MICROCEL 102		The risk analysis is presented as a tabular,
	MICROCEL 112		spreadsheet-like display in the Excipients
	MICROCEL 12		Risk Assessment Results area, which is
	MICROCEL 200	~	immediately below the <b>Select Options</b> area.

Select Options		E	Explore Options													
Current Select	ted Options: Cellulo	ose, Microcrystallin	e (MCC) / Tablet - oral / Bind	ler - direct d	ompression / Blen	ding - ribbon / Avic	el PH-101			Excipie	nt	~ Explore				
			Functionality						V	ew Valid Grades						
			Functionality	Man	uracturing Meth				Valid View							
	Excipient Dosage Form Grade											View Other Data				
	Reset		Manufacturin	g Method	Functiona	lity				Risk Assessment	Prope	erty Measurements	Supplier	rs		
Explore Risk Asse	essment Results															
Show 50 v er	ntries				First Previous	1 Next Last			Search:							
Excipient *	Dosage Form 🌣	Functionality \$	Manufacturing Method 🗘	Grade 0	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 M		Rank								
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-101 IZ	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	н	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	м	4	Batches that do	4	MCC is a plastic	3	¢		
Show 50 v er	ntries		Showing 1 to 3 o	of 3 entries							Firs	t Previous 1 Next	Last			
														~		
C.													-	2		

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.

		First Previous 1	Next Last					Search:		
Grade 🗘	Failure Mode 🗘	Effects of Failure Mode	RPN ¢	Rank ≎	L ¢	L Justification 🗘	P ≎	P Justification \$	D ¢	D Justification \$
Grade	Failure Mode	Effects of Failure N	RPN	Rank		L Justification	Ρ	P Justification		D Justification
Avicel PH-101 IZ	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	н	5	Batches that do	4	MCC is a plastic	4	Over blending c
Avicel PH-101 IZ	Lubricant Over Blending	Capping or lami	48	м	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.

	First Previous	1 Next L		Search:								
Failure Mode 🗘	Effects of Failure Mode	RPN \$	Rank ≎	L ^	L Justification 🗘	Р \$	P Justification \$	D ¢	D			
Esthura Mada	Effects of Eathers 1	DDN	Deek		L			×				
Failure Mode	Effects of Pallure 3	KPIN	Капк		Severity of Loss	s (L) is	a value from 1 to	6 with				
Lubricant Over Blending	Capping or lami	48	м	4	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							
Poor Blend Uniformity	Content uniformi	15	L	5								
Lubricant Over Blending	Delayed or inco	80	н	5	primary function; Loss of all safety Margins, 1 failure away from a catastrophe, severe damage, severe injuries, max 1 possible death).							
wing 1 to 3 of 3 entries					the failure may operation and p	result i ossible	n complete unsafe multiple deaths)		ıs			
							. ,	//				

#### 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.

×

			First Previ				Search:					
Grade \$	Failure Mode 🗘	Effects of Failure Mode	RPN \$	Rank ≎	L ¢	L Justification 🗘	Р \$	P Justification \$	D ¢	D Justification 🗘	Referen	
Grade	Failure Mode	Effects of Failure %	RPN	Rank		L Justification	Р	P Justification		D Justification	Referenc	
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	н	5	Batches that do	4 Ful	MCC is a plastic	4	Over blending c	-	
Avicel PH-101 🖻	Lubricant Over Blending	Capping or lami	48	м	4	Batches that do	MCC is a plastic material and very sensitive to over lubrication, poor mixing procedures make over					
	Showing 1 to	o 3 of 3 entries	blending a problem, a ribbon blender is higher shear than a tumbling blender									
							-				h	

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.

#### Explore Property Measurements for Excipient Grades

O Down	load	Clear Filters T No-V	Vrap					
Show [	50 ~	entries				First Pre	vious 1 2 Next I	Last
ID ≓		Excipient \$	Grade ≎	Lot Number 🗘	Property Measurements 🗘	Humidity \$ [%]	Temperature ≎ [°C]	Test Method \$
		Excipient	Grade	Lot Number	Property Measurements	Humidity (*	Temperature [°:	Test Method
1		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Shear Cell 🖻	31.60	24.53	Schulze Shear C
2		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Shear Cell 🗷	32.58	24.89	Schulze Shear C
3		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Shear Cell 🖉	33.39	25.01	Schulze Shear C
10		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Poured/Tapped Bulk Density II	21.40	23.64	Poured/Tapped B
13		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Apparent Density 🗷	55.00	23.00	Helium pycnome
14		Cellulose, Microcrystalline	Avicel PH-101	P108819435	Apparent Density 🗷	55.00	23.00	Helium pycnome
21		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Particle Size Distribution 🖻	21.50	23.89	Laser Diffraction 🗷
22		Cellulose, Microcrystalline	Avicel PH-101	P109821003	Particle Size Distribution 🗷	21.50	23.89	Laser Diffraction 🗷
23		Cellulose, Microcrystalline	Avicel PH-101	P1098 Measuremen	t Data PSD Graphs and Raw Data	01.50	00.00	
25		Cellulose, Microcrystalline	Avicel PH-101	P1098 Frequency Distribution	Chart Hans II No-Hop Hill Charts	Frequ	iency Distribution	C Riscol Devriced Otor
26		Cellulose, Microcrystalline	Avicel PH-101	P1088	1.2			MesoremerCID - 21
33		Cellulose, Microcrystalline	Avicel PH-101	P1098	1.0			
34		Cellulose, Microcrystalline	Avicel PH-101	P1088	20.6	-		
41		Cellulose, Microcrystalline	Avicel PH-101	P1098		0	0	
42		Cellulose, Microcrystalline	Avicel PH-101	P1098	0.0			
57		Cellulose, Microcrystalline	Avicel PH-101	P1098	· · · · · · · · · · · · · · · · · · ·	a. 6.	size [µm]	4. h. h. h.
79		Cellulose, Microcrystalline	Avicel PH-101	P1098 Meas.	Distribution     Other Distribution     Distribution	r Size © Midpoint Of	Volume / Mass     Porcentare	Search: Frequency 0 Cumulative 0 Polympia P61
90		Cellulose, Microcrystalline	Avicel PH-101	P1098	[hu] [hu]	[µm]	[%]	fuel [16]
91		Cellulose, Microcrystalline	Avicel PH-101	P1098	VolumeNass 3,0020 4,3650	r Size Bound Midpoint Of Size	e Interval Volume / Mass Percentage	Frequency     Oumulative     0.0710     0.0400
94		Cellulose, Microcrystalline	Avicel PH-101	P1098	Volume/Mass         4 2650         5 0120           Volume/Mass         5 0120         5 7540	4.6880 5.3830	0.0500	0.1380 0.1300 0.2700

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 <a href="https://pharmahub.org/excipientsexplore">https://pharmahub.org/excipientsexplore</a>; that content will not be described in this User Guide.

vious 1	Next	Last			S	earch:	
on 🗘	<b>P</b> ≎	P Justification \$	D \$	D Justification \$	References \$	Mitigation 🗘	Submitter 🗘
	Ρ	P Justification		D Justification	References	Mitigation	Submitter
)	4	MCC is a plastic	3	Over blending c	-	Having a good b	Stephen Hoag
	1	This grade has	3	Full Text Having a good ble best way to avoid	nding procedure I soft and weak f	that is robust is tablets	the Hoag
J	4	MCC is a plastic	4				Hoag
						First Previous 1	Next Last

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

Explore Options								
	Excipient   Explore							
	Excipient							
	Dosage Form							
View Valid Grades	Functionality							
	Manufacturing Method							
	Grade							
View Other Data								
Risk Asse	ssment Property Measurements Suppliers							
	Notifications							

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.

I Manufacturing Methods Catalog					
O Download X Fullscreen     O Clear Filters I No-Wrap					
Show 50 - entries		First Previous 1 Next Last		Search:	
Manufacturing Method	≜ Excipients ≎	Dosage Forms \$	Functionalities 0	Submitter	\$
Blending - high shear	Lactose Anhydrous Celluidose, Microcrystalline (M Tranium Dioxide Polysthylene Oxide (PEO) Pregelatinized Starch Starch Lactose Inhalaton Povidone Matitol Lactose Monohydrate Sucrose Lactose Spray-dried Cotioidal Silicon Dioxide Sodium Starch Glycotate Croscarmellose / Hydrov Proyf Calcium Phosphate Dibasic D Hydroxypropi (Celluidse (HPC)) Polysthjene Glycol (PEG) Crospovidone Xylitol Calcium Phosphate Dibasic A	Tablet chewable Tablet - buccal ADF Formulation Dry Powder inhalers (DPI) Bead - multiparticulate Tablet - oral Tablet - mini Capsule Pill Tablet - orally disintegrating Film - sublingual	Pigment Gidant Diluent Diluent Binder - direct compression Io Antiadherant Sweetening Agent Cheitang / Complexing Agent Elander - wet Modified - release agent matix. Drug Stabilisation Agent Flavoring Agent Antimicrobial Preservative Viscosit-Increasing Agent Binder - direct compression Binder - edirect compression Binder - direct compression Carrier PH Modifier Coloring Agent ADF Barrier Liquid Inhaler carrier Complexing Agent Binder - dry Lubricant Anticaking agent Anticaking agent	Stephen Hoag	

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.

🖽 Manufacturing Methods Catalog				
Download     X Fullscreen     O Clear Filters     X No-Wrap			suspension	
Show 50 v entries		First Previous 1 Next	suspension	Search:
Manufacturing Method	Excipients 0	Dosage Forms		¢
		suspension		
		Fo Ex To To CI	ollowing filter options are also supported, act matches, use ": (e.g. tekyword) o ignore a specific word, use ": (e.g. tekyword) o ignore a pattern, use "! (e.g. tekyword) lick on the search box to list all the entries in the column Antioxidant Complexing Agent	
Hot melt extrusion	Hydroxypropyl Cellulose (HPC) Polyethylene Oxide (PEO)	Tablet - mini Film - sublingual Suspension - oral ADF Formulation Bead - multiparticulate Tablet - buccal Capsule Tablet - oral	Solvent Sovening Agent Drug Stabilisation Agent Antimicrobial Preservative Biosadhistift, Enhancer Biosadhesive Modifide - release agent matrix Pigment Colonic drug delivery agent Disintegrant Emulsifting agent - suffactant Vehicle Gelling Agent Chelaten (Complexing Agent)	

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).

Excinients Catalog

Download S Fullson	reen 🛛 🐵 Clear Filters 🗍 🎞	No-Wrap							
Show 50 v entrie	es	First Previo	ous 1 Next Last					Search:	
Excipient 0	CAS Number 0	Chemical Name 🔅	Description $\diamond$	Narrative 0	Image *	Functionalities 0	Dosage Forms 0	Manufacturing Methods 🗘	Submitter 0
		Chemical Name		Narrative	Image				
Cellulose, Microcrystalline (MCC) 2	9004-34-6	Microcrystalline cellutose	A colloid-forming, athrited mixture of Microcrystalline Cellulose and Carboxynethylecullose Sodium. It contains not less than 750 percent and not more than 1250 percent of the labeled amount of carboxynethylecullose sodium, calculated on the dired basis. The viscosity of its aqueous dispersion of percent by weight stated on the label is not less than 60.0 percent d'mat tated on the label in centpoises.	MCC narrative @	6	Binder - direct compression Binder - direct compression 10 Binder - dry	Bead - multiparticulate Capoule Tablet chewable Tablet - mini biblet - orali kiblet - orali / disintegrating	Elending - high shear Elending - ribbon Blending - ribbing Direct compression Fill - direct Fill - plug Granulation - roller compaction Stugging Tablet compression	Stephen Hoag
Lactose Anhydrous 🗗	63-42-3	O-β- d-Galactopyranosyl- (1→4)-β-d- glucopyranose	Anhydrous Ladose is O-β- D-galactopyranosyl-(1-4-9-D- glucopyranose (β-ladose) or a mixture of O-β-D-galactopyranosyl-(1-4-9-D- glucopyranose)-(1-4-9-D- glucopyranose)-(1-4-9-D- glucopyranose (α-ladose)	LactoseNarrative 🗗			apsule rophil Powder ablet - buccal ablet - hwable ablet - mini ablet - oral ablet - orally disintegrating ransdermal patch	Blending - high shear Blending - ribbon Blending - urmbing Direct compression Fill - direct Fill - plug Freeze dry Granulation - roller compaction Slugging Tablet compression	Stephen Hoag
armahub.org/app/site/	collections/excipients/	excipients/microcrystalline	Lactose Monohydrate is a natural disaccharide, obtained from milk, which cellulose.ong one glucose and one			Diluent	Capsule Lyophil Powder	Blending - high shear Blending - ribbon Blending - tumbling Direct compression	

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.

Explore Options
Excipient v Explore
View Valid Grades
Valid View
View Other Data
Risk Assessment Property Measurements Suppliers Notifications

List of Suppliers

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.

Download X Fullscreen      O Clear Filters	I No-Wrap		
Show 50 v entries		First Previous 1 2 3 4 5 Next Last	Search:
Grade	Excipient	Supplier	
(Tristar 149) STASMP	Stearic Acid	American International Chemical Inc (United St	ates) www.aicma 🖻
(Tristar NF) STTQMP	Stearic Acid	American International Chemical Inc (United St	ates) 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 <u>all possible valid "next" choices</u>, 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.

Current Selected Options: Cellulose, Microcrystalline (MCC) / Tablet - oral	
Functionality Manufacturing Method Excipient Dosage Form	Grade
Reset Manufacturing Method Functionality	

NIPTE-FDA Excipients Risk Analysis Tool

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.

Explore Risk Asse	ssment Results												
Show 50 v entries First Previous 1 2 3 Next Last Search:										^			
Excipient *	Dosage Form \$	Functionality $\diamond$	Manufacturing Method 🗘	Grade ≎	Failure Mode 🗘	Effects of Failure Mode	RPN ≎	Rank ≎	L ≎	L Justification \$	Р \$	ΡJι	15
Excipient	Dosage Form	Functionality	Manufacturing Method	Grade	Failure Mode	Effects of Failure N		Rank		L Justification			
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	91
Cellulose, Microcrystalline (MCC)	Tablet - oral	Binder - direct compression	Blending - ribbon	Avicel PH-101	Lubricant Over Blending	Delayed or inco	80	н	5	Batches that do	4	мсс	is ~
<												>	

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.

III List of Risk Assessments with current selections

Download X F	ulscreen    Clear Filters	II: No-Wrap												
Show 50 • e	ntries		evious 1 2 3 Next Last									Search		
Excipient ^	Dosage Form 🗘	Functionality $\diamond$	Manufacturing Method 🗘	Grade 🗘	Failure Mode 🗘	Effects of Failure Mode	RPN ¢	Rank 0	L ¢	L Justification 🗘	P ¢	P Justification \$	D¢	D Justification 0
Excipient	Dosage Form	Functionality	Manufacturing Method	Grade	Failure Mode	Effects of Failure	RPN	Rank	L	L Justification	Ρ	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	н	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	м	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	н	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.

First	First     Previous     1     Next     Last       Search:									
Failure Mode 🗘	Effects of Failure Mode	RPN \$	Rank ≎	L ¢	L Just	tification \$	Р \$	P Justification 0	D ¢	DJ
Failure Mode	Effects of Failure	RPN	Η	L	L Just	tification	Ρ	P Justification	D	D
Lubricant Over Blending	Delayed or inc	80	н	5	Batche	atches that d 4		MCC is a plast	4	Ove
Lubricant Over Blending	Delayed of mc	or incomp	olete disso	olution	Batche	Batches that don't meet their dissolution specification must be			4	Ove
Lubricant Over Blending	Delayed or inc	80	н	5	Batche	For patien can cause	ts, dela sub the	yed dissolution erapeutic doses	4	Ove

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.

					First
Functionality \$	Manufacturing Method 🗘	Functionalit	y 🌣 Manufacturing M	lethod 🗘 Grade 🌣	Failure Mode 🗘
Functionality	Manufacturing Method	Functionality	Manufacturing Me	thod Grade O	Failure Mode
Binder - direct compression	Blending - ribbon Blending - tumbling	Binder - direct compression	Blending - ribbon	Avicel PF Avicel PF Avicel PF	H-101 H-301 H-102
Binder - direct compression	Blending - ribbon	Binder - direct compression	Blending - ribbon	Avicel PH 301	1-302 ▼ r 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.

io	ous 1 Next Last Search:											
	RPN \$	Rank 🗘	L ¢	L Justif	ication ᅌ	P 0	P Justification 🗘	D \$	D Justification 🗘	Ref		
	RPN	L	L	L Justifi	L Justification Batches with p		P Justification	D	D Justification	Re		
	15	L	5	Batches			This grade has	3	With a good P	-		
	15	L	5	Batches	Full Text With a good PAT or traditional sampling plan blend uniformity problems can be detected, but most blend							
	15	L	5	Batches	samples are bulk samples from a stagnate powder blend, and segregation can be hard to detect in these systems							
			_					-				

Previous 1 2 3	4 5 Ne:	xt Last	<90			
ffects of ≎ ailure Mode	RPN \$	Rank		tic		
Effects of Failur#	<90	Rank	L	L Justification		
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.



List of Valid Grades with current selections

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.

Cownload X Felscreen @ Clar Filter X No.Wap							
Show 50 v entries		Search:					
Excipient	≎ G	Grade	٥				
		Grade					
Cellulose, Microcrystalline (MCC)	A	vicel PH-101					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-102					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-103					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-112					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-113					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-200					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-301					
Cellulose, Microcrystalline (MCC)	Av	vicel PH-302					
Cellulose, Microcrystalline (MCC)	E	MCOCEL 50M					
Cellulose, Microcrystalline (MCC)	E	MCOCEL 90M					
Cellulose Nicrocrystalline (MCC)	F	MCOCEL 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.

#### III List of Valid Grades with current selections

E List of Valid Grades with current selections

Download    X Fullscreen    @ Clear Fitters    X No-Wrap							
First Previous 1 Next Last		Search:					
Dosage Form 0	Grade	0					
	Grade						
Tablet - oral	Avicel PH-101						
Tablet - oral	Avicel PH-102						
Tablet - oral	Avicel PH-103						
Tablet - oral	Avicel PH-112						
Tablet - oral	Avicel PH-113						
Tablet - oral	Avicel PH-200						
Tablet - oral	Avicel PH-301						
Tablet - oral	Avicel PH-302						
Tablet - oral	EMCOCEL 50M						
	First Previous 1 Next Last Dosage Form  Dosage Form  Tablet-oral	First Previous 1 Next Last         Dosage Form       Grade         Dosage Form       Aricel PH-101         Tablet- oral       Aricel PH-102         Tablet- oral       Aricel PH-103         Tablet- oral       Aricel PH-113         Tablet- oral       Aricel PH-200         Tablet- oral       Aricel PH-301         Tablet- oral       Aricel PH-301         Tablet- oral       Aricel PH-302         Tablet- oral       Aricel PH-302         Tablet- oral       Aricel PH-302         Tablet- oral       Brice Occl. Foldy					

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.

Countait X Fullowers 0 Care Files I to Wrap							
Show 50 v entries First Previous	1 Next Last			Search:			
Excipient 0	Dosage Form $\diamond$	Functionality 0	Manufacturing Method	Grade ≎			
				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.

⊕ Download X Fullscreen      ⊕ Clear Filters	Download X Fullscewa @ Ckar Fitzer X No-Wrap								
Show 50 v entries	First Previous 1 Next Last			Search:					
Grade 0	Excipient \$	Dosage Form 0	Functionality 0	Manufacturing Method $\diamond$					
Grade									
Avicel PH-200	Cellulose, Microcystalline (MCC)	Bead - multiparticulate Capsule Tablet chevaole Tablet - mni Tablet - orally disintegrating	Binder - direct compression fow moisture Binder - direct compression	Blending - high shear Blending - high shear Blending - hibbin Direct compression Fill - direct Granutation - roller compaction Stugging Tablet compression Dry - fluid bed Dry - tray Fill - bitser Siewing Siewing Siewing					
EMCOCEL 90M coarse	Cellulose, Microorystalline (MCC)	Bead - multiparticulate Capstue Tablet - mini Tablet - mini Tablet - orally disintegrating	Binder - direct compression	Blending - high shear Blending - high shear Blending - humbing Dirst compression Fill - shed Fill - shed Granulation - roller compaction Stupping Tablet compression Dry - had Sed 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.



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: Capsule / 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 01:47:39 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: - / 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: - / Grade: -2017-07-29 09:00:05 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -2017-07-29 09:00:05 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -2017-07-29 09:00:05 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -2017-08-25 11:13:20 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Powder / Functionality: - / Manufacturing Method: - / Grade: -2017-08-25 11:13:20 Incomplete path: Excipient: Lactose Monohydrate / Dosage Form: Lyophil Po

# 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 <a href="https://pharmahub.org/excipient-risk-analysis">https://pharmahub.org/excipient-risk-analysis</a>.

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	AutoSave (• Off) 🚽 🕤 T 💣 T M			ts v8					
	File Human Install Department Fu		D-1-	D					
	File Home Insert Page Layout Fol	mulas	Data	Kevi					
H:	$10  \overline{}  =  \times  \sqrt{f_x}$								
1	A	В	C						
1	Excipient								
2	Hydroxypropyl Cellulose (HPC)								
3	Calcium Stearate								
4	Calcium Stearate								
5	Colluloso Microspistallino (MCC)								
7	Sodium Starch Glycolate								
0	Crossarmallasa Sadium								
9	Crospovidope								
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								
	- ·								

Examples of partial master lists are shown below.

,	AutoSave 💿 Off) 🖬 🕤 🗸 🔿 -	₹ M	Master List Manufacturing Methods v8				
F	ile Home Insert Page Layou	ıt For	mulas	Data	Review	View	
125	$5  \cdot  :  \times  \checkmark  f_X$	:					
	А	В		с	D	E	
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						

	AutoSave 💽 Off 🔲 🕁 🗸	· @ - =	Ма	ster List Grades with Excipients and Suppliers	v8 [Compatibility Mode] - Exce
	File Home Insert Pa	age Layout	Formulas Data Revi	ew View Add-ins 🖓 Tell me what yo	ou want to do
D	32 · : ×	✓ f <sub>x</sub>	Peter Greven		
	А	В	С	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 of
3	Hydroxypropyl Cellulose (HPC)	RT-J	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product of
4	Hydroxypropyl Cellulose (HPC)	RT-L	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product of
5	Hydroxypropyl Cellulose (HPC)	RT-M	H-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product of
6	Hydroxypropyl Cellulose (HPC)	LH-20	L-HPC	China RuiTai International Holdings Co. Ltd	http://www.ruitai.com/product of
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)	Н		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 <a href="https://pharmahub.org/excipient-risk-analysis">https://pharmahub.org/excipient-risk-analysis</a>.

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

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	А	В					
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					

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	A	В	С	D	E	F	G	н	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)	М	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	One of the most common risk assessment methods in the pharmaceutical
Effects of Failure Mode	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
	Tailure away from a catastrophe, severe damage, severe injuries, max 1
	pussible upduit.
	o. catastrophic (product becomes moperative; the failure may result in complete upsafe eneration and possible multiple deaths)
	complete unsale operation and possible multiple deaths)
LJustification	Justification for the L rating.

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# 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.

