PROJECT NO: FP6-513121

POS BEADD

*The development of **pos**itive-**bead**s for **d**rug **d**elivery in the embolotherapy of uterine fibroids*

Co-operative Research (Craft)

Horizontal Research Activities Involving SMEs

Final Activity Report
Date of issue: August 2007

Start Date: 15th November 2004 Duration: 28 Months

Lead Contractor: Biocompatibles Plc

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PROJECT INFORMATION

PROJECT NO: FP6-513121

CONTRACT NO: COOP-CT-2004-513121

TITLE OF PROJECT: *POS-BEADD – The development of positive-beads for drug delivery in the embolotherapy of uterine fibroids*

COORDINATOR: Biocompatibles Plc

SME EXPLOITATION MANAGER: Biocompatibles Plc

***SME CONTRACTORS*:**

1 Biocompatibles Plc

3 Joline GmbH & Co KG

4 CellMed AG

5 S & S Plastics

6 DMC Medical Ltd

RTD PERFORMER CONTRACTORS:

2 Fraunhofer TEG

7 Pera

8 Biomatech

PUBLISHABLE EXECUTIVE SUMMARY

This report covers the work carried out in the entire duration of the project.

The main body of this report is a précised overview. However more detailed appendices are attached to cover the technical work programme.

The proposed CRAFT research project, **POS-BEADD**, proposes the development of positively charged beads for drug loading and delivery in the embolotherapy of uterine fibroids. It also includes; the chemical synthesis of alginate polymer beads, the development of a novel bead management technology for mixing polymer beads with physiological saline prior to delivery and finally a new catheter system to permit a uniform delivery of beads into blood vessels in metered doses.

The technical work has been completed for all Work Packages.

Project Management, Co-ordination, Exploitation were on going through the life of the project. All the tasks in all Work Package are now complete and good results have been achieved. Technical Reports on each of these tasks have been attached to this document.

Regular Technical Meetings and Interim meetings, to discuss IPR and exploitation were held every 3 months, Periodic progress and management meetings at months 6, 9, 12, 15, 18 and 24 followed, interspersed with working party meetings. A final meeting was held at the end of the project. All Meetings were well attended throughout the life of the project, with all partners showing a high level of commitment and enthusiasm.

Problem:
Uterine fibroids are benign tumours whose symptoms include any combination of; excessive bleeding, severe pain and disfigurement. Indeed, some women with large fibroids may appear to be pregnant. Untreated, the symptoms will persist until menopause.

Previous treatment options for uterine fibroids include treatments with steroids have been attempted but generally only alleviate symptoms and do not affect a cure. Therefore, until recently, only surgery has proven effective. In the US and EC together over ten million women seek treatment annually for uterine fibroids. It is estimated that over 600,000 invasive surgical procedures, including 400,000 hysterectomies (surgical removal of the uterus) and 200,000 myomectomies (surgical removal of the fibroids) are performed each year because of fibroids. There are major drawbacks to these surgical approaches; hysterectomies result in the patient being unable to have (further) children, analgesia must be continued for up to two weeks post-operatively and each procedure requires a hospital stay of 3-5 days and a recovery period of 6-8 weeks. In attempts to overcome these problems, the process of uterine fibroid embolization (UFE) has been developed.

The Consortium:
The project partners, lead by the coordinator Biocompatibles, are spread throughout four member states. Biocompatibles, S & S Plastics and Pera from the United Kingdom, Fraunhofer, Joline GmbH and CellMed AG from Germany, Biomatech from France and DMC Medical from Ireland. The geographic locations of the companies, who make up the consortium, provides this project with an even spread across Europe.

Objectives:

The Societal and policy objectives of this project are to benefit European society by improving embolotherapy for fibroids using drug-eluting beads and reducing: the length of fibroid treatment by 90 %; the number of women having hysterectomies by 5%; the pain experienced by women by 50%; and the post-operative infection rate by 50%.

Results Achieved to date:

The consortium has just completed the two-year research and development project. The project progressed extremely well, and according to plan.

This project has generated new technologies including product a novel bead mixing system, new catheter equipment and alginate bead polymer synthesis for drug delivery. For more information, relating to this project, please contact Dr. Anup Patel at Pera. anup.patel@pera.com

SECTION 1 - SUMMARY OF OBJECTIVES AND ACHIEVEMENTS

1.1 Overview of General Project Objectives

Scientific Objectives:
The scientific objective of this project is to enhance the scientific understanding of polymer bead synthesis chemistries in respect of the ability of co-polymerisation technologies to allow the development and synthesis of alginate polymer beads for drug delivery. The project aims to enhance the understanding of technologies for introduction of alginate polymer beads into new catheters for delivery to the uterine artery in an ergonomic and timely manner, using a novel bead mixing system. Finally, the project aimed to research existing pre-clinical test procedures for bead delivery technologies and to adapt these to the development of a pre-clinical model for testing bead delivery.

Technological Objectives:
The technology objective of our work is to provide Europe‘s medical industry with an innovative technology capable of competing globally to secure their market. We aim to provide a polymer bead synthesis method, catheter design technology and an innovative drug delivery system to improve the quality of life of European women. The demands are for the ability to accurately and independently verify the surgical operation so that length of treatment, pain during surgery and post-operative infection rate can be is reduced or totally eliminated. To achieve these objectives, the following operational targets need to be met:

- synthesis of alginate based polymer beads;
- novel catheter design that are compatible with all drug/bead combinations;
- a bead mixing device to enable a uniform flow through the catheter when mixed with surgical saline and contrast agent;
- to increase our understanding of the relationship between co-polymerisation and its ability to form 0.5 mm to 2 mm spherical beads that have a deformability of 30 +/- 5 kPa unloaded;
- to develop our scientific understanding of the syringe and catheter technologies to enable delivery of polymer beads of 0.5-2 mm diameter to the uterine artery with 1 ml of contrast agent whilst maintaining uniform dosages over time;
- to research the possibility of adapting the alginate polymer bead technology to use of existing apparatus.

Societal & Policy Objectives:
The societal and policy objectives of this project are to improve the health and quality of life of women with uterine fibroids. To benefit European society by reducing the length of fibroid treatment by 90 %, by a minimum of 5% the number of women having hysterectomies by 2010; by at least 50% the pain experienced by women undergoing fibroid treatment; by at least 50% the infection experienced by women undergoing bead fibroid treatment. In addition, the relatively low cost of the POS-BEADD technology will enable the increasing use of embolization treatments in all European countries including the candidate countries and this will support the policies of the European Union to bring the health of eastern Europeans up to the same standard as those of the 15 states.

Economic Objectives to Improve Competitiveness:

The economic objective of this project is to give Europe a significant lead in the international market place, especially against USA and Japanese companies that are currently actively involved in developing the healthcare technology sector. The economic objectives of the project are for the participants and subsequent licensees to:

- make the POS-BEADD products for less than €40 per unit for the management system and €15 for the drug-loaded beads;
- sell the POS-BEADD products at €100 per unit for the bead management system and €30 per unit for the drug-loaded beads (depending on the drug);

  and make these inroads into their target markets by 2010:
- gain a 5% share of the €2 Billion p.a. global market for UFE products by 2010 and generate 65 new jobs in Europe;
- gain a 5% share of the remaining €1 Billion global market for bead embolization products generating a further 25 new jobs in Europe.
- gain a 5% of the €200 Million global market for chromatography consumables generating a further 10 new jobs in Europe.

Enabling Innovation Related Objectives:

In order to achieve the societal and economic objectives that come from the dissemination and exploitation of the research results, we have defined an enabling set of Innovation-related objectives as follows:

- to collate and prepare the results of the project into a suitable format and apply for patent protection of the low cost, bead embolization and drug delivery system by the end of 2006;
- to transfer knowledge from the RTD performers to the SME participants through three technology transfer events and interactions. This will result in three secondments and placement of four staff providing a total of 120 hours of technology transfer;
- to disseminate the results and benefits of the knowledge and technology developed beyond the consortium to potential users such as pharmaceutical companies, healthcare providers, sports systems companies and specifically:
  - to contact the top 50 pharmaceutical firms and 50 other firms contacted to promote the project results;
  - make presentations at three trade or sector specific shows;
  - stimulate 10 firms to apply or use the science and technology results in their future product strategy;
  - engage with four firms for detailed knowledge or technology transfer by the end of 2010;
  - to stimulate 10 licensees to adopt the results in the generation of new products or systems by the end of 2010.

1.2 Summary of Recommendations from Previous Reviews

None

1.3 Summary of Project Objectives & Major Achievements for Project

The specific objectives for the project are summarised in the table below.

Deliverable	Task	Objective	Progress Towards Achieving Objectives
D1	1.1	Scientific understanding of polymerisation chemistries	Literature investigated on technologies for the synthesis of polymer beads.
D2	1.2	Research scientific literature	Literature searches have been conducted in the areas of with polymer bead technologies
D3	1.3	Enhance scientific knowledge	Test-rig constructed and chemical synthesis and of negative polymer beads achieved.
D4	1.4	Pre-clinical models	Pre-clinical models of embolization therapy for adaptation to beads have been accomplished.
D5	1.5	Holistic QFD assessment	A thorough initial QFD risk assessment for the total project has been conducted.
D6	2.1	Polymer bead synthesis	The design and synthesis of two types of positive beads have been accomplished.
D7	2.2	Test physical properties	The two types of positive polymer bead have been analysed and found to be of high purity.
D8	2.3	Bead dye technology	The bead dye technology and lyophilisation techniques have been investigated.
D9	2.4	Drug loading and elution	Successful drug loading and elution studies have been conducted on different beads.
D10	3.1 3.2	Bead management technology	Designs for the bead mixing device have been accomplished and a prototype vibration motor bead system has been constructed.
D11	3.3	Catheter system	New catheter technologies have been designed and developed.
D12	4	Develop alginate bead synthesis	The alginate polymer bead synthesis has been investigated and accomplished.
D13	4	Lyophilisation technologies	The lyophilisation technologies have been investigated.
D14	5	Prototype integrated system	The prototype system has been successfully integrated and tested.
D15	5	Prototype system for pre-clinical trials	Pre-clinical trials for the prototype have been designed.
D16	6	Model systems for pre-clinical testing	Animal model systems for the project have been thoroughly researched and identified.
D17	6	Pre-clinical testing of technology	Pre-clinical testing of the Joline catheter has been achieved.
D18	6	Drug elution delivered *in vitro* and *in vivo*	Pre-clinical testing of the alginate polymer beads has been accomplished.
D19	7	Competitive patents and a plan for patent application(s)	Thorough patent searches have been made through the course of the project.
D20	7	Support material for transfer of the knowledge	Knowledge and communications have been transferred to all the partners involved.
D21	7	Report on the standards and regulatory exploitation of the results	The standards and regulatory aspects of the exploitation of the results have been discussed.
D22	7	Plan for using and disseminating the knowledge	Plans for dissemination of knowledge have been made during the course of the project.

1.4 Issues During the Project

The project start date was 15th November 2004, however in order to ensure that all partners could attend the kick-off meeting this was delayed until 27th January 2005.

The planned schedule has been adapted to better reflect the predicted timescales of the tasks based on the new knowledge that has been gained during the first part of the project. The new timetable of activities and amendment of the Annex 1 also allows the tasks for the new partners to be accomplished. The new timescales allow research to be completed properly and scientifically, to provide the maximum benefit to all partners in the consortium. The work that the two new partners must contribute to do not involve or affect the first 12 months of the project, their involvement will merge into the project during the latter period.

The plan to catch up is combined with the 4 month extension to the project will provide sufficient time to complete the project. All the specified tasks are planned for completion, the correct knowledge and expertise is available at each respective partner of the consortium. Most tasks in each work package will be conducted in parallel rather than in series, this multiple completion of tasks will enable the consortium to complete all task in the modified anticipated timeframes. As illustrated in the work programme the majority of tasks will be conducted at the same time after month 18, to ensure all work may be finished. The deadlines for the individual deliverables will be met. All partners are well motivated and enthusiastic for the successful completion of the project, they also understand the situation. The two new partners show strong early commitment to the project, their contribution is vital and their role in the project is well defined and understood so they will able to deliver the task.

SECTION 2 - WORK PACKAGE PROGRESS REVIEW

2.1 Work Package Objectives

The specific work package objectives for the full duration of the project are summarised in the table below.

Work Package	Work Package Title	Lead Contractor	Person Months	Start Month	End Month	Deliverable
1	Development of Scientific Knowledge for WPs 2-4	TEG	7	1	6	D1-D5
2	Development of POS-BEADD Chemistry	Pera	8.8	7	22	D6-D9
3	Enhancement of Bead Management and Catheter Technologies	Joline	12.5	12	24	D8-D9
4	Development of Prototype Bead Processing, Storage and Transport Systems	Biocompatibles	21.4	18	26	D10-D11
5	Integration of POS-BEADD Technology	Biocompatibles	21.2	22	28	D12-D15
6	Pre-Clinical Validation of POS-BEADD Technology	Biomatech	11.7	22	28	D16-D18
7	Innovation Related Activities	Biocompatibles	15.7	1	28	D19-D22

2.2 Overview of Technical Progress

Work Package 1 – Development of Scientific Knowledge for Work Packages 2-4

Task 1.1 Enhancing Scientific Understanding of Bead Chemistries
Task Leader Pera

Objectives:
To enhance the scientific understanding of co-polymerisation chemistries for generation of positively charged beads.

Progress:
The literature has been researched on PVA, ion-exchange chromatography for further examples of the use of PVA co-polymerisation technologies for the production of positively charged beads. The world patent databases have been researched through ESPACENET to discover published patents and applications concerning the use of co-polymerisation technologies. Enhanced knowledge has been gained on chemical approaches to the development of positively charged PVA beads. Co-polymerisation technologies have been reported for generation of positively charged beads to be disseminated to the other participants.

Deliverable Status (D1):
This deliverable has been completed.

Task 1.2 Increasing Understanding of Impact of Co-polymerisation Technologies on Physical Characteristics of PVA Beads
Task Leader Biocompatibles

Objectives:
To enhance our understanding of the effects of co-polymerisation on physical properties of PVA beads

Progress:
The literature has been researched concerning the effects of co-polymerisation and cross–linking of PVA on the uptake of other chemicals including drugs and dyestuffs. Examples from the scientific literature of the effects of co-polymerisation and cross-linking on the deformability of resulting polymeric structures and the further effects of drug and dyestuff take up on these characteristics, have been identified. The literature has been scrutinised for details of the effects of co-polymerisation and cross-linking on the ability of PVA co-polymers to allow drug and dye-stuff elution and how the kinetics of elution are affected by the degree of co-polymerisation and cross-linking. The effects of co-polymerisation on physical properties of PVA beads have also been reported.

Deliverable Status (D2):
This deliverable has been completed.

Task 1.3 Enhancing Understanding of Beads Processing Technologies
Task Leader Pera

Objectives:
To enhance scientific knowledge of reactive dyes, sterilisation, lyophilisation and re-hydration technologies for application to POS-BEADD development.

Progress:
Reactive dye development and chemistry has been identified that will react with positively charged co-polymers of PVA. The literature has been researched on lyophilisation of PVA polymers in the presence and absence of drugs, dyestuffs and other chemicals. Technology used to re-constitute lyophilised PVA polymers has also been investigated. The negative PVA polymer beads have been successfully lyophilised. The test-rig has been constructed and the chemical synthesis for negative beads has been accomplished. This provides a good platform for the completion of subsequent work packages. Successful lyophilisation has also been conducted on the negative beads.

Deliverable Status (D3):
This deliverable has been completed.

Task 1.4 Researching Pre-clinical Models for Testing of Bead Delivery Technology
Task Leader Biomatech

Objectives:
The aim is to research the pre-clinical models of embolization therapy for the adaptation for bead delivery.

Progress:
The literature has been researched for examples of pre-clinical testing of embolization procedures and these have been adapted to PVA beads. A preliminary protocol for the model to be used in this project has been constructed and the pre-clinical models of embolization therapy have been reported.

Deliverable Status (D4):
This deliverable has been completed.

Task 1.5 Risk Assessment & Contingency Management
Task Leader Fraunhofer TEG

Objectives:
To undertake the initial QFD assessment of the risks associated with the total project and the individual work packages.

Progress:
The initial QFD assessment has been undertaken, the different levels of the participants' expectations, the expected outputs from individual work packages and their related impacts, the technical requirements and targets including measurable specifications, technical concepts and solutions has been all linked in a methodical way into a 'House of Quality' (HoQ). The resulting HoQ documents have been disseminated to all the participants following their input at the 3 Month Meeting along with guidelines for their use and updating throughout the project.

Deliverable Status (D5):
This deliverable has been completed.

Work Package 2 – Development of POS-BEAD Technology

Task 2.1 Design and Synthesis of Prototype Positively Charged Beads
Task Leader Pera

Objectives:
The aim is to design and implement protocols for the generation of POS-BEADD using co-polymerisation technologies. Design flow chart for laboratory synthesis of positively charged beads. Develop acid/base titrimetric assay for charge on beads. Implement protocol for synthesis of beads. Estimate degree of cross-linking and charge using titrimetric assay developed above. Modify protocols and re-iterate until technical objectives are met.

Progress:
A chemical protocol has been designed for the synthesis of positive beads from the Nefilcon B macromer. This methodology uses an *azo* initiator for the radical reaction, which then reacts with the cross-linker DMAP that in turn reacts with the macromer to form the required spherical beads. The bead synthesis has also been successful with APTA which is a quaternary amine, as opposed to a tertiary amine with DMAP. These conditions have been designed for the optimum synthesis of positive beads. As an addition to the work package alginate polymer beads have also been synthesised, which could have the potential to treat tumours. Alginate polymer beads possess a negative charge and it would also be possible to have these drug loaded. Overall, three different types of beads have been successfully synthesised. All sets of beads will be available for drug

loading and lyophilisation studies, to deduce which type of bead has the better up-take and elution properties.

Deliverable Status: (D6):
This deliverable has been completed.

Task 2.2 Test Physical Properties of Positively Charged Beads
Task Leader Biocompatibles

Objectives:
To develop test procedures and analyse the effects of co-polymerisation on physical properties of positively charged PVA beads. Develop and implement assays for deformability of beads using Instron Model 4411 system for measuring modulus. Assess the effects of increased cross-linking on deformability of positively charged PVA beads and ability to meet technical objective of a modulus: 30+/-5 kPa for unloaded beads. Assess ability of positively charged POS-BEADDs to migrate down 1.7 Fr catheter compared with existing micro-spheres in solutions of saline and commonly used contrast agents.

Progress:
The physical properties of the beads have been determined using an Instron 4411 system with a modified staging unit, to measure the *in-vitro* compressibility of the beads. High Performance Liquid Chromatography on residuals of the beads indicates the purity of the beads. Residual analysis has been conducted on both DMAP and APTA beads, showing the following results;
805BB/86: <0.1ug/ml APTA; <0.1ug/ml NAAADA
805BB/90: <0.1ug/ml DMAP; <0.1 ug/ml NAAADA
The APTA beads using the quaternary cross-linker have <0.1ug/ml excess APTA and <0.1ug/ml NAAADA starting material. The DMAP beads using tertiary cross-linker have <0.1ug/ml excess DMAP and <0.1ug/ml NAAADA starting material. Overall, both sets of results are within the specification limits for residuals showing low levels of impurities and starting material of the beads, this indicates that they are suitable for further study such as drug loading, lyophilisation and potential animal research.

Deliverable Status (D7):
This deliverable has been completed.

Task 2.3 Develop Bead Dye Technology
Task Leader Pera

Objectives:
To examine the binding of reactive dyestuffs to positively charged POS-BEADD. Develop protocol for in-process dying using existing reactive dyestuffs. Implement protocol for in-process dying of beads. Determine degree of dye elution over time and degree to which dying process limits cross-linking and restricts overall bead charge using assays developed earlier. Modify protocols and re-iterate until technical objectives are met.

Progress:
Anionic compounds have been used to determine the charge on the DMAP beads both the anions 4-nitrophenol and phenolphthalein can bind onto positive beads. The binding of 4-nitrophenol gives the

beads a yellow colour and hence illustrating that the beads synthesised are positive. This similar methodology could be used to bind dyestuffs onto the positive beads. Further investigation shows that the drug loading step will inevitably give the beads a characteristic tint and hence would eliminate this step. This would work to out to benefit further as it reduces the toxicity of the beads posed by using a dye. Supplementing with a dye would increase the toxicity and hence the beads would be more likely to fail in the pre-clinical trials, the dye used in previous methods was reactive blue 4.

Deliverable Status (D8):
This deliverable has been completed.

Task 2.4 Test Drug Loading of Alginate Polymer Beads, and Drug Elution
Task Leader Biocompatibles

Objectives:
To develop and implement a protocol for the synthesis and purification of a drug for the selected alginate polymer bead candidate. To develop the synthesis of the alginate polymer bead in the absence of any drug. Develop the synthesis of the alginate polymer bead incorporated with a drug. Investigate analysis of the alginate polymer beads in presence and absence of a drug. To study the quantity of a drug loaded on alginate polymer beads and the elution kinetics of the alginate beads containing a drug. Investigate analysis to investigate the quantity of ibuprofen loaded on each bead. Test physical properties of alginate polymer beads in the absence and presence of a drug.

Progress:
The drug loading on polymer beads has been thoroughly researched for this application. A number of various drugs have been investigated such as is lidocaine and dexamethasone. To acquire a deeper understanding of the scientific knowledge relevant to the developments taking place in the project our main ideas how to develop beads of appropriate size and composition to be easily modified or loaded with the respective substances has been summarized. Several types of beads have been evaluated focusing on previous experimental work in our own facilities in order to contribute to the development of beads carrying positive charges throughout. Literature research from and evaluation of work within was conducted to identify suitable particles for reversible nucleic acid and drug immobilisation. Three types of particles which also have been used previously (for nanotechnological purposes) were looked at more closely. The most appropriate due to the simple preparation of particles in various sizes, their stability, colourability and highly flexible surface chemistry were determined as silica particles. In addition, to our knowledge, no adverse reactions of the human body against silica particles have been reported.

Deliverable Status (D9):
This deliverable has been completed.

Work Package 3 – Enhancement of Bead Management and Catheter Technologies

Task 3.1 Development Novel Bead Management Technologies
Task Leader DMC

Objectives:
The aim is to use CAD CAM system for designs of various mixing devices using three different methods for the aggregation for the beads. To construct a prototype bead mixing device based on

one of the mixing design ideas. This includes the electronics, batteries and switches and will establish the methodology and proof of principle. To use CAD CAM system to design three ergonomic bead mixing devices based on the prototype device. Obtain feedback from a surgeon and/or interventional radiologist for the prototype bead mixing device. To build test rig and test flow of prototype beads. Determine optimal and refine prototype devices. Deliver prototype components of in-line bead management device. Develop the bead mixing ideas further and construct a prototype model.

Progress:
The most practical idea was to design a vibration device to mix the beads inside the syringe, as this would eliminate the additional step of having a pre-sterilised bead inside the syringe. The administrator (delivery) syringe is attached onto a plastic casing containing a vibration motor (similar to the motors in mobile phones). This is a hand-held and portable device that is battery operated. The syringe size would be designed to fit inside the clips. When the motor is switched on this will cause tiny vibrations causing the hydrogels beads to move. A prototype device has been constructed that operates using a vibration motor in order to establish the basic principle of the methodology. Initial mixing experiments have been conducted with contrast agent and it concludes that bead mixing is possible using this application. As this mechanism for bead is valid the actual hand-held case will need to be designed and appropriate mould tools made for this application.

Deliverable Status (D10):
This deliverable has been completed.

Task 3.2 Produce Prototype Delivery System
Task Leader DMC

Objectives:
To build prototypes of the in-line bead management device and to build a prototype bead management devices using prototype tools.

Progress:
A prototype device has been constructed that operates using a vibration motor in order to establish the basic principle of the methodology. Initial mixing experiments have been conducted with contrast agent and it concludes that bead mixing is possible using this application. As this mechanism for bead is valid the actual hand-held case will need to be designed. A CAD drawing of the bead block syringe was designed, to illustrate how the mixing device would be constructed and housing involved. The technical drawing also gives ideas for the dimensions and size of the object.

Deliverable Status (D10):
This deliverable has been completed.

Task 3.3 Develop New Catheter Technologies
Task Leader Joline

Objectives:
To create prototype catheters capable of delivering the drug/bead combinations developed in work package 2, through uterine arteries.

Progress:
The most suitable design for catheters for the POS-BEADD project has been investigated. The present range of catheters available at include the double and triple lumen silicon catheters. The double lumen silicon catheters or D-LINE LT catheters are designed for short and long term during extracorporeal treatment, mainly in haemodialysis. The catheter designed by Joline for the project has a balloon device near the tip. The balloon sheath will able to block the peripheral circulation and from that improves the flow in to the liver and to the suprarenal aorta. The increased blood pressure and perfusion will need are investigated and explained further in work package 6.4. The balloon catheter will able to measure the effect of liver peripheral circulation occlusion on arterial blood pressure and on hepatic artery and aortic blood flow.

Deliverable Status (D11):
This deliverable has been completed.

Work Package 4 – Development of Prototype Bead Processing Storage and Transport Technologies

Task 4.1 Develop and Refine Alginate Polymer Bead Synthesis
Task Leader CellMed

Objectives:
To conduct alginate based polymer bead synthesis and drug loading studies and using laboratory scale equipment, test response of alginate polymer beads. To formulate and manufacture the alginate polymer material, determine its chemical composition and subsequent manufacturing process.

Progress:
The alginate polymer bead synthesis has successfully been conducted on a laboratory scale. The formulation and manufacture of the alginate polymer material has been thoroughly tested. The chemical composition has been determined and the manufacturing process investigated and optimised.

Deliverable Status (D12):
This deliverable has been completed.

Task 4.2 Adapt Sterilisation Technologies to POS-BEADD Production
Task Leader DMC

Objectives:
To develop protocols which ensure the sterility of beads with and with out drug when delivered to the radiologist for use. To develop the lyophilisation and sterility methods for the polymer bead technology.

Progress:
The lyophilisation was carried out both with hydrogels in saline and hydrogels separated from saline by filtration followed by a washing step with water. Prior lyophilization, the hydrogels were separated from the liquids by filtration using membrane filters (pore size 0,45 µm). The PVA polymer also serves as cryoprotectant, the addition of other cryoprotectants were not necessary. The lyophilisation process consisted on three steps. The samples were frozen at -25 ℃ under atmospheric pressure on cooled shelves inside the ice condenser chamber for 3 hours. The samples were frozen in layers of

about 5 mm. First drying at low temperature (-25 ℃) under vacuum up to $4x10^{-1}$ mbar for 48 hours, the ice was removed by sublimation. Second drying at room temperature under strong vacuum (usually 10^{-3} mbar) could not be performed because the strong vacuum could not be reached by the used vacuum pump. After the first drying the process was usually finished..

Deliverable Status (D12):
This deliverable has been completed.

Task 4.3 Develop the Bead Mixing Technologies
Task Leader DMC

Objectives:
To use the bead mixing technologies to enable the testing the mixing ability of alginate polymer beads in saline and/or appropriate contrast agent. To enabling the testing of the entire POSBEADD bead delivery system that includes syringe, mixing device and catheter.

Progress:
The bead mixing technology has been tested using polymer bead in saline and also with increasing quantities of omnipaque contrast agent. The entire delivery system operates very well together and the delivery of beads causes no blockages or malfunction to the various systems involved. The novel bead mixing system contains; a vibrating plunger barrel with off-set motor, AAA battery, connected to a push button switch on the head of the plunger. The casing consists of two parts the main barrel section which is joined onto the head by a thread. The new mixing system will be demonstrated to people involved in the embolization surgery (interventional radiologists and surgeons).

Deliverable Status (D13):
This deliverable has been completed.

Task 4.4 Develop Bead and Catheter Packaging, and ID Technologies for the POS-BEADD System and Test with End-Users
Task Leader DMC

Objectives:
To integrate and test the entire POSBEADD bead delivery system that includes syringe, mixing device and catheter. Test the ability of the system to deliver and administer beads in a uniform manner with any malfunction or blockage to the system.

Progress:
The POSBEADD system has been integrated so that the whole unit is operational as a system. The bead mixing device has also been tested using the alginate polymer beads and catheter system. The polymer beads are in a solution with saline and omnipaque contrast agent as mentioned earlier. The bead mixer provides a continuous and uniform flow when administered. There is found to be no blockage of the catheter or the syringe when the beads are administered. The different components of the POS-BEADD technology have been incorporated and operate very well as a single unit.

Deliverable Status (D13):
This deliverable has been completed.

Work Package 5 – Integration of POS-BEADD Technology

Task 5.1 Production of Prototype beads
Task Leader Biocompatibles

Objectives:
To implement production protocols for alginate polymer beads. To synthesise beads on a laboratory scale according to protocols developed in work package 2, sterilise and package according to protocols developed in work package 4 to provide alginate polymer material for bead synthesis.

Progress:
The work has been conducted on one type of bead with the aim to establish technologies that can rapidly be transferred to all kinds of beads with similar features. The features of the beads should be largely inert structures (silica, polymers etc.) and positively charged surface or surfaces with functional groups on which surface architectures can be built by chemical means to introduce positive charges. The work described below especially with regard to chemical modification of beads and nucleic acid loading of beads represents general methods which can be applied rapidly to a large variety of beads as defined above. Overall, prototype alginate polymer beads have been synthesised.

Deliverable Status (D14):
This deliverable has been completed.

Task 5.2 Test Integration of Beads, Bead Management Components and Prototype Catheters
Task Leader Pera

Objectives:
To test compatibility of elements of POS-BEADD system when fully integrated. To test the ability of the alginate polymer beads through the designed catheter.

Progress:
An even bead suspension over a 30 second time period was noted after 3-5 minutes of mixing. It was not possible to assess bead aggregation or clumping properly due to the slightly opaque nature of the syringe. For beads in saline and water the deliverability was smooth with slightly more resistance on second and third deliveries. This may be because beads were already in the catheter. Overall, no blockages occurred in all deliveries. An interventional radiologist should have no difficulty delivering the alginate beads, prepared by CellMed, in the POSBEADD sheep uterine artery embolization study. The bead mixing device (work package 4.3) has also been tested using the alginate polymer beads and catheter system. The polymer beads are in a solution with saline and omnipaque contrast agent as mentioned earlier. The bead mixer provides a continuous and uniform flow when administered. There is found to be no blockage of the catheter or the syringe when the beads are administered. The different components of the POS-BEADD technology have been incorporated and operate very well as a single unit.

Deliverable Status (D14):
This deliverable has been completed.

Task 5.3 Assemble Optimised Prototype POS-BEADD System
Task Leader Biocompatibles

Objectives:
To assemble optimised prototype bead sets for pre-clinical trials. To supply and assemble components for pre-clinical trials

Progress:
The fast degradation of alginate beads for sheep uterine embolization and *in vitro* testing was measured and optimised. The degradation of alginate beads is dependent on the cross linking agent, the M/G ratio and molecular mass distribution. The cross linking agent is achieved by using Ca^{2+}, which has a lower affinity than Ba^{2+}. The synthesis of alginate polymer beads has been optimised for the project.

Deliverable Status (D14):
This deliverable has been completed.

Work Package 6 – Pre-Clinical Validation of POS-BEADD Technology

Task 6.1 Establish In-Vitro Physiological Model of Uterine Arterial Injection
Task Leader Biomatech

Objectives:
To develop *in-vitro* and *in-vivo* models of uterine artery embolization. To develop an *in-vitro* model of POS-BEADD delivery using perfused arteries in the organs of butchered animals – probably sheep or pigs. Model to include: exposed small artery (diameter = that of uterine artery in humans) connected to capillary network in organ with a draining vein that can be used to detect output drug. Liver may be most appropriate organ

Progress:
The literature has been reviewed and the most suitable models listed. A preliminary / feasibility study has been conducted to confirm the selection of the sheep uterine artery model, optimization of surgical techniques and choice of instruments, training of investigators.

Deliverable Status (D15):
This deliverable has been completed.

Task 6.2 Test Embolization with Beads
Task Leader Biomatech

Objectives:
To evaluate the local tolerance of three alginate bead formulations, following injection in the subcutaneous tissue of rat has been investigated. To evaluate the local tolerance of three test articles following subcutaneous injection after 1 week and 12 weeks in the rat in comparison with a reference article.

Progress:
The microscopic results illustrated that after one and 12 weeks of implantation all the four types of beads for testing were non-irritant. Signs of inflammation were decreased slightly after 12 weeks. Bead types A and B were found to have the least inflammation. Evaluation of the inflammatory reaction: One week: (less inflammation) A = B < Ref < C and at 12 weeks: (less inflammation) A = B < C < Ref. Product C showed signs of peripheral fragmentation and degradation. Signs of tissular integration ranking: One week: Ref = C > A = B and at 12 weeks: similar observations.

Deliverable Status (D16):
This deliverable has been completed.

Task 6.3 Test Drug Elution
Task Leader Biomatech

Objectives:
To test four types of alginate polymer beads *in-situ* during the embolization procedure. To investigate the effects of alginate beads in animal models, to determine the rate of necrosis and any irritation effects of the alginate polymer beads.

Progress:
Four types of alginate polymer beads have been tested in the study. The total duration of the study was 12 weeks so the intervals were; 1 week, 4 and 12 weeks. The beads types are High G, High M, High G pre-degraded and High M pre-degraded. The surgery was performed under angiography. The aortography was performed to identify the internal iliac arteries. Selective catheterization was conducted of the internal iliac artery and super selective catheterization of the uterine artery. The embolization was distally into the uterine artery and angiogram performed immediately after the procedure. At the 4 week stage there were no significant macroscopic signs of necrosis could be observed. The organs were removed and examined. Leading to the conclusions that not enough embolization agent was used or the beads have already degraded. This pre-clinical study is currently in the process of being written for publication.

Deliverable Status (D17):
This deliverable has been completed for the 4 weeks stage.

Task 6.4 Establish *In-Vivo* Physiological Model of Uterine Arterial Injection & conduct Tests on the Joline Catheter
Task Leader Biomatech

Objectives:
The effect of peripheral circulation occlusion with the Joline balloon sheath on the aortic blood pressure and on hepatic artery and aortic blood flows was studied. The aim of the work was to assess whether the Joline balloon sheath is able to block the peripheral circulation and subsequently improve the flow in the liver and in the suprarenal aorta. To investigate the increase in blood pressure and/or perfusion are instantaneous and reversible.

Progress:
The concluding preliminary results showed the effectiveness of the Joline balloon sheath to block the peripheral circulation. The study illustrated the increase in the aortic blood pressure during occlusion. A slight increase in the hepatic artery flow during occlusion was also observed, together with a decrease in aortic artery flow during occlusion. These haemodynamic changes were instantaneous and reversible. However, the mean hepatic blood flow showed regular increases cascade like.

Deliverable Status (D18):
This deliverable has been completed.

2.3 Deviation from the Plan and Corrective Actions

Here is a summary of deviations from the work programme, with the corrective actions taken or suggested. The nature and reason for the problem and identity of contractors involved has been stated.

Work Package 1 Scientific Knowledge

Deviations from Plan
There was an important requirement to explore other avenues of drug delivery as the treatment of uterine fibroids may not have a large impact on the market by the end of the project. To investigate the treatment of tumours and drug delivery systems to the brain, the synthesis of both positive beads as well as alginate beads would be better for the project.

As a result, the pre-clinical evaluation experiments on alginate beads in the intra cerebral location have been conducted. The implantation tests were designed to evaluate the local pathologic effects of implanted materials on living tissues and give a macroscopic and microscopic evaluation. The macroscopic results showed that there was no difference in terms of local intolerance were seen between the test or reference articles. The microscopic results illustrate that after one and 12 weeks of implantation, all products were considered as non irritant and inflammation signs decreased slightly at 12 weeks. Due to these results the alginate polymer beads would prove to be an ideal bead candidate for the project. The appropriate drug candidate would have to be selected to compliment the use of alginate beads.

This change was implemented as alginate polymer beads could be used on tumours associated with the brain and nervous system, as opposed to positive beads being used on uterine fibroids.

Corrective Action
The impact of this is that an alginate material supplier will be needed in the consortium. The new partner CellMed will able to provide such alginate polymer material for the synthesis of alginate polymer beads. CellMed through its knowledge of formulating and manufacturing of alginate based polymer material, it will able to help Biocompatibles guide the design and development of the alginate polymer beads. Secondly, they will consult on the use of the alginate polymer, its chemical composition and the subsequent manufacturing process including their implementation.

This will have an impact on the drug loading and drug elution studies that will be carried out at Fraunhofer. The candidate drug will need to loaded on to alginate polymer beads and/or positive beads. Moreover, Fraunhofer will able to provide the candidate drug that will be used to test the ability of POS-BEADDs to bind these drugs and will then test the elution of the drugs following *in vitro* and *in vivo* assays of POS-BEADD activities. Fraunhofer has worked in the field of methodical development in medical device technology for seven years using an interdisciplinary team of engineers and medical doctors and is well placed to support the consortium. They have the expertise and skilled personnel to conduct such studies.

This also has an impact on Biomatech who will have to conduct the final clinical trials mentioned in work package 6 on alginate polymer material. Biomatech possess the knowledge, facilities and capabilities of conducting the research on alginate polymer material, so will not be a large problem.

Work Package 2 Development of POS-BEADD Chemistry

Deviations from Plan

The bead dye technology for positive beads may not need to be developed. There was a risk to the process of dyeing of the beads, due to the presence of the positive charge prior to dye being used. It may become necessary, assuming that the cross-linkage works all right to change the dye for a non-charged dye. Best of all would be the use of a positively charged reactive dye. However for reasons of the evolution of the reactive dye industry, there has been little need for positively charged reactive dyes. Reactive dyes are necessary in this bead product as traditional dye approaches lead to leaching (i.e. they are not colourfast) which is probably unacceptable in regulatory terms. The other solution to the problem of dyeing is to use the tertiary amino cross-linker (rather than the quaternary salt), and perform the dyeing stage at a high pH, where the amino group is effectively uncharged. The only remaining issue on this would be the molar ratio of negatively- charged dye present in the beads compared to the number of cross-links. There would need to be significantly more positive charges present to outweigh the presence of the sulphonate groups present.

Further investigation shows that the drug loading step will automatically give the bead a characteristic tint and hence would eliminate this step. This would work to out to benefit further as it reduces the toxicity of the beads posed by using a dye. Supplementing with a dye would increase the toxicity and hence the beads would be more likely to fail in the pre-clinical trials, the dye used in previous methods is reactive blue 4. The drug loading of doxorubicin on beads gives a red tint. Therefore, it is anticipated that drug loading onto positive and/or alginate polymer beads would also have a similar effect. Alginate polymer material is already brown so the respective beads would also be of similar pigmentation, therefore the dye step would serve no purpose.

Corrective Actions

This will not have a large impact on the project research; rather it will make things move more swiftly. The drug loading and elution studies conducted by Fraunhofer will able to operate without hindrance of the dye attached to the polymer bead. The facilitation of loading the drug will be better and the elution of dye during the drug elution studies will not occur.

The alginate polymer material will be provided by the new partner CellMed, who have specialist expertise in formulating and manufacturing alginate.

The pre-clinical trials that will be conducted by Biomatech in work package 6 should show promising results as there will be no toxic dye loaded on the beads. These beads are more likely to be biocompatible and biodegradable in the body of the patient as no dye is present that would be toxic. It is also likely to cause less irritation and inflammation in the body of the patient. The dose administered by the surgeon would also not be limited as the toxicity would be the minimum amount.

Work Packages 4 - 8

Deviations from Plan

The consortium partners Steripack and Melitek have had to withdraw from the POS-BEADD project, due to their respective valid reasons. The consortium has worked very hard to replace these partners with valid new SME's to the project. These two partners have been replaced by two new partners to the project, they are CellMed AG and DMC Medical Ltd;

CellMed AG is a German medical technology company developing medical device and drug delivery products.

DMC Medical have spent many years servicing the healthcare industry on a global basis. The team at DMC are drawn from a background of medical device manufacture, quality assurance, product development, customer service and distribution.

Both new companies are ideal for this project and would provide an integral part towards the successful completion.

As the partners have changed the work programme has also altered to fit these two companies, but the major aims and objectives of the project still remain the same. These changes to the work packages have been stated and defined in the modified Annex 1 document.

Corrective Actions

This has a significant impact on the future of the project, it has been agreed that all members of the consortium will work very hard to provide research for the success of the project. The Annex documentation has been modified and up-dated to meet the requests of the project and new partners. The new partners will also be contributing towards work in the project. This also means the bulk of man months will be transferred towards Biocompatibles as the coordinator, who can confidently conduct more work towards the project, due to the expansion of the consortium. Biocompatibles will generally be involved on all the tasks in every work package to foresee that everything is completed and contributions are high.

CellMed AG´s advanced technology addresses the market's urgent need for innovative approaches for proteins with short biological half-life, high systemic toxicity or limited transport across the blood-brain barrier. CellMed will bring its special brand of expertise to the design and development of two parts of the POS-BEADD technology.

DMC Medical's main role in the POS-BEADD project is to supply a range of sterile polycarbonate syringes which will store the drug-loaded beads in saline, this will amalgamate with the catheter and bead delivery components.

The Fraunhofer have the facilities and capabilities to conduct the lyophilisation research of beads mentioned in work package 4, this can easily progress without the Melitek in the consortium. Early studies on lyophilisation conducted at Fraunhofer have already proven to be very successful and provide a good platform for this research.

Both new partners will provide ideal and vital input to the project and enough people power to drive the project forward. The consortium is confident to provide high quality results, which in turn will provide the man months target for the project. For every partner involved in each respective task the resources and capabilities are available to provide the work anticipated. All members of the consortium are very motivated and will able to provide the man months required to fulfil the requirements of the project.

2.4 Work Package Deliverables Update

Deliverable No.	Deliverable Title	WP No	Lead Partici-pant	Estimated Person Months	Nature	Delivery Date	Complete
D1	Report on co-polymerisation technologies for generation of positively charged beads	1	TEG	7	R	6	100
D2	Report on effects of co-polymerisation on physical properties of PVA beads	1	TEG	-	R	6	100
D3	Report on potential for adaptation of current bead processing technologies to POS-BEADDs	1	TEG	-	R	6	100
D4	Report on pre-clinical models of embolization therapy	1	TEG	-	R	6	100
D5	Holistic QFD assessment of POS-BEADD project	1	TEG	-	R	6	100
D6	Report on optimal synthesis protocols for POS-BEADDs	2	Pera	8.8	R	13	100
D7	Report on physical properties of positively charged PVA beads	2	Pera	-	R	13	100
D8	Protocols for dying POS-BEADDs	2	Pera	-	R	13	100
D9	Report on loading of POS-BEADDS with example drugs	2	Pera	-	R	22	100
D10	Prototype mould tool and prototype in-line bead management device	3	Joline	12.5	P	22	100
D11	Prototype catheters with lumens at 1.7-9 Fr. capable of delivering the beads from WP2	3	Joline	-	P	22	100
D12	Lyophilisation, syringe sterilisation and re-constitution protocols	4	TEG	21.4	O	23	100
D13	Bead and catheter packaging, and ID technologies	4	TEG	-	O	23	100
D14	Report on prototype integrated POS-BEADD system	5	Pera	21.2	R	28	100
D15	Prototype POS-BEADD system for pre-clinical trials	5	Pera	-	P	28	100
D16	Model systems for pre-clinical testing of POS-BEADD technology	6	Biomat	11.7	D	28	100
D17	Report on pre-clinical testing of POS-BEADD technology	6	Biomat	-	R	28	100
D18	Report on drug elution from POS-BEADDS delivered *in vitro* and *in vivo*	6	Biomat	-	R	28	100
D19	Report on potentially competitive patents and a plan for patent application(s)	7	Biocomp	15.7	R	28	-
D20	Production of support material for transfer of the knowledge to the partners through a web site, case studies and a generic design guide	7	Biocomp	-	D	28	-
D21	Report on the standards, ethical and regulatory aspects of the exploitation of the results	7	Biocomp	-	R	28	-
D22	Plan for using and disseminating the knowledge	7	Biocomp	-	R	28	-
D23	Six month progress reports, Mid Term Assessment Report and Final Report. Submission of the cost statements at mid term and end of projects. Organise kick-off, mid term and final meetings	8	Biocomp	3.7	R	28	-
D24	Provision of audit certificates and bank guarantees and amended consortium agreement (if applicable)	8	Biocomp	-	O	28	-
D25	Report on gender, societal and ethical issues of exploitation	8	Biocomp	-	R	28	-
D26	Non confidential summary report	8	Biocomp	-	R	28	-

2.5 Work Package Milestones Update

Milestone No	Milestone Name	WP No	Date Due (Month)	Actual Delivery Date (Month)	Lead Contractor
M1	End of research phase (WP1)	1	6	6	TEG
M2	End of chemistry development phase	2	18	18	Pera
M3	Development of catheter and bead management device	3	23	23	Joline
M4	Complete bead processing protocols	4	23	28	Biocompatibles
M5	Production of ergonomic & safe packaging protocols	5	23	28	Biocompatibles
M6	Complete prototype POS-BEADD system	6	28	28	Biomatech

SECTION 3 - CONSORTIUM MANAGEMENT

3.1 Consortium Status

The consortium is working well together providing valuable input and direction for the research programme. We have had a good start to the project with very constructive technical and commercial discussions at the meetings, as described in the minutes, and regular communication has taken place between the Partners. The Partners are working very well together, communicating and meeting regularly. In addition to the formal meetings a number of working party meetings have occurred to discuss the technical aspects of the project. The consortium partners Steripack and Melitek have had to withdraw from the POS-BEADD project. More specifically:

Steripack – Shane Healy from Steripack has subsequently left the company since the project started. This leaves the remaining team at Steripack short of staff and unable to devote the human resources (actual time and expertise) needed for the project. We are currently seeking a partner with comparable expertise and facilities to replace their role within the project.

Melitek – Melitek specialise in the supply of lyophilisation equipment and services, they were going to be an important part of the production process for the POS-BEADD product. Since the project started their business focus has changed and they no longer plan to provide lyophilisation services. Consequently they have less of a role in the POS-BEADD supply chain and have decided to leave the project. Subsequent to leaving the project both partners have issued formal letters of withdrawal and waived any ownership to any IP generated by the consortium.

The consortium has successfully recruited two new partners to the project. They are CellMed AG and DMC Medical Ltd;

CellMed AG is a German medical technology company. Several therapies are in development using its proprietary and broadly applicable CellBeads®-Biopolymer biodegradable bead technology. The company was founded in 2000 by Dr. Peter Geigle and Olaf Althaus. CellMed AG´s advanced technology addresses the market's urgent need for innovative approaches for proteins with short biological half-life, high systemic toxicity or limited transport across the blood-brain barrier. CellMed will bring its special brand of expertise to the design and development of two parts of the POS-BEADD technology. Firstly, through its knowledge of formulating and manufacturing of alginate based polymer material, it will able to help Biocompatibles guide the design and development of the alginate polymer beads. Secondly, they will consult on the use of the alginate polymer, its chemical composition and the subsequent manufacturing process including their implementation in WPs 4 and 5.

DMC Medical represents Distribution, Manufacturing & Consultancy and utilizes a team of professionals, all of whom have spent many years servicing the healthcare industry on a global basis. The team at DMC are drawn from a background of medical device manufacture, quality assurance, product development, customer service and distribution. All the finished medical devices are manufactured, tested, sterilized and approved to the highest international standards. Manufacturing is BS ISO 9002/EN 46002 certified, while the product range is tested and evaluated in accordance with ISO 10993. Sterilization is by EtO and Gamma Irradiation, performed to ISO 11135/EN550, ISO 1137/EN552 respectively. CE marking is carried out in accordance with the Medical Device Directive 93/42/EEC assuring the customers that quality is not an issue at DMC but a fact. DMC Medical's main role in the POS-BEADD project is to supply a range of sterile polycarbonate syringes which will store the drug-loaded beads in saline, this will amalgamate with the catheter and

bead delivery components. They will greatly contribute to the implementation of the packaging phase in WP4 as well as in the integration of POS-BEADD technology in WP5.

Both companies are ideal for this project and would provide an integral part towards the successful completion.

Project Management Structure

The project is controlled by a Technical Board, which in turn is headed by the Co-ordinator (Biocompatibles), who will have the ultimate responsibility for the project, and act as Chairman. Each task has been allocated to the partner or RTD performer with the most appropriate skills or requirements relating to that particular task and they will be responsible for delivery of that task to plan. The task leaders are detailed in the work programme and report to the Co-ordinator.

3.2 Project Timetable & Status

Work Schedule	Lead	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	Months
WP1 Scientific Enhancement	**2**																													7
1.1 Scientific Understanding	1, 7	X	X	X																										
1.2 Co-polymerisation	1, 7				X	X	X																							
1.3 Bead Processing	1, 2, 7	X	X	X	X	X	X																							
1.4 Preclinical Testing Research	1, 7, 8				X	X	X																							
WP2 Bead Chemistry	**7**																													8.8
2.1 Design & Synthesis of Beads	1, 7							X	X	X																				
2.2 Test Physical Properties	1										X	X	X	X																
2.3 Develop Dye Technology	1, 7										X	X	X	X																
2.4 Test Drug Loading & Elution	2																		X	X	X	X	X							
WP3 Bead Technology	**3**																													12.5
3.1 Bead Management Device	5, 7												X	X	X	X	X	X												
3.2 Prototype Delivery System	5																		X	X	X	X	X							
3.3 Develop Catheter Technology	1, 3, 7														X	X	X	X	X	X	X	X	X							
WP4 Prototype Beads																														21.4
4.1 Lyophilisation Technologies	2																		X	X	X	X	X	X	X	X	X			
4.2 Sterilisation Technologies	1, 2																		X	X	X									
4.3 Re-constitution Technology	1, 2, 7																		X	X	X									
4.4 Bead & Catheter Packaging	1, 3, 5																					X	X	X	X	X	X			
WP5 Integration of Technology																														21.2
5.1 Production of Prototype Bead	1, 7																		X	X	X	X	X	X						
5.2 Test Integration	1, 3, 7																		X	X	X	X	X	X						
5.3 Optimised Prototype	ALL																					X	X	X	X	X	X			
WP6 Pre-clinical Validation	**8**																													11.7
6.1 Physiological Model *In-Vitro*	8																					X	X	X	X	X	X	X	X	
6.2 Test Embolization	8																					X	X	X	X	X	X	X	X	
6.3 Test Drug Elution	2, 8																					X	X	X	X	X	X	X	X	
6.4 Physiological Model *In-Vivo*	8																					X	X	X	X	X	X	X	X	
WP 1-6 RISK ASSESSMENT	**2**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WP7 Innovation Activities																														15.7
7.1 Develop Exploitation Strategy		X	X	X																										
7.2 Protection of Results	1, 7							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
7.3 Absorption of Results	ALL													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
7.4 Dissemination of Results	ALL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
7.5 Technology Transfer	ALL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
7.6 Socio-Economic Impact	ALL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WP8 Consortium Management	1																													3.7
8.1 Knowledge Management	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
8.2 Technical Activities	1, 2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
8.3 Overall Administration	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
8.4 Co-ordination of Other Issues	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

3.3 Clarification of Changes to Work Programme

The consortium partners Steripack and Melitek have had to withdraw from the POS-BEADD project, due to their respective valid reasons. The consortium has worked very hard to replace these partners with valid new SME's to the project. These two partners have been replaced by two new partners to the project, they are CellMed AG and DMC Medical Ltd;

CellMed AG will consult on the use of the alginate polymer, its chemical composition and the subsequent manufacturing process including their implementation in WPs 4 and 5.

DMC Medical will greatly contribute to the implementation of the packaging phase in WP4 as well as in the integration of POS-BEADD technology in WP5.

Both new companies are ideal for this project and would provide an integral part towards the successful completion.

As the partners have changed the work programme has also altered to fit these two companies, but the major aims and objectives of the project still remain the same. These changes to the work packages have been stated and defined in the modified Annex 1 document.

3.4 Meetings & Communication

There have been nine project review meetings since the start of the project. These have all combined technical, management and exploitation issues.

Project Review Meetings Held

	Date	Type of meeting	Venue
1	27.01.2005	Kick-off Meeting	Biocompatibles
2	23.03.2005	Month 3 Management Meeting	S & S Plastics
3	28.06.2005	Month 6 Management Meeting	Biomatech
4	05.10.2005	Month 9 Management Meeting	Biocompatibles
5	14.12.2005	Month 12 Management Meeting	Joline
6	01.03.2006	Month 15 Management Meeting	Pera
7	27.07.2006	Month 18 Management Meeting	Biocompatibles
8	31.10.2006	Month 24 Management Meeting	CellMed
9	20.03.2007	Month 28 Management Meeting	Biomatech

All meetings have been characterised by good attendances and open discussion, thus exploring broad views on the direction and content of the technical work. Partners have also carried out technical presentations at these meetings and have brought technical knowledge to the project consortium. This clearly illustrates the positive commitment of the partners.

Very constructive technical and commercial discussions have occurred at the project meetings, as described in the minutes and regular communication has taken place between the partners. The partners are working very well together.

In addition to the formal meetings a number of working party meetings have occurred to discuss the technical aspects of the project and specific project issues to focus the work programme.

Project Technical Meetings

	Date	**Type of meeting**	**Venue**
1	15.02.2005	Technical / Bead Chemistry	Biocompatibles
2	28.02.2005	Technical / Bead Mixing System	S & S Plastics
3	18.04.2005	Technical / Bead Mixing System	Pera
4	20.09.2005	Technical / Bead Mixing System	S & S Plastics
5	27.09.2005	Technical / Catheter	Joline
6	28.09.2005	Technical / Management QFD	Fraunhofer
7	22-23.11.2005	Technical / Bead Chemistry	Pera
8	30.01.2006	Technical / Bead Mixing System & Catheter	Devon & Exeter Hospital
9	09.03.2006	Technical / Bead Mixing System	DMC Medical
10	17.01.2007	Technical / Catheter pre-clinical trials	Biomatech
11	14-16.02.2007	Technical / Bead pre-clinical trials	Biomatech

The venues for all meetings have been rotated at different partner-sites to give the consortium an opportunity to learn more about how the host partner operates. A tour of the facilities has always followed the meetings.

3.5 Dissemination Activities

Management of Knowledge and IPR

In the project the industrial partners have agreed and requested that no specific dissemination activities are undertaken. It is envisaged that patent applications will be made.

A number of different types of Intellectual Property Rights (IPR) are likely to be developed in any project of this type. These include patents, designs (both registered and unregistered), copyright, software and database rights, and (secret) know-how. In the POS-BEADD project, the most important of these are the inventions that can be patented as these will form the basis of future licensing revenues. The following are novel, involve an inventive step and are capable of industrial application and are therefore deemed to be patentable:

- development of bead management systems, including catheters and valves capable of delivering a wide range of drug-loaded beads;
- positively charged PVA and alginate polymer beads for embolization, drug delivery and chromatography applications;
- applications of POS-BEADD chemistries to other applications including ink-jet printing.

The SME participants in the POS-BEADD project will take steps to secure the IPR in their inventions and a sum has been put aside to cover the costs of this task. The Exploitation Manager will manage the Innovation Related Activities and will co-ordinate:

- absorption of the results by the participants;
- dissemination of the knowledge beyond the consortium;
- activities promoting the exploitation of the results;
- studies on socio-economic aspects;
- transfer of best practices for the early use and exploitation of technologies;
- activities that promote or enable synergies with education.

Routes to Exploitation

A number of different types of Intellectual Property Rights (IPR) are likely to be developed in this project. These include patents, designs (both registered and unregistered), copyright and (secret) know-how. The management of these different types of IPR will be allocated to the Exploitation Manager as part of the overall Exploitation Strategy (see below). Through consultation with Patent Attorneys and following close examination of the advice issued by the IPR-Helpdesk (e.g. 'A Tutorial On The Intellectual Property Regime of the Sixth Framework Programme' and 'The creation of an entity in charge of the exploitation of RTD results - What are the best choices?') and the sample consortium agreements supplied, the partners have produced a draft Consortium Agreement that comprehensively addresses the IPR issues in the POS-BEADD project.

The partnership has already developed an Exploitation Strategy for the management of knowledge, intellectual property and of its inter-relation with the various innovation-related activities planned. The basis of the strategy is to allow the new scientific knowledge created by the project to be actively disseminated amongst academic communities to validate it and extend science and technology understanding and promote science and technology cohesion. However, prior to the programme of innovation related activities, the industrial partners will patent the technological capabilities developed and the product, process and system applications they in turn enable. Hence, the full range of scientific, technological and product, process and system specific dissemination, demonstration and

training activities can be enabled without compromising the protection of the foreground IPR. This strategy includes a joint policy of the partnership concerning rights of ownership, rights of defence and rights to exploit.

In summary, the SME participants in the POS-BEADD project are confident that they form a strong supply chain that, through its Exploitation Board is highly capable of the initial exploitation phase. Backed by strong project results leading to high quality and robust manufacturing and marketing processes, the participants are also confident that they can meet the requirements for international scale up of exploitation in new and diverse market sectors.

Assimilation and Exploitation of the results by the SME proposers

The members of the POS-BEADD consortium form a close network of scientists, engineers and managers all working toward the common goals of the project. Technical meetings, design discussions, prototype manufacture, validation and trial work will all result in project personnel being seconded to multiple sites throughout the project. A fluent and convenient exchange of project reports and data has been achieved. All of these activities will promote rapid assimilation and retention of knowledge between the partners which will continue beyond the end of the project.

The SME partners will form an Exploitation Board and come together at specified meetings to co-ordinate and harmonise all the exploitation activities. This committee will generate an Exploitation Plan which will link companies, both in and outside the consortium, into an agreement that will specify confidentially, licensing intentions and intellectual property protection. The Exploitation Board will meet on a frequent basis to review the EP, analyse market potential, sales forecasts and supply chain capability. The partners will identify additional technology applications and market areas as well as disseminate the project results to a wider audience. After the project, the committee will continue to plan and co-ordinate project developments and exploitation to ensure that the commercial collaboration and legal activities are continued and maintained.

Validation of the Technology

It is important that the product, process and applications are validated. To assist in this, an application and technology application facility will be produced to highlight the prototype system performance in simulation. Subsequently, clinical trials of the POS-BEADD system will be implemented in collaboration with clinicians. Additional meetings of the Board with trade associations will stimulate market exploitation and identify new and emerging applications for the technology.

Dissemination Method

Through conventional procedures such as publications in healthcare magazines, scientific journals and the popular media, organisation of workshops, seminars and conferences, the consortium will seek to encourage the use of the POS-BEADD technology in the broadest possible range of medical, industrial and commercial applications. All participants will play an active role in technology transfer and dissemination, promoting the technology development to customers, and through networks of industrial contacts. Where possible, links will be established with existing EC funded projects involving therapeutic applications. Trade Associations throughout Europe will be used to network the results and help demonstrate the technology to end users in a variety of industry sectors. The numbers of events, publications, etc. will be determined by the Exploitation Board in collaboration with the Sponsor Group.

Exploitation & Dissemination Activities Undertaken

The partnership has already developed an Exploitation Strategy for the management of knowledge, intellectual property and of its inter-relation with the various innovation-related activities planned. The basis of the strategy is to allow the new scientific knowledge created by the project to be actively disseminated amongst academic communities to validate it. However, prior to the programme of Innovation Related Activities, the SMEs will patent the technological capabilities developed and the product and process applications they in turn enable. Hence, the full range of scientific, technological and product-specific dissemination activities can be enabled without compromising the protection of the foreground IPR.

Exploitation & Dissemination Activities Planned

This Exploitation Strategy will be developed into an Exploitation Plan by the forth project milestone. The plan will cover the dissemination and exploitation of all the project results to companies outside of the consortium. The plan will also cover collaboration between the partners to fully facilitate exploitation of the foreground technology. This will encompass agreements in respect of the patent applications made and go on to determine the terms and conditions under which licensing of the technology can take place. This licensing to third parties is seen as critical to the roll out of the technology across the EU and beyond, speeding the proliferation of the technology and penetration of the markets by sector or geographically distant from the partners'.

You should provide a coherent and detailed disssemination and exploitation plan where you describe clear plans of how the consortium is going to take the project outcomes forward.

In the project the following technologies have been successful; positively charged PVA beads for embolization, synthesis of drug-loaded alginate polymer beads, development of bead management systems and new catheter technologies. The consortium aim to take the mentioned technologies further as explained:

Positively charged PVA beads for embolization.

The project has developed revolutionary chemistry for the production of positively charged PVA beads that will enable delivery of; painkillers, nucleic acid-based drugs or chemotherapeutic drugs that do not bind to current beads. This chemistry has the many potential uses in the medical and pharmaceutical industries. The development of positively charged beads predominantly made from PVA. It will enable lyophilised beads carrying drugs at concentrations between 20 and 100 mg/ml of re-constituted beads and will have a catheter flow rate of 10ml/min +/- 1ml/min with beads of 0.5-2.0 mm diameter. This will be exploited through the production and sale of the bead mixing device and similar medical devices to health authorities, medical practitioners and directly to interventional radiologists. The design and concept, once protected as a registered design, can also be disseminated.

Synthesis of Drug-Loaded Alginate Polymer Beads.

The project has already successfully synthesised two types of positive beads; quaternary and tertiary beads. As an addition to the project the synthesis of alginate based polymer beads will enable to increase the scope of the application. This change was implemented as alginate polymer beads could be used on tumours associated with the brain and nervous system, as opposed to positive beads being restricted to uterine fibroids. Commercial alginates are extracted from seaweed. Certain bacteria's, however, also produce alginates. Alginates are used in food products. Purified qualities of alginates are also available for biomedical use, and it is used extensively as a mold-making material in dentistry and prosthetics. The target would be to have drug-loaded alginate polymer beads that are also biodegradable. In this way, the target is not only restricted to uterine fibroids, increasing the market area. These criteria will be fulfilled by Biocompatibles and CellMed. This will be exploited through the production and sale of the bead mixing device and similar medical devices to health authorities, medical practitioners and directly to interventional radiologists. The design and concept, once protected as a registered design, can also be disseminated.

Development of Bead Management Systems.

The project has developed specialist bead handling and catheter technology enabling; micro fluidic mixing and in-line bead delivery, variable speed of delivery, compatibility with, and introduction of, contrast agents and uniform delivery of beads to ensure correct drug delivery kinetics. The system will be used by surgeons and radiologists to enable a more accurate delivery and dosage of the medication. It is anticipated that this medical device will be marketed through S & S Plastics and Biocompatibles with the remaining consortium forming a commercial supply chain for the design and production equipment. It is expected that the conservative temperament of the medical industry will need to be overcome before there is wide uptake of new instruments and suitable medical testing and approval will be required. It is predicted that the technology developed during the project can be exploited through the production and sale of other related products, as yet undefined. Markets for the bead mixing system will be investigated further. For markets beyond the importance of the consortium, the patent protected intellectual property can be licensed to alternative third parties. The

knowledge, once patent protected, will also be distributed. It is likely that patent protection for the technology will be sought in 2008, once the processing circumstances and requirements are more entirely recognize. This could be exploited through the production and sale of the polymer beads and similar medical devices to health authorities, medical practitioners and directly to interventional radiologists. At this point in time, several patent searches have been conducted and have not identified any patents which this technology breaches or violates

New Catheter Technologies

The novel technology will involve a dedicated catheter that allows the delivery of standard, negatively charged beads, the addition of drugs to the beads will create a unique surface in terms of charge, viscosity and frictional characteristics that will alter the ability of standard catheters to deliver the beads in a uniform and unimpeded fashion to the uterine artery. The drug-loaded beads will increase the surface viscosity of the beads (once re-hydrated) and this will make them slow to pass through standard catheters and potentially could create a catastrophic blockage during the UTE procedure. The new catheter system that is compatible with each (or all) drug and bead combination(s) is anticipated. To date, a preliminary search of registered designs and patents has identified no areas of potential infringement. The knowledge, once patent protected, can also be disseminated. The marketing of these will be through Joline GmbH, as it fits with their principal business.

The Medical Device Technology 2006 exhibition was attended by representatives of Pera in February. It was with very little technical content and keeping all potential intellectual property confidential and protected, to generate interest in the technology, and to start to identify potential licensees and further developmental applications. In this initial phase dissemination was informal and very limited in extent. Future exhibitions for the medical industry near the end of the project epoch are anticipated to create interest and awareness of the products prior to launch.

Some information and evidence should be provided on the development of material for Technical Files for submission to regulatory bodies.

For the POS-BEADD project the SME's (Biocompatibles, CellMed, Joline, S&S Plastics and DMC Medical) have started to and will complete to finalise the route to CE marking. The route to CE marking will be undertaken using the Technical File route. The letters CE on a product are the manufacturer's claim that the product meets the requirements of all relevant European Directives.

The standards that will be adhered to will be;
EN60601-1-1 General requirements for safety.
EN60601-1-1 Part 1.1 General requirements for safety – Collateral standard: Safety requirements for medical systems.

The design process will take into consideration these standards to pre-empt problems occurring at product test. The Technical file started will essentially provide the necessary evidence that the design is in accordance with relevant requirements. The file will identify the product and the requirements and it will describe the assessment-activities, and contain the results of these activities.

The Technical file will contain a stringent layout that each SME will adhere to for the relevant part of the product.

Suggestions for Technical File-elements are:

* Name of the company responsible for the design
* Name and function of the employee responsible for the file
* Name (of the product)
* Type
* Description:
  - photographs, brochures
  - technical construction drawings
  - material compositions
  - schematic diagrams
  - parts lists of components
  - descriptions of components

Furthermore, all different versions shall be described, as far as relevant:

- Copies of the users manual and service instructions, as far as applicable
- List of applicable EU-directives
- List of normative technical documents or standards used for the conformity assessment
- Design calculations
- Hazard analysis

It is vital that in the process that a description of measures to reduce or eliminate hazards is addressed. Any of the pending evaluation and test reports will indicate; which evaluations and tests were performed, the methods of evaluations and the tests, the evaluation and test-equipment, any results of evaluations and tests and finally the acceptance criteria.

Finally, a conclusion will be drawn up indicating that the product complies with all relevant requirements. If considered appropriate, descriptions and explanations to properly understand the documents shall also be provided. It is agreed that it is the responsibility of the manufacturer to decide about the assembly of the file.

In Summary, for POS-BEADD the following will be included in the Technical files.

- Function Requirement Specifications
- Test Case Protocol
- Test Results
- Technical Documentation
- Risk Analysis
- Support Documents
- Process Description
- Scientific Documents

An economic objective detailed in the final activity report is that of producing a POS-BEADD product for less that 40E per unit - this is not addressed later in the reports or deliverables. Some critical commentary should be provided based on the prototype developed in this study.

The envisaged economic objectives of the project are for the participants and subsequent licensees to:

- make the POS-BEADD products for less than €40 per unit for the management system and €15 for the drug-loaded beads.
- sell the POS-BEADD products at €100 per unit for the bead management system and €30 per unit for the drug-loaded beads (depending on the drug).

Financial benefits to the SME consortium have been calculated using projected sales as a function of market size, estimated manufacturing costs, calculated overhead costs, and target retail price. Discussions with members of the consortium helped to provide manufacturing and overhead costs while market size and retail price have been determined from market research/data. Figure 1 shows the break down of the financial outlay for the POS-BEADD device from the perspective of full scale production and individual manufacturer selling price/mark-up.

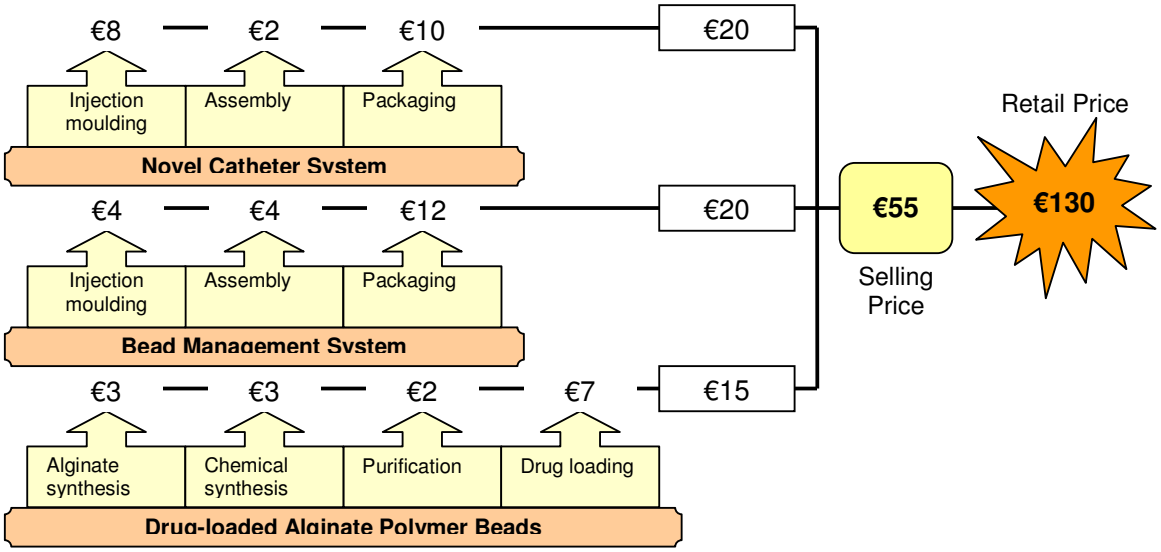

Figure 1 Full Scale Production Cost Outlay

The cost outlay can be used to estimate the profit that would follow after POS-BEADD enters the market. With regards to the actual selling of the POS-BEADD device a profit margin of a minimum of €75 would be made per POS-BEADD product. The estimated costs are the maximum envisaged as per discussions with the relevant manufacturers which allows us to set the statement 'minimum' return. A price tag of €130 is very competitive with regards to the retail price of medical devicess of similar technical excellence which is reassuring from the point of view that the selling price and/or retail price can be increased if the need arises. To calculate the financial returns for the other SME's is less obvious and requires some market data to facilitate the ability to calculate a five year return.

4.0 - OTHER ISSUES

4.1 Conclusions

The project has developed correctly and initiating a number of novel technologies, which will unlock new market opportunities, for the consortium, and provide substantial social benefits. The consortium has worked very well together, steering the research partners, providing guidance, assistance and the specialist knowledge needed for the success of the project.

The formal start date for the project was the 15th November 2004, however in order to ensure that all partners could attend the kick off meeting this was delayed until 27th January 2005. The project started two months late, because of this it has resulted in the actual delivery dates behind schedule. Relentless effort has been made to correct this. All work activities were at least two months behind schedule due to the time period set, required to amend documentation and recruit the new partners; CellMed AG and DMC Medical Ltd. It was vital to the project that these two new partners were admitted, as their contribution was very important to the progress of the project and for the successful completion of the tasks. They bought their respective specialist expertise to the consortium. This 2 month time period was been agreed to be reimbursed and an additional 4 month extension to this was been requested. The total of these time periods enabled enough time to successfully complete the project and accomplish the designated tasks. This means that the project commenced till March 2007. All partners have attended the meetings throughout the year and the final meeting was very successful.

The planned tasks in each work package have progressed well and show promising results. The initial pre-clinical models of embolization procedures have been tested for adaptation of POS-BEADD technology. The synthesis of positive beads has been achieved two types of cross-linker; tertiary and quaternary which provide clear results. The residual analysis conducted on the beads indicates that they are of high purity. The compressibility of beads is currently being tested. Overall, three types of beads have been synthesised including alginate polymer beads which is an addition to the project.

The design of the bead mixing system has progressed extremely well and a prototype mixing device constructed that uses a vibration motor to circulate the beads within the syringe. The original design had a unit containing the vibration motor attached to the syringe

This prototype device has evolved in to a more ergonomic design. The bead mixing system has been constructed to be vibrating syringe plunger. The plunger contains a vibrating motor which mixes the beads. The end of the vibrating plunger has a push-switch for easy operation for the surgeon and radiologist performing the embolization surgery.

The balloon catheter designed and developed in the project has been used to delivery the alginate polymer beads. This delivery was very successful and there were no blockages from experiments. The catheter has also successfully undergone pre-clinical testing experiments to test its performance. The novel catheter has received a CE mark and a patent application has been achieved by the original surgeon who came up with the design. A publication for the pre-clinical research on the catheter has also been anticipated.

The pre-clinical trials on alginate polymer beads have also been conducted. This study has been very informative. Four types of alginate beads would be tested for the study. The total study duration is 12

weeks so the intervals for tests would be; 1 week, 4 and 12 weeks. The results of this pre-clinical study would be written for publication. The paper would consist of the work conducted in the consortium collaboration.

The research in all the work packages provided an excellent foundation for work in the subsequent work packages which will involve the integration of the different aspects of the project.

The project has continued as envisaged; partner attendance has always been excellent at all of the organised meetings, also including the working party meetings. The consortium also shows enthusiasm and is highly motivated