Producers versus regulators? An enquiry into pharmaceutical quality information systems

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Abstract

Given rising costs and declining R&D productivity, the pharmaceutical industry needs information systems and processes that contribute to business efficiency and cost reduction without compromising fundamental quality and safety principles. This study investigated quality information systems in the pharmaceutical industry and the relationship between the industry and its regulators. The data demonstrated a risk-based approach to information management and a quality-by-design philosophy in the industry, aiming to satisfy the needs of product regulators, optimise manufacturing process efficiencies, and give patients reliably consistent medicines and devices. The data also revealed a problematic perception of regulatory oversight, with highly significant correlations between level of regulator contact and 'difficulty' with regulators (r=0.92) and between difficulty with regulators and delays in IT implementations (r=0.87).We propose that emerging trends in standards-based interoperability offer a new paradigm for the industry and its regulators.

Keywords: pharmaceutical, quality, regulator, standards.

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1.0 Introduction

The pharmaceutical manufacturing industry is heavily regulated and quality driven. This requires the gathering of considerable amounts of data and information to prove product quality. The secondary use of this data also supports continuous process improvement initiatives, dealing with process optimisation, reliability and efficiency aspects of the manufacturing environment. Data integrity, security and traceability are of paramount importance to guarantee product safety. The principal regulatory authorities are the US Food and Drugs Administration (FDA), the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Japan Pharmaceutical Manufacturers Association (JPMA). Joint projects involving the pharmaceutical industry and all its global regulators are coordinated through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

This paper reports a project that examined pharmaceutical product quality information to identify and assess significant issues for regulators, quality compliance professionals and process improvement experts.

The overall aim was to discover whether the pharmaceutical industry is using best practice to manage information and whether the regulatory bodies are having a positive or negative effect on information management.

1.1 Product quality information

Registration of a new product with the regulators includes defining the set of critical quality information that is declared to be imperative to the outcome of the product. This is derived from the stages of drug development, validation, and transfer to production processes. For example, the whole process of tablet production can include: mixing the active pharmaceutical ingredients with excipients such as binders, filler and colouring material, forming the mixture into granules and finally compression into tablet form (Cole, 1998). Each item added to the mixture must be measured and inspected, the vessel itself must be at a specified temperature and also inspected, the weight of the final product must be noted and many other more scientific measurements as well.

Product quality information is information identified from critical stages in the production process of a product. Such information as the pressure a tablet breaks during the compression stage, temperature of a room, weight of a device, signature of completion, and quantities. This data is stored in batch records, compliance records, laboratory data, manufacturing data, training records, calibration tracking records, and audit trails. General automated procedures along the production line will collate and import data into a database. This information is usually printed out, signed, and counter signed and attached to a batch of product, to provide traceability for regulatory bodies. Other bespoke software will manage documentation, quality, product lifecycle, audit, training, bill of materials, and submissions management.

Pharmaceutical companies strive to meet stringent regulations to deliver the highest quality possible. Failure in delivering a satisfactory product can result in prosecution and product recalls. The substantial expense of bringing a new product to market is not recovered when a product is withdrawn from sale. Product recalls can result from patient complaints, regulatory observations or a manufacturer identified problem.

1.2 Regulatory initiatives

Regulators set the information standards for pharmaceutical production and have emphasised the need to ensure that computer systems that run throughout the process of drug production are as safe and secure as the production process and materials themselves.

Part 11 of the FDA's Code of Federal Regulations (CFR) requires pharmaceutical manufacturers to provide controls utilising audits, validation systems, and documentation. These control systems are part of operations and product development. Part 11 also highlights the need to have procedural controls such as training, Standard Operating Procedures (SOP), and administration to support this code. Part 820 further presents the need for a robust quality system in the manufacture of pharmaceuticals.

The Process Analytical Technology (PAT) initiative is a system for designing, analysing, and controlling manufacturing through measurements primarily during processes. Its ultimate goal is to ensure the product manufactured is of sufficient quality (FDA, 2011). The key objectives of PAT are to reduce the production cycle times by using measurements and controls, preventing rejects, scrap, and re-processing. Another key objective is to increase automation to improve operator safety and reduce human error whilst facilitating continuous processing to improve efficiency and manage variability. The tools that assist in this movement are multivariate data acquisition and analysis tools, process analysers or process analytical chemistry tools, along with process and endpoint monitoring and control tools. All of this endeavours to achieve continuous improvement and improve existing manufacturing and associated regulatory practices that do not adequately support or facilitate innovation and continuous improvement. The sole focus of the PAT is to understand and control the manufacturing process.

Additionally there are site inspections; the MHRA, for example, has three types of inspection. The first type scheduled inspections that UK Market Authorisation Holders (MAHs) undergo on a periodic basis. The second is 'For Cause' national inspections (MHRA, 2011). These are *ad hoc* inspections that are triggered as a result of, for example, safety issues, suspected violations of legislation relating to

monitoring of the safety of medicines, referrals by other EU Member States. Finally the last is the Committee for Medicinal Product for Human Use (CHMP) requested inspection (MHRA, 2011). The CHMP may request inspections of MAHs in association with specific centrally authorised products.

1.3 Financial pressures

Whereas the overall research and development cost of bringing a new drug to market has increased from around US$800m in 2003 to something in the order of US$1.5bn in 2009, productivity has declined disproportionately (Collier, 2009). This context demonstrates the pharmaceutical industry's need for information systems and processes that contribute to business efficiency and cost reduction without compromising fundamental quality and safety principles.

1.4 Methods

The methodology chosen for this study comprised two parts. A semi-structured interview was conducted with a Lean Six Sigma process improvement specialist in a major UK pharmaceutical manufacturer, with qualitative analysis based on a hybrid of Soft Systems Methodology (SSM) *(*Checkland, 2006) and Effective Technology and Human Implementation of Computer Supported Systems (ETHICS) (Mumford, 1996). The quantitative element used a survey. This paper reports primarily the quantitative findings, with some illustrative explanatory data from the qualitative work included in the Discussion section.

The survey was distributed via the Human Resources department of a UK-based pharmaceutical manufacturer. As this study is primarily exploratory, a sample size of 30 was judged to be adequate, with interpretive emphasis given to the qualitative interview data. The survey primarily used standardised closed-ended questions to allow stable data to analyse. This simple survey was to substantiate and clarify qualitative findings from the interviews. Quantitative survey data was analysed using SPSS and Microsoft Excel, with Likert scaled items coded to numeric values. Confidence intervals (CIs) and Pearson correlations were calculated for some responses and interrelationships.

Survey questions 1-4 were demographic items, covering gender, employment status, age group and job role. The substantive questions are listed below:

- Q.5: How many times have you been in direct or indirect contact with regulators such as the FDA or MHRA?
- Q.6: How many projects have you been a part of where you had difficulty in meeting regulatory requirements?
- Q.7: Has your company adopted the PAT initiative? (Process Analytical Technology)
- Q.8: How important do you feel regulator involvement is in projects you have been a part of?
- Q.9: If IMPORTANT, please explain why?
- Q.10: Have you or your manager postponed implementing IT solutions because you feel you may not comply with regulations?
- Q11: If YES, please explain why?
- Q.12: I fully understand regulations affecting me in my day to day work.
- Q.13: If No, please explain why?
- Q.14: Does the company you work for support and encourage IT innovation?
- Q.15: How many projects roughly in the past year have you been involved in where information technology was a key component?

2.0 Results and Analysis

Thirty survey responses were received. The sample comprised 27 male and 3 female staff, mostly in full-time employment. Figure 1 shows the age distribution of respondents and Figure 2 shows the range of job roles represented.

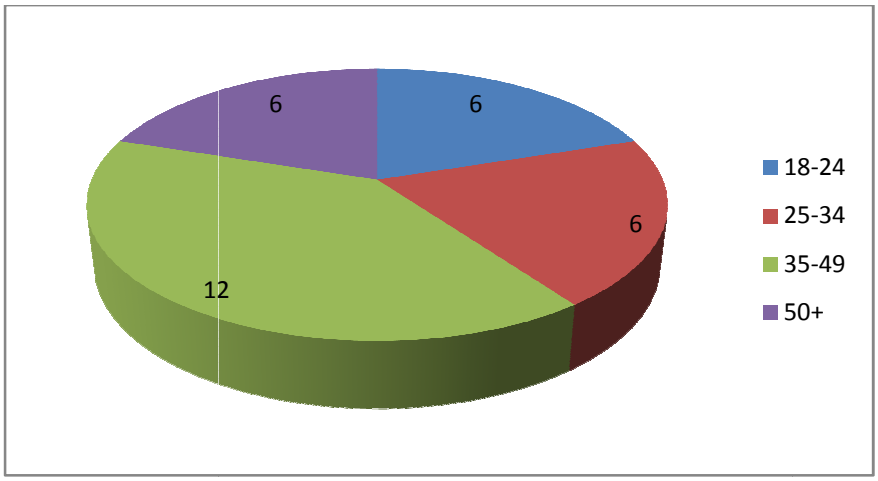


Figure 1. Age distribution.

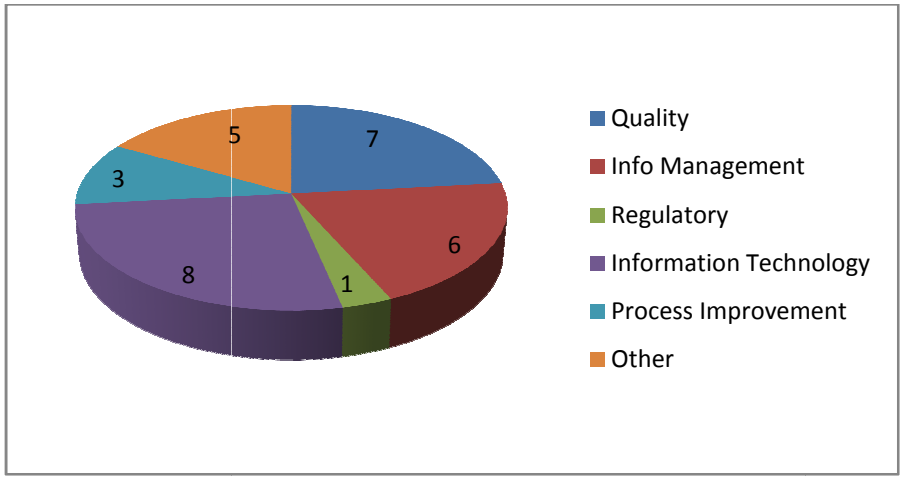


Figure 2. Job roles.

The remainder of this section presents a selection of the most interesting findings.

2.1 Q.5 Contact with Regulators vs. Q.6 Difficulty with Regulators

The Pearson correlation between the difficulty respondents had with regulators and the amount of contact a respondent had with regulators was found to be both substantial and statistically significant with **r(28) = .92, p < .01**. On average, quality professionals spend the most time interacting with regulators at a rate of 21.25 times in their current working career. The survey also indicates they have high rates of difficulty in meeting requirements. This could be due to the fact in quality roles, tasks can be detail orientated and essentially the main aim is to comply with regulators and make sure the product or process is safe and efficient. On average, information technologists have had the most difficulty in meeting regulatory requirements. This could be due to the fact they are not as knowledgeable as quality professionals in regulatory requirements. This could also suggest that IT and Quality have a poor relationship or the business infrastructure doesn't support this interaction. As the correlation is high at .92 it is fair to state that the difficulty respondents had increased when contact with regulators, direct or indirect, occurred. This may suggest that there are weaknesses with the communication between the two parties and therefore may need further improvement as to accomplish a sophisticated communication system. Another area which this highlights is the lack of or poor connection between business and IS strategy. Without a close relationship with the two strategies, gaps in communication and focus can allow conflicting ways of working throughout a company.

2.2 Q.7 - Has your company adopted the PAT initiative?

50% of respondents are aware their company has adopted the PAT initiative from the FDA. This suggests that companies are taking this process analytical technology seriously and or see a serious benefit it can make to the business. The 26% of respondents who 'Don't know' may be as a result of their area of work and they may not be required to know about this FDA initiative

2.3 Q.8 - How important do you feel regulator involvement is in projects you have been a part of?

The 95% CI was 3.49 – 4.24 (on a Likert scale where 'Definitely unimportant' was coded as 1 and 'Definitely important' was coded as 5). This suggests a perception of the regulator as a necessary stakeholder rather than a negative interference. Another area of interest is the two extremes of the Likert scale. None of the respondents chose "Don't Know", this indicates a strong feeling or that it was a simple straight forward question. On the other side of the scale only one person stated that regulator involvement was definitely unimportant; looking in more depth the respondent's role was of a process improvement type. Process improvement can be a difficult role when detailed systems engineering tasks sometimes create friction with regulators.

2.4 Q.8 Importance of Regulators vs. Q.4 Job Role

Table 1 demonstrates the relationship between how the respondents perceive regulator importance within projects and their job role. As the table shows, the majority of respondents opted for 'mostly important'. The purpose of this cross tabulation is to identify if job role relates to what they feel about regulators.

The most interesting result came from the Process Improvement staff, the weight of their answers being in the unimportant category. This may be due to the difficult tasks of re-engineering processes and encompassing strict regulatory rules whilst trying to improve the system.

Job	Definitely Unimportant	Mostly Unimportant	Neutral	Mostly Important	Definitely Important	Don't Know
Quality	0	0	2	3	2	0
Info Management	0	0	1	4	1	0
Regulatory	0	0	0	0	1	0
Information Technology	0	0	1	4	2	0
Process Improvement	1	1	0	1	0	0
Other	0	1	1	2	1	0

Table 1. Importance of Regulators vs. Job Role.

2.5 Q.9 - If IMPORTANT, please explain why?

This question leads from Q.8 and the overall response was that regulators are there to help and ensure products are produced in a safe manner and do what they say they are supposed to do, thus providing substantiated evidence. Another comment states “It is useful to have such a well-developed governing body but at the end of the day we ensure product safety and are always proactive in achieving the best.” This highlights the appreciation of regulators but the industry governs itself and utilises the regulators as a last resort. Two negative responses occurred stating “It is important but sometimes I feel there are too many rules and regulations” and “It can be a hindrance at times.” These responses may be the result of a negative experience in the past and therefore appreciate the importance but believe there could be room for improvement.

2.6 Q.10 Postpone Implementing IT vs. Q6 Difficulty with Regulators

The Pearson correlation between the difficulty respondents had with regulators and the amount of respondents who felt they had to postpone IT projects due to regulatory compliance was found to be substantial and statistically significant with **$r(28) = .87$, $p < .01$**. Although there could be many other factors which may defer respondents implementing IT, this Pearson correlation demonstrates one factor which suggests regulatory involvement in IT projects has stopped innovation. As the correlation is high at .87 it is fair to state that there is a significant issue relating the difficulty a

respondent had and a resulting postponement of IT projects. It is important to state that the postponement of IT projects can have many reasons, however the high correlation suggest there is an issue with how regulators are impacting the adoption of new technologies and systems.

2.7 Q.11 - If YES, please explain why?

This question leads from Q.10 and the purpose was to find out in more detail why the respondent felt they put off implementing IT. The major point identified was that validation was sometimes difficult and complex. One interesting comment stating "CFR part 11 is a pain." This demonstrates that regulatory issues were impacting IT projects and predominantly at the validation stage.

2.8 Q.12 - I fully understand regulations affecting me in my day to day work

The response to this question highlights the majority of respondents believe that they fully understand regulations. Whether their belief is justified could be a possible avenue of further enquiry. However 83% gives a good indication that they are comfortable with regulations and that they perceive them to be understandable.

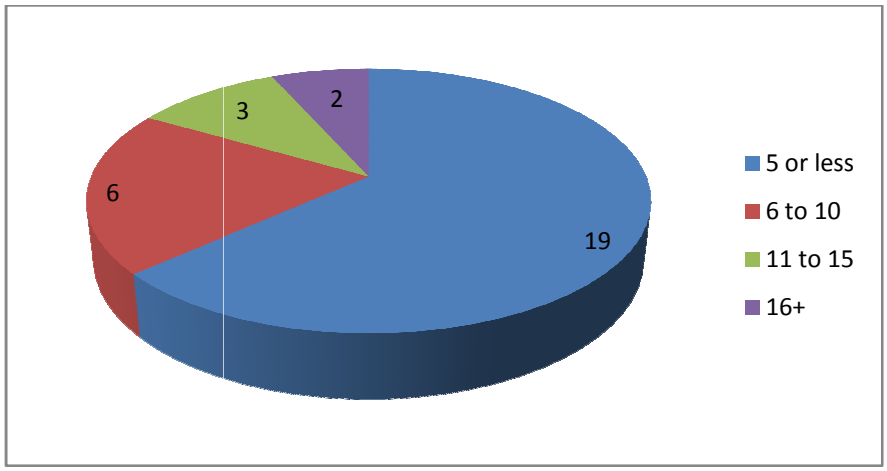
2.9 Q.13 - If No, please explain why?

This question leads from Q12 and tries to identify the knowledge of regulations in a respondent's daily task. The main point presented by the respondents was that it all seems complex. One respondent said "I get informed of big new regulations. The rest is just built into your work from the beginning so you're not really aware all the time." This suggests that significant initiatives such as PAT are presented effectively, however the basic tasks that come from "cGMP" (current Good Manufacturing Practice) are built into the work and therefore do not take much precedence in the respondents mind. From a consultant's perspective the respondent suggests a way they handle regulations. "I take each project as it comes and rely on the company knowing the rules. Close consultation with validation, quality, and the head of the department assist in my understanding. Most of my knowledge is old from when I worked in Pharmaceuticals."

2.10 Q.14 - Does the company you work for support and encourage IT innovation?

76% of respondents agreed that IT innovation is encouraged. 16% of respondents stated they did not know, which suggests they are either not involved with IT as much as the others or that their company does not demonstrate IT innovation effectively.

2.11 Q.15 - How many projects roughly in the past year have you been involved in where information technology was a key component?



63% stated they were involved with five IT projects or less, while there is also a minority of staff who are involved with very high numbers of projects each year. This confirms that IT projects are viewed as routine and are integral to pharmaceutical operations.

3.0 Discussion

It might be expected that regulation is the primary driving force controlling the pharmaceutical manufacturing industry and its technology through strict rules and compliance audits. The qualitative part of this study indicated that although regulation had a formative influence on technology adoption it is no longer the principal factor in the way pharmaceuticals work. Relevant extracts from an interview illustrate this point. The first quotation is recalling the state of the industry in the 1970s-80s:

> "Although I was subsequently in a responsible position in this manufacturing department, I don't recall seeing the 'Systems Requirements Specification', if there ever was one. Regulation of computer systems was limited and relied on

> the expertise of a few individuals. I doubt if there was a formal validation report; whether the computer equipment and its use was verified and properly controlled... The regulators recognised the importance of quality critical information management during the processing of this product, but they put more emphasis on the quality of the end product as determined by various laboratory tests."

This can be contrasted with a subsequent quotation about progress since the 1990s:

> "There was a growing emphasis on process reliability and waste reduction in our Company in an attempt to move towards 'World Class' standards... This was made up of a combination of "Lean Manufacturing" waste elimination and "Six Sigma" process reliability principles. We wanted to move from failure rates of about 99% (analogous to 200,000 wrong drug prescriptions every year) to a six sigma level of 99.99966% (equivalent to 68 wrong prescriptions a year)... The regulatory bodies are now recognizing the mutual benefits of using data, information, knowledge and understanding of processes; to design and make consistently effective drug products... the Pharmaceutical Industry and the regulatory authorities are now growing even closer in achieving their mutual interests: cost reduction and consistently effective and reliable products. But this may come at the result of high initial costs. Some small pharmaceutical companies have limited resources to invest time and money into high quality regulatory compliance and may not be able to adopt the full principles of the PAT philosophy."

The survey data above has indicated that regulator involvement is now perceived to be associated with delays in information system implementations. The drive for process and quality improvement is seen to be vested in the interests of the pharmaceutical industry itself, not something that has to be externally imposed.

The survey results suggest that fifty percent of the respondents are aware that their company is using the PAT initiative and even higher percentage state that their company is encouraging the use of IT in innovative ways. This indicates that, from the historical '*that'll do*' mentality mentioned in an interview, there has been a shift to companies actively pursuing a 'best-in-class' mentality. Although, as suggested, regulators are now working hard to assist in pharmaceutical manufacturing, the

evidence from the survey results portrays a different view. The data shows that respondents who had more difficulty with regulators were then inclined to postpone IT projects. However it is imperative to mention that there could be many other factors that could impact IT projects. Although this is important to be aware of, the close relationship between these two variables suggests that regulators are not always perceived to be having the desired effect on innovation. This is an area that merits further investigation.

As mentioned in the survey research the significance of the correlation is quite substantial and therefore the importance of the result must impact the project. With technology now driving regulation as discussed above, with the PAT initiative, the issue the findings present of the difficulty and postponement of IT projects shows that although regulators are embracing the importance of technology there are still areas most notably communication that need enhancement. This would greatly increase the implementation of IT in the pharmaceutical manufacturing industry. An increase of successful projects would also increase due to the reassurance that the IT systems would comply with regulations. This brings to the forefront the consideration that IT developers and staff must always incorporate the safety of the systems they implement. To conclude, the importance in technology is of great interest to this industry as it can increase production speed, reduce waste, and ultimately ensure quality. This realisation of IT supporting the manufacture of medicine and devices has now led to regulators having to become more aware of technology and enable IT innovation to work its way into moving the pharmaceutical industry into a sophisticated technology driven.

Recent developments in information standards offer a new cooperative paradigm for the industry and its regulators. A good example is the “Identification of Medicinal Products” (IDMP) standard. This was a joint project run by ICH with HL7 (the global authority on standards for interoperability in healthcare IT), CDISC (the Clinical Data Interchange Standards Consortium, who provide file formats for regulated research), ISO (the international organization for standardization) and CEN (the European standards body). The aim of IDMP is to enable harmonized specification of medicinal products, and thereby standardize information flows between regulators, manufacturers, sponsors and other stakeholders. The same organizational

collaboration has also produced information standards for adverse event reporting ("Individual Case Safety Report", ICSR) and is also working on standards for clinical trial registration and results (CTRR). By working in a collaborative and aligned way, the regulators have had a constructive rather than constraining effect on industrial innovation and progress.

We suggest this offers a good pattern for converging and aligning the business, technical and quality interests of the regulators and manufacturers. This kind of cooperative standards-based approach could be transferable to more general regulatory concerns and indeed to helping the industry move away from what is, anecdotally, a needlessly over-partitioned information environment to a more open culture of knowledge and information sharing.

4.0 Conclusions

This study has shown a problematic perception of pharmaceutical regulatory oversight, with highly significant correlations between level of regulator contact and 'difficulty' with regulators (r=0.92) and between difficulty with regulators and delays in IT implementations (r=0.87).We propose that emerging trends in standards-based interoperability offer a new paradigm for the industry and its regulators.

References

Checkland, P. Poulter, J. (2006). Learning for Action. Chichester: Wiley.

Cole, G. C. (1998). Pharmaceutical Production Facilities : Design and Applications [Electronic Version]. CRC Press.

Collier, R. (2009). Rapidly rising clinical trial costs worry researchers. CMAJ, 180(3), 277-8.

ICH. (2011). Harmonisation for better health. Retrieved from http://www.ich.org/home.html

MHRA. (2011). Medicines and Healthcare products Regulatory Agency. Retrieved from http://www.mhra.gov.uk/index.htm

Mumford, E. (1996). Systems design: ethical tools for ethical change. Basingstoke: Macmillan.