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GMP Production of an Encapsulated Cell Therapy Product: *Issues and Considerations*

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One of the major concerns facing relatively young biotechnology companies once a lead product has been identified is the issue of manufacturing. Usually this involves the upscaling of a lab-scale process while at the same time, complying with good manufacturing practice (GMP) to ensure a reproducibly-produced and consistent product. It also involves the establishment of specific and robust assays in process controls and release criteria.

This issue has become more acute in the EU since 2004 due to the EU Clinical Trials Directive requiring GMP-certified production of investigational medical products even for phase I trials. Start-up biotech companies are often limited in their finances and resources, as well as being bound by tight milestones. Quite often the expertise in upscaling and GMP-compliant production as well as the facilities and equipment required are not available in-house. Companies have to decide early on whether they will embark on costly, labour-intensive and time-consuming in-house production or rather, partner with a GMP specialist contract manufacturing organisation (CMO).

In-House Development or Outsourcing: Some Key Issues

A major advantage of in-house production is the ability to secure absolute product and process control as well as the maintenance of trade secrets and know-how. It also ensures a maximization of future revenues. In contrast, outsourcing of GMP manufacturing can reduce the risk of not getting GMP implemented if the CMO chosen is a reputable partner. Additional benefits include cost reductions since it negates the requirement for major capital investment in facilities and recruitment of manufacturing and quality control teams well before an investigational drug has proved itself in the clinic.

Outsourcing usually speeds the process development and scale-up so that an efficacious and safe investigational drug should make it to the market place quicker, as well as allowing production of the drug in sufficient quantities to meet the market demand. Both of these advantages should thus prevent a reduction in revenues from lost or delayed sales.

Nevertheless, there are a number of risks associated with outsourcing, including maintaining a high priority ranking for your lead product in comparison with products from other companies, and ensuring the timely scheduling of your activities. This can be the case particularly when the assigned CMO also works for larger, more established biotech and pharma companies with more financial clout.

Indeed, more and more companies are turning to outsourcing.[1,2] More often than not, the CMO is based some distance away in another city or even country. The further away the CMO, the more difficult it can be to perform the necessary monitoring of the facilities, not to mention the scheduling of project meetings. Another potential caveat is technology transfer—generally, the more unique the technology, the more difficult the transfer. Technology transfer should ideally occur in sufficient detail to ensure large-scale GMP production. But this raises issues about confidentiality and being able to protect trade secrets pertaining to the technology. Adequate documentation and compliance can still be issues even when production is outsourced and can never be taken for granted—in the eyes of regulatory authorities, this is still the responsibility of the contractor.

Outsourcing is advisable in a number of circumstances including: a) when a company is developing a product for the first time; b) there are limited technical and monetary resources available in-house; c) the product pipeline is small; d) there is a need for process develop-

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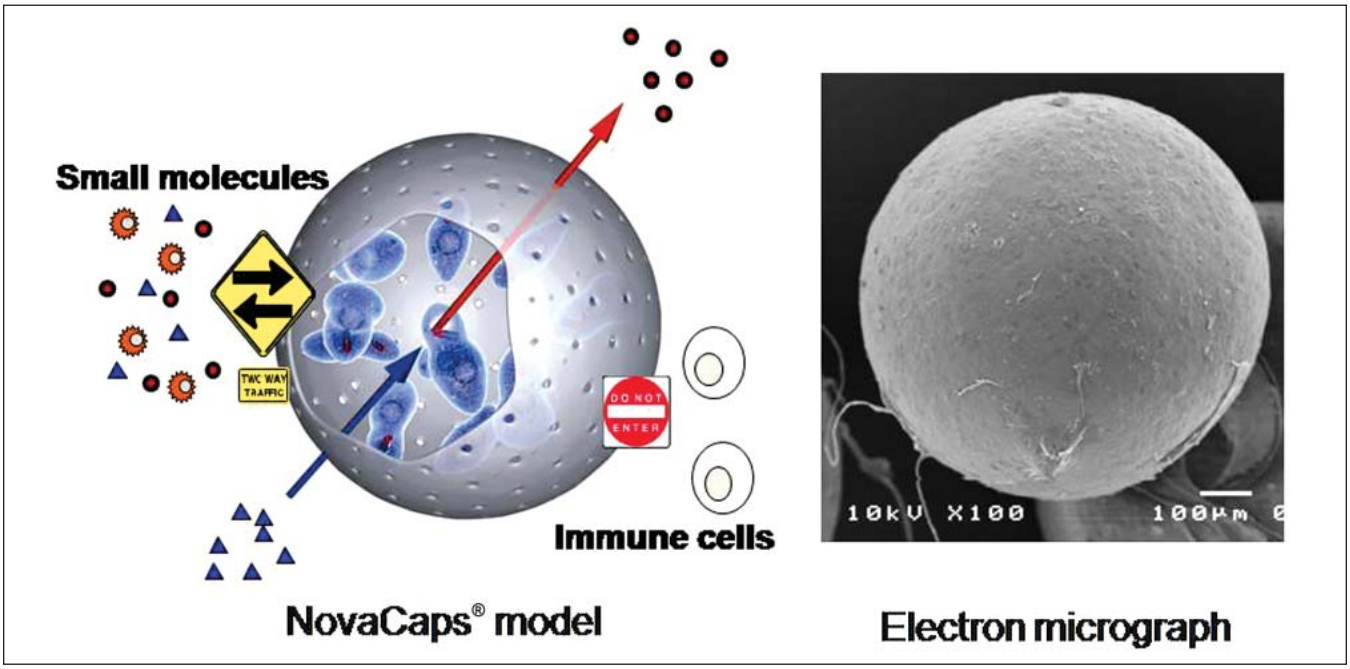


Figure 1. Schematic representation and electron micrograph of NovaCaps®. Shown on the left is a representation of a single capsule or bead with a cutaway showing cells inside of the capsular structure. The capsule membrane is semi-permeable and thus, small molecules such as nutrients can enter the structure and metabolites can leave the capsule. However, the pores of the capsule are small enough so that cells of the immune system cannot enter. NovaCaps® for the treatment of pancreatic cancer carry cells that have been genetically modified to over-express a cytochrome P450 that is particularly efficient in activating ifosfamide (triangles) to its toxic, anti-tumour form (circles). Shown on the right is an electron micrograph of the outer surface of a capsule.

ment assistance and advice; e) there is a need to meet milestones for gaining additional financing; and f) at least parts of the technology being developed are outside the core competence of the contractor but are an area of expertise for the CMO.

The Austrianova Experience: Lead Product NovaCaps®

Background

NovaCaps® is a novel, cell-based therapeutic that has been developed for the treatment of solid tumours like pancreatic cancer.[3] The product consists of cells genetically modified to overexpress cytochrome P450 and encapsulated in biologically inert cellulose sulphate polymers (Figure 1). In pancreatic cancer patients, NovaCaps® are delivered by supraselective catheterisation into a groin-area blood vessel and guided to the pancreatic tumour where they lodge in the smaller blood vessels.[4,5] The patient then receives low doses of the chemotherapeutic agent, ifosfamide, which is locally converted by NovaCaps® to its active, tumour toxic products at the site where it is needed. Thus, NovaCaps® functions as a targeting device, increasing therapeutic efficacy while at the same time, reducing the side-effects associated with more standard doses of chemotherapy (Figure 2).

Safety and proof of principle have been demonstrated for NovaCaps® in a phase I/II clinical trial in which 14 patients received the encapsulated cells and ifosfamide.[4,5] Key indicators of therapeutic benefit in the study included: a) an improvement in quality of life; b) 4/14 tumour reductions with stable disease for the remaining ten patients; c) a twofold improvement in median survival over a control group (Figure 3); and d) one-year survival rates that were twice as high as with the current gold standard treatment, gemcitabine.[4,5]

NovaCaps® has been designated an orphan drug in Europe and is the first of a new class of therapeutics called "advanced therapy medicinal products." A pivotal clinical trial has been designed together with the EMEA and will commence soon.[6] A prerequisite for this study is the large-scale GMP-compliant production of NovaCaps® in sufficient quantity to supply the whole market for pancreatic cancer treatment.

Challenges in GMP Manufacturing of NovaCaps® at Industrial Scale

NovaCaps® is novel, and is quite a complex product to manufacture reproducibly at large-scale, even though the lab production process is, in principle, rather simple. The active components of NovaCaps® are the genetically modified cells over-expressing cytochrome P450. Here, the issues faced were a bit more straightforward since there are guidelines and precedents for the production of large amounts of such cells. A master cell bank (MCB) and working cell bank (WCB) are created and tested for identity, sterility, stability and freedom from adventitious agents. Depending on the origin of the cell line and its history, there may be additional issues that have to be resolved. After a vial of frozen cells from the WCB has been thawed and allowed to grow in cell culture, they are then harvested and encapsulated using a novel, continuous process followed by a maturation step which is, in essence, a fermentation

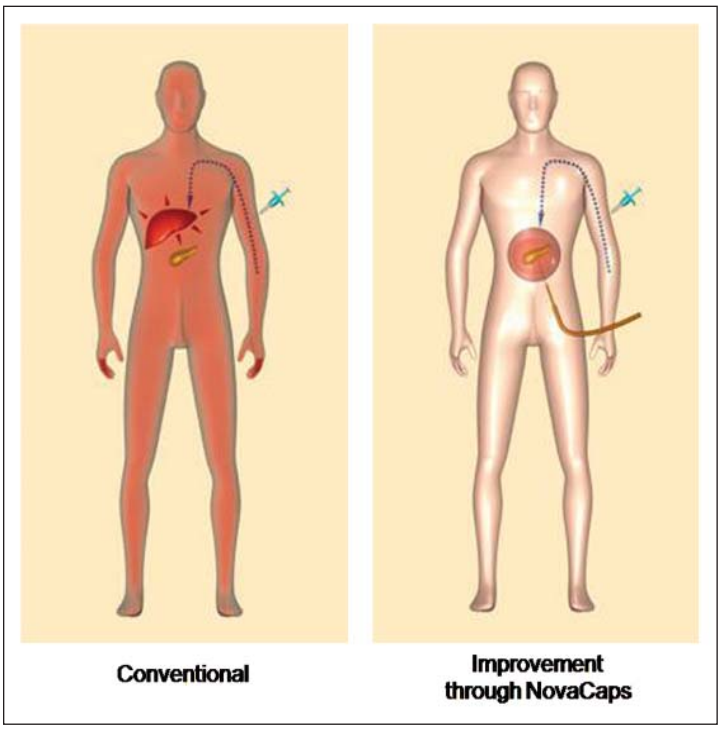


Figure 2. NovaCaps'® principle to enhance anti-tumour efficacy of chemotherapeutic agents while reducing debilitating side-effects by reducing systemic doses. Depicted on the left-hand side is the usual situation when tumours are treated with chemotherapeutic agents like ifosfamide, where the chemotherapeutic agent is injected as an inactive form systemically. The agent reaches the liver via the bloodstream where a number of cytochrome P450 enzymes activate it to a short-lived active form which is toxic for dividing cells. This form is shipped around the body and attacks all dividing cells, including tumour cells. However, since it has a short half-life and the pancreas is the last organ on the circulatory system from the liver, the results are relatively poor anti-tumour effects coupled with debilitating side-effects. The right-hand panel shows how NovaCaps® can be used to enhance antitumour efficacy using lower doses of ifosfamide. A catheter containing 300 NovaCaps®, each with a diameter of 0.7 mm, is placed in a vessel leading from the groin area and is guided to vessels leading to the pancreatic tumour (supraselective catherisation). The capsules are then released and are pushed by the blood flow into smaller vessels where they become lodged. Two days later, the patient is given low-dose ifosfamide (1 g/m^2 compared to 2.5 g/m^2) systemically which reaches the NovaCaps® via the circulatory system. It is metabolised by the cytochrome P450 enzyme (which the cells overexpress) to its active anti-tumour form at the site where it is required—next to the tumour.

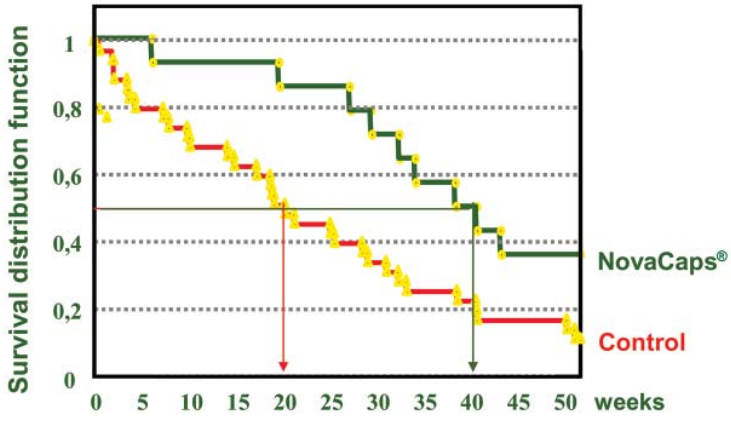
process. After maturation, the encapsulated cells are aliquotted into vials which are then stoppered and crimped before being frozen at -80°C. The scale of manufacture has to be large enough to comfortably meet the estimated demand in the EU.

In 2004, there were 55,000 new cases of pancreatic cancer in the EU[7] and it is estimated that around 70% of these cases could eventually be eligible for treatment with NovaCaps® plus ifosfamide. Nevertheless, a more realistic initial market share penetration is likely to be of the order of 12,000 doses per year. This can easily be covered with four campaigns of 3,000 vials each per year. It is relatively easy to increase this to 48,000 vials per year by using all four positions of the biofermenter for the maturation process instead of a single unit. An important factor here is that the final product can be frozen for long-term storage without appreciable loss of activity. Thus, shelf life has become less of an issue for this product, although the logistics of shipping a frozen product have to be overcome.

Initially, NovaCaps® will be used for a pivotal clinical trial in Europe aimed at obtaining market approval, as well as for additional trials in the USA, Australia and Southeast Asia.

A relatively young biotech company, Austrianova is located on a university campus (the University of Veterinary Medicine in Vienna, Austria). The campus is just over ten years old, with state-of-the-art facilities and generous space available. Nevertheless, while setting up GMP production of NovaCaps® would be possible at the location, it was decided that such a goal would be too time consuming and costly. Austrianova elected to produce a suitable, genetically-modified cell clone over-expressing the cytochrome P450 enzyme in-house, but to outsource production of the MCB and WCB.

The company also determined the optimal parameters for the GMP-



Treatment	n	Phase	Mean survival	% 1 year survival
Control	36	-	>30 weeks	11%
NovaCaps®	14	I/II	>45 weeks	36%
Gemzar	63	III	n.d.	18%

Figure 3. Kaplan Meier plot showing survival of patients in a phase I/II clinical trial of Novacaps®.

compliant encapsulation of the cells using a custom-built encapsulation machine for the maturation process, in-house. Austrianova co-developed the upscaling process with an expert CMO who is experienced in GMP-compliant production of cell and gene therapy products. Thus, the CMO provides the GMP facilities and the quality environment as well as bringing suitably trained staff to the project. They have a good knowledge of the regulations and compliance issues, having had prior dealings with both regulatory agencies and local competentcy authorities. The CMO also has previous experience in the production of cell therapeutics and the confection of the final product.

Initially, as mentioned above, each production run will result in a batch size of 3,000 vials. In general, batch size is dependent on the feasibility of the upscale process. Austrianova is using a continuous process for the actual encapsulation, thereby ensuring that, in contrast to the lab-scale process, each capsule is treated in exactly the same fashion. Continuous processes have a number of advantages over classical batch processes, or parts of the process being carried out as parallel batches (Figure 4). Problems can be encountered if a continuous process cannot be established, primarily arising from the consequent need for pooling criteria such as quality, variation and composition parameters.

When the pooling must occur during the production process (Figure 4, center lines labeled 2), necessary pooling criteria become critical in the timing of the whole process. Here, companies have two alternatives: 1) pooling with minimal testing to ensure quality and microbiological safety; or 2) pooling after extensive testing. In particular, sterility tests are time-consuming because they require relatively long incubation periods. During this time, the batches can be "on hold" if this does not lead to spoilage or loss of potency. The alternative is to pool batches before the sterility and quality results are known, but this enormously increases the risk that the whole production run has to be rejected. Unfortunately, this is costly, both in terms of finance and time. Thus, the risk is much greater in non-continuous production systems consisting of batch production with subsequent pooling.

Often major changes are necessary to move a lab-scale production into a large-scale production, including alteration of process parameters like temperatures, amount of reagents, extended process duration, length of stability of the process, equipment and machinery, logistics, etc. There are a number of other important points to bear in mind when considering basic raw materials.

One issue is to ensure the continuity of supply of such materials. If at all possible, it is prudent to ensure that more than one supplier is available, just in case a supplier decides to discontinue offering certain products. This can often be controlled by making sure that a good contract is in place. Inter-batch variations needs to be minimized and multiple batches should be validated. Each supplier should be regularly audited.

As well as having sufficient amounts of the basic raw materials, the actual quality of these reagents is of importance. If at all possible, starting materials should be pharmacopeial grade, or failing this, should emulate parameters defining the nearest similar reagent listed in the pharmacopoeia. They should be produced under GMP, or as close as possible to this standard.

For Austrianova's NovaCaps® product, the primary raw capsule material is not commercially available, so it was necessary to establish a qualified manufacturing procedure. This involved the establishment of release and quality criteria based on the nearest similar pharmacopeial entry, as well as auditing of the process and quality control.

A further issue with respect to the raw materials is lot size for the inter-lot variation analysis. If the size of each individual lot is too large, batch variation analysis becomes expensive and cumbersome, requiring the purchase and storage of huge amounts of each

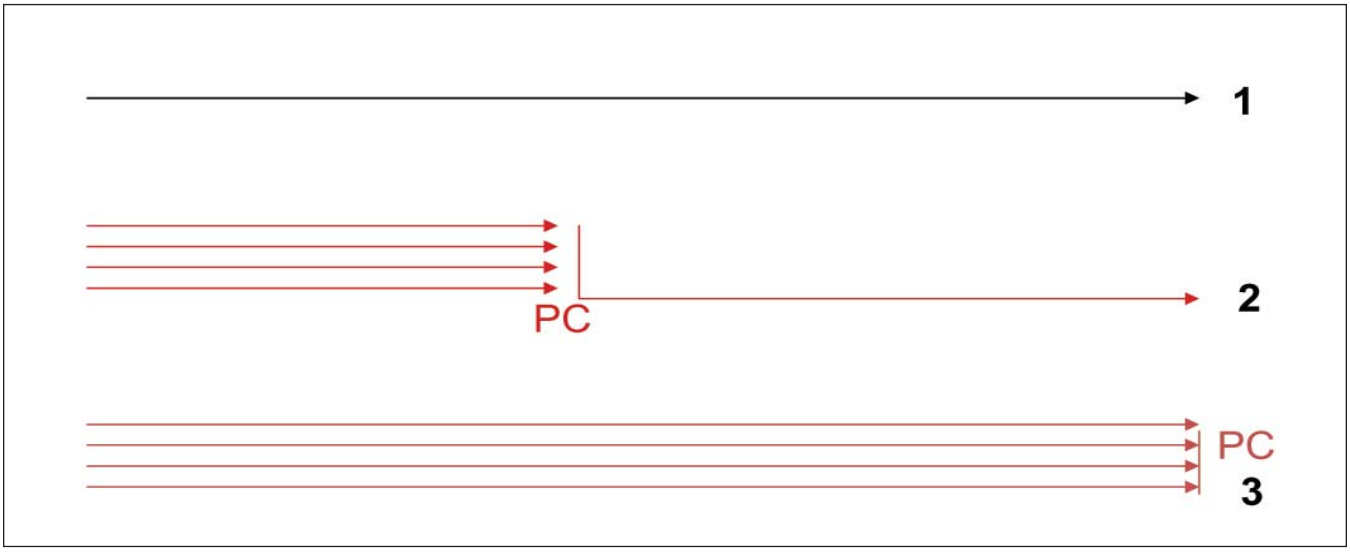


Figure 4. The problems of pooling. 1 (top): Indicates a continuous production process. 2 (center): A production process in which part of the production results from the mid-process pooling of four parallel sub-batches which require pooling criteria (PC) before the process can be taken to completion. 3 (bottom): Four parallel production runs which are pooled at the end of the process after PC have been met.

Figure 5. Various steps in the continuous process required to produce NovaCaps®. After unfreezing a vial from the working cell bank, cells are cultivated (top two panels), harvested, and encapsulated[23] using a custom-built GMP-compliant encapsulation device (left, second panel). The encapsulated cells (right, second panel) are washed and transferred to a biofermenter in cell culture medium (left, third panel). They grow within the capsules to fill the available space, but without breaching the confines of the capsules, thereby attaining a confluent state in three dimensions (right, third panel). They are then aliquotted (left, bottom panel) into vials (right, bottom panel) and frozen at –80°C.

lot. The only way around this is to have the supplier provide lots that have been specially confected in smaller amounts. On the other hand, if the size of each individual lot is too small, these lots realistically need to be pooled prior to analysis. Otherwise, carrying out analyses on each individual lot will become prohibitively expensive. Some of the reagent ingredients necessary for the production process (*e.g.*, cell culture media) may have confidential formulations which suppliers are unwilling to reveal. Such formulations must be disclosed under confidential disclosure agreement (CDA)—at the very least to the regulatory authorities, if not to the contractor.

A number of ingredients and their concentrations must be known by the manufacturer given that they need to be used as identity parameters when checking incoming supplies.

Process Scale-Up

The maximum possible scale-up factor is dependent on a number of details such as:

a) the necessity for standard and/or specialised machinery and equipment, and their availability;

b) the process itself, including limiting parameters such as dissolved oxygen, pCO_2 and pH temperature, physical and chemical process parameters, etc.;

c) time issues that have an impact on survival (half-life) or consistency of biologics during the process;

d) turnaround time for the whole process, allowing for matters like in-place cleaning or reusable versus single-use machine parts; and

e) facility-specific constraints such as the type of workspace available (class) and the type of machinery.

In the specific case of Austrianova's NovaCaps®, there was a conscious decision to move from a batch process (small-scale, lab production) to a continuous encapsulation process. This meant linking the four necessary activities (cell culture, encapsulation, maturation, and aliqotting into vials) in a continuous and timely fashion (Figure 5).

In addition, new and unique manufacturing equipment was required for the encapsulation process. This included a custom-built encapsulation machine (Figure 5) in which all parts coming into contact with the final medicinal product are manufactured from materials that comply with the relevant quality class (*e.g.*, synthetic materials should be USP class VI-compliant, stainless steel, V2A, *etc.*) with well-documented origin and all necessary certificates. Specially designed gamma-radiation-sterilised tube-sets and a fermentation vessel were also designed for the process (Figure 5).

Confection, Storage and Shelf Life of the Final Product

Preferably, confection of the final medicinal product should be an automated process. The type of packaging

is dependent on storage conditions as well as the clinical application procedure. It is important to ensure that the storage container and any other components (stoppers, *etc.*) are inert and biocompatible. Likewise, if the final product is in solution, it is important to ensure that the liquid does not react with the container or stoppers, or that leaching will not be a concern.

The labeling of the final product has to be in accordance with the regulatory guidelines. If a vial is used for the final product and there is not enough space to provide all information on the directly-applied label, some of it can be provided on the outer packaging. EU guidelines specify that product information has to be given in all the official languages of the EU.

The confection process must be developed and set so that it is reproducible within certain tolerances, and the final product also has to be sterile.

The conditions required for the optimal storage and shelf-life of NovaCaps® is very specific. Storage can be at various temperatures: room temperature, +4°C, –20°C, or even –80˚C. Biological therapeutics such as cell lines, vaccines, and virus vectors often require cold chain logistics. The ability to reproducibly freeze a product while maintaining viability often requires a controlled cooling rate and cryopreservative agents. This complicates not only confection, but also brings with it certain logistic requirements when freezing cells. The shelf life has to be determined and specified. This can be achieved during the process as well as during further development steps and clinical trials where it can be continually revalidated and extended.

In the specific case of NovaCaps®, the confection process is quite demanding—the final product consists of living cells that have to be frozen at –80˚C. This makes demands on both packaging and ease of product handling in the clinic. Moreover, the necessity to freeze the final product and the use of a cryopreservative means that the aliquotting of NovaCaps® into vials is under quite specific time constraints while having to maintain reproducible filling. Furthermore, labelling of frozen vials is difficult, so the vials or containers are prelabelled before confection and freezing to avoid this problem, as well as to gain time for aliquotting and freezing. All unused, prelabeled vials are destroyed.

In-Process Assays and Release Criteria

The production process is required to be controlled by in-process assays, such as viability and/or metabolic activity assays, at certain critical steps, usually at stages where a "go"/"no go" (abort) decision is needed. If the choice has been made to outsource production, the relevant assays needed for monitoring the process may or may not be available. If available, they can be transferred to the CMO; otherwise the CMO has to develop these, and all of them must be qualified and validated. In addition, lot release tests and specifications should be established, and all methods and specifications should be listed.

It is a good idea to provide the CMO with any unusual or product-specific methods to facilitate an accurate timeplan and reasonable pricing of the production activities. The entire development of the production strain/cell line and the manufacturing process needs to be fully documented and should include: a) the complete strain/cell line history; b) all relevant development data; c) the exact specifications of materials and equipment used in the final process; and d) all relevant procedures in the final form of SOPs, as well as a complete set of analytical data specifying the final product.

Progressing Towards a Manufacturing Licence

After the initial technology transfer and setup phase where all specialised machinery is installed and qualified, and the individual process steps are established for the complete process, a number of test runs are performed. Depending on the outcome, fine adjustments are made to the process. This is followed by a risk assessment and a number of verification runs and further adjustments which then result in a detailed validation plan with the specifications being defined. Only then can the validation (or consistency) runs take place. Traditionally, a minimum of three consecutive runs are required that meet specifications. Once this data has been obtained, the relevant authorities can be approached for a licence to manufacture the clinical product.

Cell Encapsulation in Cellulose Sulphate: A Technology Platform to Produce a Plethora of Products

The establishment of the GMP production process by Austrianova sets guidelines for producing other encapsulated cell products. This is an extremely important asset since, in principle, any cell type can be encapsulated in cellulose sulphate polymers under similar GMP conditions. We have already demonstrated proof of principle for a number of different cell types (Table 1). Encapsulated cell products can be used to treat a wide spectrum of diseases with diverse causes (Table 2).

The encapsulation technology can also be used to produce missing enzymes and growth factors, or to augment their production. The immune system also can be bolstered by the production of cytokines from encapsulated cells. With this aim in mind, it has been demonstrated that encapsulated cells can produce interleukin-2 and granulocyte macrophage colony-stimulating factor (unpublished data). Additionally, depending on the site and route of application (Table 3), local or systemic delivery can be achieved. Another attractive feature of the encapsulation technology is that physiological regulations of the released therapeutic agents can be

Table 1. Primary and/or established cell types that have been successfully encapsulated.

Fibroblasts[11]
Epithelial cells[3, 4, 5, 12]
Hybridomas[13, 14, 15]
Islet cells[16, 17]
T cells (unpublished)
Hepatocytes (unpublished)

Table 2. Some possible therapeutic uses of implanted cellulose sulphate-encapsulated cell products.

DISEASE	FACTOR PRODUCED	COMMENTS	REFERENCES
Solid tumours	Anti-tumour toxic agents	Suicide gene/prodrug combinations	3, 4, 5, 18, 19, 20
	Anti-angiogenic factors e.g. angiostatin e.g. endostatin e.g. GBP-1	Prevents growth of tumour neovasculature	
	Monoclonal antibodies	Directed against tumour-specific antigens	
Diabetes	Insulin	Shown for established islet cells	17
		Shown for primary porcine islets	16
Parkinson's Disease	Neuron survival factors e.g. GDNF, Neuturin		
Haemophilia	Factor VIII, Factor IX	~1% usual levels can provide a benefit	
Hypocholesterolaemia	ApoE	~2.5% usual levels can fully reduce plasma cholesterol	
Infectious diseases	Monoclonal antibodies	Passive immunity to treat - viral diseases - bacterial diseases	15
Vascular diseases	Proangiogenic factors e.g. VEGF, bFGF	Stimulation of new blood vessel growth	

achieved in response to a metabolic stimulus.[8] If desired, it is also possible to design gene expression constructs that allow manipulation of expression levels, for example using antibiotic dependent switch mechanisms (for reviews of the various systems available see [9,10]). Austrianova is seeking partners to exploit the potential of this promising technological platform.

Table 3. Encapsulated cells are well-tolerated *in vivo* after implantation at many sites in different species.

SITE OF IMPLANTATION	MEANS OF DELIVERY	SPECIES	REFERENCE
Intra-arterial	Supraselective catherisation	Pig	21, 22
		Human	4, 5
Intratumoral	Direct injection in/near tumour	Mouse	3, 12, 18, 20
		Dog	19
Subcutaneous	Direct injection	Mouse	13
Intraperitoneally	Direct injection	Mouse	13
		Rabbit	23

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