



UNIVERSITY of MARYLAND  
SCHOOL OF PHARMACY

**NIPTE** The National Institute for  
Pharmaceutical Technology and Education  
*Improving quality and lowering costs of pharmaceuticals™*

# Research needs in pharmaceutical excipients: implications of a global supply chain

**FY 2015 GDUFA Regulatory Science Initiatives**

**Part 15 Public Meeting**

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Stephen W. Hoag, Ph.D.

University of Maryland, Baltimore; School of Pharmacy

**A NIPTE Institution**

Email: [shoag@rx.umaryland.edu](mailto:shoag@rx.umaryland.edu)



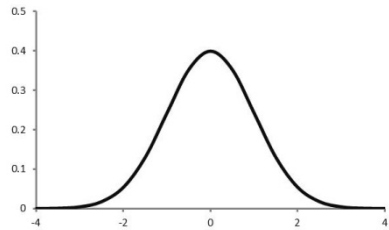
# Outline

- Introduction
- Research needs for excipients:
  - Fundamental research
    - Material science and process understanding
  - Risk management metric development
    - Identify excipient metrics
      - That relate excipient properties to clinical performance
      - Facilitate change control
  - Cataloging material properties
- Summary

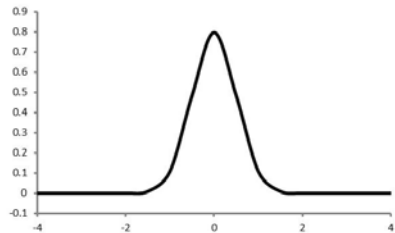
Should be  
done  
together

Topic #6. Strategies for enhancing quality and equivalence risk management during generic drug product development, during regulatory review, and/or throughout the drug product's lifecycle following initial approval.

# Dosage Form Variability

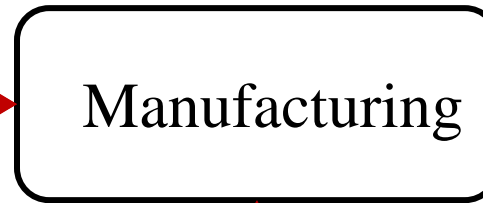
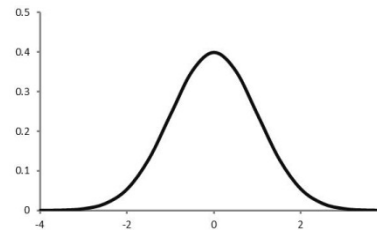


Excipients

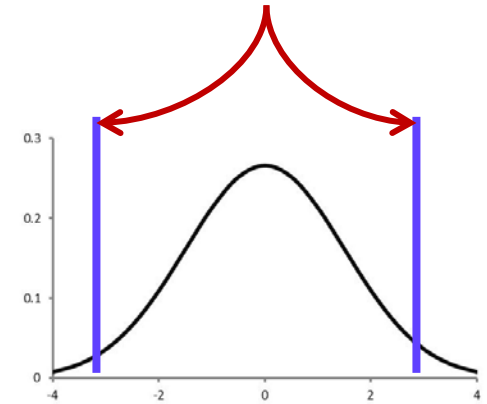


API

Processing  
Conditions



Spec. range



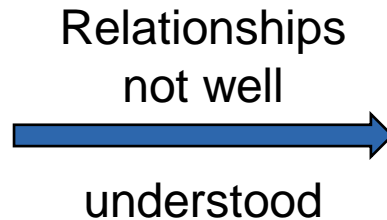
Dosage  
Forms

$$\sigma_{Tot} = \sigma_{Exc} + \sigma_{API} + \sigma_{PC} + \sigma_{Int} + \sigma_{Mes}$$

# Excipient Property Relations

## Material Properties

- Particle size
- Molecular weight
- Degree of substitution
- Bulk, true density
- Etc.



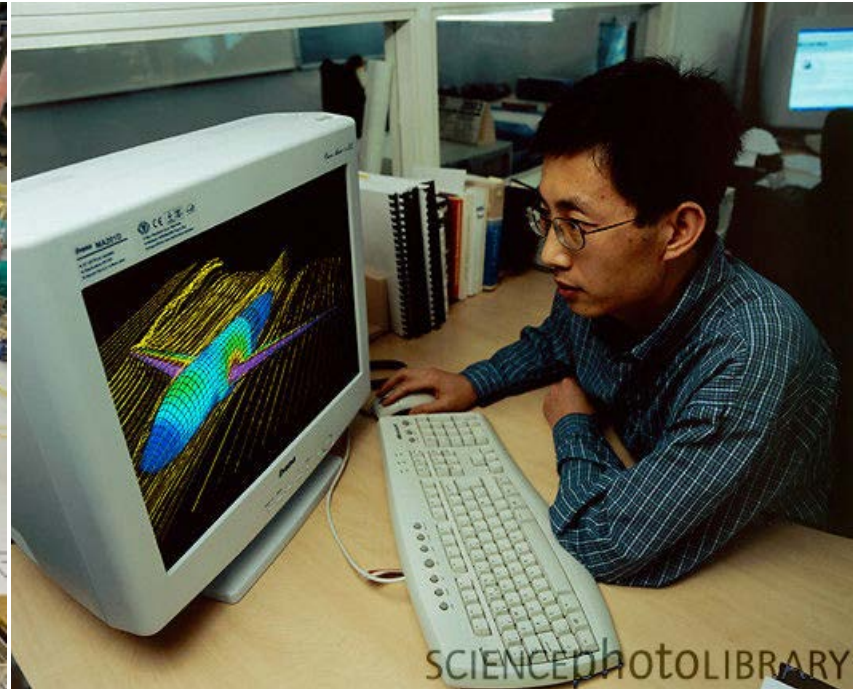
## QTPP

- Clinical use factors
- USP specs.
- PK/PD performance
- Bioavailability
- Misuse risk minimization
- Shelf life

## Lack of knowledge makes risk management difficult & empirical

- Empirical analysis is only as good as studies done to develop risk models
- Excipient variability complicates studies that need to be done
  - Lot-to-lot, grade, manufacturing site, manufacturer, etc.
- Makes change control difficult

# Fundamental Research → Ideal End Point

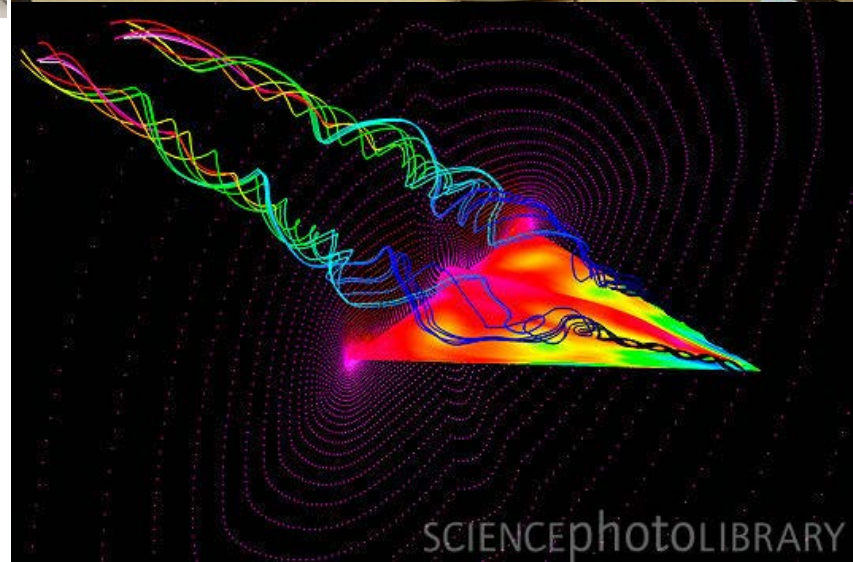


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-Determining material properties and material variation is essential to reach desired end point

-FDA should partner with other agencies to support this research

Image source: <http://www.sciencephoto.com/media/350843/enlarge;>  
<http://www.sciencephoto.com/media/350846/enlarge>  
<http://programminggeeks.com/building-airplanes-on-a-computer/>



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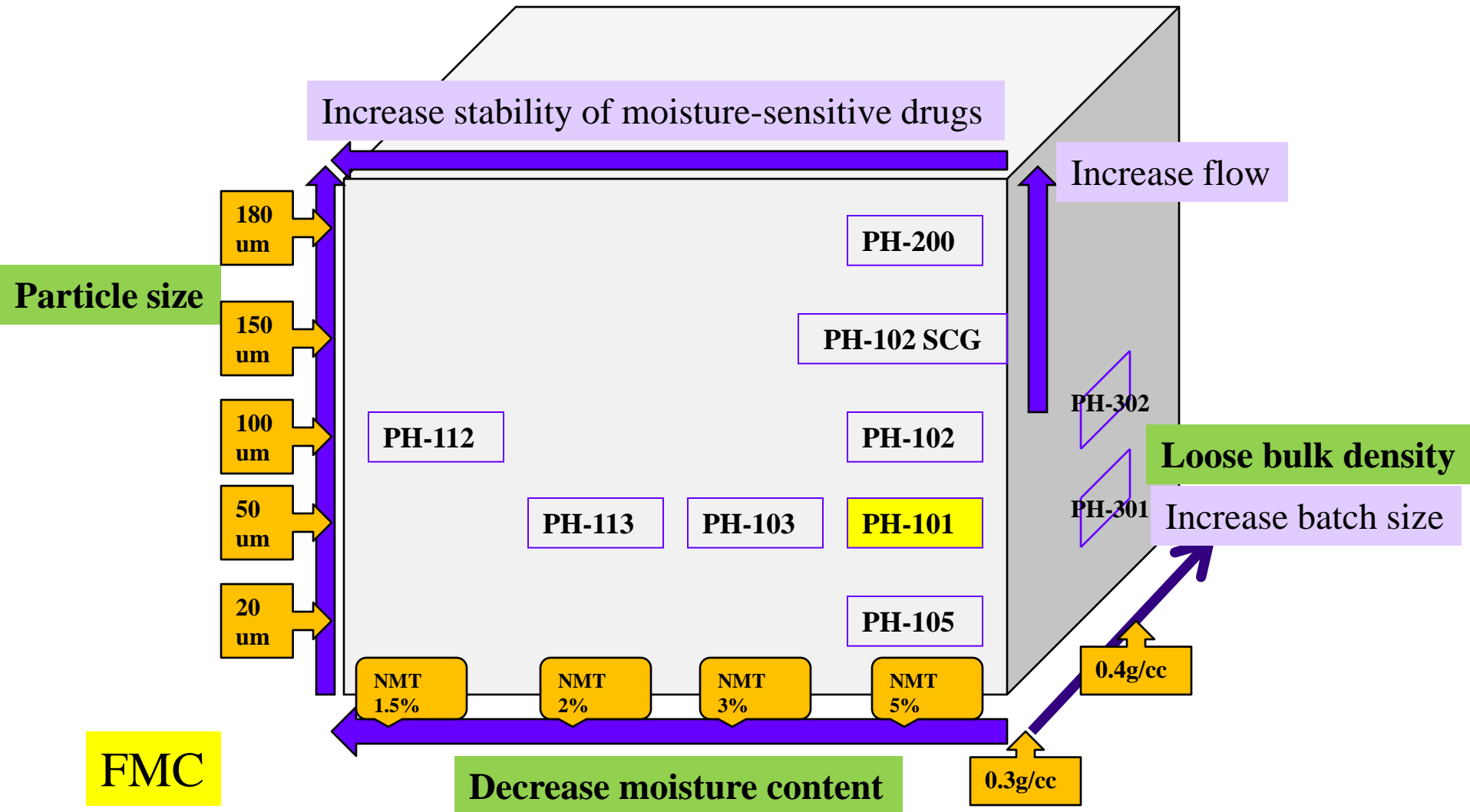
# Identifying Performance Metrics

- By nature excipients are highly variable materials
  - Thus, material science is key to process understanding
  - For each dosage form type: need to identify properties that affect QTPP
    - For some properties this is well known
      - E.g., particle size and flow
    - For most properties this is not well known
      - E.g., water activity and stability
      - Degree of substitution on a polymer and bioavailability
  - Should develop risk evaluation scheme for excipients section of the CMC
    - Should be open to public and built with input from FDA, industry and academics

# Global Supply Chain

- With globalization of the supply chain there has been a dramatic increase in the kinds and sources of excipients
  - Excipient vendors from all over the world now sell excipients in many markets
    - Products are now manufactured all over the world and imported to the USA, often using local excipient suppliers
  - In an effort to meet drug manufacturers needs excipient vendors have developed many new excipients
    - E.g., new excipients for low solubility drugs

# Comparison of different grades of MCC



NMT= not more than



# Comparison of different grades from different manufacturers--MCC

FMC\_ = FMC BIOPOLYMERS

JRS = J Rettenmaier & Söhne GmbH and Co.KG

AKC = Asahi Kasei Corporation

Manufactures	Grades	Particle Size, $\mu\text{m}$	Moisture, %	Loose Bulk Density, g/cc
FMC	Avicel PH101	50	3.0-5.0	0.26-0.31
JRS	Vivapur 101	65	--	0.26-0.31
	Emcocel 50M			0.25-0.37
AKC	PH-101	50	2.0-6.0	0.22
	UF-711			0.21
	KG-802			0.12
	KG-1000			0.29
FMC	Avicel PH-102	100	3.0-5.0	0.28-0.33
JRS	Vivapur 102	100	--	0.28-0.33
	Emcocel 90M			0.25-0.37
AKC	PH-102	90	2.0-6.0	0.30

# Change Control in a Global Supply Chain

- Often excipients are considered an interchangeable commodity item
  - In addition to the Certificate of Analysis, one needs to identify critical material attributes that need to be the same for a change not affect the patient
    - Key material attributes depends on the type of dosage form
  - Given our knowledge of excipient properties, assessing what changes won't affect the patient can be difficult
- Industry, FDA and academics should develop a set of metrics for assessing excipient changes

# Cataloging Material Properties

- Risk assessment methods are expensive and time consuming to develop
  - It would be very beneficial if all these efforts could be cataloged into a central location
- This information should be cataloged into a database that can track excipient properties:
  - Different vendors
  - Lots
  - Grades
  - Etc.
- The database should have tools to take information from the database and use it in a risk analysis
- Also, we are entering the area of “Big Data”
  - It would go a long way to improve product quality to be able to data mine excipient properties to identify unknown properties that affect product performance
  - Data mining can be used to guide theoretical studies on excipients

## Nomenclature











- Compendial Name
- CAS Number
- Chemical structure
- Common & Product Name
- Description & Functional Category

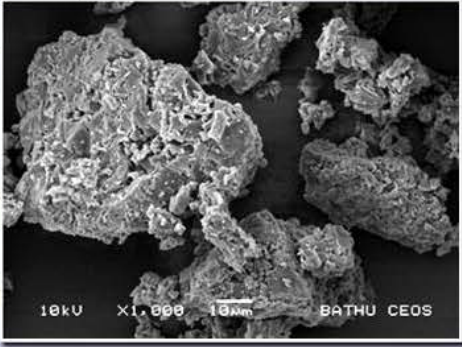
## Property Measurements

- Traceable
- Searchable
- Sortable
- Organized data into families by
  - Measurement type or chemical class

**Excipients Catalog**

Show 10 entries First Previous 1 2 Next Last Search:

ID	Compendial Name	CAS Number	Chemical Name	Description	Narrative	Image
1	<a href="#">α Lactose Monohydrate</a>	5989-81-1	Lactose	-	<a href="#">LactoseNarrative</a>	
2	<a href="#">Anhydrous α-Lactose</a>	63-42-3	Lactose	-	<a href="#">LactoseNarrative</a>	
3	<a href="#">Anhydrous β-Lactose</a>	63-42-3	Lactose	-	-	
4	<a href="#">Microcrystalline cellulose</a>	9004-34-6	Microcrystalline cellulose	-	-	
5	<a href="#">Partly Amorphous Lactose</a>	63-42-3	Lactose	-	-	
6	<a href="#">Lactose Monohydrate</a>	5989-81-1, 10039-26-6, 64044-51-5	O-β-d-Galactopyranosyl-(1→4)-α-d-glucopyranose monohydrate	-	-	
7	<a href="#">Anhydrous Lactose</a>	63-42-3	O-β-d-Galactopyranosyl-(1→4)-β-d-glucopyranose	-	-	
8	<a href="#">Lactose, Spray-Dried</a>	5989-81-1, 10039-26-6, 64044-51-5 and 63-42-3	mixture of α-and-β-lactose, and O-β-d-galactopyranosyl-(1→4)-d-glucopyranose monohydrate	-	-	
9	<a href="#">Maltodextrin</a>	9050-36-6	Maltodextrin	-	-	
10	<a href="#">Mannitol</a>	69-65-8	D-Mannitol	-	-	





# Summary

- Greatest needs
  - Fundamental material science research on excipient performance
  - For each dosage form type identifying performance metrics that relate to product efficacy and can be used in a risk analysis
  - Develop risk analysis schemes for excipient change control for excipients coming from different sources
  - Cataloging excipient information in a database or knowledge management system