Anticipation of scale up issues in pharmaceutical development
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Anticipation of scale up issues in pharmaceutical development

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Abstract

We present a methodology to evaluate the robustness of pharmaceutical batch processes on scaling up. The Scale Up Risk Evaluation (SURE) is applied on new processes that are part way through their development. During a SURE study one first collates current process understanding and then extrapolates this understanding to evaluate scenarios at larger scale. The output of the SURE study is a ranked list of scenarios that development teams use to prioritise further development.

Keywords: Batch Process, Process Development,
Scale up, Risk Assessment, Robustness & Reliability.

1. Introduction

The pharmaceutical industry is currently expanding the role of process engineers from their traditional roles in chemical manufacturing and capital projects. Significant process engineering populations can now be found in process development, which has typically been the domain of the synthetic and development chemists. Some drivers for this trend are the regulatory push for increased process understanding, and the frequency at which scale up issues occur in processes moving to commercial scale (Sherlock & Brewis 2006).

From a process development point of view, the life cycle of an active pharmaceutical ingredient (API) consists of a series of campaigns executed at scales starting at 10's of grams for discovery, then kg scale for early clinical work then 10-1000 kg for late stage clinical work culminating in commercial manufacture. Although engineers do contribute to kg scale campaigns, typically, significant engineering contribution is made to campaigns for 10's Kg onwards when development teams are formed, drawing on chemistry, analytical, pilot plant and engineering.

The aim of a development team is to invent and scale up a synthesis in order to generate an API for use in clinical trials. The pilot manufacture typically takes place in multi-purpose batch reactors. As outlined by J Double et al. (2005), batch reactors have a degree of flexibility unsurpassed when executing partially developed often multiphase (typically S-L) processes.

The development team starts by identifying the "Route"; i.e. fixing starting materials and intermediates. The process for a given Route is separated into stages; a stage covers either the conversion of starting material or intermediates, or in case of a "Pure's" stage the (re-) crystallisation of the API.

Carey et.al. (2006) give an analysis of typical reactions used in pharmaceutical synthesis and conclude that most pharmaceutical routes are "simple constructions from complex fragments", so called modular convergent synthesis. A typical pharmaceutical route consists of 2-4 in-house stages forming intermediates, a stage to form the Crude API and a Pures stage to achieve the desired quality of the API. (the Pures stage may also be combined with the Crude stage).

For each stage a process[1] is developed. This involves identification of solvent(s) and reagents conditions (T, P) and the order in which operations are executed. Once a suitable process is identified, it is optimized and scaled up to pilot scale in order to generate the required quantity of API. The "process description" document describes the required operations of a stage in detail.

A typical process consists of 20-40 operations; e.g. charge, heat, hold, cool filter, wash and dry. The responsibilities of the engineers are typically related to (i) scale up of operations (ii) minimization of environmental impact and hazard, and (iii) configuration of the flexible (pilot) plant for the processing of a stage.

The extent to which engineers need to address scale up of operations depends very strongly on the interaction between the chemist and the engineer. For example if a chemist working on a process considers a mixture to be "thick" he may decide to dilute the process with solvent, thus resolving the issue. If an engineer had been present he might have concluded that mixing was not sufficient and suggested using an alternative agitator, thus also solving the issue. In reality, a good chemist will have "chemi-neered" out the majority of the scale up issues before an engineer gets involved.

Unfortunately, the chemist's solution is not always robust with regards to scale up. Internal studies with regard to "Right-First-Time" indicated that a significant proportion of processes run at pilot scale gave unforeseen results; i.e. a scale up incident had occurred[2]. The severity of these scale up incidents ranged from simple deviations (more added, longer times etc) that still gave "in-spec material", to material that had to be reworked or even product that was totally unusable.

Roughly 30% of the scale up incidents occurred during reaction operations, 30% involved crystallisation (slower, or unwanted nucleation) and 40% were related to other work up operations. From this data it was estimated that about 1% of process operations led to a scale up incident. It was also noted that scale up incidents are more likely to occur if the mixture in the batch vessel is multi phase.

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[1] In this paper a "process" refers to the sequence of operations that is required to transform the input material and reagents for a **stage** into the product of that **stage.**

[2] A scale up incident is defined as an event during a development manufacture that had not been expected based on the experimental laboratory data; e.g. an unexpected nucleation or the formation of a new by-product.

2. Scale Up Risk Evaluation (SURE)

In order to help chemists and engineers identify the 1 in a 100 operation that is going to cause a problem a Scale Up Risk Evaluation (SURE) methodology was developed. This methodology aims to anticipate scale up issues early on in the development of a new compound. Note: the SURE study is thus **not** a problem resolution technique like those proposed by Keppner and Tregoe (1981) and the Britest consortium ("Driving Force Analysis" Britest 2007, Sharratt and Borland 2003)

The principal of SURE is based on that of a hazard and operability study (HazOp): for each operation in a process recipe various scale up/down scenarios are identified, where a scenario is defined as an unplanned change in conditions. The potential impact of a scenario on the process is then assessed as a "threat" or an "opportunity" and subsequently scored on:

(i) The likelihood the scenario will occur on a change in scale
(ii) The likelihood the scenario will affect product quality or process operability.

The output of a SURE study is a risk matrix, and a summary table of the threats and opportunities that provide development drivers for the development team. The key elements of a sure study are:

Participants
The evaluation of a 'Process' works most effectively with a cross functional team. The minimum team requirements are a process owner (typically a chemist), an engineer and a study facilitator. The facilitator brings a number of skills to the SURE study: a consistent approach, knowledge of the tool, an independent eye and experience of other projects. The inclusion of too many team members or observers can detract from or slow down the study.

Timing
The study can be performed at anytime in the development of a 'Process' but is best done once both reaction and work up have basic definition. .

Excel tool
The application of a rigorous approach allows a consistent format to be applied and the output can then be correlated against other studies. An Excel based tool is used to capture the 'Process' and SURE information.

The study is performed using a number of elements: description/capture of current knowledge, possible challenge scenarios are tested, the impact of any meaningful scenarios are measured.

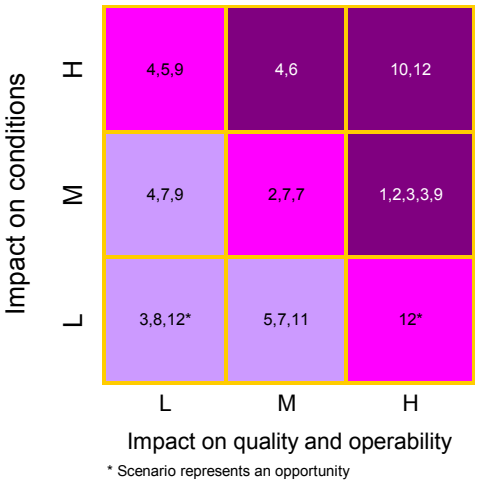
Capturing understanding
The sequence of operations in the process description are described and recorded in order. The operation to add a reactive reagent for example would be described by documenting: (a) reagent name, concentration, amount (actual or by reference to other key material) and time scale (rate) (b) the complexity of the reaction mass, e.g. rheology, the number of phases (present, formed or destroyed). (c) the intended change or mechanism (A>B reaction), (d) physical properties (boiling / melting point) and (e) experimental data (heat data/ reaction profile).

A more simple operation, e.g. to heat or cool, would require much less description.

Risk Evaluation

For each step possible 'Scenarios' are generated using classic (HAZOP type) guidewords; e'g longer time, higher temperature. Any scenario that generates a meaningful outcome is documented, noting the mechanism involved and the nature of impact (e.g. yield, quality, operability). The scenarios are then weighted on two scales: (i) the likelihood to change on scale and (ii) the potential impact on operability or quality of product. The risk are indicated as low, medium or high. The score is a subjective one, which represents the view of the team. If the assessment of the risk is difficult because information is lacking, it scores automatically as "High" to drive the development team to generate of understanding in this area. The distribution of risk over various scenarios is not reported in this paper.

Figure 2.1: Example of a risk matrix for a stage with 12 operations



Output generation

The excel tool automatically populates a pictorial risk matrix (see figure 2.1) and a results summary table. The range of risks identified can vary significantly but the later in the development lifecycle and the more development resource applied the lower the balance of risk profile should become.

3. Analysis of SURE study output

The output from 16 SURE studies, resulting in 591 scenarios was analysed. For all operations we counted the number of times a specific scenario occurs. Rather than listing each specific scenario (i.e. higher, lower Temperature), they where classed into a number of groups (e.g temperature; see table 3.1). The data suggests that 62% of the scenarios relate to time, temperature, more/less, agitation, physical properties and the presence of a new compound. Hulshof (2000) identified the main cause of scale up problems to be related to mass transfer and mixing, followed by longer processing times and heat transfer. Clearly we identified the same issues, though not in the same order of importance. In addition this work demonstrates that physical properties (or lack there of!) and new materials appearing in the plant (O_2, water, Fe, Ni) are also considerable sources of concern.

Table 3.1: Number of times a scenario is encountered

scenario type	Total number	
none	81	13.7%
Time	78	13.2%
more/less	63	10.7%
Temperature	61	10.3%
PhysProps	55	9.3%
Agitation	54	9.1%
New Compound	43	7.3%
Crystallisation	33	5.6%
Concentration	33	5.6%
Heat transfer	24	4.1%
Particle	19	3.2%
Other Scenarios	18	3.0%
Omit	13	2.2%
Mass transfer	12	2.0%
RM quality	2	0.3%
Profile	2	0.3%

In contradiction to Hulshof(2000) we find that heat & mass transfer, raw material quality and reaction profiles figured low in the scenarios generated (This data set does not contain a hydrogenation though) This probably reflects the degree to which these issues are "chemineerd" out. Chemists, very much aware of potential scale up and hazard issues, avoid complex rheologies, ensure heat generation/removal rates are low and use reactive gasses only as a last resort (other then hydrogen for which purpose built equipment may be available on site).

Table 3.2: Mechanisms affected by the key scenarios

Time (13%): • Reaction (degradation, by-product formation, conversion/yield) • Reaction profile • Particle (Super-saturation, nucleation, growth, attrition and form) • Gas evolution and foaming • Distillation	Temperature (11%) • Reaction (Decomposition, hydrolysis, impurity formation) • Solids (melting, solidification of liquids) • Crystallisation (Faster, thicker mixtures)
More/less Species, Shear(10%) • Reaction (Rate, Concentration, Degradation,) • Filtration (compression) • Phase split, emulsion • Others: Gas evolution, evaporation, solubility, Impurities to next stage	Agitation (9%) • Solid suspension • Emulsification • Blending, reaction selectivity • Inclusion
Physical properties (9%) • Crystal (form, hydrate, nucleation) • Oiling out • Solubility • Density	New Compounds (7%) • Ingress (O_2, MOC, tap water vs distilled)

In table 3.2 we list what mechanism was affected for each of the main scenario types. In addition to Hulshof's original list other sources of significant risk are: (i) a lack of understanding in reaction mechanisms, (ii) crystallisation & nucleation and (iii) agitation requirements. Of these three, nucleation is the most difficult to scale up. Especially as one is not always aware the system is supersaturated….

Finally in table 3.3 we show the distribution of the generated scenarios over the various process operations. Clearly the charging operations generate by far the most scenarios. This reflect the fact that many operations include a charge (e.g. reactions, phase separations, filtration washes, drown out crystallisations). Similarly, the "hold" operation is typically executed in order to complete reaction or crystallisation; both operations that carry a high level of risk.

Heating and cooling, as well as typical "work up" operations like "wash", "Distill" and "phase separate" account also for a significant part of the scenarios. More detailed analysis revealed that the risk these operations pose falls in a few categories:

- Wash (filtrations): Insufficient removal of impurities, impurities precipitate, residual wash liquor concentration is high, degradation (hydrolysis)
- Distill: super-saturation, nucleation too early, wrong final composition, degradation
- Phase sep: Wrong split, phase inversion, emulsification
- Heat/Cool: unexpected nucleation, degradation, over reaction (more impurities), more evaporation

4. Participant's feedback

Clearly, a robust approach like SURE requires a significant investment of time from the development team. To ensure the SURE process develops and made best use of people's time, feedback on the methodology is always discussed at the end of a SURE study. Typically, both chemists and engineers are enthused by the process. For many engineers it was the first time they discussed all aspects of a process in detail, which gave them a much better insight in what is planned, and why it is required.

Table 3.3: Distributions of the scenarios types over typical batch processing operations

scenenario type	Charge	Hold	Cool	Phase Sep	Distill	Wash	Heat	Transfer	React	Agitate	Filter	pH check	Crystallise	N2 flow	Change P	Screen	EOR	Grand Total	Gra
none	36	6	9	6		11	5	1		2	1	1		1	2			81	14%
Time	27	11	5		11	1	3	8	5	2	1	1	1	1			1	78	13%
more/less	32	1	3	9	8	1	1	1	2		2			1	2			63	11%
Temperature	26	7	7	1	3	5	4	2	3		2		1					61	10%
PhysProps	24	3	3	15	2	1		2		2		2	1					55	9%
Agitation	29	11	2	3	1		2	2	1			2	1					54	9%
New Compound	19	5				3	3	4	2	1		1	1	4				43	7%
Crystallisation	9	2	6		5	2	3		1	1	1		3					33	6%
Concentration	14	2		3	6	3	1	1		2		1						33	6%
Heat transfer	9		2				9	2					1		1			24	4%
Particle	4		3			4	2	1			2	2				1		19	3%
Other Scenarios	6	6			1	3			1		1							18	3%
Omit	5	5		1		1					1							13	2%
Mass transfer	3	2				1	1	1	1	2					1			12	2%
RM quality	1						1											2	0%
Profile	1				1													2	0%
Grand Total	245	61	40	38	38	36	35	25	16	12	11	10	9	7	6	1	1	591	
	41%	10%	7%	6%	6%	6%	6%	4%	3%	2%	2%	2%	2%	1%	1%	0%	0%	100%	

Chemists are key contributors to the discussions, providing most of the information. They generally find the methodology useful as it gives them additional areas to focus on and increases the development team's confidence in the process

5. Conclusions

This paper presents a new methodology to assess the scale up risk of batch processes under development: Scale Up Risk Evaluation (SURE). This methodology is has been applied successfully to 16 processes in AstraZeneca providing the development teams with a ranked list of scenarios that could be a possible threat to robust scale up.

The various threats to robustness can be evaluated by looking at the nature of the scale up scenarios generated. The most frequent deviations from lab conditions relate to changes in time, temperature, agitation, physical properties and the number of species. The reason these deviations generate potential scale up risk lies in the mechanism affected. The paper presents a whole range of important mechanisms. The paper highlights two key sources of risk: (i) (unwanted) reactions and (ii) the unpredictable nature of nucleation of a new phase. Surprisingly heat and mass transfer do not rank high. The view is that experienced development chemists avoid these issues during process design.

Another interesting point revealed by this study is the fact that most deviations of anticipated behaviour are expected when charging additional material to the batch; This reflects the fact that compositional changes that occur on a charge lead to reaction and nucleation. Typical work up operations (wash, distill, filter) also generate a significant number of potential scale up issues.

The SURE methodology is generally seen as a valuable addition to the development community as it addresses process robustness in a rigorous way. An additional benefit is that after a SURE study, the process is generally better understood by the development team as a whole.

6. Aknowledgements

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