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GLOBAL UPDATE ON THE CELL & GENE THERAPY REGULATORY LANDSCAPE

SPOTLIGHT

EDITORIAL

New Gene Therapy CMC Guidance from the FDA – A Breakthrough in Regulation or Something More Generic?

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Since his appointment as Commissioner of the FDA in May 2017, Dr Scott Gottlieb has expounded his perspectives with greater panache than most of his predecessors. After surviving combative commentary on his prior pharmaceutical affiliations, in venues ranging from CNN to the New England Journal of Medicine [1], he has emerged as a utilitarian voice of reason. All this in an era when, perhaps for the first time in human history, we can make more effective drugs than we can afford. Recent pricing of cell and gene therapies has driven many headlines. But, despite the Commissioner's background in industry, it is now his job to ensure the 'safety, efficacy and security of human…drugs' [2]. The set of revised guidance for cell and gene therapies has, therefore, been much anticipated. These were promised at the Alliance for Regenerative Medicine RMAT Policy Briefing, in May of this year, and delivered – faster than promised – in July [3]. Pre-eminent was the Chemistry, Manufacturing and

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Controls (CMC) draft guidance [4], the first significant update in this area in over a decade.

This latter fact has itself been a bone of contention between practitioners in the field and regulators for most of that decade. With the definitive understatement within the new guidance being "The field of gene therapy has progressed rapidly since we issued the April 2008 guidance", it is regretful indeed that such time elapsed between updates. However, looking forward, does this revision debut a new era in the regulation of these much-heralded and complex therapeutics? The answer, like the answer to many questions in this field, is 'yes, and no'.

The most definitive organizational change to guidance, relative to the 2008 document, is systematic adoption of the Common Technical Document (CTD) organizational structure. This set of dossier specifications, for the submission of information about new drugs to regulators, is maintained by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). While law in many countries, ICH guidelines were for a long time only guidance relative to the FDA. At last this is changing, along with increasingly mandated electronic submission [5].

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This significant organizational change is concisely explained in Section I. of the new document, followed by more background, referencing the appropriate sections of the CFR in Section II. Section III., referencing Module 1 of the CTD, 'Administrative Information', provides exactly that. The often ephemeral nature of cellular Drug Substance is addressed with clarity in Section IV. B. of the guidance, along with brief commentary on combination products (Section IV. C.) and chain of custody (Section IV. D.).

Then come the big changes. The 2008 guidance divides between 'Product Manufacturing and Characterization…' (Section III.) and 'Product Testing' (Section IV.). The 2018 document has a single section for 'Manufacturing Process and Control Information' (Section V., which corresponds to Module 3 of the CTD), divided into a Drug Substance sub-section (A., corresponding to 3.2.S in the CTD) and a Drug Product sub-section (B., corresponding to 3.2.P in the CTD). This CTD-formatted section devotes 28 pages to Drug Substance and a further 12 pages to Drug Product, out of a total of 52 pages.

But beyond significant reorganization of the document, are there material changes to guidance? Unfortunately, no. In fact, much of the 2008 guidance is essentially cut and pasted into the 2018 document, and much of the new material is lifted directly from the verbiage in the CTD guidance itself.

There are multiple, unexploited areas in which the FDA had an opportunity to introduce clarity and

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simplification into the regulation of these complex products.

One area of confusion is the FDA's description of gene-modified cell therapies as 'gene therapies'. The ideal way in which to segregate regulatory guidance of Advanced Therapy Medicinal Products (ATMPs), to use the European (EC No 1394/2007) definition, is:

- **Cell Therapies** which are 'Pure Play' (non-gene-modified): these are almost always allogeneic in origin, often embryonic stem cell products, or different flavours of mesenchymal lineage cells manufactured from sources such as bone marrow, peripheral blood and placenta. This commonality results in their sharing many manufacturing and quality challenges, warranting distinct and detailed guidance, especially around tissue procurement, control of expansion, differentiation into desired phenotypes, and limit tests for critical impurities. For the latter example, the new guidance's Section V. B. 5 'Control of Drug Product', corresponding to 3.2.P.5.2 of the CTD Module 3, could very productively be expanded in this area

- **Gene-modified Cell Therapies**: these can equally be autologous or allogeneic in origin, but the majority of the CMC regulatory challenges reside in the gene modification itself, be it virally or otherwise mediated. Again, this distinction warrants its own separate guidance, providing specific recommendations about tissue procurement and supply chain integrity, the vector and transduction, and, for autologous products, product consistency and control. For the above example of supply chain integrity, the new guidance's Section IV.D. should provide much deeper insight into the critical issues around software, hardware and human factors contributing to distribution of autologous raw materials, equipment and products

- **Gene Therapies** which are 'Pure Play': in these products, the gene-modifying vector is itself the product. Recently dominated by viral vectors such as AAV, in this class of product the cell is relegated to the position of host early in the manufacturing process, more reminiscent of its place in monoclonal antibody production. But, once more, a distinct set of regulatory challenges, many centred around genetic integrity and stability, and reversion to replication competence, warrant their own deep but clear guidance. Here, for example, more contemporary molecular genetics and analytics guidance around Section V. A. 4. b 'Analytical Procedures', corresponding to 3.2.S.4.2 of the CTD Module 3, would be welcomed by industry

This set of guidance documents will have to remain dynamic, as the field is evolving in real time. For example, gene editing technology is already permeating cell therapy, and there exist multiple examples of 'autologous gene therapies' in development, particularly exploiting neoantigens in cancer. While there are obvious commonalities between the above three classes of ATMPs,

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regulation of which could still be captured in a more general guidance such as the CMC 2018 draft just released, the clarity and benefit which the above three proposed, focused documents would bring is considerable.

Not to neglect bacteria and other organisms' use as therapeutics, but these should, for now, be grouped into an 'everything else' guidance, at least until one or more of these approaches grows enough for its own document.

Arguably the most significant therapeutics-related events of the Gottlieb era FDA have been the approvals of the cell and gene therapies Kymriah®, Yescarta® and Luxturna™. All three drugs were approved from relatively small clinical trials. The basis for the Office of Tissues and Advanced Therapies' approval for Yescarta® was a Phase 1/2 clinical trial (ZUMA-1) which treated 101 patients, for Kymriah® was a Phase 2 trial (ELIANA) which treated 68 patients, and for Luxturna™ was a Phase 3 trial which treated 29 patients. These statistics show clearly that the approvals were achieved with quite unusually low patient numbers in, mostly, unusually early stage clinical studies.

This trend is likely to continue in multiple areas of cell and gene therapy. The products in this field are suddenly reaping the benefit of decades of diligent work, generating stunning efficacy data at earlier points in the clinical development process than regulators are accustomed to. The problem is that products obtaining their commercial license out of small, mid-phase trials are unlikely to have commercial grade CMC.

A sobering example of the corporate and medical risks involved is the recent report of manufacturing problems with Kymriah®. In their Q2 2018 earnings call, Novartis disclosed that they have 'seen some variability in our product specifications' [6]. From what little Novartis has divulged, it seems that the FDA mandated an increase in the Kymriah® cell viability specification, between the ELIANA trial and commercial production. This appears to have resulted in an unanticipatedly high failure rate for adult DLBCL patient products, whose manufacturing is performing worse than the pediatric ALL products on which the original approval was based. Presumably, the design space built around the pediatric product, whose cells might well be expected to grow better, was not large enough adequately to accommodate all adult patients' products. In fact, Novartis, in their earnings call, made only the modest claim of being able to deliver the therapy 'to the majority of patients'. One hopes that is actually significantly more than 50%. But one must also note that the Kymriah® manufacturing success rate during clinical development already hovered between 91 and 94%, as opposed to a 99% success rate for Yescarta®.

Whatever the resolution of this emerging issue, it is clear that, to some extent at least, pre-licensure

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manufacturing methods for Kymriah® have not fully supported commercial manufacturing and clinical line extensions.

So, one critical area in which the FDA could impact this field is a crystal-clear definition of the 'CMC Must Haves' for cell and gene therapy licensure. One could envision scenarios wherein the CMC kernel is insisted on pre-Biologics License Application (BLA), and post-approval commitments are made to complete the package. A hypothetical example might be an approval package including several qualified, semi-quantitative release assays, and a commitment for them to be rendered fully quantitative and validated two years later. A more concrete example could readily be constructed around the Kymriah® viability issue. If a clear threshold for acceptable viability in clinical development, and an equally clear, raised threshold post-approval, had been promulgated, perhaps Novartis could have stepped ahead of the problem. This would have been a preferred outcome for all.

CMC development funding is never unlimited, and more significantly, neither is the time available, especially with rapid clinical achievements from small trials such as those listed above. What is needed is guidance on where to focus this pre-BLA CMC spend. While in no way should the field expect, or even want, approval of drugs with watered down CMC, there is a genuine thirst for regulatory opinion on appropriate focus.

Commissioner Gottlieb's recent tweetorial on 'what FDA is doing to modernize clinical trials' [*sic*] [7] is a clear and eloquent call for compression of the clinical trial process, using methodologies including hub-and-spoke Master Clinical Trial Protocols (MAPs) [8] such as I-SPY 2, and Seamless Trials [9] for breakthrough-designated drugs. It outlines a roadmap for meritocratic, evidence-based streamlining and compression of the approval process. The days of the classical Phase 1, Phase 2, Phase 3, BLA approval process are clearly numbered, especially for ATMPs.

Approvals out of (what will soon formerly be known as) Phase 1 or Phase 2 will become the rule rather than the exception. Look for patient numbers in the ZUMA-1 and ELIANA range, for future therapies as effective, or more so, than the trailblazers which were Kymriah®, Yescarta® and Luxturna™.

And poor old cell and gene therapy CMC? Will it be left behind in the dust, always on the critical path,

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standing between patients and this new generation of therapies? Yes, it will. Unless the innovative spotlight of enlightened regulators is focused on CMC as much as it is being focused on, for example, the statistics of trial design. If there can be a Clinical Trials Transformation Initiative (www.ctti-clinicaltrials.org), why should there not be a Cell & Gene Therapy CMC Transformation Initiative? And why should not the FDA lead boldly and further in this direction?

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