Translation of 3D bio-printing into medical practice: learning from related fields to focus our efforts.

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Our community has a great and important vision – the routine use of customised living 3D bio-printed living products that will transform medicine by permitting new approaches to patient care. Conferences, publications and this new journal exemplify both the promise and the scientific energy of the field.

Our hope is that we will be able to build upon earlier successes. 3D printing is becoming routine in surgery planning. This as a consequence of the energy of the people involved, clear application pull and a commercial environment with business led leadership – in particular a strong company that has shaped and pioneered the field. It is also a consequence of the engineering community understanding its fit with the practice of medicine, those who practice medicine and the necessary regulatory pathway. Conventional 3D printed materials are now beginning to be applied in medical device settings of increasing complexity. This is once again a consequence of a clearer understanding of the principles of the regulatory pathway that allows them to be used – that the properties of the materials and structures made by 3D printing /additive manufacturing are equivalent to the properties achieved for the product via conventional manufacturing. We are also seeing significant benefit from the application of 3D printing techniques to personalised and customised prosthetics, delivered by a regulatory pathway for manufacturing extending that of traditional craft processes carried out in hospital settings. We have demonstrated that we understand our fit as a community with medical device regulatory pathways for both products and manufacturing and we have understood how we add value to the practice of medicine and have identified our fit with the practice of medicine.

We do however need to be careful on how excited we get about our more visionary products – they are much more complex –and in many cases have 3D printed forms, include living cells and complex micro and macro structures, and are customised – ultimately with the ambition of creating organs for transplant that are physiologically equivalent to human organs. Many also see the logical setting for their manufacture as in a number of specialist hospitals rather than in a conventional centralised “factory”. As a community we need to be prepared for the effort that will be required to translate these new and emerging technologies from the laboratory bench to the bedside - this is the only way we will bring benefit a to large number of patients.

Translation of a medical technology requires some fundamental questions to be addressed by a developer taking account of the perspectives of a range of important stakeholders:

- Technology – does your product work and can you make it?

- Regulation – how is it interpreted and applied to your product, product approval including clinical trials, and Good Manufacturing Practice (GMP) manufacturing?
- Reimbursement and cost of goods – is anybody going to pay for it? This is especially important in our cost constrained healthcare systems. Will we be able to generate a profitable margin?
- Adoption and clinical pull – will anybody use it and will they be able to persuade somebody to buy it?
- Will anybody invest, and under what business model - pharmaceutical, device, combination product, service or procedure?

For 3D bio-printed products some of these questions are particularly testing and will particularly exercise a community with manufacturing roots like 3D printing. Significant challenges fundamentally derive from the likely regulatory classifications of 3D bio-printed products if they include living cells within some form of “scaffold”. In the US these are likely to be combination products including a biologic and in the EU, combination products including an Advanced Therapeutic Medicinal Product (ATMP). The regulatory pathways for ATMP’s using cells alone are particularly complex and challenging to navigate. In the 3D printed case there are the added complexities to the product regulatory pathway of a scaffold including a macro or micro structure, essentially resulting in the combination product designation, there are also many challenges in customised regulated (GMP) manufacturing.

It is important to recognise that ambiguities and uncertainties in regulation considerably impacted the closely related field of cell therapy, these ambiguities only being resolved in Europe in 2007. Getting regulatory clarity and moving from “case by case” product regulation is still an important focus for the cell therapy, this was product focussed at first but is now increasingly addressing manufacturing. 3D bio-printing requires similar clarity.

Key manufacturing complexities arise from customisation in particular the Computer Aided Design-Computer Aided Manufacturing (CAD-CAM) model compilation and code generation steps that generate the instructions for the printing machine. The sensible expectation that such products will also be delivered in a number of different and distributed clinical centres is also complex to address when the expectation is that the products will be the same in the different hospitals. These are extremely challenging under Good Manufacturing Practice ((GMP) in the EU and cGMP (c is current) in the US) and require demonstrable reproducibility of process – executing the same process in the same way “again and again” – and comparability – ensuring that the process is the same after a change. The key target for reproducibility is the management of biological variation, see Therman-Newall et al (1), and for change is ability to execute the same process in a different site.

However the most challenging step from a regulated manufacturing perspective is the validation (proving that the process does what it should) of the CAD-CAM code

generation step to ensure that it consistently delivers 3D printed living product – remember cells are alive and not conventional “inert” engineering materials with and without customisation of geometry. Without this validation we cannot be sure, for example, that we are not creating necrosing (dying) tissue that could be subsequently transplanted. These issues are discussed in full in Hourd et al 2015 (2).

The message of this discussion is that medical technology researchers must take a translational perspective in order that their ideas reach patients. For 3D bio-printing there is a particular need to tackle regulatory science for manufacturing by addressing research questions raised by the regulatory framework that protects patients. The output of this pattern of work – especially if pre-competitive – will inform regulators and industry as they work to develop these products to address clinical need and deliver patient benefit. The scientific community must work together to define the key questions that need to be addressed and reach out to developers, regulators and clinicians to ensure the methods they use to address the questions are endorsed, their results appropriately reviewed, and the outcomes fit with evolution in the practice of medicine and relevant clinical pathways – this is the only way research outcomes will be accepted and applied.

References

1. Jamie Therman-Newall, Jon Petzing and David Williams, Quantification of biological variation in blood-based therapy – a summary of a meta-analysis to inform manufacturing in the clinic, Vox Sanguinis, 109 (4), 394-402, 2015
2. Paul Hourd, Nicholas Medcalf, Joel Segal and David Williams, A 3D bioprinting exemplar of the consequences of the regulatory requirements on customized processes, Regenerative Medicine, **10** (7), 863-883, 2015

Word count 1187.