Impact statement - Interfaces/Gaps in Knowledge

Background

The Pharmaceutical industry is, and to my mind pretty much always has been, in a state of development and continuous improvement. Those of us who have been fortunate enough to be heavily involved in the discovery / development and / or introduction of new and often revolutionary types of pharmaceutical products and processes can rightly feel very proud of our achievements. So too can those who take older, well established products and continue to develop their manufacturing processes in order to retain a cost-effective supply chain of safe and effective medicines, which in turn provide real patient benefit.

The recent PHSS annual meeting (which was held virtually) concentrated on some of the newer types of medicines – Advanced Therapeutic Medicinal Products (ATMPs). Great steps forward in medicine are being made with these types of product, but such innovative products and the processes involved in making them are not necessarily straightforward and it can be relatively easy to focus on the sophisticated technology involved at the expense of some of the more basic aspects of current Good Manufacturing Practices (cGMP). This was particularly highlighted in the presentation "GMPs for ATMPs - A Changing Landscape" presented by Philip Rose, Senior GMDP Inspector, MHRA

So, what are the issues/ concerns?

In terms of ATMPs Mr. Rose laid it out very clearly: -

- The rapid increase in use of ATMPs from 200 patients in 2018 to a projected 2,500 patients in 2021
- 93 ongoing ATMP clinical trials in 2019 (up 9% from 2018)
- A resultant increase in new ATMP facilities. Meaning that the GMP footprint for ATMPs is up by 343% over the last three years
- That the AMTP 'Part IV' is a supplement to the existing EU GMPs
- The teams involved in these projects are usually technically very strong in terms of their understanding of the product but...there can often be significant weaknesses in that
    - New facilities may not have an established Pharmaceutical Quality System
    - Personnel will often be new to GMP
    - Many of the issues raised at inspection relate not so much to the product itself but are more in the issues of basic GMP such as but not limited to
        - Change Control
        - • Lack of documentation
        - • Risks not adequately considered
        - • Timeliness – after event
        - • Effectiveness checks
        - Operators do not sufficiently understand GMPs e.g. Annex 1
        - Facilities not designed in alignment to annex 1.

MBH / PHSS comment

These are exciting times but, to my mind, this is not necessarily new nor restricted to ATMPs. In my many years working in the research-based Pharma industry and as a consultant, I would often come across the same issue when helping take new products and processes from R&D into routine production. In the early days R&D would often develop a new product or process and then literally "throw it over the wall" into the manufacturing site for them to get on with it, whilst R&D moved on to the next, now more important project. Their job was considered as done!

Behaviours were seen where manufacturing did not like to have R&D present in their plant and R&D did not like to be asked "Why do it this way?". The more enlightened companies soon learned that each side had much to learn from the other and introduced the concept of new product / process introduction teams which led to faster more efficient product/process transfer. It also sometimes led to the more permanent transfer of personnel as Subject Matter Experts between R&D and Manufacturing & vice versa.

Also, the introduction of Pre Approval Inspections (PAI) particularly by the USFDA helped cement this team approach to new product and / or process introduction to a manufacturing site, not only up to the satisfactory conclusion of such an inspection, but on an ongoing basis as trusting relationships were formed in both camps. Though it often came as a surprise that a 5 day PAI often for a non-biological product spent at least 75% of the time focused on GMP. Though this is not the case for biological pre-PAI

I have also, particularly as a consultant, seen issues in the area of other new (not necessarily ATMP) innovative products or combination product/delivery devices. These can and do involve issues as to how the product is classified and what regulations apply. In such cases, the MHRA Innovation Office provides free and confidential expert regulatory information, advice and guidance, so prepare as much information from a product and GMP standpoint as you can and then call them for advice as to decision making and future direction. It really does make sense to do so.

Opportunities.

ATMPs and innovative medicinal products are exciting new fields in pharmaceuticals. They are probably well served in terms of R&D resource but could well be lacking in GMP and PQS knowledge and experience across the spectrum of activities from plant design and construction through GMP Subject Matter Experts (SME) to the Qualified Person (QP) who has in depth understanding of the industry, its regulation and has the legal responsibility to certify batches of medicines prior to release

Whilst ATMP manufacturing processes may be complex, or may appear daunting to an individual who has a long career and experience in conventional pharmaceutical products, in reality they are not when broken down to high level unit operations such as propagation/production, separation/purification, formulation etc. In fact, many of the techniques used in an ATMP manufacturing process e.g. chromatography, filtration etc. may be very familiar to such an individual. What, however is definitely true, is that fundamental understanding and application of GMP is certainly a directly transferrable skill; and based on the feedback from Mr. Rose, something some ATMP manufacturing companies may well be crying out for in a potential future employee.

Could this offer you as an individual the opportunity of an exciting new career in this branch of medicines production or as a regulatory inspector?

Prepared by Malcolm Holmes C Chem. MRSC - PHSS Regulatory SME November 2020