What is PAT?

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Introduction

In 1990 I drew a cartoon that suggested that NIR stood for "Nearly Impossible Results". Continuing with this line of thought, PAT stands for "Possible Analytical Theory", but officially it stands for Process Analytical Technology. There are slight variations on the theme but the aim remains the same. Last year there was a European meeting on PAT. In June this year there will be a two-day conference on PAT in London (www.iqpc.co.uk) and in August Tom Fearn and I are giving a workshop on chemometrics to a pre-International Diffuse Reflectance Conference (IDRC) conference on PAT in the Pharmaceutical Industry. Clearly PAT is a current buzz-word, but what is it about?

Outline of PAT

I am not really sure who actually invented the term, but it has been championed by Dr Ajaz Hussain, Deputy Director of Pharmaceutical Sciences, CDER, FDA, and I heard him speak at the last IDRC (August 2002). This was when I first became aware of the acronym and what it was intended to mean. PAT is not like PCA, PLS or SIMCA, it is more like "Chemometrics" but larger! It has to be larger because chemometrics is one facet of this many sided idea that may be a jewel but could end in tears. In its simplest form, PAT will allow manufacturers to deliver a product which will not require post-process testing, because it will have been produced by a process controlled to produce in-spec product. A definition of PAT is given in Box 1.

Figure 1 indicates the present manufacturing framework within which the FDA regulate the pharmaceutical industry[a] and this can be compared with Figure 2 in which some of the aspects that might go into a PAT scheme are indicated. The important point that should be obvious from this diagram is that the "Analytical" in PAT should have a very wide interpretation. It is not just analytical chemistry but the analysis of all the other topics as indicated (and probably several more). The second point is the presence of a feed-back loop in which manufacturers learn about the variability of the manufacturing process so that it can be investigated and the efficiency of the operation improved.

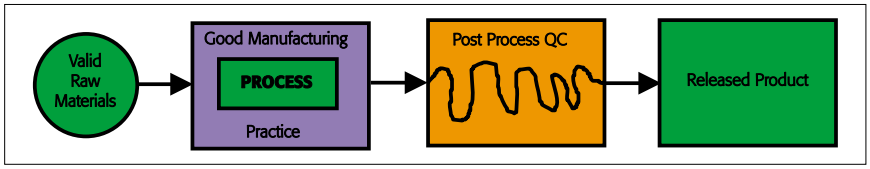

Figure 1. Current FDA regulation of a pharmaceutical process.

Box 1. Proposed Definition of PAT

Systems for the analysis and control of manufacturing processes based on timely measurements, during processing of **critical** quality parameters and performance attributes of raw materials and in-process materials and processes to assure acceptable end product quality at the completion of the process.

Ajas S. Hussain, Deputy Director, Office of Pharmaceutical Sciences, CDER, FDA

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Why is it important

PAT is important because, if it is successfully introduced, it will pioneer a new concept of how regulation should be organised in the 21st century. As it is being driven by the regulators (well some of them), it does have a reasonable chance of, at least partial, success. Some of the larger global pharmaceutical companies are being very encouraging but others are less keen, probably because of the learning curve they see in front of them. But how is the FDA trying to sell it?

Advantages of PAT

The FDA believes that if they introduce PAT, not only will they achieve better regulation while diminishing their costs, they will at the same time make the US pharmaceutical companies more efficient at producing higher quality products and that this will be good for everyone (in the USA). Of course, it extends worldwide because pharmaceuticals may be produced anywhere in the world, but if they are going to be marketed in the USA then the FDA has to be satisfied about their manufacture (www.fda.gov/cder/OPS/PAT.htm). Other regulators cannot afford to be left behind and so this would appear to be a snowball with a long downhill path and plenty of snow; it could become VERY large!

Spectroscopy and PAT

Just for the record, most of you will have already seen the possibilities for spectroscopy; this could be a very important development for spectroscopy. While not all the on-line or near-line analysis will be done by spectroscopy, it will be a large percentage. I will go further: not all the spectroscopy will be near infrared (NIR) but my guess is that more than 50% of the spectroscopy will be NIR. [Especially if you include FT-NIR Raman as NIR spectroscopy (I do!).] So this is an area where spectroscopists should be studying; their contributions are going to be important and if you do not know much about NIR spectroscopy, this could be a good time to learn! (See the

[a]Some pharmaceutical companies have been employing PAT-like processing before the PAT initiative was formulated. But this may well have been carried out without the involvement of FDA as the previous FDA requirements were for post-process quality testing.

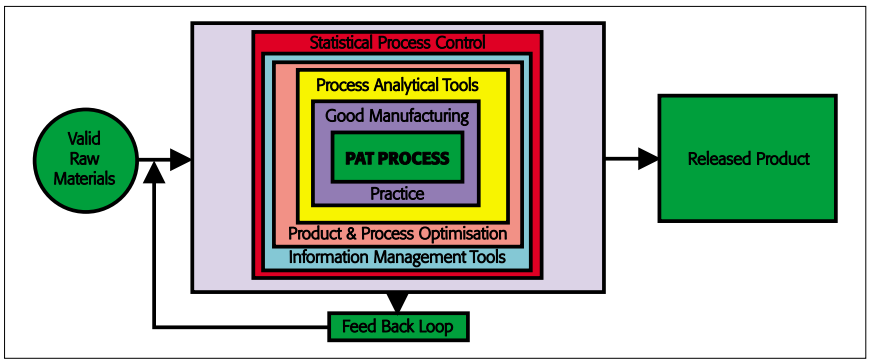

Figure 2. Indication of some of the requirements for PAT.

ICNIRS website for more information: www.icnirs.org.)

Problems of PAT

There have already been problems with the attempt to write regulations for PAT. The FDA is a very large organisation and not everyone in the chain of command has a good understanding of (for example) PCA! Attempting such a large change in the outlook of the regulators creates a need for internal education. At the same time, the snowball can be slowed, if not stopped, by those people and companies who are worried by the idea of change.

If we look in detail at a small scale production and see the requirements for PAT, as in Figure 3, another problem becomes visible. PAT is going to require a large input of chemometrics and some of this effort will be localised and continuous. This will require a large number of staff in production plants with sufficient knowledge and experience to make chemometric-based decisions and be able to justify them to the regulators, in addition to their own management. Where are these chemometric operators going to come from? At present in the UK, only a handful of people per year acquire the required level of chemometric knowledge and I suspect that it is not much better in the majority of European countries. In 2002, Harald Martens put together a proposal for major EU funding for what he called "FoodMetrics". It had the backing of just about every European chemometrician who had done any work in the food sector. It had many exciting proposals but the main thrust was the need to educate far more students in data analysis. It fell on deaf ears in the EU. Some aspects may get funded but the grand design is lost for another decade. It seems clear to me that if PAT is to be successful, then the FDA and the pharmaceutical industry needs an equivalent "PharmMetrics" programme. Who is going to alert the educators? Perhaps this will be debated in June and I hope there will be a positive out come.

If there is not, then I suspect that PAT will remain a "Possible Analytical Theory".

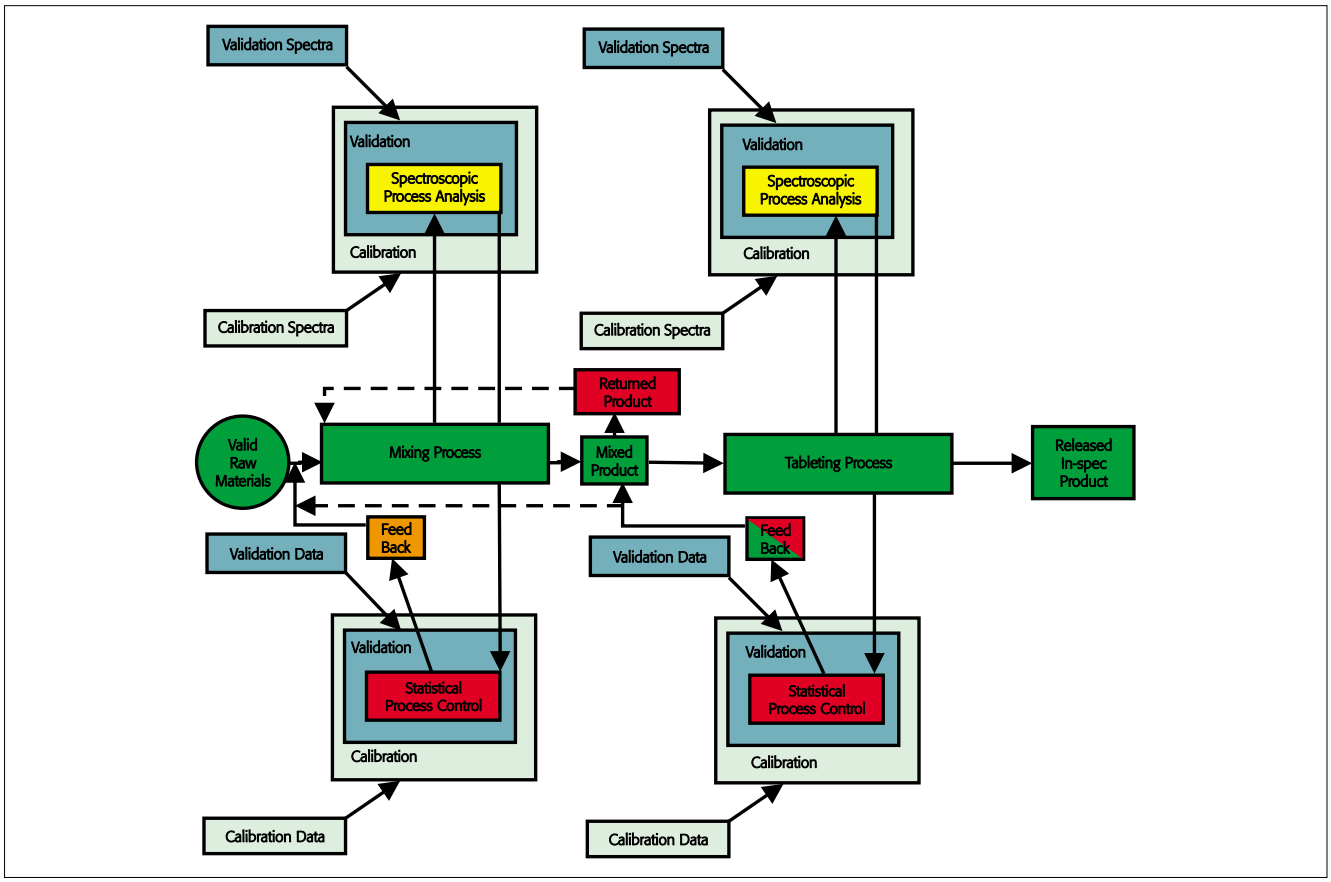

Figure 3. An outline of some of the chemometric operations required for a PAT two-stage process of mixing ingredients and forming the mixture into tablets.