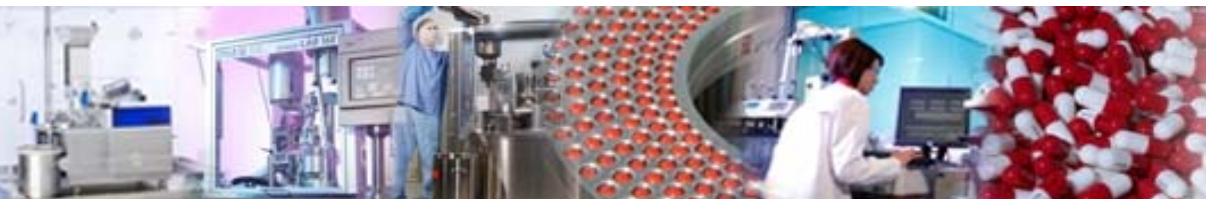


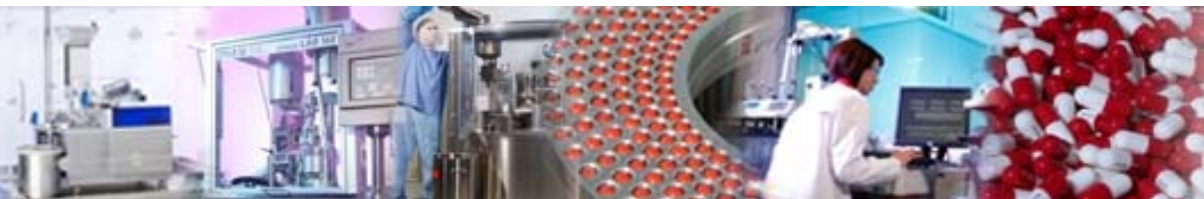
Evaluating Capsule Manufacturing & Comparator Blinding Techniques for Clinical Trials



Agenda



- Almac Introduction
- Industry Perspective
- Blinding and Over-encapsulation
- Preparation of blinded investigational medicinal products
- Evaluation of manufacturing techniques and technologies
- The importance of analytical assessment
- Case study
- Alternative approaches
- Q & A



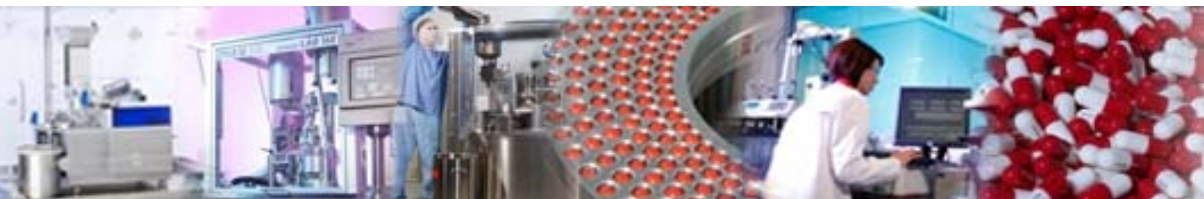
Industry Perspective



- The pharmaceutical industry is in a state of change
 - Faster, more effective, more value for outsourcing due to internal and external pressure
 - Move by Pharma/Biotech to introduce virtual models requiring strategic outsourcing

- Continued globalization of trials
 - Purchase of global comparator supply
 - Choice of materials used in excipient / shells

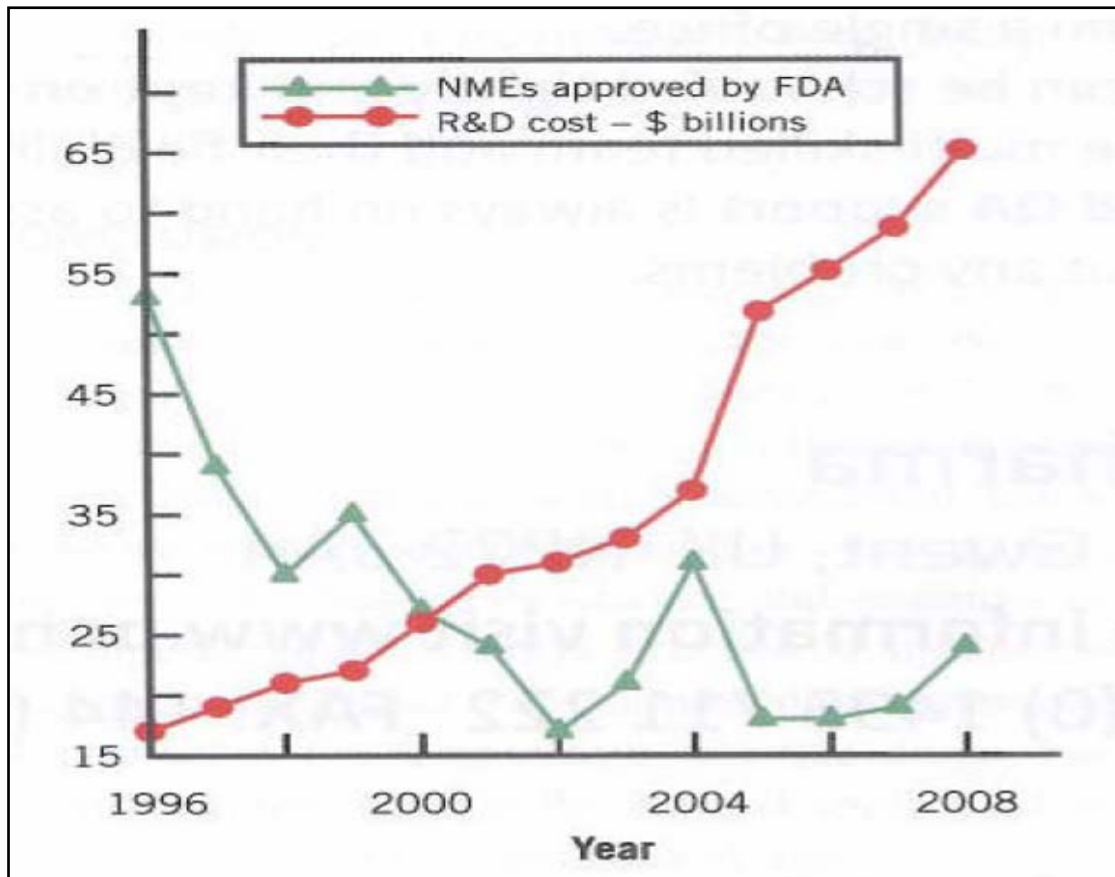
- Increasing complexity of trials and dosing regimes
 - Customized nature of many clinical supply requests



Industry Perspective



R & D expenditure for Pharma Companies Compared to New Molecular Entities Approved by the FDA



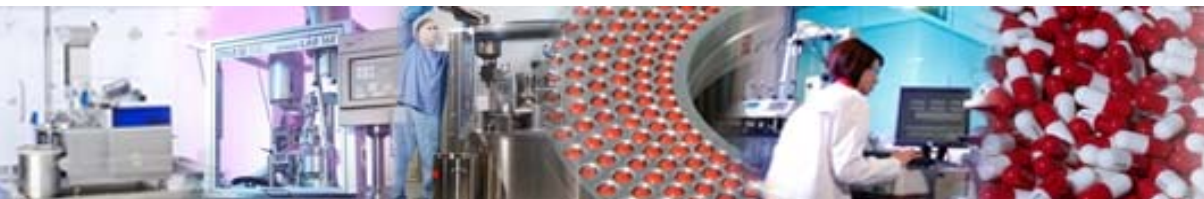
Source : International Clinical Trials May 2009

Relevance to over

- encapsulation / blinding ?



- Over-encapsulation can be over-looked as part of the supply chain
 - Over-encapsulation may be managed by a manufacturing group and not clinical supply teams
- Complexity of dosages can require specific unique solutions that may not be on the agenda for clinical teams or built into timelines
- Comparator supply can be challenging – increases with intensity as the trial progresses from start up to maintenance
- Important to select backfill that will not impact upon product or processing
- Build efficiency in from the outset



Definitions



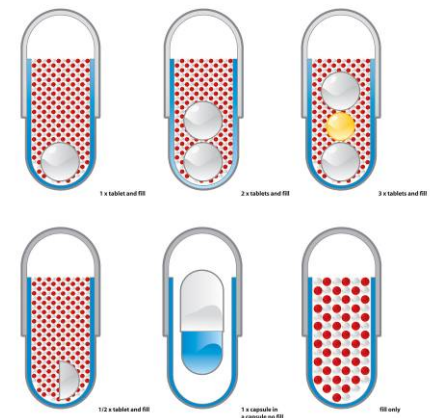
Blinding

- A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).¹
- In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the product in accordance with the instructions of the sponsor.¹

Over-encapsulation

- Placing a product or multiple products into a hard gelatin/ HPMC capsule, which may or may not be filled with inactive bulk agent or excipient.

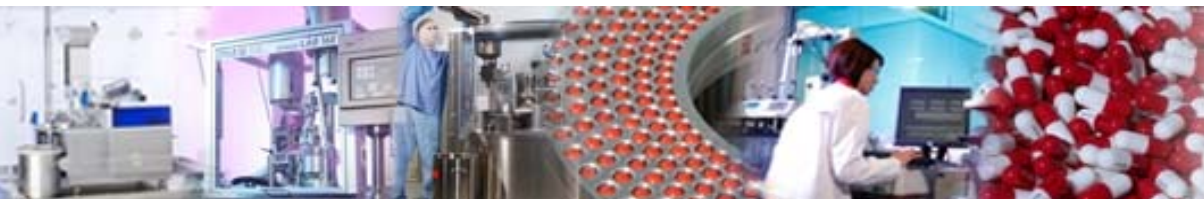
1 Rules and Guidance for Pharmaceutical Manufacturers and Distributors - Annex 13



Benefits of over-encapsulation



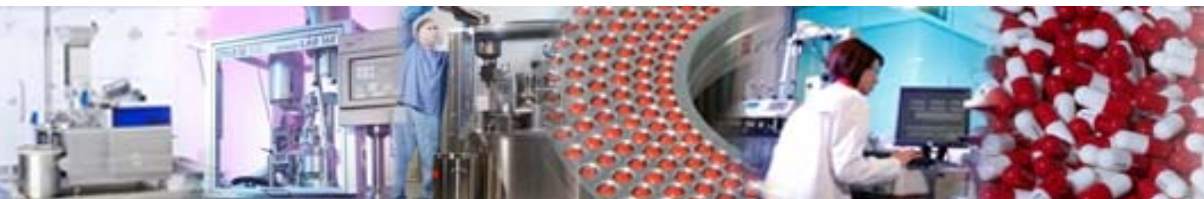
- Widely accepted blinding technique
 - Opaque colours used to obscure input components
- Provides visually identical product
 - Investigational Medicinal Product (IMP), Comparator and Placebo
 - Removes the potential for study bias and maintain study integrity
 - Standardisation of future packaging design



Impact & Requirements of GMP / Annex 13



- Understanding and maintaining GMP is critical to successful over-encapsulation
- Over-encapsulation removes bias, but raises other challenges
- Annex 13 defines data required to support this process and assign expiration dates
 - e.g. Stability, Comparative Dissolution, Bioavailability
- Critical to demonstrate no significant change to product characteristics following over-encapsulation

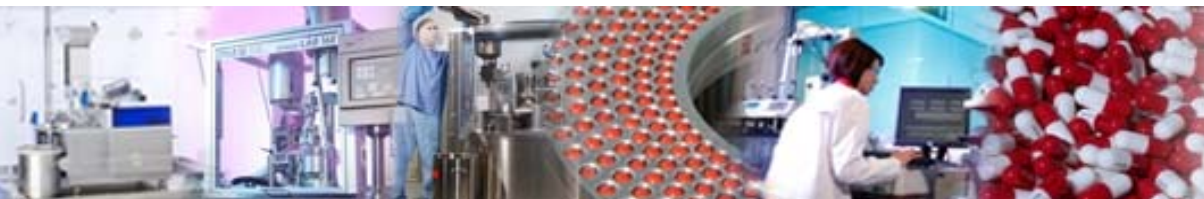


Key Considerations

Comparator Selection



- Market leader typically selected
- How available is this product
 - Consider lead-time for delivery and expiration dates
 - Can it be used across global markets?
- Is it a suitable candidate for over-encapsulation e.g.
 - Controlled release/enteric coated product
 - Physical shape and size
 - Friability/Hardness of the input product will determine feasibility for automation

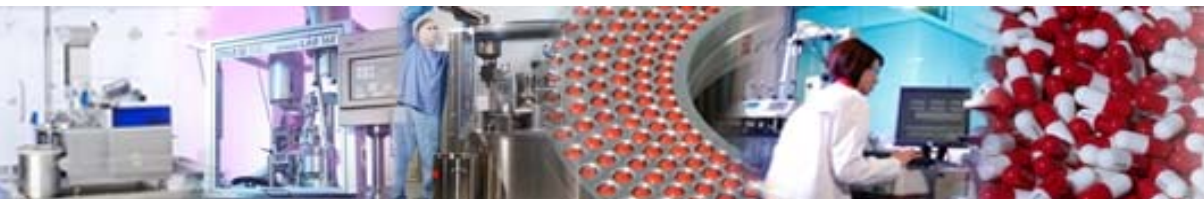


Key Considerations



Blend / Excipient Usage

- Used to prevent rattling and fill capsule void
- What excipient should be used?
 - Important that this be inactive
 - Various off the shelf products available e.g. Powder, Pellets, Sugar Spheres
 - Blends may be utilised e.g. Lactose and Magnesium Stearate
 - Excipient chosen may impact upon machine type used

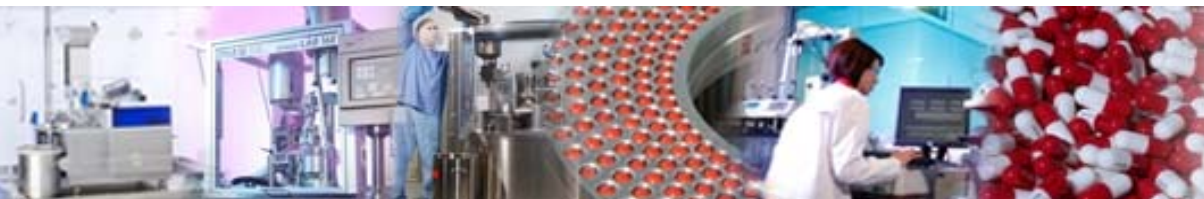


Key Considerations



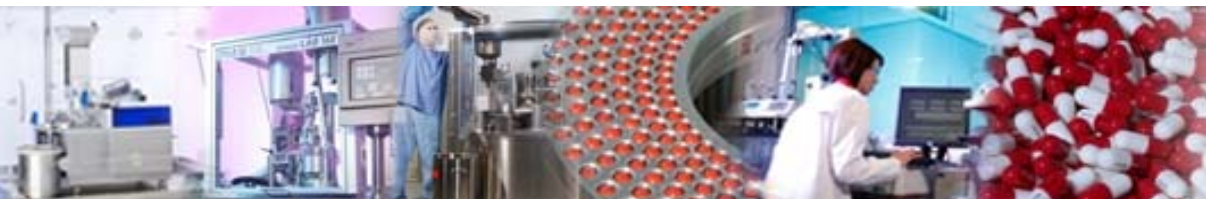
Capsule Selection

- Wide range of hard gelatin capsules available
 - Wide bodied, opaque capsules designed for use within clinical trials
 - Important to ensure colour chosen completely obscures input material
 - Does the comparator/IMP fit within capsule shell without distorting shape?
 - Is the shell a universally accepted colour
 - What is an acceptable daily intake for the capsules/courants?
 - Always useful to view a representative sample



Evaluating Capsule Manufacturing Techniques

Manual Processing



Manual Encapsulation		
		Manual
Batch Size		100 – 2,000
Applications	Active Fill	✓
	Placebo to Match	✓
	Comparator / Overencap & Backfill	✓

Manual Encapsulation

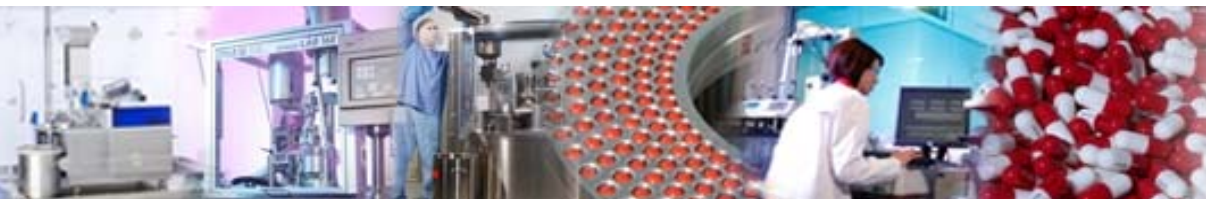


- Batch Size 100-2000 caps
- Hand-Filling (Analytical balance)
- Applications
 - Formulation development
 - FiH supplies
 - Early stage clinical batches



Advantages	Limitations
Fast set-up	Time consuming
No clean-down verification method	Balance accuracy
	<5mg challenging

Evaluating Capsule Manufacturing Techniques **Semi Automated Processing**



Semi Automated Encapsulation Technology

		Capsule Boards	Elanco
Batch Size		500 – 5,000	500 – 500,000
Applications	Active Fill	✓ *	✓
	Placebo to Match	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓ *

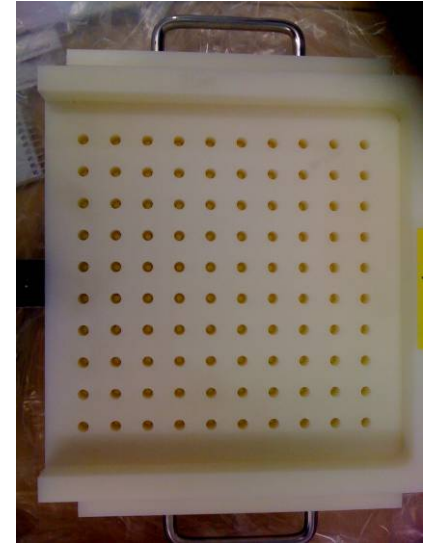
Semi Automated Encapsulation Technology

		Capsule Boards	Elanco
Batch Size		500 – 5,000	500 – 500,000
Applications	Active Fill	✓ *	✓
	Placebo to Match	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓ *

Capsule Boards



- Batch size 500-5000
- Applications
 - Formulation Development
 - Early stage clinical trials



Advantages	Limitations
Faster than hand filling	Precision engineering required
No clean-down verification method	Demixing / Adhesion
	<100mg challenging

Semi Automated Encapsulation Technology

		Capsule Boards	Elanco
Batch Size		500 – 5,000	500 – 500,000
Applications	Active Fill	✓ *	✓
	Placebo to Match	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓ *

Elanco



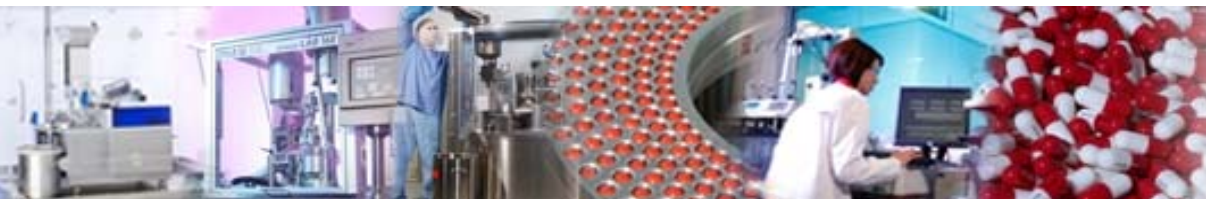
- Batch size 500 - 500,000
- Applications
 - All stages of Clinical Trials
 - Single and Multi-product filling



Advantages	Limitations
Tool Sets for all capsule sizes	Specific tool sets may be required for each input unit shape & size
Handle all shapes & sizes of input unit	
Suitable when breaking a large input unit in 2 to fit in shell	

Evaluating Capsule Manufacturing Techniques

Automated Processing



Automated Encapsulation Technology

		Xcelodose / Xcelodose 600	Intermittent Motion Dosator IMA Lab 16 / IMA Zanasi 40	Harro Hofliger Modu-C	MG2
Batch size		100 – 5,000	10,000 – 1,500,000	20,000 – 1,500,000	750,000 +
Applications	Active Fill	✓ *	✓ *	✓	✓
	Placebo to Match	✓	✓	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓	✓ *	✓ *

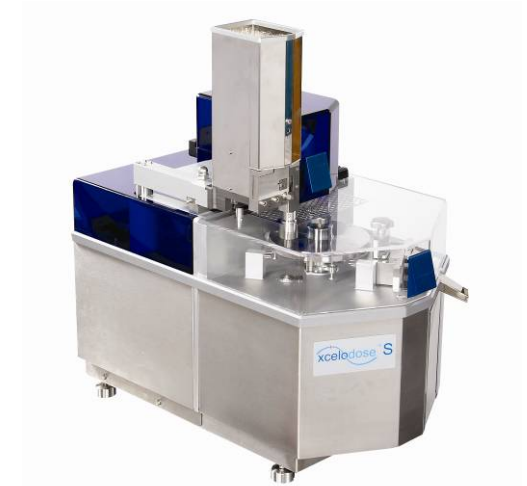
Automated Encapsulation Technology

		Xcelodose / Xcelodose 600	Intermittent Motion Dosator IMA Lab 16 / IMA Zanasi 40	Harro Hofliger Modu-C	MG2
Batch size		100 – 5,000	10,000 – 1,500,000	20,000 – 1,500,000	750,000+
Applications	Active Fill	✓ *	✓ *	✓	✓
	Placebo to Match	✓	✓	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓	✓ *	✓ *

Xcelodose



- Batch size 100 – 5,000
- Applications
 - FiH
 - Early clinical trials



Advantages	Limitations
High accuracy	Development for each blend / API
Low dose (0.1mg)	200 – 600 capsules per hour
No cleaning verification method required	

Automated Encapsulation Technology

		Xcelodose / Xcelodose 600	Intermittent Motion Dosator IMA Lab 16 / IMA Zanasi 40	Harro Hofliger Modu-C	MG2
Batch size		100 – 5,000	10,000 – 1,500,000	20,000 – 1,500,000	750,000+
Applications	Active Fill	✓ *	✓ *	✓	✓
	Placebo to Match	✓	✓	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓	✓ *	✓ *

I.M.D.P Machine



Zanasi Lab16

- Batch size 10,000 – 1,500,000
- Application
 - All stages of clinical trials



Advantages	Limitations
Up to 16,000 capsules per hour	Cleaning verification methods required
Good scalability	Generally >100mg fill
Powders / tablets / pellets	Minimum blend 1Kg

Automated Encapsulation Technology

		Xcelodose / Xcelodose 600	Intermittent Motion Dosator IMA Lab 16 / IMA Zanasi 40	Harro Hofliger Modu-C	MG2
Batch size		100 – 5,000	10,000 – 1,500,000	20,000 – 1,500,000	750,000+
Applications	Active Fill	✓ *	✓ *	✓	✓
	Placebo to Match	✓	✓	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓	✓ *	✓ *

Harro Hofliger Modu-C



- Batch size 20,000 – 1,500,000
- Applications
 - All stages of clinical trials



Advantages	Limitations
Dose input units or excipients only	Longer set-up time
Dose accuracy	Only 1 type of input unit can be inserted
Dose down to 25mg for inhalation	

Automated Encapsulation Technology

		Xcelodose / Xcelodose 600	Intermittent Motion Dosator IMA Lab 16 / IMA Zanasi 40	Harro Hofliger Modu-C	MG2
Batch size		100 – 5,000	10,000 – 1,500,000	20,000 – 1,500,000	750,000+
Applications	Active Fill	✓ *	✓ *	✓	✓
	Placebo to Match	✓	✓	✓ *	✓ *
	Comparator / Overencap & Back Fill		✓	✓ *	✓ *

MG2



- Batch size 750,000 +
- Application
 - All stages of clinical trials



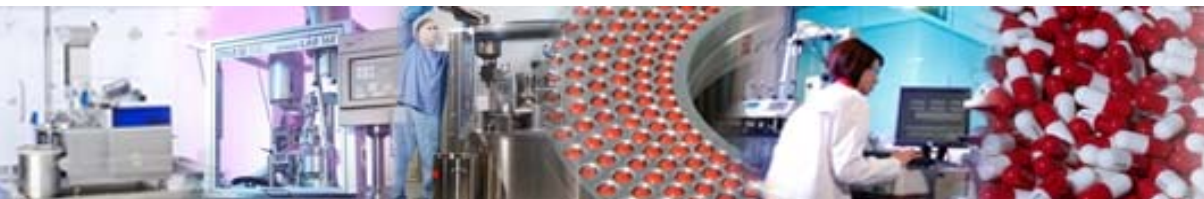
Advantages	Limitations
Can be used for dosing input units or excipient only	Excipient must contain a lubricant (commonly Mag Stearate)
High speed continuous motion –up to 20,000 capsules per hour	Input units must be round biconvex & specific change parts are required
Weight controlled automatically	

Evaluation of Manufacturing Techniques & Technologies

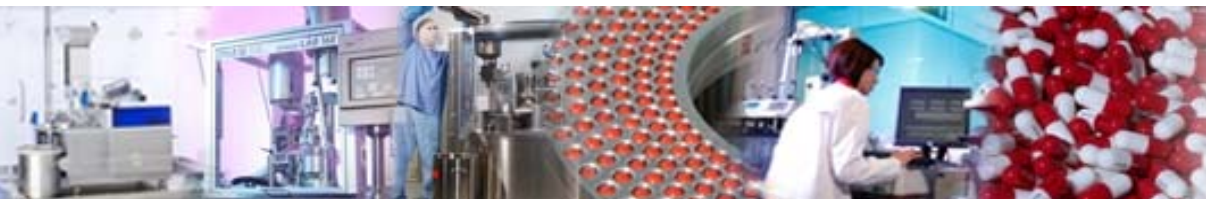


Finish off checks performed on completion of all operations:

- Checkweigh
- Dedusting
- Metal check



The Importance of Analytical Assessment



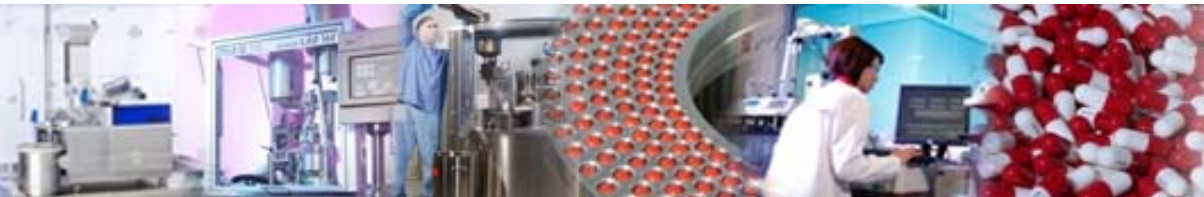
Stability



Additional stability assessment of OE product should be considered

- Excipient interaction
 - Usually limited by selecting a backfill from tablet excipients
 - Although, additional backfill concentration may still impact stability

- Capsule shell
 - Moisture from capsule shells may support degradation
 - Capsule shell may be incompatible with the API



Analytical considerations



- Comparator Analytical Method Sources
 - Pharmacopeia
 - Verification?
 - Published articles
 - Limited Validation
 - Full Method development
 - Stability indicating
 - Limited Validation



- Analytical Reference Standard Source?
 - Pharmacopeia
 - Commercial source
 - e.g. API supplier / Sigma
 - Comparative to reference sample



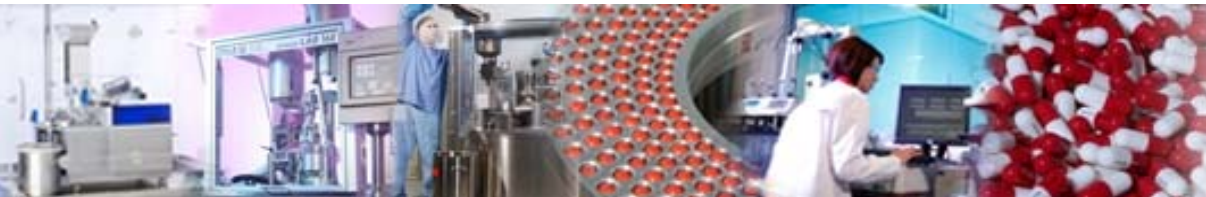
Analytical Method performance

Validated Analytical Methods may be effected by OE format

- Specificity
 - Addition of excipient (backfill) and capsule shell may cause interference
 - Care when selecting Shell colours

- Sample extraction
 - Accuracy / Repeatability of recovery may be effected

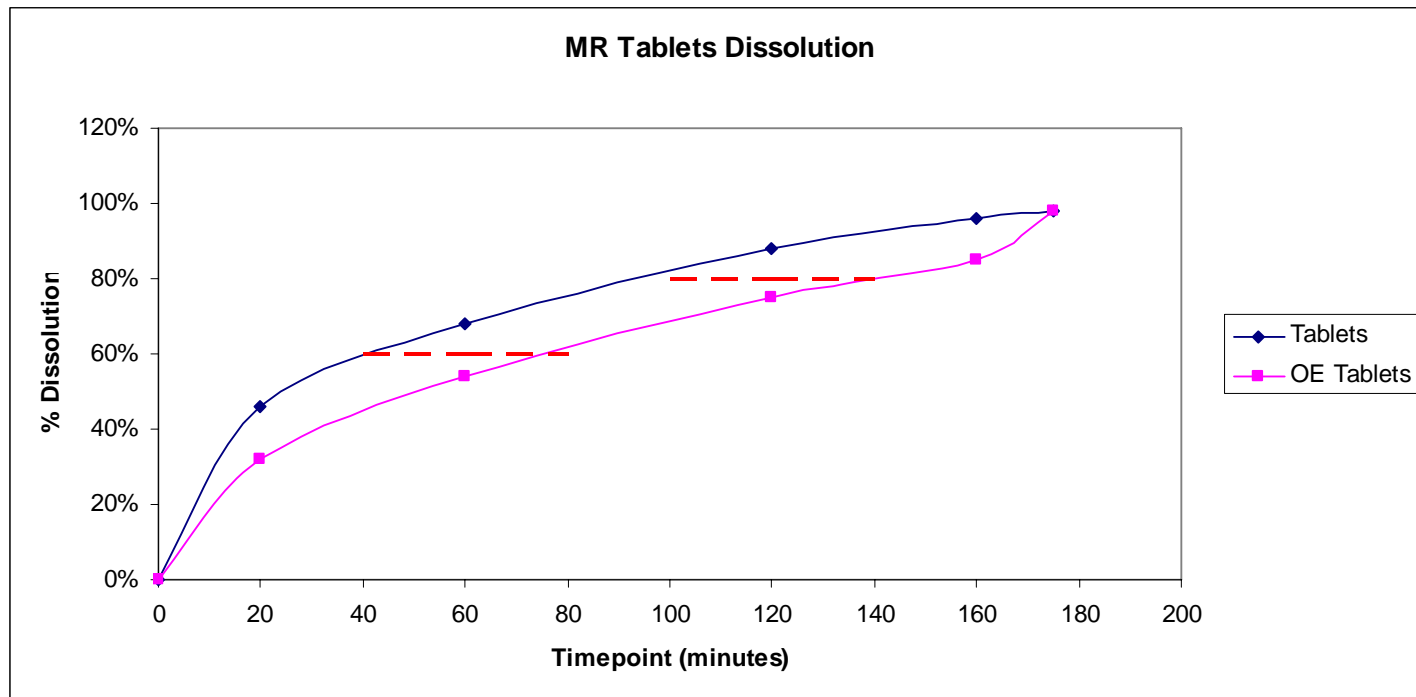
Recommend – Limited validation of above parameters



Dissolution

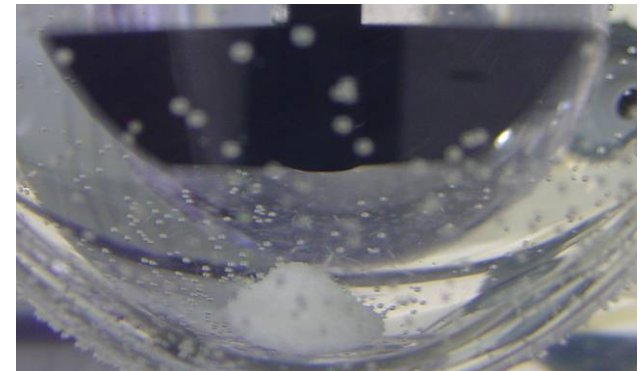
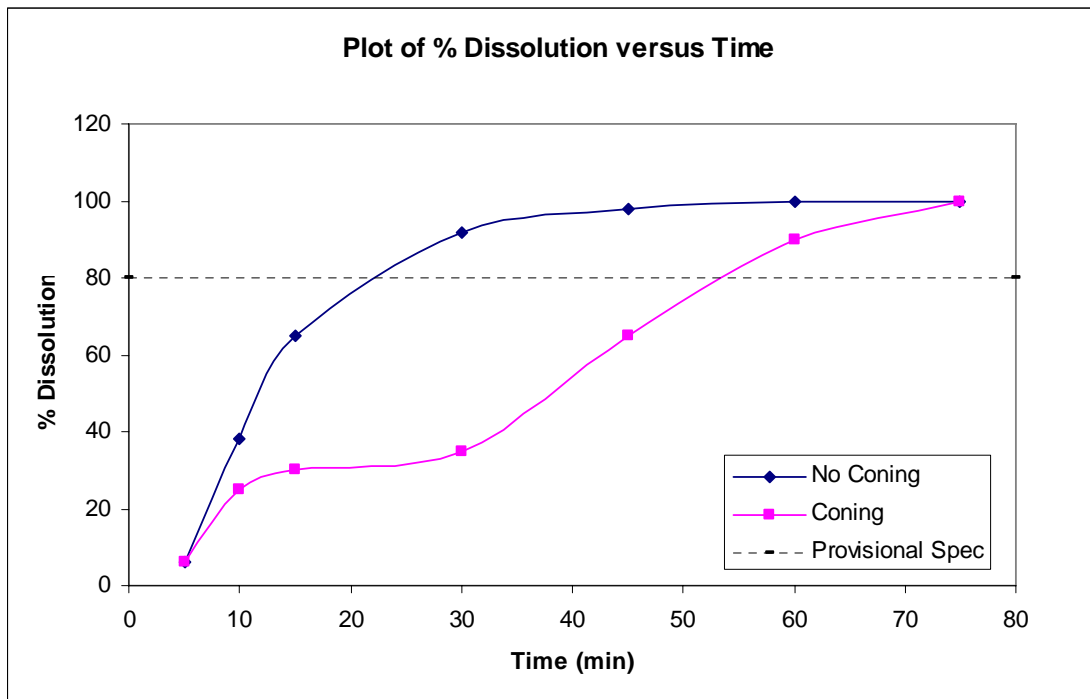


- Capsule Shell / Excipients may delay dissolution
 - Resulting in specification failure – Bio relevance?
 - Comparative assessment is required



Dissolution

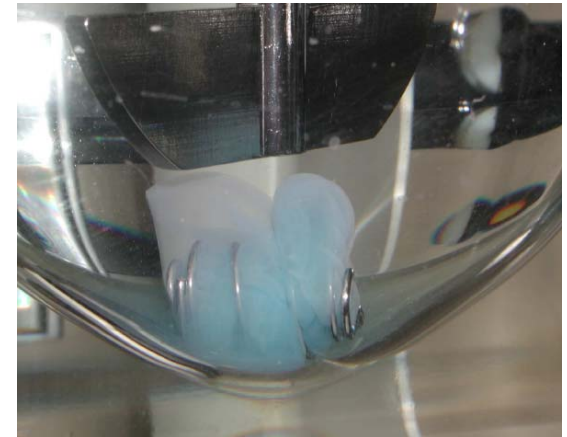
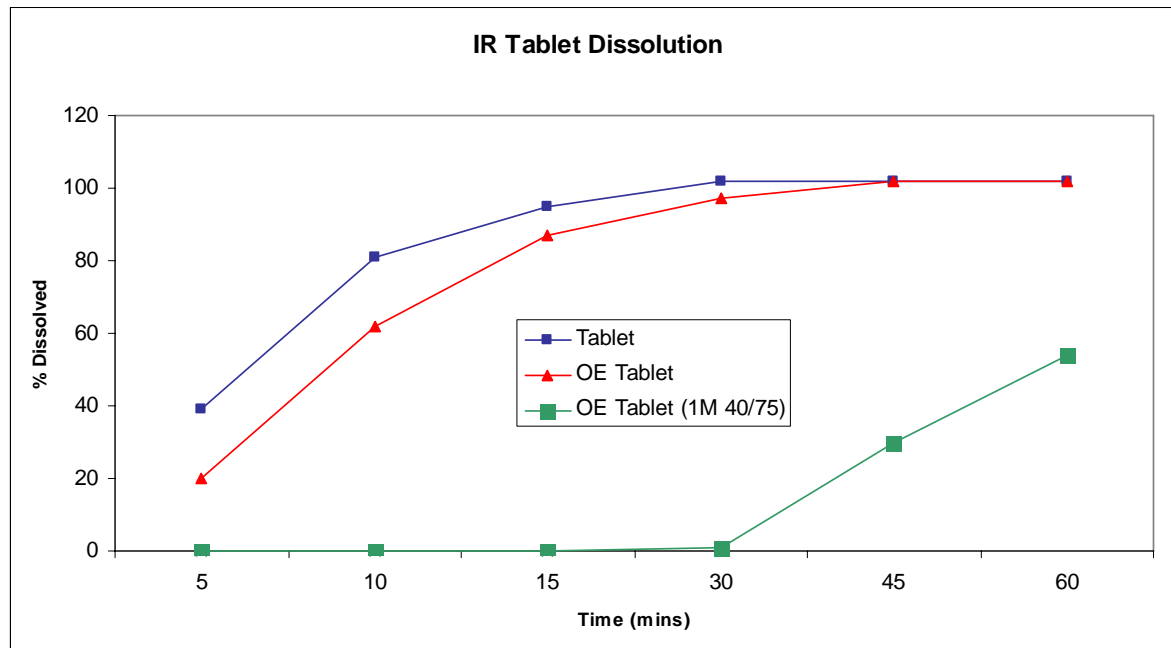
- Apparatus parameter modifications
 - Additional excipient backfill may cause coning



Dissolution

Cross linking

- Gelatine can be incompatible with some materials
- Shell solubility can reduce on storage



Alternative Blinding Techniques



Technique	Concept	Pros	Cons
Mill and Fill	Grinding of tablets prior to placing a controlled volume of ground tablets into a capsule.	<ul style="list-style-type: none">• Allows selection of smaller capsule shell• Blinding method for tablets that would not fit into available capsule shells	<ul style="list-style-type: none">• Content uniformity analysis required• Substantial analytical support needed to confirm product quality• Cannot be used in conjunction with enteric coated tablets• Rarely used within the industry
Tablet Splitting	Split tablets into two halves, prior to placing into a capsule	<ul style="list-style-type: none">• Allows selection of smaller capsule shell• Blinding method for tablets that would not fit into available capsule shells	<ul style="list-style-type: none">• Analytical support required to confirm quality i.e. comparative dissolution, stability testing and bioavailability• Cannot be used in conjunction with enteric coated tablets

Alternative Blinding Techniques



Technique	Concept	Pros	Cons
Film coating	Coating tablets with a film to obscure commercial markings	<ul style="list-style-type: none">• No over-encapsulation required	<ul style="list-style-type: none">• May have an effect on dissolution profile• Will not hide embossed or debossed markings• May need several coats to completely obscure marking• Not suitable for friable products
Removal of markings	Use of a solvent to remove commercial markings or logos from tablets or capsules	<ul style="list-style-type: none">• No over-encapsulation required	<ul style="list-style-type: none">• Analytical testing required to confirm absence of solvent following processing• Not suitable for enteric coated product• May see colour variations between areas where solvents have and have not been used

Preparation of Blinded IMP



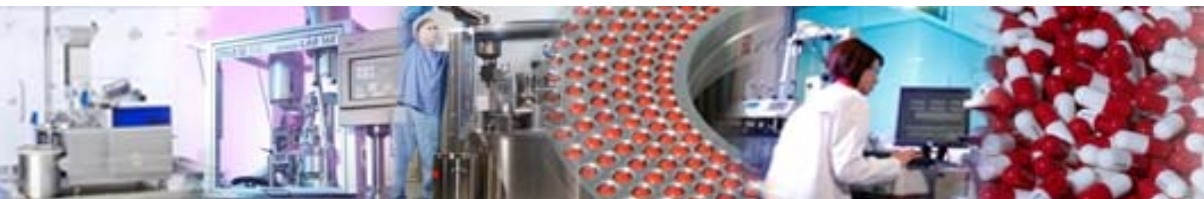
Case Study

- Placebo capsules for inhalation
- 25mg fill weight +/- 10%
- Size 3 shell weighing 50mg +/- 4mg
- Checkweigh would not detect under or over filled capsules
- Specially manufactured drum dosator used
- Weights monitored and controlled by enhanced IP checks

Conclusion



- Changing Industry requirements – greater levels of outsourcing
- Over-encapsulation/blinding is central to double blind clinical trials
- Key considerations
 - Input Product, Blend/Excipient and Capsule Shell
 - Understand equipment and process used
 - Analytical data is critical to support integrity of study results
- Each product is different but the same principles can be applied!



Presenters



If you have any further questions or would like to contact any of today's presenters directly please find contact emails below:

- Colin Lorimer, Senior Formulation Scientist
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