

MAINTAINING A STRONG SAFETY CULTURE IN A DEVELOPMENT FACILITY WITH RAPID CHANGEOVER AND MAJOR ACCIDENT POTENTIAL[†]

SJ Harding, BL Fox, SD Whittingham and CF Blyth
AstraZeneca, Macclesfield, UK

A challenging regulatory environment and internal drivers to deliver drugs to market more quickly means that there is a constant pressure to reduce development timelines and development costs for new drugs. Process R&D supplies the development function of AstraZeneca with API (Active Pharmaceutical Ingredient) to ensure a supply of drug substance for use in clinical trials, toxicological studies and formulation development. This requires scaling up laboratory processes to pilot plant scale, often with limited time to develop process understanding. It follows that changes often need to be made throughout the manufacture, either as a result of identified process improvements or responding to unexpected scale-up effects. In a rapidly changing environment, Process R&D Macclesfield has maintained a strong safety culture for many years, while consistently delivering to challenging project timelines. This paper describes the three “pillars” which support this safety culture: (i) ensuring the right risk assessment and change control procedures are in place, both for chemical processes and plant equipment; (ii) putting in place an organisational structure which supports the smooth operation of these procedures, monitors performance and addresses issues effectively; and (iii) cultivating the right behaviours in all staff, at all levels in the organisation, to create an open, honest, no-blame culture where safety is a top priority.

INTRODUCTION

Culture in organisations is hard to define and hard to measure, although guidance is available (HSE, 2008). In an extensive literature review Bell & Healey (2006) conclude that the behaviours associated with major accidents and how to change them are poorly understood. Mearns (2001) concludes that unsafe behaviour such as rule breaking and risk taking behaviour was related to perceptions of pressure for production. As the pharma industry faces pressure to become significantly more efficient (EFPIA, 2008) due to pressure from generics and reducing R&D approvals, a potential risk is that the safety culture is undermined.

This paper gives a high-level overview of the Process Risk Assessment (PRA) procedure which has contributed to maintaining and improving an excellent safety record at Macclesfield. It also emphasises the importance of supporting the procedure with the right organisation, behaviours and SHE-centric culture to ensure that potential increases in throughput do not lead to a reduction in safety standards.

In order to put the risk assessment procedure into context, a brief overview of the Process R&D organisation within AstraZeneca is given below.

PROCESS R&D WITHIN ASTRAZENECA

Process R&D within AZ is organised across four sites; three in Europe and one in India. The sites are globally aligned with respect to governance, high level processes and best practice but with significant site autonomy to allow flexibility and continuous improvement at a local level.

The sites all have kilo-lab facilities, and the three European sites also have pilot plant capability up to 6300 L scale. The functional structure within Process R&D consists of projects management, Analytical & Process Chemistry, Process Engineering & Development Manufacture with QA support. SHE is fully integrated into all functions & processes, with specialist advice & support provided from a central SHE department. The core purpose of PR&D is to ensure supply of API via robust manufacturing processes to support the wider drug development programme.

Process R&D Macclesfield has several multi-purpose pilot plant manufacturing units, ranging from 250 L to 6300 L scale. The pilot plant facilities are located alongside (and share some services with) commercial manufacturing plants, and the area as a whole is subject to COMAH regulations. Because of the attritional nature of drug development, the fact that development of the process is ongoing alongside the need to deliver campaigns of material for clinical and other studies, and the relatively small quantities of materials involved (compared to full-scale commercial manufacture), it is important that the pilot plant is flexible, able to handle a wide variety of chemistry, and that changeover between processes is rapid. In 2008 the pilot plant in Macclesfield manufactured 31 different chemical intermediates, which means that 31 changeovers were required from one process to the next. Changeover encompasses cleaning the manufacturing unit to the required level of cleanliness as dictated by GMP, and reconfiguring the unit for the following process, which will usually involve some temporary modifications to the plant. Because of the rapid throughput of different processes, it is vital that each new chemical

[†]AstraZeneca retain all registered and unregistered Intellectual Property Rights.

process is risk assessed appropriately, and that the Process Risk Assessment (PRA) is supported by a robust, efficient change control process to control modifications to the equipment.

PROCESS RISK ASSESSMENT

PURPOSE

The purpose of the PRA is to demonstrate that any potential SHE risks arising from the accommodation of a new process into a specific manufacturing unit have been identified, and any necessary control measures identified and implemented to reduce the risks to an acceptable level. A key feature is ensuring an appropriate level of detail is considered, given that it is not possible or desirable to run a full HAZOP study for each new process. The PRA is designed to consider the specific risks arising from the new chemical process, based on sequences of established unit operations in well-maintained and reliable equipment.

OUTLINE

The process can be broadly categorised into three parts (Figure 1), centred around the PRA meeting itself where the risk assessment takes place. If the pre-work is carried out thoroughly then in our experience this considerably reduces the burden during the meeting, and allows the meeting to focus on the critical aspects of the process and its accommodation into the manufacturing unit.

FUNDAMENTALS OF THE PRA PROCESS

There are a few “fundamentals” which we believe provide the foundation for a successful and efficient PRA. It is worth considering these briefly before going into the mechanics of the PRA process in more detail.

The PRA is a cross-functional activity. Specific involvement will vary depending on local ways of working, but in general the process needs input from pilot plant staff (to accommodate the process, co-ordinate activities and provide operational knowledge), process chemists (providing knowledge of the chemical process) and process engineers (ensuring compliance with environmental regulations, checking materials compatibility, generating temporary modifications and other activities). In addition, the chemical hazard assessment is generated by and the PRA meeting itself chaired by people who are not directly involved in the manufacturing campaign. Most of the people involved in the above activities will also attend

the PRA meeting itself, to ensure that the risk assessment is truly a team-based activity.

There is a degree of independent review at key stages. Every new process must undergo a full evaluation for chemical hazards, which will typically involve measuring the heat of reaction at all key points in the process by appropriate calorimetry, evaluation of thermal stability of the materials and reaction masses, stability of the product under typical drying conditions and measuring any gas evolution throughout the process. The assessment is carried out by a specialist group within AstraZeneca and provides a basis of safety for the process which the PRA team is expected to implement.

Additionally, the PRA meeting itself is chaired by an “independent” PRA leader, who is an experienced member of the department, with formal risk assessment training and with no other involvement in the proposed manufacture. The PRA leader is the sole approver of the outcome from the PRA, and ensures that all the necessary actions have been completed and documented before processing can commence on plant.

A defined chemical process is the basis for the PRA. It is a pre-requisite of good risk assessment that the boundaries of the process are defined; it does not mean that further process changes are not possible after the PRA meeting. Any such process change after the PRA is subject to a defined change control procedure (see section 2.6) and is risk assessed appropriately.

The PRA meeting agenda is driven by a consistent checklist. The checklist is based on a standard AZ procedure and has been subject to continuous improvement to address site-specific learning over many years. This ensures that there is a globally consistent approach to PRA within AZ for new chemical processes, with the flexibility which recognises local differences in plant, ways of working or organisation which are a largely historical but which may also reflect different legislative standards in different countries.

PRE-MEETING ACTIVITIES

The PRA meeting should be the final review of a series of pre-manufacturing activities which constitute an ongoing assessment process. These activities are co-ordinated by the Campaign Manager, who is part of the pilot plant staff and effectively project-manages the delivery of the manufacturing campaign. Prior to the PRA meeting, the Campaign Manager will work closely with the Process Chemist and, in particular, the Process Engineer to produce a draft accommodation of the process, ensuring all recommendations from the chemical reaction hazard assessment have been implemented, and that any relevant safety-critical information has been incorporated into the draft batch record. The draft batch record is a key input into the PRA meeting, as it is the “set of instructions” used by the operational staff to carry out the process, and will therefore reflect any specific control measures. This is carefully reviewed in the PRA and amended as necessary before processing is undertaken.

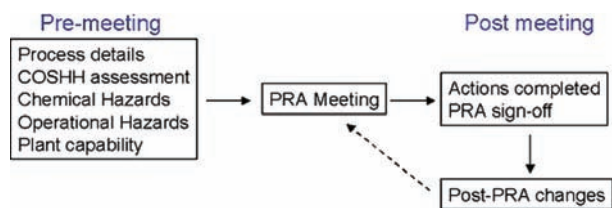


Figure 1. Schematic of the PRA process

PRA MEETING

The PRA meeting is chaired by an “independent” PRA leader, and the agenda is fairly rigidly determined by the PRA Checklist. This ensures a consistent, structured approach which will consider all significant risk areas. It is not possible to describe the checklist in detail here, but each of the major topics will be mentioned briefly in order to demonstrate the key areas discussed in the meeting. The assessment usually requires 2–3 hours, depending on the complexity of the chemical process. The content of the meeting is described in Table 1.

It is worth noting that because most of the material to be manufactured is destined for clinical trials, a GMP assessment is also required to ensure the quality of API produced. This assessment is carried out separately to allow the PRA to focus solely on SHE-related matters.

POST PRA CHANGES

Processes in pilot plants are by definition not fully understood and development activities are often ongoing alongside manufacture. Frequently it is necessary to make changes after the PRA meeting, and often during manufacture. Often the operator must make process decisions during manufacture with only limited knowledge of the process. It is important that any changes are assessed in a structured way, while allowing changes to be made without undue delay to a process where the effect of a prolonged hold may not be known.

A “Post PRA Checklist” has been developed, which is effectively an abbreviated version of the PRA checklist. An operational chemist can complete this relatively quickly, but the correct thought processes are prompted (for instance, if more solvent needs to be charged, is the vessel volume still

Table 1. Major PRA topics

Major areas for assessment	Points to review
1. The chemical process	Chemistry, including any unwanted chemistry, by-products, critical charges and potential hold points (or parts of the process where it would be undesirable for a prolonged unplanned hold to occur)
2. Manufacturing history and learning	Previous manufacturing experience (focussing on any problems encountered during previous campaigns, either in the kilo-lab or pilot plant). Proposed changes from the “fixed” process; e.g. addition of reagents in a slightly different way, or over longer times, or additional line wash requirements not in the original process. Any changes must be assessed against the process which was subjected for Chemical Hazard Assessment, to ensure they still fall within the scope of that assessment.
3. Chemical reaction and operational hazards (key element)	Chemical reaction hazard assessment and proposed control measures. Operational (fire & explosion) hazards, including the measures in place to prevent generation of a flammable atmosphere and all materials being compliant with the area classification of the manufacturing unit. Potential Major Accident Hazard scenarios (COMAH requirements) and proposed control measures. Basis of SHE (BoSHE) for the manufacturing plant, i.e. the “base state” risk assessment for the pilot plant, listing all the control measures ensuring safe plant operation (e.g. fire prevention, alarms, trips, ways of working etc).
4. Human Factors	Potential sources of human error e.g. incorrect charges leading to a potential hazard, potential for ambiguity, any additional training or instruction requirements, etc. Other processes operating simultaneously in the area, and whether any interactions between different processes could lead to any additional hazards (e.g. some units share services such as effluent receivers or vacuum pumps).
5. Environmental considerations	Effluent streams from the process and the appropriate routes of disposal. Check measures are in place to ensure compliance with IPPC legislation, i.e. emissions are within permitted quantities for the site. Abatement systems (e.g. liquid scrubbers or carbon treatment) with respect to additional hazard potential
6. Occupational Health	Associated COSHH assessment against the appropriate level of containment needed.
7. Materials of construction	All process materials against the materials of construction of the plant to ensure compatibility; extends to drums for process waste and any consumables which are being used (e.g. filter cartridges). Cleaning solvents are also included.
8. Cleaning	Potential interaction of cleaning solvents with residual process materials.
9. Detailed assessment	Review the draft batch record, to ensure that it adequately reflects the output from the rest of the PRA. It is also an opportunity to ensure that any ambiguity or lack of clarity in the instructions is removed, and it is important to have representation from the operational team at this point.
10. Action review	Ensure all the actions have been captured, and responsibilities and timings have been agreed.

appropriate?). There is also a prompt to ensure assistance is sought if the change does not fall within the scope of the original PRA. If the change is significant then the PRA team may be reconvened to assess the change more formally.

All changes to the process are reviewed and documented after manufacture is complete to ensure learning is captured for future process development and also for continuous improvement of the PRA checklist.

ORGANISATIONAL STRUCTURE

It is important to support good procedures with the right organisation. In this section a brief overview of the Development Manufacture organisation within AZ is given, highlighting those roles which are key to delivering a safe and robust change control process.

The Development Manufacture organisation is shown below. Although the kilo-lab team provide delivery of small quantities of API (up to 5 kg) and scale-up learning for pilot plant manufacture, the figures for throughput given in this paper refer to the pilot plant area only. The structure gives clear defined accountability for the different roles in the function (Figure 2).

There are obviously various roles within the pilot plant team, encompassing many responsibilities associated with the safe manufacture of development API in a GMP environment. Three key roles, however, are described below which are pivotal to the successful implementation of the change control procedures described in the section above.

CAMPAIGN MANAGER

The Campaign Manager project-manages the manufacture, and is responsible for ensuring that all process changes

have been adequately assessed. The role has already been described above in the context of the PRA process.

PILOT PLANT CHEMIST

The pilot plant operating team consists of a mix of technicians and graduate / PhD chemists, all of whom have operationally-focussed roles. The pilot plant chemist role, however, is particularly important in ensuring an adequate transfer of understanding about the process and associated risks takes place. In an environment where the chemical processes are not fully developed, it is essential that the people operating the process are able to understand the chemical risks, and respond effectively to unexpected scale-up effects which are a natural part of development. Pilot Plant Chemists are able to make informed decisions during processing, with the aid of systems such as the Post PRA Checklist described above, to make relatively minor process changes in an efficient manner with little or no additional technical support. The chemists are involved in many of the pre-manufacturing activities to provide operational expertise, and an atmosphere of what has been called “creative mistrust” is encouraged (Mitchell, 2008) – in other words, the ability to challenge established procedures and ways of working. This “creative mistrust” of equipment, human factors and other processes is an important element of developing the safety culture in the organisation.

PLANT CO-ORDINATOR

The Plant Coordinator role is key in terms of plant and process safety (in a wider context than the chemical process itself). The Plant Coordinator controls all Safe

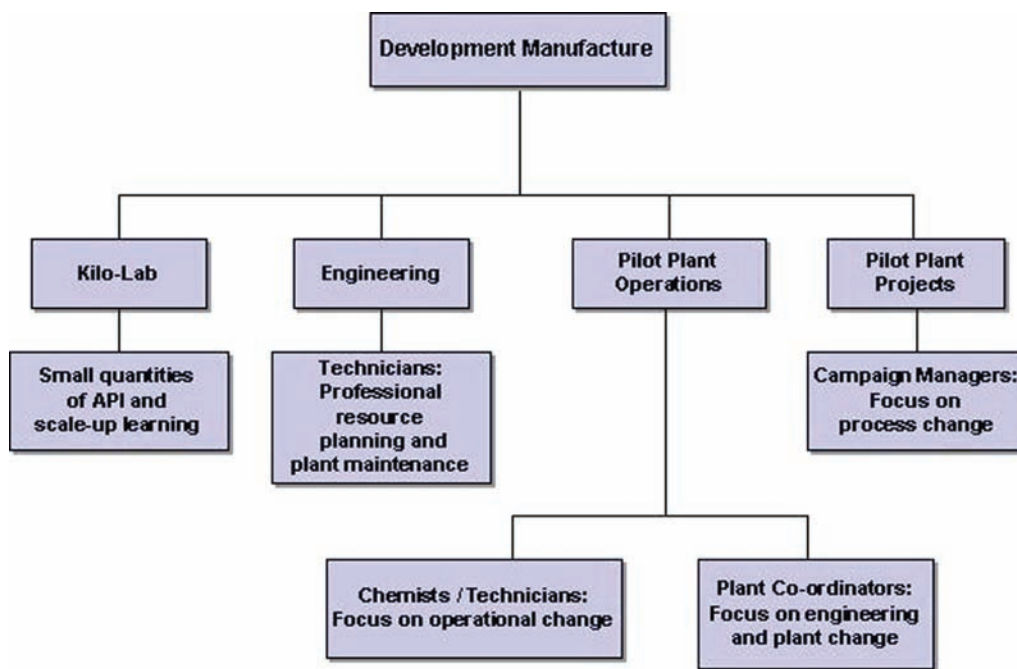


Figure 2. Development manufacture change-focused roles

Systems of Work across the manufacturing units. They are trained to issue all work permits including flame, height & entry. The Plant coordinator is the liaison between production and engineering in coordinating and controlling all scheduled engineering maintenance, breakdowns, changeovers and stage specific modifications. The role ensures that there is a high degree of plant ownership and overview across all manufacturing units, reducing the risk of a conflict between engineering and production requirements in this high change environment.

BEHAVIOURS AND CULTURE

The third “pillar” which supports the safety culture of the organisation is the behaviour of its staff and leaders. Any procedure or organisation is only as good as the people who operate within it, and while it is clearly important to establish robust training systems, it is equally important to establish the right behaviours.

Leadership and engagement are the key elements in making up the safety culture of our organisation. Inevitably the discussion is mainly of a qualitative nature, but quantitative measures have been introduced where appropriate.

LEADERSHIP

Leadership is vital in setting the tone and culture of any organisation. The importance of leadership is acknowledged in recent major incident investigations (Buncefield, HSE 2008; Baker Panel Report 2007). Conchie and Donald (2006) argue that management has the biggest impact on safety climate and associated safety behaviours. For our organisation safety is lead by a SHE (safety, health and environment) committee. Responsibilities of the committee are to ensure views on SHE from all levels are taken into account, to review SHE performance and to drive improvement. The committee is led by the Head of Function, and has representation from all levels of the organisation. A range of measures, both lead and lag, are reviewed by the committee. Additionally the committee owns a SHE improvement plan for the area and reviews learning from accidents and near misses.

This formal SHE management system with direct leadership input is necessary, but not sufficient, to ensure a strong SHE culture. It is essential that leaders within the organisation are visibly directly involved in SHE related issues, for instance leading investigations, authorising permits and engaging in routine SHE inspections, alongside other staff.

ENGAGEMENT

A key part of the overall system for ensuring process safety performance is engagement of all staff with SHE. The Baker Panel Review (2007) noted that “A good process safety culture requires a positive, trusting, and open environment with effective lines of communication between management and the workforce, including employee representatives.” All

staff are included in carrying out audits and safety tours and have personal objectives which include SHE specific actions. There are also two members of staff who act as Safety Representatives, who have completed IOSH certified safety training along with all managers within the operational team.

An important part of engagement in our organisation is the STOP system for reporting SHE learning. STOP is a behaviours-based SHE programme which encourages employees to report and take personal action on SHE issues at work. To encourage this, as well as our SHE committee reviewing learning from STOP cards (Figure 3), we make small awards for the best examples, and try to focus on behaviours rather than outcomes. We have, for example, rewarded those who report personal mistakes where the consequences could have been more severe rather than criticising or disciplining.

A particular issue with high hazard installations such as ours is that where there are significant high consequence but low frequency events we need to ensure that the consequences and likelihood of incidents are understood; often employees underestimate the overall risk because of perceived low likelihood (Fleming, 1999). We have used learning from real incidents and near-misses locally to combat the “couldn’t happen here” mentality as well as using our corporate SHE function to run learning sessions based on the unfortunate reality of investigation of fatalities within the wider AstraZeneca organisation.

QUANTIFICATION

Accident rates are the easiest measure of SHE performance but are extremely unreliable and can miss important “below the radar” issues. As the Baker Report (2007) noted “Preventing process accidents requires vigilance. The passing of time without a process accident is not necessarily an indication that all is well and may contribute to a dangerous and growing sense of complacency.” For our accident statistics specifically (Figure 4), it is important to note that these are for a very small population and are not statistically significant. Also that we mandate and encourage reporting of even the most minor incidents, where there is not reliable data for comparison. In the dataset shown, there are zero process related reportable or lost time injury accidents.

Internal surveys are often operated by large companies to give a quantitative snapshot of employee morale and other indicators. AstraZeneca runs a survey known as “Focus” biennially which includes questions relevant to SHE culture. Results for our local function show some evidence of a strong SHE culture, although the sample size of approximately 60 together with changes to the questions renders the results not statistically significant over time.

PERCEPTION OF CONFLICT WITH EFFICIENCY

As referred to above, it is an acknowledged risk that focussing on production can cause a perception of a lack


 Lets Accidents and Prevent Hurt, Harm or Alarm			
REFERENCE			
DATE			
What did you see?	Please tick box	Act	Condition
	Safe	<input type="checkbox"/>	<input type="checkbox"/>
	Unsafe	<input type="checkbox"/>	<input type="checkbox"/>
What did you do immediately?			
Where did the incident occur?			Date Occurred?
What are the next steps/actions to complete?	By Whom?	When by?	
Observer's Name: _____ Manager's Name: _____			
Manager has read stop card and added to actions if required (Y/N): _____			
Actions have been completed or added to an action tracker (Y/N): _____			
Further investigation required (Y/N): _____			
Trending Data (tick box)			
Behavioural	Housekeeping	Tools & Equipments	PPE
Environmental	Procedures	Site/Building	Other

Figure 3. A STOP card, used to report near misses within AZ

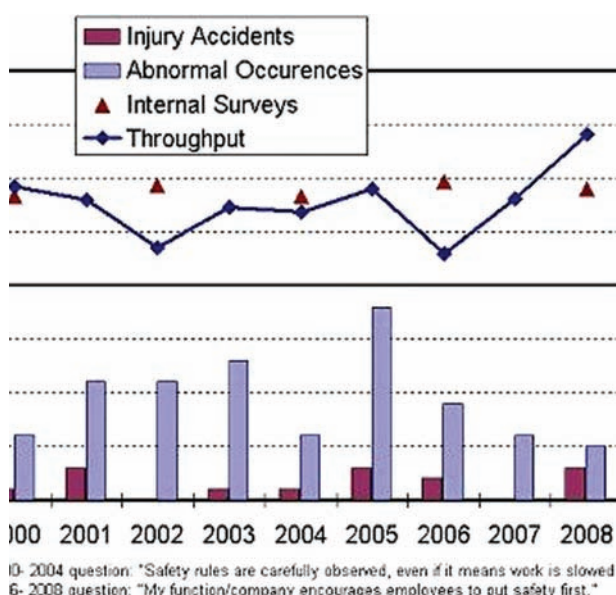


Figure 4. Accident data for AZ macclesfield pilot plant

of commitment to safety, which in itself leads to workers taking more risks. Whilst this is undoubtedly true, we believe that a focus on the efficient operation of our change and safety systems, using the same approach as that for improving production efficiency can simultaneously raise efficiency and maintain if not improve safety culture and performance. In AstraZeneca we are currently implementing the "Lean Sigma" (George et al, 2003) change methodology for efficiency, and also applying this to changeover and SHE procedures. We believe that a more efficient, well defined and executed change and SHE management process can add to the overall safety culture rather than be in conflict with it. The most recent data shows that despite significant increases in volume, there is no apparent trend in either abnormal occurrences (typically process related) or injury accidents (typically minor and non process related).

CONCLUSIONS

Safety culture is developed and built gradually over time and is vital to overall safety performance. We have

described three “pillars” upon which the safety performance in our organisation is built. The first is a consistent procedure for process risk assessment which takes account of corporate learning over many years, and which is also subject to continuous improvement. The second supporting pillar is an appropriate organisational structure with clear SHE accountability, both in terms of the PRA process and the wider organisation. The third pillar (and arguably the most important) is to instil the right behaviours in all staff and leaders such that SHE can be discussed in an open and honest way. Our systems are not perfect, but offer a model others may wish to use as a benchmark. While acknowledging that the sample size is small, the data we have presented indicates a consistently low level of injury accidents despite a relatively wide variation in throughput over the last 9 years. We hope that by presenting this case study of safety management and culture we can encourage learning from other organisations and continue to improve our own systems.

REFERENCES

- HSE, 2008, Leaflet INDG277, Leadership for the major hazard industries, rev1.
- Bell, J. and Healey, N., 2006, The Causes of Major Hazard Incidents and How to Improve Risk Control and Health and Safety Management: A Review of the Existing Literature, HSL/2006/117.
- Mearns, K., Flin, R., Gordon, R. and Fleming, M., 2001, Human and organizational factors in offshore safety. *Work and Stress*, 15: 144–160.
- EFPIA, 2008, The Pharmaceutical Industry in Figures – Edition 2008.
- HSE, 2008, The Buncefield Incident 11 December 2005: The final report of the Major Incident Investigation Board.
- Baker et al., 2007, The Report Of The BP U.S. Refineries Independent Safety Review Panel.
- George, M.L., Rowlands, D. and Kastle, B., 2003, What is Lean Six Sigma? McGraw-Hill, ISBN 0-07-142668-X.
- Fleming, M. and Lardner, R., 1999, *The Chemical Engineer*, 8th July 1999, 14–15.