CONTINUOUS MANUFACTURE: A REAL TIME APPROACH TO MANAGING QUALITY AND ENHANCE SUPPLY CHAIN EFFICIENCIES

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CONTINUOUS MANUFACTURE: A REAL TIME APPROACH TO MANAGING QUALITY AND ENHANCE SUPPLY CHAIN EFFICIENCIES

- Overview of Epsilon Pharmaservices

- Who we are

- Overview of our work in the area of continuous processing & PAT Technology

- Run though some examples (whilst maintaining client confidentiality)

- Give an overview of continuous processing technology including benefits and challenges

- Hopefully you can relate the use of PAT to your applications
EPSILON BACKGROUND & SUMMARY OF EXPERIENCES

- Pharmaceutical Design & Integrations Consultancy
- Founded in 1997
- Independently owned Company
- Based in Leicestershire, United Kingdom
- Business model based on – difficult to execute process related projects…. over 750 to date
- 15 years experience mostly repeat business
- Cut and carve high risk projects
- Project capability £1K to over £3 million
- Focus on equipment and process improvement with associated facilities work
- Majority of work is within existing facilities
- Involved in a number continuous projects – both solid and liquid processing technologies
Client responsibility

Traditional Engineering Company Role

Client responsibility

**EPSILON RESOURCES PROVIDED TO MATCH NEEDS**

- Establish project targets
- Test & evaluate available technology
- Produce formal project scope & costing
- Develop project details
- Analyse project H&S impacts
- Project implementation
- Project finalisation
- Post project support
CUSTOMER REFERENCES

Ware Harlow Crawley
BACKGROUND WORK

- Epsilon have an understanding of the issues & concepts in continuous processing and Process Analytical Technology
  - Developed design study for installation at a blue chip client
  - We understand:
    - Granulation/drying from first principles
    - Drying rates/mass balance transfer equations
    - Fluidization calculations (when applicable!)
  - High level review of patents
  - Ongoing detailed review with a number of equipment suppliers
  - Detailed design with suppliers, universities and conduct of trials
  - Controls requirements understood & partnering with Optimal Automation to develop PAT systems
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

- Recent investment on many clients' sites has focussed on:
  - Regulatory and compliance issues (e.g. Hazardous Area Zoning)
  - Process improvements and reductions in production costs

- For a number of clients we have:
  - Investigated and compared traditional manufacturing methods (e.g. wet granulation and fluid bed drying)
  - New continuous manufacturing streams…….
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

We have identified:

- Alternative, proven continuous processing equipment suitable for manufacture high volumes of Pharmaceutical products, to a sufficiently lower unit cost

- That incoming and outgoing materials handling is often overlooked when design of a continuous process is put together. We have worked with our clients on material routings, improving the supply chain for raw materials and the release of product

- Continuous processing has been used in other industries for many years and Epsilon Pharmaservices are developing technologies based upon those used in other industries

- Continuous and High Throughput Manufacturing is aimed at increasing Overall Equipment Efficiencies and reduction in unit production costs by development of High Throughput Processing methods and techniques, complimented by continuous processing

- We have worked on a project with one client where there is an opportunity to increase production capacity.
EXAMPLE 1 - PROJECT SUMMARY BASED UPON CURRENT BATCH PROCESS

Client Came to Epsilon with a Requirement to Raise production Output:

- Our client wanted a new production suite for an extra 1,000 tonnes/annum of product

This production capacity was over and above of their current output:

- They were manufacturing 18 sections per day (180 kg/section) approx 3.3 tonne per day (with 2 operators – 24hr/5day week)

- With Machine downtime, cleaning etc this only equated to a maximum of 500 tonnes/annum.
EXAMPLE 1 - PROJECT SUMMARY BASED UPON CURRENT BATCH PROCESS

What were the main drivers for the client?

These will probably be familiar to most people in the audience today:

- Lower the Unit Cost
- Increase Profitability

By increasing production volume, overheads are shared with other Products…

Therefore there is a Net reduction in unit cost for ALL products on the same site, not just the

Examples of these overheads include:

- Laboratory
- Quality Control
- Quality Assurance
- Warehouse
- Personnel Departments
- Site/Production Management
EXAMPLE 1 - PROJECT SUMMARY BASED UPON CURRENT BATCH PROCESS

- Our client requested that the new system was capable of 1,000 tonnes/annum at 60% utilisation, so allowing for:
  - Clean down
  - 5 day manufacturing/week
  - 3 shift (24hr) operation
  - Overall Equipment Efficiency (OEE)
  - Assume equipment utilisation of 60%

The design basis out of the suite would be 8 tonnes/day (24hr).
(Work back up to an theoretical 365/24/7 Operation = 2920 tonnes/yr)

Design Basis MUST be higher than required to give the desired production capacity
THE FOLLOWING PROCESSES WERE CONSIDERED FOR OUR CLIENTS’ PROCESS

- **Roller Compaction**
  Many high volume, low cost products have a high active concentration within a tablet/capsule
  Material is not particularly plastic
  If higher quality actives are required then costs can be prohibitive
  Roller compaction can, however, form part of a modular system

- **High throughput wet granulation**
  High efficiency suites allow for pre-loading & fast discharge to minimise rate limiting process (granulation and subsequent drying)

- **Fluid bed spray granulation** was discounted early on based on low throughput capability

- **Continuous manufacturing**
  Known technology on the market incorporating:
  - Screw granulators
  - True continuous drying
  Controls incorporating:
  - NIR PAT
  - Control System
  - Data Capture
  - Analysis Software
EXAMPLE 2 - CONTINUOUS PROCESSING USING LIQUID BASED FORMULATIONS

We have run extensive trials with another client on a new process:

- Currently producing 15 to 20 tonnes/day
- Half of which is subcontracted – internal capacity utilised.
- Resulting in High Production costs

A step change in the processing method is required to enable 40 tonnes/day manufacture.

Currently using a powder blending process which has issues with:

- Stratification
- Variable product quality
- Large material handling requirements
EXAMPLE 2 - CONTINUOUS PROCESSING USING LIQUID BASED FORMULATIONS

We have run extensive trials with another client on a new process

One of the raw materials can be purchased as a liquid – saving the company over €3M per annum

We developed a continuous mixing system to:

- Automatically Feed
- Analyse Compositions
- Control based upon composition analysis

Final product is then solidified, milled and bagged.

A trial showed that product quality could be controlled within 1% of specification. Resulting In:

- Better Product Quality
- Lower Production Cost
- Higher throughput capability
CONSIDERATIONS FOR CONTINUOUS PROCESSING

Continuous processing technologies are:

- Existing mature pharmaceutical processes
- A number of companies offer continuous granulators and continuous driers

But Epsilon have been engaged to link these processes

- Often a short trial can quickly determine the correct arrangement for your product
- Drying residence times and PAT probe positioning can also be determined which are functions of:

  the product composition
  moisture content (in and out)
  density
  flowability
  particle size
  morphology
SHORT SUMMARY OF CONTINUOUS GRANULATION & CONTINUOUS DRYING

- Utilises existing screw granulation technology
- Utilises existing drying technology
- Technology is well known outside the pharmaceutical industry
- Unit manufacturing (loading/granulation/drying) well understood
- There are a number of lines already in operation
- Small footprint and lower facilities cost
- Reduces manual handling and labour costs
- Lower cost alternatives can be developed which are better suited to high volume manufacturers
- Low volume alternatives available
- Easily expandable
- PAT for online release (reduced analyst/personnel costs)

We will pick up on some of these in a just a moment
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

- So, we have found many Clients fall into one of the following categories:
  1. Those who have each operation in a separate room:
     - Raw Material Dispensary 20 mins
     - Charging of Granulator 10 mins
     - Granulation Followed by Discharge through Mill into an IBC 40 mins
     - IBC Docked and Fluid Bed Dryer charged from IBC 15 mins
     - Product Dried in the Fluid Bed Dryer 30 mins
     - Fluid Bed Dryer discharged to IBC 15 mins
     - Excipients Added + Additional Blending 30 mins
     - IBC Docked onto Compression Machine 10 mins

Dispensary to Compression Machine Takes Approx 2.8 hrs (Without Testing!)

**Of which approx 1.5 to 2 hrs is spent transferring material**

(Times may also include transfer to and from a warehouse whilst product testing is performed – we will look at this in more detail in just a moment)
EXAMPLE LAYOUT OF A TRADITIONAL GRANULATION SUITE
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

2. Those who have a streamlined operation:
   - Raw Material Dispensary 15 mins
   - Charging of Granulator from Holding Hopper 5 mins
   - Granulation 15 mins Section 2 Dispensed
   - Fluid Bed Dryer charged from Granulator through Mill 10 mins
   - Product Dried in the Fluid Bed Dryer 30 mins Section 2 Gran’ Start
   - Fluid Bed Dryer discharged to IBC 15 mins
   - Excipients Added + Additional Blending 30 mins Section 2 in FBD
   - Vacuum Transfer Direct to Compression Machine 10 mins

Dispensary to Compression Machine Takes Approx 2 hrs

Of which approx 1 hr is spent transferring material
(What about product quality testing – again we will look at this in more detail in just a moment)
EXAMPLE LAYOUT OF A STREAMLINED GRANULATION SUITE
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

3. Those who have a continuous operation:
   - Raw Material Dispensary: Operators Top Up Charge Stations when required
   - Charging of Granulator: N/A – Continuous
   - Granulation: N/A – Continuous
   - Dryer charged from Granulator: N/A – Continuous
   - Product Dried: N/A – Continuous
   - Fluid Bed Dryer discharged to IBC: N/A – Continuous
   - Excipients Added + Additional Blending: N/A – Continuous
   - Vacuum Transfer Direct to Compression Machine: N/A – Continuous
   - Tablet/Capsules from Compression Machine: Operators Remove Product when required (IBC/Drums etc)
EXAMPLE LAYOUT OF A CONTINUOUS GRANULATION SUITE
CONTINUOUS & HIGH THROUGHPUT MANUFACTURING OVERVIEW

On the previous slides we have discussed various process methods and many of our clients have one or a combination of these, but.....

What About Product Quality and Quality Assurance?

How do you know that each tablet has the required:

- composition?
- weight?
- hardness?
- solubility?

Etc.....
PROCESS ANALYTICAL TECHNOLOGY (PAT)

PAT allows us to control quality in real time

But also….

PAT can provide an ASSURANCE that the previous controls have worked

With PAT we move away from a Process Parameter driven system

And Instead…..

We concentrate on the Material Attributes
PROCESS ANALYTICAL TECHNOLOGY (PAT)

Control By Material Attributes e.g.

- composition
- moisture content
- particle size

In order for PAT to work for us:

- Control system with data acquisition is key to good use of PAT
- Data can be analysed to give:
  - A better understanding of the product and
  - The effect of process parameters on product quality

- Favourable regulatory acceptance
- Online release (reduced analyst/personnel costs)
- Needs to be affordable - Optimal SynTQ is a good alternative to Siemens, better suited for the high volume, low cost market
- System is CFR21 Compliant
- Automated, electronic batch records
PROCESS ANALYTICAL TECHNOLOGY (PAT) – A FEW THOUGHTS

PAT is not only suitable for continuous systems

Batch systems also benefit from the technology to look at... Material Characteristics e.g.

- composition
- moisture content
- particle size

This allows us to better our understanding of:

- How process parameters affect material properties
  
  e.g.  Do fluctuations in the speed of the granulator affect the granule?
  How does the speed of the granulator affect how the granule compresses?
  Is the temperature of the fluid bed dryer critical?

- End point determination – What is the optimum time for granulating or drying?
Residence Time Considerations in Continuous Processing

A lot of fuss has been made – but what does it mean for the Product Quality? What effect does this have on the customer?

For many mature products where Material Characteristics are well known, they are not measured at the moment.

A good example is Paracetamol

A lot of data exists in the Public Domain e.g.:

- Material properties
- Quality of raw materials
- Temperature and Moisture Stability
- Flowability (Particle Size/Shape)

We can use this data to determine an appropriate level of PAT
Residence Time Considerations in Continuous Processing

If the drying time through a continuous drier is 1hr you may want:

Approx 85% of the tablet wt. to have been dried for 54 to 66 minutes
Of the remaining 15% you would want to demonstrate 12% had been dried no longer than 90mins.
Of the remaining 3% no more than 0.6% has been dried longer than 2hrs.
Of the remaining 0.6% nor more than 0.12% had been dried more than 4hrs,
Of the remainder no more than 0.024% had been dried more than 8hrs.
We could argue that below this and number becomes insignificant.

Therefore some stability data for product dried up to 8hrs would be required to show that the product would meet specification.

This becomes your control to ensure material characteristics remain consistent and may be gauged from:

- Air flow Rate
- Temperatures
- Humidity

(Process Parameters)

Material Characteristic = Moisture Content of the Product
PROCESS ANALYTICAL TECHNOLOGY (PAT)

Don’t over complicate your PAT…

Make The Important Measurement

Don’t make your Measurements Important
OTHER CONSIDERATIONS

The Wider Effects of Continuous Processing Upon Existing Operations

Material Movements & Logistics

Using the previous example – 8 tonnes/day assuming API content of 75%

Assuming the client has a traditional granulation suite where material is moved between equipment:

This means we have:
- 6 tonnes/day of API
- 2 tonnes/day of Excipients
- 10 tonnes/day of Granulated Product (Including Water)
- 8 tonnes/day of Dried Product (For Lubricant Addition)
- 8+ tonnes/day of Final Product

i.e. a total of 34+ tonnes/day of material movements in the facility.

If excipients are in 25 kg sacks, operators would be discharging
80 bags per day

On top of moving 32+tonnes

Continuous processing halves this to 16 tonnes!
OTHER CONSIDERATIONS

The Wider Effects of Continuous Processing Upon Existing Operations

Supply Chain

Use your process to determine the correct container size for your application:

Can FIBC’s or kegs be used instead of 25 kg sacks?

This is key to:

• Facility Design – Building and Equipment layouts

• Raw Material & Product Handling
  Can we use our lorry as the warehouse with live testing of raw materials and live release of product?

• Containment – Ease of loading/unloading?

• Personnel Requirements for your process
  (Analysts to Warehousing)

Ultimately all of these aspects affect your unit price and profitability
OTHER CONSIDERATIONS

The Wider Effects of Continuous Processing Upon Existing Operations

Rethink our Batch Control

Consider what is classed as a ‘batch’

We can take an example from the food industry where a ‘batch’ is the individual sachet, packet or pot

Our batch control becomes a **time stamp**

And...

Because of your PAT you would know the **material characteristics**

And...

**The PAT Data Becomes Key**
OTHER CONSIDERATIONS

Scale Up and Speed to Market

We have established that with PAT we can gain a good understanding of material properties.

This makes scale up a lot easier.

With continuous systems:

- Trials can be conducted easily
- Good Scale up Correlation
- Run the system longer for full production
- Some development required depending upon current licensing of the product
OPPORTUNITIES

Back to examples 1 & 2, Epsilon concluded that high throughput processing should be considered for our clients.

In these instances for the client and the key issues were:

- Timing – some product development required for a continuous solution
- Mindset – ‘best follow a traditional path’ and least risk
- Cost of continuous manufacturing represents good-value
- Change in license may be required for some products
- A step change in the method of manufacture is required to remain competitive

Epsilon are also developing processes to provide a lower cost integrated continuous manufacturing lines based on:

- High throughput 300kg plus/hr
  and
- Low throughput micro continuous line for up to 10kg/hr max
CONTINUOUS PROCESSING WITH PAT IS HERE

Our aim is to Provide a Step Change in Pharmaceuticals

By...

Providing low cost proven alternatives to the market

To...

Drive down unit cost and increase profitability for our clients
Thank you for listening…

Any Questions?

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