

Obtaining Manufacturing Approval for the First Culture-Expanded Adult Stem Cell Therapy under an Evolving Regulatory Framework: Challenges and Opportunities

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Abstract

In 2002, the Australian Government committed to a new framework to allow biological products to be regulated as a distinct class of goods. The new legislation was passed by the Senate in 2010 and will be implemented by 31 May 2011. Administered by the Therapeutics Goods Administration (TGA), and known as the "Biologicals Framework" it will radically reshape the regulatory environment applying to cellular therapies for both existing licence holders and potential applicants. Products will be divided into four categories based on degree of manipulation, intended use and risk.

Mesoblast Limited have developed a proprietary technology for extraction and expansion of mesenchymal precursor cells (MPCs). MPCs can be isolated from a variety of sites in human adults and grown to large numbers relatively quickly, while retaining their capacity to differentiate into bone, cartilage, heart muscle and other tissues. Following on from a successful clinical trial in long-term repair of long bone fracture, the company submitted a licence application to manufacture autologous MPC for clinical use.

Preparing a licensure submission is demanding at any time; doing so in the context of an evolving regulatory framework, and with a novel therapy, compounds the challenges involved. We present our experiences in navigating this pathway and discuss the challenges and opportunities that we have encountered in the process.

Mesoblast Clinical Trial Results

Table 2: Provides a summary of results from the CTN Phase I clinical trial for the treatment of delayed healing and non-union of tibial and femoral fractures requiring secondary surgical intervention

CTN Trial Patient ID	CC9 Expression at Passage 2 %	CC9 Expression at Harvest %	Cell Dose Received x 10 ⁶	Union Achieved #	Time to Union Achieved #
M103	92.8	62.1	212.0	Yes	3 months (11 weeks, 5 days)
M108*	76.5	N/A	N/A	N/A	N/A
M111	84.0	74.4	110.0	Yes	4 months (19 weeks, 5 days)
M112	96.0	47.4	98.3	Yes	9 months (36 weeks, 5 days)
M113	88.8	78.8	115.5	Yes	4 months (18 weeks, 6 days)
M117	93.1	76.6	82.3	Yes	3 months (10 weeks, 0 days)
M118	85.9	93.3	122.0	Yes	10 months (41 weeks, 2 days)
M119	82.5	53.6	147.0	No	Not united at 12 months
M120	97.5	67.2	111.0	Tibia Yes Femur No	9 months (39 weeks, 2 days) Not united at 12 months
M121	58.2	13.1	84.8	Yes	12 months
M122	93.4	51.3	89.0	Yes	2.5 months (10 weeks, 0 days)

*Cells not implanted
#Data provided by Mesoblast Ltd

Challenges

A significant challenge for our facility and the auditors during the manufacturing licence application was undergoing the initial audit process under a draft regulatory framework and included the following issues;

- Different parts of legislation become applicable at different times – Code of GMP, IDS and Product standards and Regulatory Framework
- Undefined regulatory timeframes – audits and audit responses
- Undefined product classification – Class 3 or Class 4
- If designated class IV – requirement for clinical product dossier
- Process validation and introduction of in-process environmental monitoring program
- Introduction of several competency programs – flow cytometry, manual cell counting, gram stain analysis
- Validation and Qualification of a flow cytometer in a research lab outside the current quality system
- Maintaining the manufacturing licence in program with a slow patient accrual rate

TGA Biologicals Framework

Table 1. Summary of "Biologicals Framework". The following table is a summary of the four classes of biologicals whereby the level of regulation is based on risk and the extent of manipulation applied to the biological and if its intended use replicates its usual biological function.

Class 1 Biological if	Class 2 Biological if
<ul style="list-style-type: none"> • Before a biological is included in class 1, a justification that the biological should not be included in Class 2, 3 or 4 and that suitable mechanisms of oversight to ensure quality, safety and efficacy will be required. • Declared in legislation to be class 1 	<ul style="list-style-type: none"> • Declared in legislation to be class 2 • Processed using only one or more of the actions of minimal manipulation; and • For homologous use
Class 3 Biological if	Class 4 Biological if
<ul style="list-style-type: none"> • Declared in legislation to be class 3 • Processed beyond minimal manipulation • Does not change an inherent biochemical, physiological or immunological property; or • For homologous use • ? MPC / MSC 	<ul style="list-style-type: none"> • Declared in legislation to be class 4 • Processed beyond minimal manipulation; and in a way that changes an inherent biochemical, physiological or immunological property; or • Not for homologous use • ? MPC / MSC

Adapted from "The Biologicals Framework: Proposed Amendments to Therapeutics Goods Regulations 1990", H Rothenfluh PhD Head Office of Scientific Evaluation, TGA, 2010

Opportunities

The pending changes in the regulation of biologicals will provide opportunities to accommodate changes in technology under the new regulatory framework. For the Mesoblast licenced manufacturing program we envisage some of the changes to include;

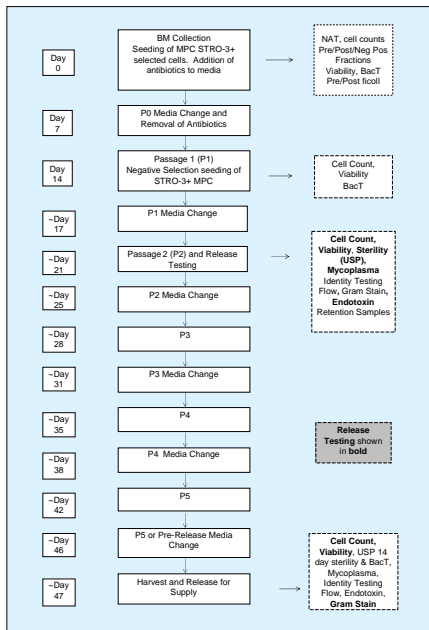
- The potential to move to or add autologous freeze banking
 - The potential to move to or add allogeneic freeze banking
 - Potential for a transferrable manufacturing program to other sites globally
- Opportunities for the greater cellular therapy community include but are not limited to the following;
- Obtain ARTG product registration in the absence of phase III clinical data
 - The potential for ISCT Australia to act as "industry body representative" – would be invaluable to have a central body.

Process Optimisation Goals Prior to Licensure

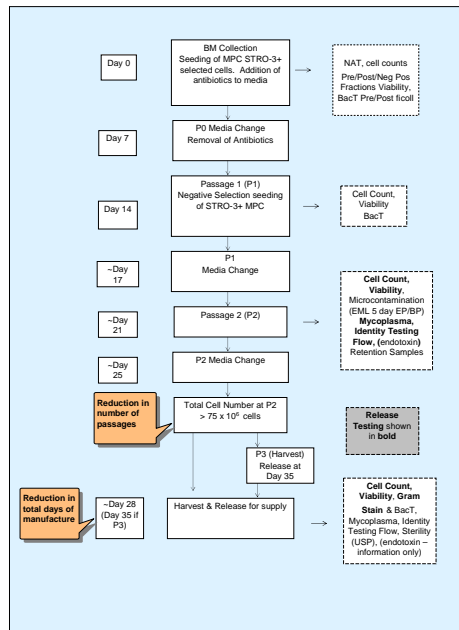
Process improvement and quality control testing opportunities have been addressed and incorporated during the engineering dry run using donor bone marrow prior to submission to apply for a licence to manufacture autologous MPCs with the TGA and include the following;

- Reduction in total number of passages
- Streamlining of all manufacturing batch records
- Introduction of clean-room verifier for all manufacturing steps
- Introduction of key core competency programs
- Introduction of process media fill validation
- Introduction of training module for collection staff at remote collection site

Initial Mesoblast Clinical Trial CTN Phase 1 Manufacturing Process



Final Mesoblast Licenced Manufacturing Process



Conclusion

While the licence application and audit process has been challenging, it has also been an exciting time providing an opportunity for stakeholders working in cellular therapies to actively engage in consultation with the TGA regarding changes to the regulations and new regulatory framework

In conclusion the manufacturing licence application and approval process has highlighted key learning's which include;

- Make friends with your regulator
- Consultation and transparency between the applicant and the regulatory agency is critical
- Anticipate additional application requirements
- The new "Biologicals Framework" will provide defined and clear guidelines in which to operate for emerging technologies
- The emphasis is on risk minimization
- The new regulatory framework will align us with other regulatory environments globally enabling wider consultation

