1. Introduction

Multi-faceted leadership in sectoral industry research in the pharmaceutical manufacturing sector, such as is evident in this monograph, is really important as we get more breakthrough therapies and as we get more complex technologies. This paper focuses on the Pharmaceutical Quality System (PQS) for Advanced Therapies (ATs) and specifically the role of QRM (quality risk management) and KM (knowledge management) within that system. I will commence by talking about what Advanced Therapies are, the challenges they pose, or, more particularly, the challenges of assuring their quality, and the current pharmaceutical quality paradigm. There will be inevitable overlap with other papers in this monograph, but it is necessary to contribute to discourses about both QRM and KM as they currently are, and as they need to be, to deal with new products into the future.

For me, medicinal products, where the active substances were genetically engineered, with well-characterised biologics, marked the dawn of a new era for medicines. In a way, we are now in a new phase of this new era, and this phase can be considered as the Advanced Therapies era as this new class of more complex biologics are rapidly coming to the forefront. Indeed, some of these ATs are personalised medicines with the various complexities associated with that concept.

In this paper I propose that, in light of the complexities of these new products, we need to look again at the PQS, albeit it is not that old, and how it is configured, particularly with respect to QRM and KM – two really critical elements of the modern PQS. I also want to draw attention to the importance of Regulatory Science Ireland and their support for research and discussion on these matters. In RSI, and particularly with the Dublin Institute of Technology (DIT) and University College Cork (UCC), we have been drawing attention to the need for critical research in regulatory science and the importance of such research for the continuing vitality of this sector in the overall national economy. One practical example where RSI may be able to contribute is in facilitating the move towards a formal certification process for QRM facilitators as mentioned in Magda Bujar’s paper.

2. The new era of complexity and Advanced Therapies

In 2017, the USA FDA (Food and Drugs Administration) approved Kymriah, Yescarta and Luxturna, three new AT medicines which illustrated to many that we have entered a new era. Indeed the FDA Commissioner Dr
Scott Gottlieb commented in a news release in December 2017 coinciding with the Luxturna approval that: “...more than 600 active investigational new drug applications related to gene therapy products. Researchers at the Massachusetts Institute of Technology estimate that about 40 gene therapies might win approval by 2022, from a current pipeline of 932 development candidates. They estimate that 45 percent relate to treatments for cancer.”

Dr Gottlieb further stated at the Alliance for Regenerative Medicine Congress in May 2018: “We’re at a key point when it comes to cell and gene therapy. These therapies have the potential to address hundreds, if not thousands, of different rare and common diseases.” So, we can forecast a dramatic change in high-technology medicines with possibly 45% of those related to treatments for cancer. Essentially, this is just the tip of the iceberg. There are a lot of other new products dealing with other medicinal problems on the horizon also. In parallel with this regulatory activity the last year or, two has seen a phenomenal growth in business interest in the area at this time, with pioneering companies in this field being acquired by more established BigPharma for eye-watering sums and new governmental initiatives, such as, the Cell and Gene Therapies Catapult in the UK.

2.1 Advanced Therapies

The term Advanced Therapies originated in the European medicines regulatory system and is incorporated into an EU Regulation issued in 2007 (Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004). Essentially the definition of Advanced Therapies includes medicinal products based on three different types of technology, namely: gene therapy, somatic cell therapy and tissue engineering. The FDA traditionally refers to these as cell and gene therapies. The term Advanced Therapies is gradually gaining broad global acceptance and is becoming more commonly used.

In this context Kymriah and Yescarta are two cell therapies, i.e. the active component of the medicine consists of living cells. They are both CAR T cell therapies, which I will explain further later. Luxturna, on the other hand, is a gene therapy whose active component is a virus that has been genetically engineered to carry a gene into the cells infected by this virus and the expression of this gene has a beneficial therapeutic effect.

Kymriah and Yescarta are both personalised CAR T cell therapies in that they are based on blood-derived T lymphocytic cells from an individual that are modified in the laboratory and then reinfused back into that same individual to achieve their therapeutic effect. This type of product has been described as an arm-to-arm therapy with the patient at its centre. A sample of the patient’s blood is taken and the T lymphocyte fraction purified from the blood plasma. These cells are then cultured in vitro in a cell culture laboratory environment during which they are activated and genetically modified using a retroviral vector to express a so-called chimeric antigen receptor (CAR): The CAR T term being the acronym of Chimeric Antigen Receptor T cell. The genetically modified T cells express this receptor on their cell surface as an integral membrane
protein. In Kymriah the receptor is directed against a particular antigen called CD 19. Different CAR Ts could (and indeed are being) generated against various other antigens as well as CD 19. However, CD 19 was selected in the first instance as it is an antigen that is expressed on the surface of B lymphocytes during their development and commonly on cancers that arise from this type of cell - notably B cell lymphomas, acute lymphoblastic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL). The majority of B cell malignancies express normal to high levels of CD19 and it appears that the CD 19 protein plays an active role in driving the growth of these cancers, making it a very desirable target for therapy. The engineered cells are cultured for a period of time to expand, or increase, the number of cells. As that process is on-going, the patient receives a preparative chemotherapy therapeutic regime that will deplete their circulating lymphocytes. Then the engineered CAR T cells are infused back into the patient. Within the patient they grow and divide, and bind to circulating cells expressing the CD19 antigen. Through this binding an immune response is initiated by the CAR T cells leading to killing of the CD 19 antigen carrying cancer cells. Clearly this is very different from the conventional therapies we are used to in the world of pharma or biopharma. The medicine is a living cell rather than a relatively simple (in the case of the classical chemical drugs) or, complex (in the case of the newer protein based biological drugs) molecular substance. Because these Advanced Therapies are so different they present certain new and different challenges in terms of how they must be dealt with to ensure that there is a consistent quality from batch to batch. Indeed, Dr Gottlieb spoke about these challenges in a 2018 presentation to the Alliance for Regenerative Medicine’s Annual Board Meeting when he stated that compared to traditional drugs the agency review is focused on the clinical part of the product, with less focuses on the product-related issues. But he continued that “I’d say that this general principle is almost completely inverted when it comes to cell and gene therapy. The initial clinical efficacy is often established early, and sometimes in small series of patients. The more challenging questions relate to product manufacturing and quality, or questions like how much you can change, or enlarge, the gene cassette that you load into a vector before the gene insert will change the conformation of the vector in ways that also fundamentally alter the entire product’s safety or performance.” So, the new challenging questions for the Regulator are around quality manufacturing and product consistency issues. As framed by Dr Peter Marks – Director of FDA’s CBER Division – who will be the primary point for review of such products, these questions would include issues like:

- Product consistency: e.g. How can the sponsor ensure the extent of lot-to-lot variation in transduction efficiency is acceptable?
- Product tracking and labelling: e.g. For a personalised medicine it is critical to ensure that the correct product is administered to the correct patient, so how does the sponsor guarantee their system is error proofed?
- Testing for potency: Assurance of consistent potency between batches is a foundational element of assuring product quality and one of the key issues for cell and gene therapeutics that may have a number of biological effects is deciding which assays are most appropriate?
- Testing for replication-competent vector: Assurance of product safety requires understanding and
control of the generation of variants of the vector that develop a capacity to replicate. There are
different assays in this area but generally all are extremely complex and possess different sensitivities
and consequently limits of detection. So, there is an onus on the sponsor to justify the adequacy of
their chosen method.

- Personalised products: For most, if not all ATs, the time window for release testing may be limited
and there may be insufficient time to execute lengthy assays (e.g. the conventional sterility test). So,
the sponsor may need to justify progressing the product to the patient before certain tests have been
completed. Indeed, for personalised products (such as CAR T cell therapies) made from biological materials from
individuals with serious life-threatening illnesses there can also be difficult decisions to be made if
some specifications fail to be met, but the product represents a ‘last chance’ for the patient.

Many other questions could be asked particularly in regards to the management of changes. Every time the
product sponsor needs to deal with different vendors, particularly of critical reagents. How can the sponsor
determine the criteria for the acceptance of specific changes that potentially could have ramifications,
particularly further along in the process? So, that is just one aspect of the challenges before us.

3. Is the process the product?

At the recent inaugural CASSS meeting on Cell and Gene Therapies in Washington, DC, the keynote speaker
CBER’s Dr Peter Marks commented that for ATs ‘the process is the product’. Interestingly, this is what was
always said in the past and was always the key differentiator between small molecule pharmaceuticals and
the biological pharmaceuticals. The concept was that small molecule pharmaceuticals can be characterised
analytically in the laboratory, whereas biological pharmaceuticals were thought of as akin to a black box. In
the context of a situation where ‘the process is the product’ the implication is that you need to control every
element of the process so that you get the same product every time. Otherwise a clinical trial would need
to be done with every batch. When rDNA derived protein biologicals became commonly available, along
with increasingly powerful analytical methods for their characterisation and routine control, there was a
push-back against the simple notion that ‘the process is the product’. As a result, over time the notion of
the well characterised protein biopharmaceutical became established leading ultimately to the acceptance
of biosimilars that are similar to, although not necessarily identical to, the originator product. When dealing
with a well-characterised molecule change was acceptable once it was done under a comparability protocol
type system which was gradually accepted by the major worldwide regulatory agencies. Consequently,
Marks’s comment seemed potentially controversial but was accepted by the audience without any significant
disagreement.

So, for advanced therapies we must start from the position that once again ‘the process is the product’ and
manage in that light the challenges of introducing changes to them, such as scaling up, changing different
vendors, and so forth, that seem highly likely to be required through the products lifecycle. In this situation
a key question is how can quality be assured without going back into clinical trials again every time a change
like those mentioned above is necessary?

It is clear that Dr Marks had not made an off-the-cuff remark as he has made similar comments in 2015
when specifically speaking about CAR-T therapies. At that time, he said that the quality challenges of CAR Ts
included product consistency: fundamentally – how can the sponsor be assured that every lot is the same
when there are so many variables that potentially effect it?

Testing for potency was another big topic at the CASSS meeting. It is a very complicated area in a context
where protection and the product are the most important things. In summary, with Cell and Gene Therapies
we are entering a new era and we must expect to face new challenges around the systems we use to ensure
that at all times the patient is protected in the context of a fit-for-purpose quality system.

4. An ideal quality system?

Can we imagine what this pharmaceutical quality system might look like? To do so we need to start with the
nature of the entities we want to control and how they differ from what the classical PQS was designed for.
Essentially the current PQS as described in ICH Q10, and as shown diagrammatically in Figure 6.1, was described
when most quality experience had been with small molecules largely (although not exclusively) formulated in
relatively simple ways and with the avalanche of protein-based biologicals looming. In transitioning from the
small molecule to the biological we went from a relatively small and manageable number of quality impacting
variables requiring control to an order of magnitude larger number. In moving to advanced therapies we add
further orders of magnitude of impactful variables.

![Figure 6.1 — The Pharmaceutical Quality System](image)
Being imaginative, one could envisage that we have gone from something like the horse and carriage via the racing car to the space shuttle as we go through these different entities.

Whatever analogy one uses the reality is that advanced therapies are both highly complex and highly diverse and it seems intuitively obvious that the level of control required, the level of education and training required to assure their control is more demanding and sophisticated than when dealing with the simpler categories of medicines.

It is also sadly the case that, if you look at the history of great technological endeavours like the space shuttle, you can have relatively simple quality and cultural defects leading to human disasters as in the case of the Space Shuttle Challenger where a defective O-ring seal led to the failure. Indeed, it is reported that some of the engineers in NASA at the time suspected the O-ring might not be adequate. Sadly, their concerns never navigated up the management levels in the organisation, which goes to the very heart of the culture in the organisation.

5. The main challenge facing us now

Ultimately, the core issue for Advanced Therapies is the challenge of the number of variables in their manufacture relative to their predecessors. How then can their quality be adequately controlled within the current, conventional paradigm which is the ICH Q10 pharmaceutical quality system and its associated documentation?

The essential thing that must be done is to ensure that the number of impactful variables is manageable and this can only effectively be achieved by continuously, iteratively ranking the variables that impact on the quality of the product. Therefore, the variables with greatest potential quality impact must be identified. These then need to be rank ordered and this order continuously adjusted as more pertinent information is acquired and translated into knowledge. This involves systematic utilisation of all the knowledge that is generated through the life-cycle.

Translating this into the workings of the current PQS approach, quality risk management (QRM) and knowledge management (KM) systems, need to be systematically used from the outset of development i.e. from the inception of the product through its discontinuation. So QRM and KM need to be placed at the centre of the PQS and applied systematically from the very earliest phase.

Arguably there is nothing particularly new about this. Indeed, in the 2003 conception of the ICH Q10 PQS it was stated that the objective of the PQS was to develop a harmonised quality system that covers the lifecycle of the product, that emphasised an integrated system of QA and science, involving both QRM and KM as enablers. So, our PQS becomes all about systematic valid data rather than a more ad hoc approach to quality that arguably preceded this. So, in a way, that was conceived at a particular point in time. The diagram in Figure 6.1 has been around for quite some time and is useful in thinking about the essentials of
6. **Operationalising QRM**

In considering the operationalisation of QRM an organisation needs to recognise that risk *assessment* is not risk *management*. Indeed, QRM is just one component in the total enterprise’s management of risk, and this should also include at least safety risk management, regulatory risk management and business risk management. A fully-operationalised QRM system should have the following three elements:

- **Infrastructural element**: including quality standards, various QRM-related processes, a library of risk assessments etc.
- **Communicative element**: a process of risk reporting, and a process for decision-making tied into the reporting process
- **Training element**: training from the introductory level up to the certification of facilitators for example, is essential with supporting tools and processes.

This need for certified training is also dealt with in other papers in this monograph. So that is what I mean by operationalising risk control.

Finally, it is also essential to have a risk control strategy associated with the product or facility concerned, and an associated risk register, all of which are subjected to systematic risk review rather than periodic review.

7. **The future**

So, the future ATM PQS will need to have QRM and KM fully operationalised within the pharmaceutical quality system. That means that there is an on-going review of the variables that are most impactful in the context of the known risks to quality and to scientific understanding of the knowledge and processes generated up to that point in time.
QRM and KM need to be co-enablers at the centre of the pharmaceutical quality system, so that they are continuously referenced in quality decision-making with all the other tools. Thus, change control processes need to systematically refer back to the risk register and so on. This approach must commence at the outset of product development and not just be added on at some later point in time.

In conclusion, ATMs are beginning to emerge as effective, highly personalised therapeutic options. This complexity requires a rethink of how they can be effectively controlled to ensure their on-going consistency and adequate quality and safety. The PQS of ICH Q10 provides a good starting-point for this, but we need to ensure that QRM and KM take their place as originally envisaged as ‘enablers’ of quality rather than merely as occasionally utilised tools within the PQS. QRM and KM need to be fully operationalised and integrated into all quality systems. Disposition decisions need to consider, not only the specific data related to that lot of product, but also the overall quality risk profile and the product knowledge profile, updated as of today.

Endnote

This contribution is merely a start and ideally will lead to more dialogue between regulators and the end-users to help define in greater detail what are the required characteristics of this type of use as an ‘enabler’. Hopefully the excellent work of the DIT group will catalyse this dialogue. Such a dialogue is merely the beginning because an effective PQS for Advanced Therapies may also need other changes. So, for example, in terms of culture, we need a culture that firstly motivates the least motivated, and secondly, ensures that knowledge and information are appropriately communicated through the organisation in a manner that is in the best interest of the patient. For regulatory science it is the essential key, and I applaud the academic work that lead to the publication of this monograph. I also applaud the colleagues who continue to give enthusiastic leadership in this regard to continue making Ireland a locus of quality manufacturing for the pharmaceutical industry.

References