

# Excipients in Nutraceuticals and Dietary Supplements

## - *Global View From a Formulation Perspective*

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**EXCIPIENT  
FEST** Americas

28 -29 April 2015 San Juan, Puerto Rico

## Introduction



- Solid dosage formulation and process design for drug products and nutrition products is similar.
- Purpose and regulatory requirements may differ..
- *Desire for a safe and effective dosage form is the same.*
- *Desire for most cost effective formulation and process is the same*
- ***Excipients are a key factor to success!***

## Formulation Goals for Nutrition

- Build in total quality
- Build in cost control
- Tablets preferred over capsules
- Direct compression first choice
- Smaller and fewer tablets per dose
- Global formula when possible
- Meet all internal quality and manufacturing process standards
- Meet global regulatory requirements for stability, ingredient acceptability and substantiation

## Formulation Challenges— What does it mean to work with plant concentrates?

- Generally large dose per daily serving
- Multiple “active ingredients” versus one or two for drug product
- Significant variation in active ingredient compression and flow characteristics within one dosage form
- Large variation in heat and moisture sensitivity of ingredients within one formula
- Significant stability challenges with multiple interaction opportunities



## Natural Bioactive Compounds



### Plant Concentrates:

Preparations of a single plant that have greater levels of macronutrients, micronutrients or phytochemicals than the feedstock

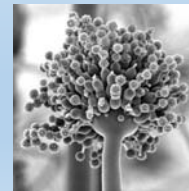
- Herbal Concentrates
- Fruit, Vegetable & Specialty Concentrates



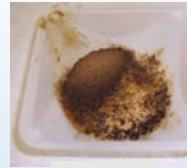
### *Other Natural Bioactive Concentrates:*

- Fungal and microbial materials are included as feedstock that can produce concentrates. ( Bio-fermentation process)
  - B12, digestive enzymes, hyaluronic acid
- Concentrates may include excipients used in production (e.g., spray drying carriers)

Aspergillus Niger



Common  
Processes



Valerian  
Extract



Valerian  
Granulation

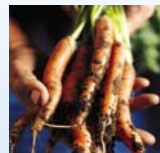
## Extraction

Retrieval of phytochemicals and essential plant phytonutrients by extraction with water/alcohol followed by spray drying with or without an inert carrier

- Powder Characteristics: Often produces hygroscopic powders with a fine particle size
- Tableting Challenges: Poorly flowing powders
  - Cause sticking during tableting

Common  
Processes

## Dehydration



Removal of water followed by milling to reduce particle size

### Powder Characteristics:

- Often results in materials that are fibrous, bulky, or spongy



### Tableting Challenges:

Generally non-compressible powders

- Difficult to incorporate into tablets at a high dose



## Excipient Assessment for Nutrition



- \* *Formulator must assess* properties of the active ingredients alone and in combination with all other active ingredient and excipients
- *Assessment is based on* the requirements of the dosage form and manufacturing processes applied.
- For Nutrition, the final formula must be robust to accommodate the varied and variable physical characteristics of natural ingredients in a complex formula.



## Key Drivers in Excipient Selection For Global Nutrition Formulations

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- 1) Meets dosage form/ process functionality requirements
  - 2) Regulatory Compliance
    - Must meet applicable compendial requirements
    - Must meet regional requirements or restrictions
- Materials and manufacturer must meet internal quality and safety, specifications and performance requirements

“One formulation’s functionality can be another formulation’s dysfunctionality” \*

- Excipient functionality can only be properly assessed in the context of a particular formulation and manufacturing process
- Excipient functionality is linked inextricably to the formulation and process, and all formulations are different, functionality is determined by the excipient user and supplier
- It would be impossible to establish a widely accepted standard for a particular excipient’s functionality in a pharmacopeia monograph.

\*R. Christian Moreton “ Excipient Functionality” *Pharmaceutical Technology* MAY 2004

## Desired Formulation *Functionalities* For Filler Binders

- Direct Compression excipients preferred
- Good Flowability of excipient and final powder blend is required
- Good compressibility is required for satisfactory tableting
  - the tablet must remain in the compact form once the compression force is removed
- ✓ ◆ Good Dilution (or carrying) potential -defined as the amount of an active ingredient that can be satisfactorily compressed into tablets
- remain unchanged chemically and physically upon compression or other processing
- ✓ Should not exhibit any physical or chemical change on ageing
- Should be stable to air, moisture and heat
- The particle size distribution should be consistent from batch to batch
- ✓ It should be relatively cost effective

## Desired Formulation *Functionalities* For Filler Binders

- ✓ It should not interfere with the disintegration or dissolution
- ✓ should not accelerate the chemical and/or physical degradation of the active components
  - It should not interfere with the biological availability of active ingredient
  - It should show low lubricant sensitivity.
- ✓ It should be compatible with all other excipients (disintegrants, lubricants, binders ,glidants etc.) present in the formulation.
  - It should be physiologically inert
- ✓ *Globally acceptable as both a nutritional and pharmaceutical excipient*

## Be Alert: Excipients Can Influence Solid State Stability

◆ Especially when formulating with multiple plant concentrates ..by

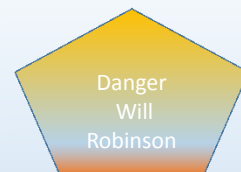
- Acting as surface catalysts,
- Acting as a source of extra moisture,
- Physical state of excipient can influence mobility of water molecules within the tablet components
- Undergoing direct chemical reactions with the extract/active components,
- Active/ excipient ratio
- Physical mixing vs. granulation,
- Granules vs compacts

Excipients may have different stability influences within different manufacturing processes

## Excipient Functionality

- For natural product formulation, excipient functionality in a particular formula is heavily influenced by the complex combination of multiple active ingredient characteristics
- Occasionally seemingly equivalent excipients are not equivalent in functionality

## Excipient Functionality vs Compendial Requirements



- ◆ The official pharmacopoeias define quality tests for the analytical characterization of the individual excipients
- ◆ Pharmacopoeial standards do not take into account particle characteristics, powder characteristics or manufacturing processes that often determine functionality of excipients

Excipient compliance with pharmacopoeial standards does not guarantee appropriate functionality for your formula





## Case in Point: What happens when you make a “one to one” excipient change?

- Excipients may have multiple functions in a product.. *or* a different function in several products.
- If produced by batch process there is a possibility of batch-to-batch variation from the same manufacturer.
- Excipients obtained from different sources that satisfy a monograph may not have identical properties with respect to use in a *specific formulation*.

Formulators must determine excipient equivalency either in final formula or before use.



## Case Study: Excipient Functionality

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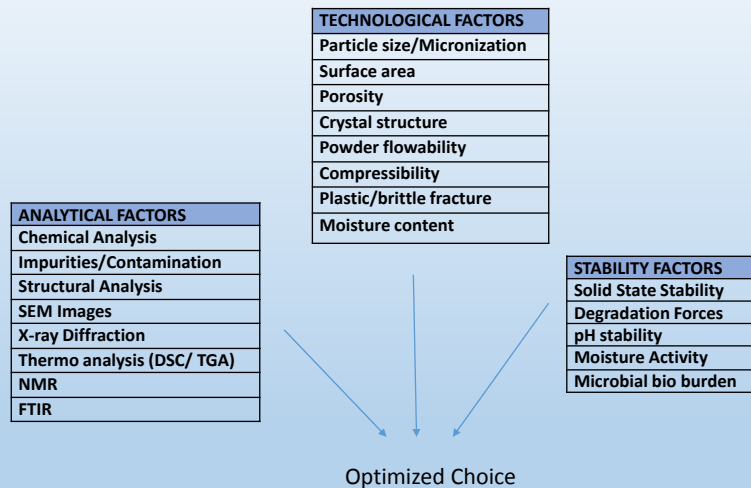
- Challenge– herbal formula capping in production trials
- Noted Change: new dextrose to meet GMO free requirements

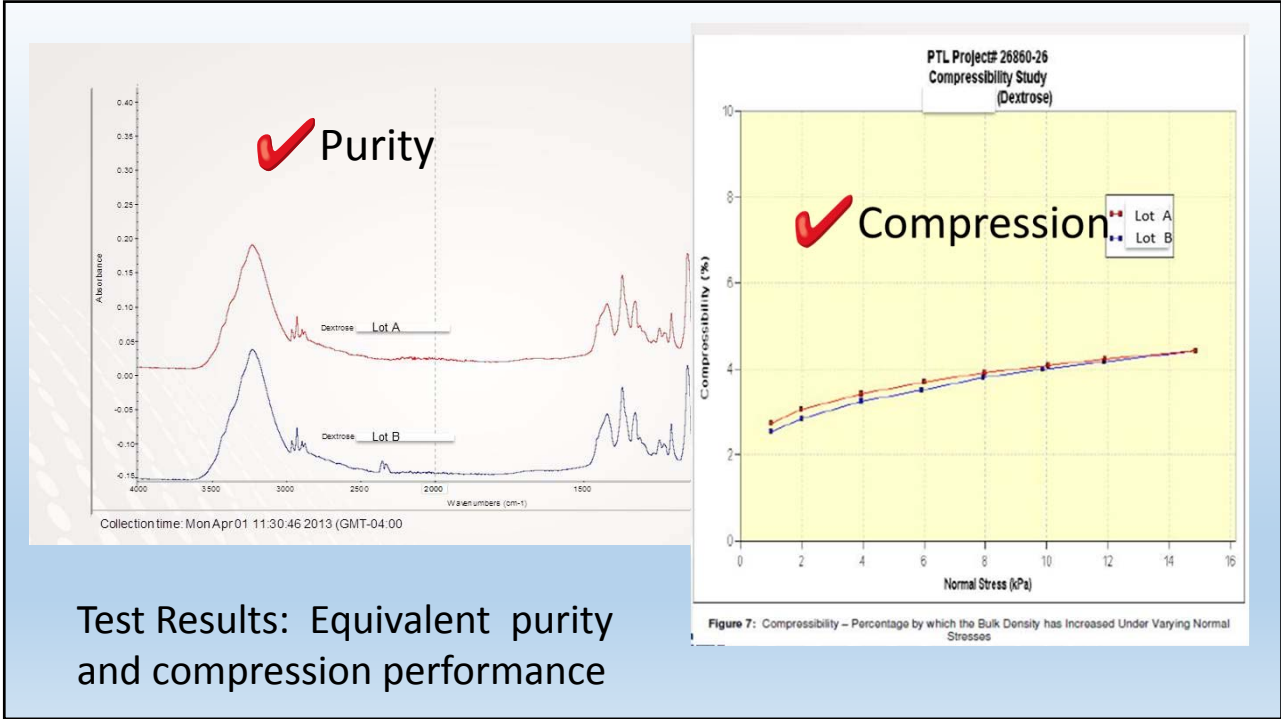


## Are the two dextrose products equivalent?

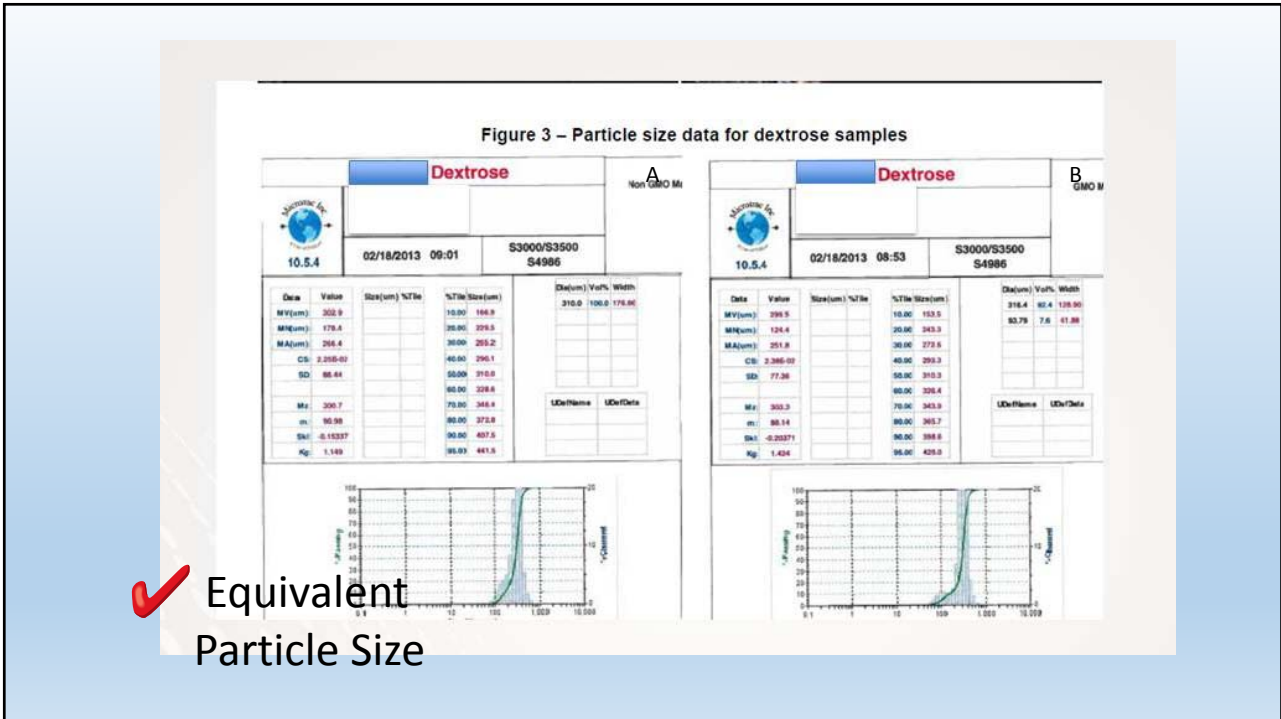
- Both meet internal specification requirements
- Both meet compendial requirements
- New dextrose meets additional regional requirements and restrictions
- ★ BUT - Negative effect on functionality and manufacturability for the herbal formula - WHY?

## Assessment of Excipient Properties





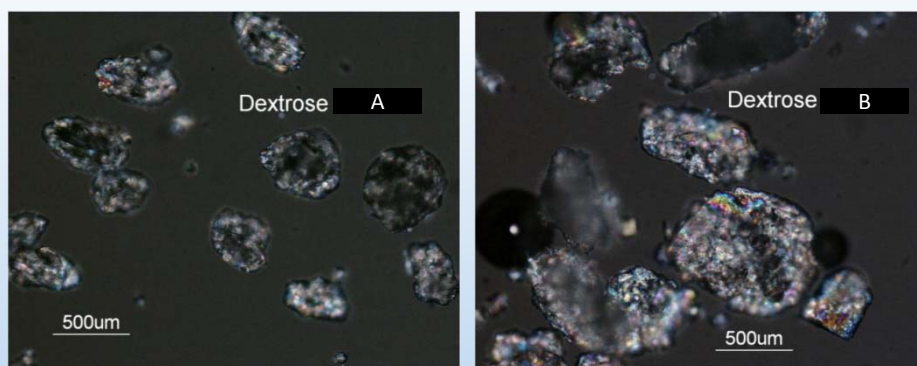
Test Results: Equivalent purity and compression performance



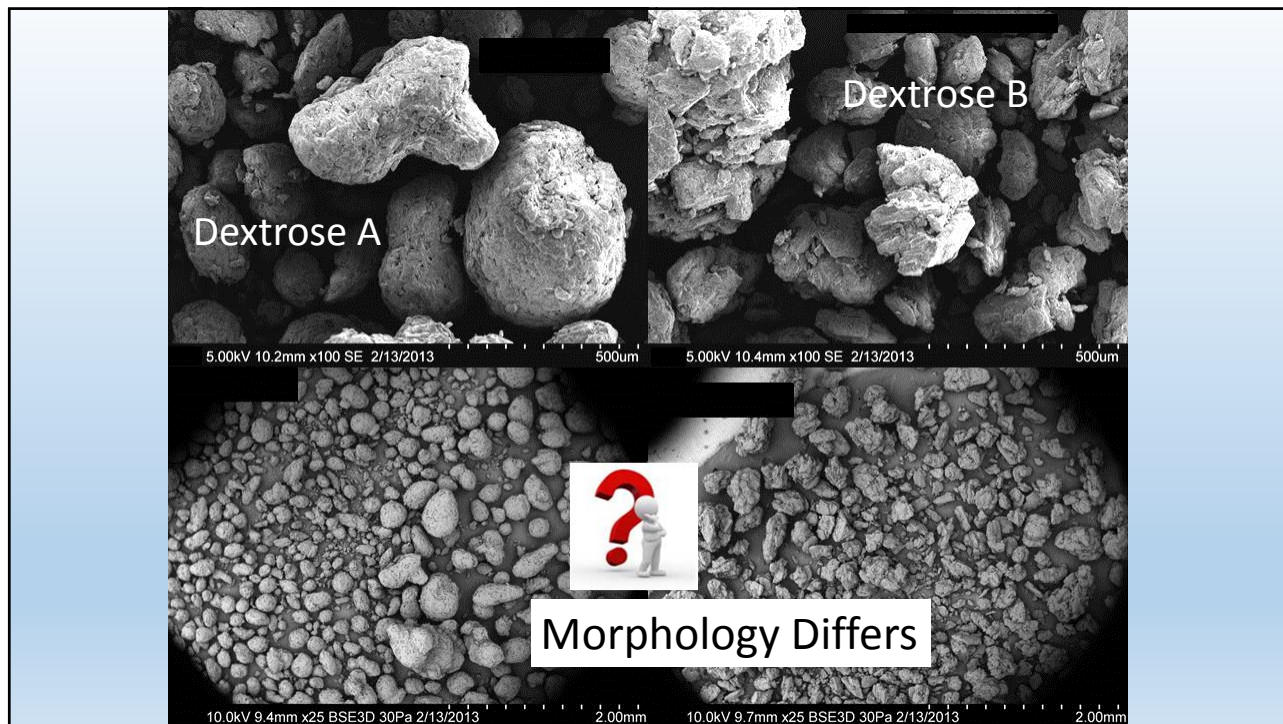
Flow Properties			
		DEXTROSE B	DEXTROSE A
Conditioned Bulk Density (CBD)	g/ml	0.64	0.71
Basic Flow Energy (BFE)	mJ	1075	365
Stability Index (SI)		1.13	1.28
Flow Rate Index (FRI)		1.17	1.03



Dextrose Lot A has improved Flow



✓ Equivalent Crystal Structure



## Case Study Outcomes – Dextrose Functionality

- Modified blending process was used to accommodate the different morphology of the Dextrose A and solve capping problem in the herbal formula
- The flow improvement from Dextrose A was realized in **other** formulas resulting in several improved run rates and related cost savings

## Co-processed excipients



The International Pharmaceutical Excipient Council (IPEC) definition of a co-processed excipient is “a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change”.

IPEC-Americas, Co-processed Excipients Workshop April 29th 2013

## *Potential of Functional- Aka (co-processed) Excipients*

### *Dosage Formulators perspective:*

- Excipient that may positively influence the physical characteristics of a powder blend containing active ingredients and /or the characteristics of the resulting finished tablets or capsules.
- Powder Bed: powder flow    Tablet: content uniformity
 

hygroscopicity	hardness
compressibility	friability
loading capacity	

## Functional (co-processed) Excipients for Nutrition

- Formed by combining two or more established excipients using an appropriate process (co-processing)
- Goal is formation of excipients with superior properties compared to the simple physical mixtures of their components
- Main aim of co-processing is to obtain a product with added value related to the ratio of its functionality/price
- *Regulatory:* Globally – for Nutrition categories, there is no uniform regulatory criteria for approval of use. Can often list co-processed material as two separate ingredients if the “intimate mixture” has no chemical change

Examples of Co-processed Functional Excipients

TRADE NAME	ADJUVANTS	MANUFACTURER
Cellactose	MCC,Lactose	Meggle,Germany
Starlac	Lactose, Maize Starch	Roquette,France
Avicel CE 15	MCC, Guar gum	FMC, USA
Prosolv	MCC, Colloidal Silica	Penwest, USA (JRS Rettenmaier , Germany)

### Key Considerations:

- Fixed ratio of components might not be suitable for all formulations
- Most are intimate mixtures in a fixed ration – not a new chemical entity
- Many functional excipients do not yet have a specific USP Monograph but rely on monographs for the individual adjuvants.
- IPEC is drafting a guideline to facilitate development and adoption of co-processed excipients

# Regulatory Considerations in Excipient choice



## Regulatory Guidances for Global Nutrition - *just a few that must be considered*

- WHO
- British Pharmacopoeia
- US Pharmacopoeia
- European Pharmacopoeia
- China Pharmacopoeia
- China GB National standards
- Canada Health- Natural and Non-prescription Health Products Directorate (NNHPD)
- Australia TGA ( Therapeutic Goods Administration)
- Japan Pharmacopoeia
- Codex Alimentarius
- ICH
- Korea HFF Codex
- Japan Positive list for use in foods (not a drug ingredient)





## Registration Certifications May Be required

Certification requirements often apply to excipients as well as active ingredients

- GMO Free
- Halal
- Kosher
- WADA Compliance
  - (World Anti Doping Agency) country and product specific



## More Challenges for Global Formulation

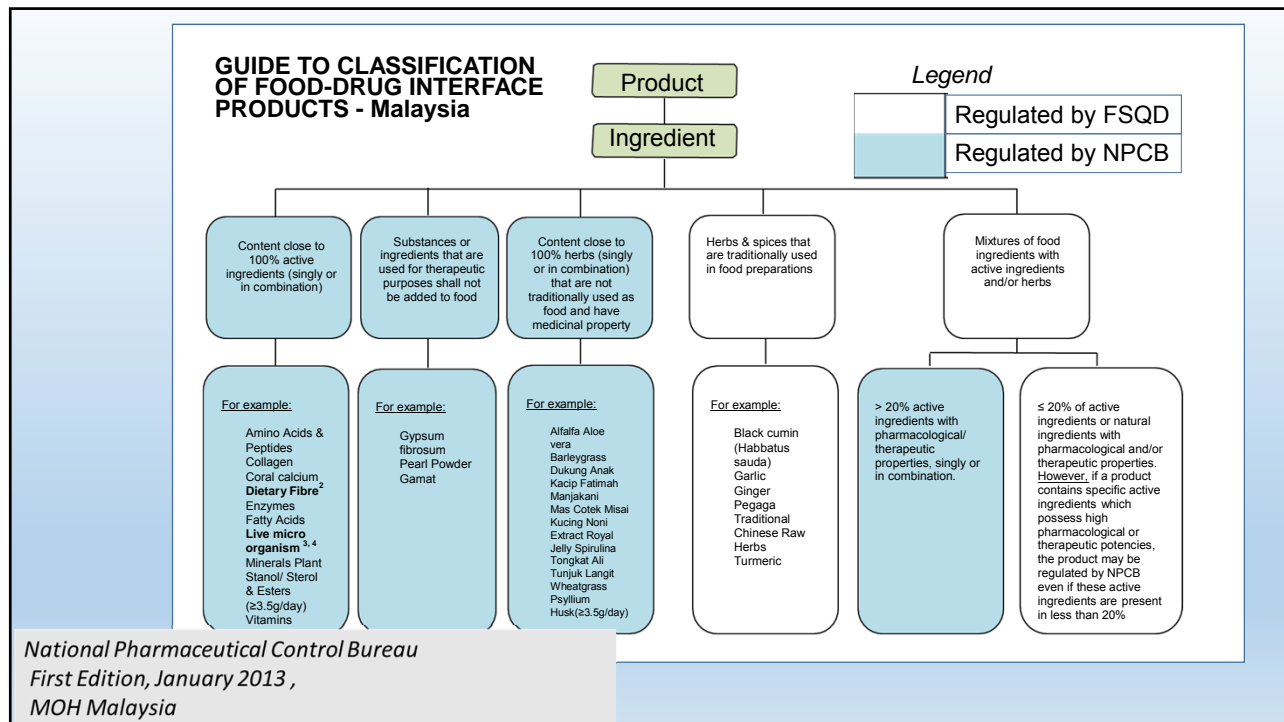
- Registration category/classification
  - According to claims and ingredients the formula may fit into different categories by country
- Registration complexity varies by category and country, dossier requirements vary greatly
- Testing requirements for finished products, as well as ingredients and excipients are not uniform

- Dietary Supplement
- Food
- NHP- Compendial
- NHP- Non Compendial
- Health Functional Food
- Tablet Food
- Health Food
- General food
- Drug
- Traditional Chinese Medicine
- OTC
- Food Supplement
- Traditional Medicine
- Complimentary Medicine
- Functional Food
- Novel Food
- Phytotherapeutic
- Food complement
- Natural product
- Natural Products, Drug
- Herbals
- Nutrient Supplement
- Food for Specified Health Uses

*Nutrition Classifications (not comprehensive)*

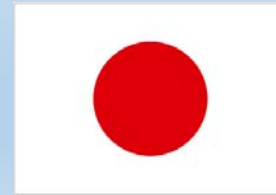
### *Example: Malaysia*

- Four nutrition categories- Functional Foods, Traditional Medicine, OTC, Health Supplement.
- Many Products fall into the Food Drug Interface (FDI)
- Depending on characteristics and ingredients, they may be regulated by the National Pharmaceutical Control Bureau (NPCB) or the Food Safety and Quality Division (FSQD) of the Ministry of Health



## Several Countries have their own testing requirements or “positive list” that impact excipient choices

- Global Markets do not always reciprocate the USP standards for excipients
  - China- CHP, MOH, GB Guobiao, or “National Standard”
  - Korea, HFF (Health Function Food Code) and MFDS (Ministry of Food and Drug Safety) re-org March 2013
  - Japan, JFHA- Japan Health Food Association (positive list for food additives)



## Towards Global Harmonization

### Global Information, Science and Regulation



- IADSA is the leading international expert association regarding the globalization of food supplement markets and increasing regulatory challenges.
- Includes food supplement associations from 6 continents,
- IADSA aims to build an international platform for debate and a sound legislative and political environment for the development of the food supplement sector worldwide.

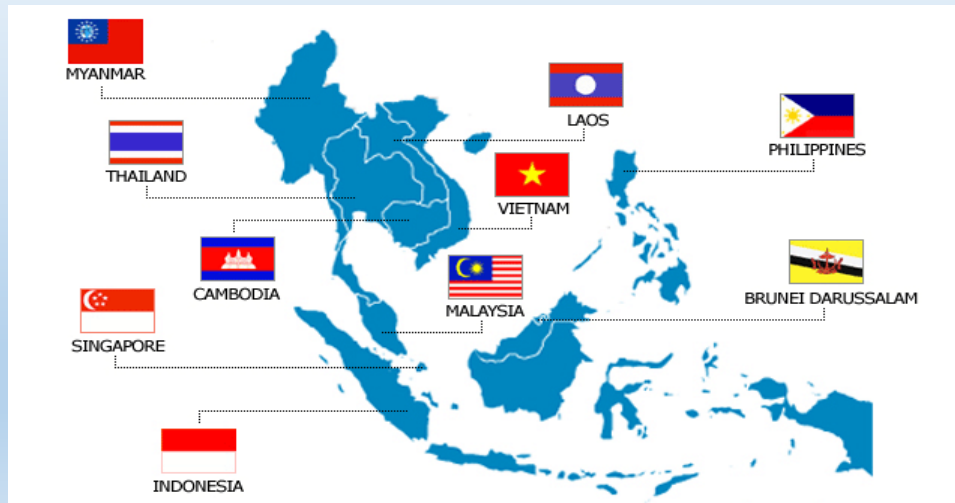
## Allowance of Ingredients

Reference: **IADSA**  
International Alliance of Dietary/  
Food Supplement Associations

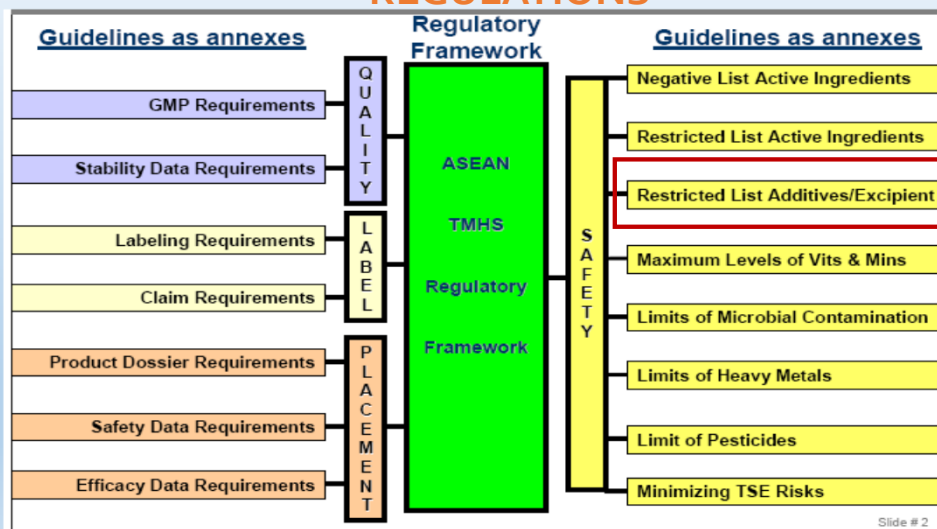
Market	Allowed "Existing" Ingredients	"New" Ingredients
<b>EU</b>	<ul style="list-style-type: none"> <li>• Used before 1997 (FS Directive)</li> <li>• Vitamin &amp; Mineral positive list</li> <li>• Other Ingredients regulated at Member States level – some Positive</li> </ul>	<ul style="list-style-type: none"> <li>• Novel Ingredient authorization</li> </ul>
<b>USA</b>	<ul style="list-style-type: none"> <li>• Used before 1994 (DSHEA)</li> </ul>	<ul style="list-style-type: none"> <li>• New Dietary Ingredient (NDI) notification (exempt from notification if in food supply)</li> </ul>
<b>ASEAN</b>	<ul style="list-style-type: none"> <li>• Negative list</li> <li>• Restricted condition of use list</li> </ul>	<ul style="list-style-type: none"> <li>• Self assessment of safety and not meet criteria for inclusion in Negative list</li> </ul>
<b>Japan</b>	<ul style="list-style-type: none"> <li>• Positive list for use in foods</li> <li>• List of not drug ingredient</li> <li>• Part of food supply</li> </ul>	<ul style="list-style-type: none"> <li>• Self or Government assessment if food or drug ingredient</li> </ul>
<b>Korea</b>	<ul style="list-style-type: none"> <li>• Health Functional Food (HFF) Code</li> <li>• Part of food supply</li> </ul>	<ul style="list-style-type: none"> <li>• New HFF Ingredient authorization</li> </ul>
<b>China</b>	<ul style="list-style-type: none"> <li>• Positive list for use in foods &amp; drugs</li> <li>• Positive list for use in health foods</li> <li>• Negative list for use in health foods</li> <li>• Part of food supply</li> </ul>	<ul style="list-style-type: none"> <li>• Must comply to regulations and process for new ingredients</li> </ul>

# ASEAN (Association of Southeast Asian Nations)

10 Member States  
Approx 520 million population



## ASEAN HARMONIZATION of Traditional Medicine Health Supplement (TMHS) REGULATIONS



## ASEAN Proposal: Global List of *Restricted Additives & Excipients*

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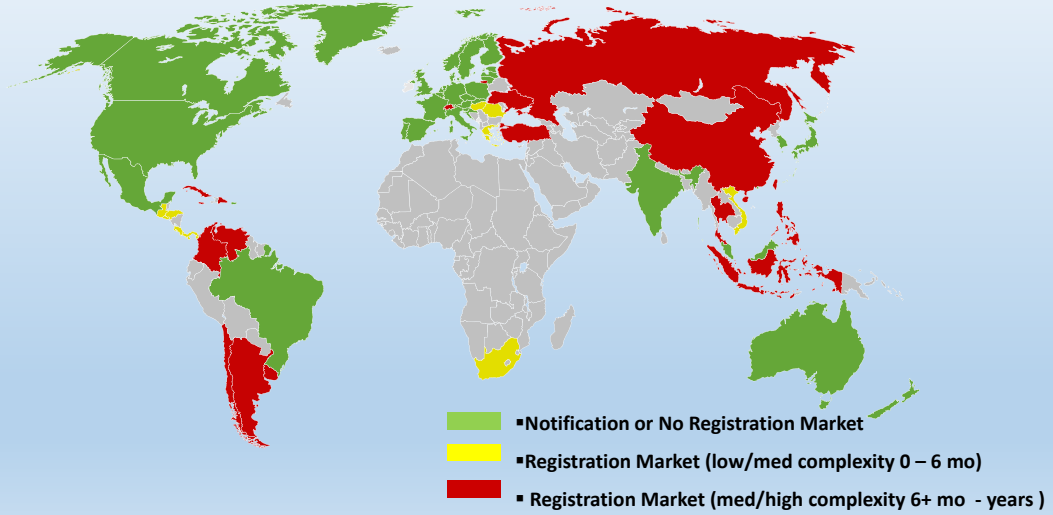


- Currently many countries and regions maintain “positive lists”
- ASEAN Guiding principles for entry of additives and excipients into ASEAN List of Restricted Additives and Excipients
  - Development stage
  - Not listed in CODEX or any international reference

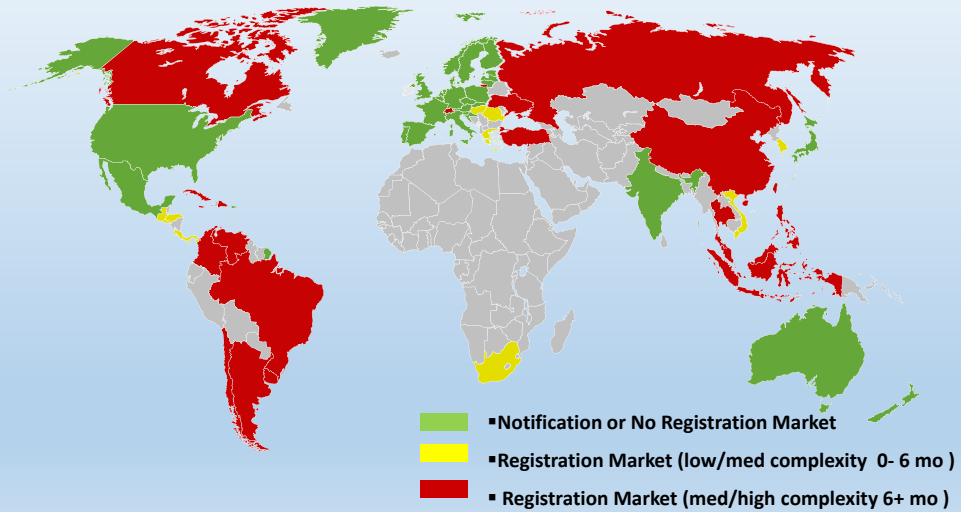
## Regulatory trends: Global Formulation (Nutrition)

- Regulatory scrutiny is increasing, but with regional differences
- Increased focus on substantiation of health claims through clinical studies
- Food safety issues will result in more restrictions
- Some regions heading towards globally harmonized rules (EU, ASEAN)
- \*However, regulatory harmonization delayed in some regions due to local interests

Nutrition – Food Products In Market Registration timing  
(Powders, Drinks and Bars)



Nutrition: Categories Excluding Food Products – In Market  
Registration Timing (Health Supplements, TCM's, Health Foods and  
items considered "Drugs/Medicines")



## Conclusions: Global Formulation



- Correct choice of excipients can be a key driver in formulation and economic success –
- Excipients have a very broad influence on tablet performance: including both physical and physiological characteristics
- If regulatory issues can be addressed, functional excipients will have a significant positive impact on formulation and process development (QbD)
- Globally, guidance for finished product specifications are not uniform.
- Globally excipient monographs and specifications are not uniform
- Globally excipient acceptability and use restrictions are not uniform

## Thanks for your Contributions to This Presentation!

- ***Kaela Napolitano***- Formulation Scientist (NBS)
- ***Mark A. Smith and Haywood Ware*** – Analytical Scientists- Forensic Analysis Laboratory
- ***Michele Stout*** - Senior Principal Regulatory Policy Coordinator ( RPI Group)





Thank you!

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