METHODS AND SYSTEMS OF PREPARING PRELOADED NEEDLES FOR BRACHYTHERAPY

A system and a method are provided for use in brachytherapy for fast and efficient preloaded needle service without the need of third-party vendors, using sterile seeds, spacers, needles and automated sterile components loading device in an aseptic environment. The system and method may be used in the treatment of, for example, prostate cancer.
METHODS AND SYSTEMS OF PREPARING PRELOADED NEEDLES FOR BRACHYTHERAPY

FIELD OF INVENTION

The present invention relates generally to radiotherapy. More specifically, it relates to systems and methods for quickly and aseptically preparing preloaded needles ready for use in brachytherapy.

BACKGROUND OF THE INVENTION

Brachytherapy is a general term covering medical treatment which involves the placement of a radioactive source near a diseased tissue and may involve the temporary or permanent implantation or insertion of a radioactive source into the body of a patient. The radioactive source is thereby located in proximity to the area of the body which is being treated. This has the advantage that a high dose of radiation may be delivered to the treatment site with relatively low dosages of radiation to surrounding or intervening healthy tissue.

Brachytherapy has been proposed for use in the treatment of a variety of conditions, including arthritis and cancer, for example breast, brain, liver and ovarian cancer and especially prostate cancer in men (see for example J.C. Blasko et al., The Urological Clinics of North America, 23, 633-650 (1996), and H. Ragde et al., Cancer, 80, 442-453 (1997)). Prostate cancer is the most common form of malignancy in men in the USA, with more than 44,000 deaths in 1995 alone. Treatment may involve the temporary implantation of a radioactive source for a calculated period, followed by its removal. Alternatively, the radioactive source may be permanently implanted in the patient and left to decay to an inert state over a predictable time. The use of temporary or permanent implantation depends on the isotope selected and the duration and intensity of treatment required.

Permanent implants for prostate treatment comprise radioisotopes with relatively short half lives and lower energies relative to temporary sources. Examples of permanently implantable sources include iodine-125 or palladium-103 as the radioisotope. The radioisotope is generally encapsulated in a casing such as titanium to form a "seed" which
is then implanted. Temporary implants for the treatment of prostate cancer may involve iridium-192 as the radioisotope.

Conventional radioactive sources for use in brachytherapy include so-called seeds, which are sealed containers, for example of titanium, containing the radioisotope within a sealed chamber but permitting radiation to exit through the container/chamber walls (US 4,323,055 and US 3,351,049). Such seeds are only suitable for use with radioisotopes which emit radiation which can penetrate the chamber/container walls. Therefore, such seeds are generally used with radioisotopes which emit γ-radiation or low-energy X-rays, rather than with β-emitting radioisotopes.

There are several examples of commonly used seeds. OncoSeed™ seeds (manufactured by Amersham Health) consist of a welded titanium capsule containing Iodine-125 absorbed onto a silver rod. OncoSeed seeds with apparent activities from 0.191 to 1.01 mCi are indicated for permanent interstitial implantation of selected localized tumours which are of low to moderate radiosensitivity. They may be used either as primary treatment (such as for prostate cancer or unresectable tumours) or for treatment of residual disease after excision of the primary tumour. Seeds in this apparent activity range may be used to treat superficial, intraabdominal, and intrathoracic tumours. Tumours of the head, neck, lung, pancreas, and prostate (early stages) are commonly treated.

OncoSeed seeds with total apparent activities greater than 1.01 mCi are indicated for interstitial treatment of tumours which have the following characteristics: unresectable, localized, and moderate radiosensitivity. These seeds may be used for selected radiation applications as temporary implants.

OncoSeed seeds are also indicated to treat residual tumours concurrent with or at the completion of other treatment modalities, such as external beam radiation therapy or chemotherapy. In addition, recurrent tumours may be implanted with OncoSeed seeds.

Another type of seed that is commonly used is EchoSeed™ (manufactured by Amersham Health). EchoSeed seeds consist of a welded titanium capsule containing Iodine-125 adsorbed onto a silver rod. The specifically designed grooves on the outer surface of the capsule allow enhanced visualization under ultrasound.
EchoSeed seeds with apparent activities from 0.297 to 0.673 mCi are indicated for permanent interstitial implantation of selected localized tumours which are of low to moderate radiosensitivity. They may be used as primary treatment for prostate cancer or unresectable tumors.

EchoSeed seeds may also be used for treatment of residual disease after excision of the primary tumor. EchoSeed seeds are further indicated to treat residual tumours concurrent with or at the completion of other treatment modalities, such as external beam radiation therapy or chemotherapy. In addition, recurrent tumours may be implanted with EchoSeed seeds.

A third example of seeds product is RAPID Strand™ (manufactured by Amersham Health). RAPID Strand consists of a number of (usually ten) OncoSeed seeds (welded titanium capsule containing I-125 adsorbed onto a silver rod) spaced at a fixed distance within polyglactin absorbable braided absorbable material. The braided material containing OncoSeed is stiffened, then sterilized by ethylene oxide. The seeds are housed in a plastic spacing jig within a stainless steel shielding tube which attenuates greater than 99% of the I-125 photons.

RAPID Strand is indicated for permanent interstitial implantation of selected localized tumours which are of low to moderate radiosensitivity. They may be used either as primary treatment (such as prostate cancer or unresectable tumours) or for treatment of residual disease after excision of the primary tumour.

RAPID Strand may be indicated for use concurrent with or at the completion of other treatment modalities, such as external beam radiation therapy or chemotherapy.

Radioactive seeds are generally loaded into needles, with the needles then being inserted into the treatment site, such as prostate, using ultrasound imaging to guide the insertion process. The radioactive seeds are either positioned independently within the needles and hence are located independently within the treatment site after they have been moved out of the needle, or they are connected in a string arrangement by being loaded within a hollow, absorbable suture member.
US 5,460,592 discloses a method and apparatus for transporting a radioactive device. The device comprises a flexible, elongated woven or braided bio-absorbable carrier material having spaced radioactive seeds disposed therein. On heating, the carrier material holding the seeds becomes semi-rigid. A length of the semi-rigid carrier material with radioactive seeds disposed therein may then be loaded into a conventional, hollow metal dispensing needle or applicator cartridge which is used to implant the radioactive seeds into or contiguous to the treatment site, for example a tumour.

Generally, seeds, such as OncoSeed seeds and EchoSeed seeds, are not sterile when shipped and must be sterilized prior to use. A sterilization method, such as steam sterilization, gamma radiation, or pulse light sterilization, can be used, after the needle is loaded.

RAPID Strand is sterilized when shipped. RAPID Strand is held within a plastic spacing jig which is inside a stainless steel shielding tube. The assembled RAPID Strand, plastic spacing jig and steel shielding tube in a plastic tray are sealed within a white sterilization pouch which is sealed in a bag. When RAPID Strand is prepared (unpackaged, cut, and loaded into sterile needles) aseptically, then re-sterilization is not needed.

There are a number of complexities involved in loading a needle by an end user. In a typical process described in U.S. Patent 5,242,373, a seed plug is assembled by hand from alternating loose seeds and biodegradable spacers (e.g. made of catgut) picked from a dish. The spacers can have any desired length and are positioned between the seeds in order to give the required separation between the seeds. The assembled plug is then implanted into a patient via needle. A problem with this method is the person making the plug is exposed to radiation from the loose seeds in the dish and is also exposed to radiation when loading the seeds into the implantation needle. A further disadvantage is that considerable numbers of seeds and spacers have to be handled individually and each configured in the correct orientation to give the desired end-to-end “plug”. The seed/spacers are so small e.g. typically 4-6 mm long, and this leads to time-consuming manual handling, with an associated radiation dose hazard. The loaded needle will then have to be sterilized before being used clinically. However, this method is used, because it has the advantage that as several seeds can be
implanted in the patient at once through pre-made plugs, the time spent in the operating room is reduced and the spatial separation of the seeds can be checked before implanting.

Due to the complexities involved and the time-consuming nature of the needle-loading process, a service for providing preloaded needles is increasingly desirable because it provides needles, loaded to prescription, to be delivered sterile for immediate clinical use.

Currently, a service for providing preloaded needles involves an end user placing an order from a seeds manufacturer according to a prescribed treatment plan (i.e., number and type of seeds). The seeds manufacturer then fills the order from its inventory, sending the required number of seeds and spacers to a third-party vendor, such as a pharmacy. By one method the third-party vendor loads the needle with seed and/or spacers using methods as described above. After loading the seeds, these preloaded needles are sterilized, using steam sterilization, gamma radiation, or pulse light sterilization. The sterilized preloaded needles are then shipped to another facility for sterility (biological indicators) testing. After sterility testing, the sterilized preloaded needles are then sent back to the third-party vendor for labelling and packaging. Alternatively, the seeds may be loaded in the pharmacy, then shipped as a loaded unit to a sterilization place. The loaded needles go back to the pharmacy, but the sterility is not verified until BIs read. Finally, the labelled and packaged preloaded needles are shipped to the end user. The entire process takes approximately seven to ten business days.

There are currently several third party companies involved in providing such a preloaded needle service, for considerable costs in both monetary value and time from order to delivery. It is thus highly desirable to provide a preloaded needle service in a fast efficient manner so that the time from order to shipment can be significantly shortened and the radioactivity lost in seeds can be minimized.

There is therefore a need for an improved method for preloaded needle service which does not suffer from all the disadvantages of the known sources, and which can preferably automate the process and load seeds and spacers sceptically in needles using an automated manufacturing process.
SUMMARY OF THE INVENTION

The present invention provides a system for fast and efficient preloaded needle service without the need of third-party vendors, comprising, for example, sterile components and an automated sterile components loading device. Preferably, the ordering and shipping process are conducted automatically.

The present invention also provides a method for quickly and cost-effectively providing preloaded needle service without the need of third-party vendors, using sterile components and an automated sterile components loading device. All the steps are performed aseptically, so there is no need for an additional sterilization step.

In one aspect of the invention there is therefore provided a method for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, comprising:

a) receiving order from an end user with device order and a needle-loading pattern, specifying the type and number of seeds;
b) supplying sterile seeds, spacers and sterile pre-plugged needles;
c) loading the pre-plugged needles with the sterile seeds according to the prescribed needle-loading pattern in a aseptic environment;
d) enclosing the pre-loaded needles in a shielded steel box; and
e) shipping the box to the end user.

In another aspect of the invention, there is therefore provided a method for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, wherein step c) of the above method is carried out using an automated seeds loading device.

In a further aspect of the invention, there is therefore provided a method for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, furthering comprising:
f) taking the preloaded needles out of the sterile packaging and using the needles for implant; and
g) returning the shielded box to the seeds manufacturer for reuse.
In yet another aspect of the invention, there is provided a system for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, comprising:

a) a computer system to receive device order and needle-loading pattern, including the number and type of seeds, from the end user and to track order fulfilling information;

b) a plurality of sterile seeds, spacers and sterile pre-plugged needles according to the order taken by the computer;

c) an automated seeds loading device loading to sterile seeds and/or spacers into the sterile pre-plugged needles according to the order taken by the computer;

d) a shielded box for shipping the preloaded needles to the end user.

The system and method of the present invention provide fast, convenient and cost-effective preloaded needle service for brachytherapy use. It is especially beneficial for orders that are of urgent nature. Further, by significantly reducing the time needed to process and ship the preloaded needle order (from seven to ten business days to one or two business days), radioactivity of the seeds are greatly preserved. Unlike current preloaded seeds services, the present method uses sterile components and performs loading in a sterile environment. Thus, there is no need to sterilize the preloaded needle assembly and no need to send the sterilized preloaded needle out to another facility for sterility testing. Therefore, it saves a lot of time and expense.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a schematic diagram of the current method.

FIG. 2 shows a view from the front of one embodiment of a automated seed loader device in a first state.

FIG. 3 shows a lateral view of the device of FIG. 2.
FIG. 4 shows a view from the front of the loader device of FIG. 1 in a second state.

FIG. 5 shows a lateral view of the device of FIG. 4.

FIG. 6 shows a lateral view of an embodiment of a magazine suitable for use with the loader device.

FIG. 7 shows a view from the end of the magazine of FIG. 6.

FIG. 8 shows a view from the front of a second embodiment of the loader device.

FIG. 9 shows a view from the front of a third embodiment of the loader device.

FIG. 10 shows the lateral view of the device of FIG. 9.

FIG. 11 shows a front view of a fourth embodiment of the loader device.

FIG. 12 shows the sterile needle package according to the present invention for delivering empty needles to a loading facility.

FIG. 13 shows an individual inner bag of the sterile needle package of FIG. 12.

FIG. 14 shows an individual inner bag of loaded needles.

FIG. 15 depicts an automated seed loading device for forming a stranded array of seeds and spacers.

**DETAILED DESCRIPTION OF THE INVENTION**

Referring to the figures, FIG. 1 represents a flowchart depicting the method of the present invention. The first step 10 involves an end user sending in an order for a device and a needle-loading pattern for the device. While the order is shown as desirably being received from a computer source in an automated or web-based system, it is also contemplated
that other known methods for transmitting and receiving an order may be encompassed by the present method.

In the next step 20, orders are then sent to the order fulfillment department of the seeds manufacturer for processing. There follows a combination of steps selected from selecting sterile seeds, 30, selecting spacers, 40, selecting calibrated seeds, 50, selecting loose seeds, 60, selecting stranded seeds, 70, and/or selecting pre-plugged needles (desirably provided with re-closable pouches), 80.

In step 90, the manufacturer would then select from either inventory stock or specially order and receive the needed seeds, spacers, and pre-plugged needles as needed. Using an order and loading plan provided according to a physician’s direction, step 100, the manufacturer may then choose among an automated seeds loading device, step 110, a manual seeds loading device, step 120, a semi-automated seeds loading device, step 130, and a shipping container, step 140, for accomplishing the aseptic loading of needles according to the loading plan, step 150.

The prepared for shipping and shipped, step 160, by labeling the loaded needles according to the plan and aseptically placing same into sterile packaging, and shipped. When the order is received by the physician and implanted, step 170, the shipping box may be returned to the manufacturer, step 180.

The present invention will now be described in more detail. As previously stated, an end user sends a device order and needle-loading pattern, which includes the number and type of the seeds required, to a seeds manufacturer.

Any conventional radioactive seed may be used as the radioactive source. These include for example the radioactive seeds disclosed in US 5,404,309, US 4,784,116, US 4,702,228, US 4,323,055 and US 3,351,049 which are hereby incorporated by reference. By "seed" is meant any sealed container, for example a metal container, containing or encapsulating a radioisotope. Suitable biocompatible container materials include metals or metal alloys such as titanium, gold, platinum and stainless steel; plastics such as polyesters and vinyl polymers, and polymers of polyurethane, polyethylene and poly(vinyl acetate);
composites such as graphite; glass such as matrices comprising silicon oxide, and any other biocompatible material. Titanium and stainless steel are preferred materials for the containers.

The radioactive seeds may also comprise a suitable radioisotope encapsulated within a polymer or ceramic matrix.

Typical radioactive seeds are substantially cylindrical in shape. Dimensions of a typical seed can be approximately 4.5 mm long with a diameter of approximately 0.8 mm.

Any radioisotope suitable for use in brachytherapy may be used in the radioactive seeds. Non-limiting examples include palladium-103, iodine-125, strontium-89, sulphur-35, cesium-131, gold-198, thulium-170, chromium-56, arsenic-73, yttrium-90, phosphorus-32 and mixtures thereof. Especially preferred are palladium-103 and iodine-125. More than one type of radioisotope may be present in the radioactive seeds for use in the invention. Examples of the common types of seeds include OncoSeed, EchoSeed and RAPID Strand.

Orders can be taken by a human representative over the phone, or more preferably, taken by a computer system which will process and keep order tracking information.

Orders are then sent to the order fulfillment department of the seeds manufacturer for processing. Sterile seeds, spacers and pre-plugged needles are provided from seeds manufactures inventory according to the order. For example, sterile EchoSeed and sterile OncoSeed are available from Amersham Health. Sterile RAPID Strand is available from Amersham Health. Sterile spacers in cartridges are also manufactured by Amersham Health. In addition, calibrated seeds and loose seeds can also be sterilized if required. Pre-plugged needles are available from CP Medical.

Spacers can be made of any non-toxic, bio-compatible, bioabsorbable material or a mixture of such materials. As used herein, a bioabsorbable material is any material of which a substantial portion will be metabolized within a patient's body and ultimately eliminated therefrom. Suitable bioabsorbable materials include poly(glycolic acid) (PGA) and poly(lactic acid) (PLA), polyester amides of glycolic or lactic acids such as polymers and
copolymers of glycolate and lactate, polydioxanone and the like. Such materials are more fully described in US 5,460,592 which is hereby incorporated by reference. Suitable commercially available polymers include polyglycaprone 25 (MONCRLY™), polyglactin 910 (VICRYL™) and polydioxanone (PDS II), all available from Ethicon, Inc. of New Jersey, U.S.A.

Other suitable bioabsorbable polymers and polymer compositions that may be used in this invention are described in the following patents which are hereby incorporated by reference: US 4,052,988 which discloses compositions comprising extruded and oriented filaments of polymers of p-dioxanone and 1,4-dioxapane-2-one; US 3,839,297 which discloses compositions comprising poly[L(-)lactide-co-glycolide] suitable for use as absorbable sutures; US 3,297,033 which discloses the use of compositions comprising polyglycolide homopolymers as absorbable sutures; US 2,668,162 which discloses compositions comprising high molecular weight polymers of glycolide with lactide; US 2,703,316 which discloses compositions comprising polymers of lactide and copolymers of lactide with glycolide; US 2,758,987 which discloses compositions comprising optically active homopolymers of L(-) lactide i.e. poly L-Lactide; US 3,636,956 which discloses compositions of copolymers of L(-) lactide and glycolide having utility as absorbable sutures; US 4,141,087 which discloses synthetic absorbable crystalline isomorphic copolyoxylate polymers derived from mixtures of cyclic and linear diols; US 4,441,496 which discloses copolymers of p-dioxanone and 2,5-morpholinediones; US 4,452,973 which discloses poly(glycolic acid)/poly(oxymethylene) ABA triblock copolymers; US 4,510,295 which discloses polyesters of substituted benzoic acid, dihydric alcohols, and glycolide and/or lactide; US 4,612,923 which discloses surgical devices fabricated from synthetic absorbable polymer containing absorbable glass filler; US 4,646,741 which discloses a surgical fastener comprising a blend of copolymers of lactide, glycolide, and poly(p-dioxanone); US 4,741,337 which discloses a surgical fastener made from a glycolide-rich blend of polymers; US 4,916,209 which discloses bioabsorbable semi-crystalline depsipeptide polymers; US 5,264,540 which discloses bioabsorbable aromatic polyanhydride polymers; and US 4,689,424 which discloses radiation sterilizable absorbable polymers of dihydric alcohols.

Bioabsorbable polymers and polymer compositions are especially useful when they comprise bioabsorbable fillers such as those described in US 4,473,670 (which is incorporated by reference) which discloses a composition of a bioabsorbable polymer and a
filler comprising a poly(succinimide); and US 5,521,280 (which is incorporated by reference) which discloses bioabsorbable polymers and a filler of finely divided sodium chloride or potassium chloride. Such fillers can provide increased stiffness to bioabsorbable polymers and polymer compositions.

Once the required components, namely, sterile seeds, sterile spacers, sterile pre-plugged needle, and/or sterile stranded seeds such as RAPID Strand, are pulled out of inventory, the needles are ready to be loaded with seeds and spacers according to the prescribed needle-loading plan in a aseptic environment in a seeds manufacturer’s facility, for example, its own pharmacy.

To perform the needle loading aseptically, sterile components, namely, seeds, spacers, needles and needle packaging, are introduced into a laminar flow hood. Needles are removed from an outer package, loaded to the implant plan and finally repackaged into an inner package. The packaging of the needles is unique in that the sterile needles are doubled packaged to provide the ability of repackaging, after loading, aseptically without additional packaging. Preferably, needles are loaded using an automated needle loading device. Details of the automated needle loading device and the needle packaging will be provided below.

Figures 2 and 3 show a frontal view, resp. a lateral view of an embodiment of the automated needle loading device. These figures are not to scale, internal features being shown unproportionally large in order to aid the clarity of illustration. The loader is intended to facilitate the preparation of seed implant needles and is not intended to be used for the direct administration of seeds to a patient. Loader 1 has an elongated body 3 with a front and a rear wide face 5`, resp 5”`, a first and a second short face 7`, resp. 7”`, and upper and lower end faces 9’, resp. 9”’. Body 3 is provided with a longitudinal through hole 11 that extends from an opening 6 in the surface of the upper end face 9’ to a dispensing outlet 8 on the lower end face 9”’ and which has stepped diameters D1, D2, D3. The diameter D1 of through hole 11 is greatest in its upper portion 13 which extends from the upper end face 9’ to an intermediate portion 15 that starts approximately one third of the distance down through hole 11. The intermediate portion 15 has an intermediate diameter D2 and extends from the lower end of upper portion 13 to approximately one half of the distance down through hole 11. The diameter D3 of through hole 11 is narrowest in the lower portion 17 that extends from the lower end of intermediate portion 15 to lower end face 9”’. Lower portion 17 is intended to act
as a seed-transporting path for guiding seeds to the dispensing outlet 8. Note that any mentions of direction in this description refer to a frame of reference where the loader 1 is in its desired operating orientation in which the upper end face 9' is uppermost and the loader held substantially vertically.

Body 3 is made of a radiation shielding material of a suitable thickness to shield an operator from radiation emitted by radioactive seeds contained within it. Body 3 is provided with a lateral opening 19 on a first short face 7'. This opening 19 leads to a recess 23 adapted to receive a standard seed magazine (not shown). Recess 23 comprises a first cylindrical portion 25 with a diameter D4 adapted to receive the body of a seed magazine, and a rectangular portion 27 adapted to receive and retain the rectangular locating arms of a seed magazine. Rectangular portion 27 intersects through hole 11 approximately one third of the distance from the lower end face 9''. The lengths and orientations of cylindrical portion 25 and rectangular portion 27 are adapted so that when a seed magazine is inserted fully into recess 23 then the seed-dispensing hole in the seed magazine (described below) is aligned with through hole 11.

The front wide face 5' is provided with a spacer-transporting path in the form of a spacer inlet opening 29 leading to a spacer receiving recess 31 that is connected by a internal chute 33 to the outlet 8 of through hole 11. Opening 29 is sufficiently large that a spacer (not shown) can be easily loaded into the recess 31. The bottom portion 35 of spacer receiving recess 31 is desirably funnel-shaped in order to facilitate the entry of spacers into chute 33. The diameter of chute 33 is greater than the diameter of a spacer so that spacers can be transported through chute 33 to outlet 8.

Through hole 11 can receive seed dispensing means such as a stepped cylindrical plunger 37, shown in a raised position in figures 2 and 3. Plunger 37 has an upper portion 39 with a diameter D5 less than D1 and greater than D2, and a length which is the same as or greater than the length of through hole upper portion 13. Upper portion 39 is connected to a concentric intermediate portion 41 with a diameter D6 which is less than D2 and greater than D3, and a length which is approximately the same as or greater than the length of through hole intermediate portion 15. Intermediate portion 41 is connected to a concentric lower portion 43 with a diameter D7 that is less than D3 and less than the diameter of the seed-dispensing hole in the seed magazine. Lower portion 43 has a length which is
approximately the same as or greater than the distance from the bottom of through hole intermediate portion 15 to the bottom surface of rectangular portion 27. The lengths of the plunger portions 39, 41, 43 and through hole portions 13, 15, 17 can be varied as desired, the only requirement is that they should make it possible to retract the plunger 37 to a seed loading upper position where lower plunger portion 43 is above the seed-dispensing hole of a seed magazine positioned in recess 23, as shown in figures 2 and 3 and they also should make it possible to depress plunger 37 to a dispensing lower position in which lower plunger portion 43 extends through the seed-dispensing hole of a seed magazine positioned in recess 23, as shown in figure 4. This makes it possible to push any seed that is positioned in the seed dispensing hole down into the through hole 11 where it then falls to, and through, outlet 8. Plunger 37 is desirably provided with a sealing means 45 such as an O-ring to prevent unwanted material entering the lower portions of through hole 11. The upper end of plunger 37 can be provided with a actuating surface 47 which has a larger surface area than plunger upper portion 39, and which can be used to lift and depress plunger 37. If desired, plunger 37 can be provided with resilient means such as a spring 49, which biases plunger 37 to the upper loading position.

The lower end of through hole is provided with adapter means such as a threaded boss 51 or a Luer needle fitting or the like, that implantation needles or a capsule or other container can be attached to. It is also conceivable to provide universal adapters.

Figures 6 and 7 show side and end views respectively of a seed magazine 53 or spacer magazine 53A that can be fitted into a loader. Magazine 53/53A has an elongated, hollow body 55 with a hexagonal cross-section. Other cross-sectional shapes are also possible, e.g. circular, square, oval, etc. When used for containing radioactive seeds, the body 55 is desirably made of a material with radiation shielding properties such as leaded plastic, stainless steel, lead glass, lead, tungsten, etc. A first, loading end of the body is closed by a removable end plate 57, while the other end is provided with a seed- or spacer-dispensing outlet 59 arranged between two longitudinally projecting locating arms 61. The outlet 59 comprises a vertical seed-dispensing hole 63 bored through the locating arms 61. Seeds 65 or spacers 65A are arranged in a row inside the magazine 53/53A and pushed towards the hole 63 by resilient means such as a spring 67 inside the magazine 53/53A. The force provided by the spring 67 is sufficiently high that the friction between the wall of the hole 63 and a
terminal seed 65 or spacer 65A in the hole 63 is enough to prevent the seed 65 or spacer 65A from falling out of the hole 63 under the influence of gravity.

Desirably, a magazine 53A used for spacers is filled with spacers 65A, desirably made of a synthetic, bioabsorbable material. Prior art spacers have been made of catgut – a material of animal origin that is undesirable from a regulatory and customer acceptability standpoint. An example of such a synthetic, bioabsorbable material is Vicryl™ that is made of approximately 90% polyglycolic acid and 10% polyactic acid. The spacer material is also desirably resistant to the temperatures used for heat sterilisation by autoclaving or dry heat sterilisation. Spacers 65A can be supplied sterile in a sterile magazine 53A in a sterile-integrity packaging material such as Tyvek™. The sterilisation can be performed in any suitable way, e.g. by heating or exposure to ethylene oxide gas (in which case a gas permeable packaging material is necessary if the sterilisation occurs after a magazine has been packaged), depending on the composition of the spacers used. The use of prepacked, sterile spacers has the advantage that the operator does not need to load his own magazines 53A with spacers 65A nor does he need to spend time sterilising the spacers before use. This ensures that sterile spacers are used.

Similarly, seeds 65 can also be supplied sterile and preloaded in a magazine for seeds 53. This magazine 53 can be supplied sterile in a sterile-integrity packaging material such as Tyvek™. The seeds and magazine can be sterilised in any suitable way, for example, in the ways mentioned above with respect to spacers 65A in a spacer magazine. Desirably a variety of pack sizes can be provided, e.g. packs containing a magazine 53 loaded with 5 seeds 65, or 10 seeds or 15 seeds, etc.

The use of a loader for loading an implantation needle will now be illustrated. An operator holds the loader 1 in an upright position or places it in a stand in an upright position. A seed magazine 53 containing seeds 65 is inserted through opening 21 until the seed-dispensing hole 63 in the magazine is aligned with through hole 11. Although not shown, loader 1 desirably has locking means such as a locking detent for releasably retaining a magazine 53 in this position. An implantation needle is then attached to adapter means 51. In order to prevent the seeds and spacers from falling out of the bottom end of the needle, the bottom end of the needle can be provided with removable closing means such as a plug or an end cap. The plunger 37 is then depressed by the operator to its lower, seed-dispensing
position. As the plunger 37 is depressed, lower plunger portion 43 passes through seed-dispensing hole 63 in the magazine 53 and pushes a seed 65 out of the magazine 53 and into the lower through hole portion 17. As the diameter of lower through hole portion 17 is greater than the diameter of the seed, the seed falls freely through the through hole 11 and out of its lower end, through adapter 51 and into the needle. The plunger 37 is then lifted to its upper, loading position. As the lower plunger portion 43 passes back up through the seed-dispensing 63 hole of the magazine 53, a new seed 65 is loaded into the seed-dispensing hole by the resilient means 67 of the magazine 53. The operator then places a spacer 65A of the desired dimensions into spacer receiving recess 31 and releases the spacer 65A. The spacer 65A falls down the internal chute 33, which has a diameter greater than the diameter of the spacer and enters the needle via adapter 51. This procedure is repeated until the desired number of seeds and spacers have been loaded into the needle. The needle can then be removed from adapter 51 and used or stored for later use. The procedure can be repeated for all the needles required for the treatment.

The use of a loader in accordance with the present invention for forming a seed plug will now be illustrated. An operator holds the loader 1 in an upright position or places it in a stand in an upright position. A seed magazine containing seeds 53 is inserted through opening 21 until the seed-dispensing hole in the magazine is aligned with through hole 11. A seed plug container is then attached to adapter means 51. This container is desirably transparent in order to allow the operator to check that the loading is proceeding without problem and to allow checking of the number of seeds and their spacing. In order to shield an operator from radiation, the transparent container and any other transparent parts of a device in accordance with the present invention, as described later, are desirably made of a radiation attenuating transparent material such as leaded acrylic. In order to facilitate checking the number of seeds and their spacing, the container is desirably provided with graduated marks. In order to prevent the seeds falling out of the bottom end of the container, the bottom end of the container is provided with a removable plug or sealed in some other way. The plunger 37 is then depressed by the operator to its lower, seed-dispensing position and, just as in the previous example, a seed is fed into the container. The operator then places a spacer 65A of the desired length into spacer receiving recess 31 and releases the spacer 65A. The space falls down the internal chute 33, which has a diameter greater than the diameter of the spacer 65A and enters the container via adapter 51. This procedure is repeated until the desired number of
seeds 65 and spacers 65A have been loaded into the container that can then be removed from adapter 51 and used or stored for later use.

In the event that the operator wishes to remove a seed 65 from the seed magazine 53 in order to, for example, measure its radioactivity, then a seed magazine 65 can be attached as normal, any suitable container placed under the loader 1 and a seed 65 ejected into the container by depressing plunger 37.

Figure 8 shows a second embodiment of a loader 101 in accordance with the present invention. For the sake of brevity, many features have a function similar to that of the first embodiment of the present invention and will not be described for this embodiment. In this embodiment, the loader is provided with a first, seed dispensing means such as a plunger 137 and a second, spacer-dispensing means such as a plunger 197 and first and second magazine receiving recesses 123, resp. 183. First magazine receiving recess 123 is adapted to receive and retain a seed magazine 53, while second magazine receiving recess 183 is adapted to receive and retain a spacer magazine 53A. As mentioned above, spacer magazine 53A contains pre-cut spacers 65A and works in a similar way to a seed magazine 53. Desirably the magazine is sterile and the contents of the magazine are sterile before being put into the magazine. It is furthermore desirable that loaded and empty magazines and the loader can be sterilised, for example, by heating in an autoclave. In order to avoid confusion, seed magazines and spacer magazines can have different shapes or sizes, this is a desired situation, especially as spacers 65A and seeds 65 often have different lengths, e.g. spacers 65A can be 5.5 mm long whiles seeds 65 can be 4.5 mm long. Alternatively, in the interests of economy it is possible to use the same magazines for seeds and spacers, in which case it is desirable to have different colours or other markings to avoid confusion. In any case it can be useful to have different colours for the different types of magazines, e.g. spacers could be supplied in a white magazine and seeds in a blue magazine. If different shaped or sized magazines are used then the diameters D4, resp. D14 of the first and second magazine receiving recesses and/or the shapes of these recesses should be correspondingly adapted in order to prevent the wrong type of magazine being retained in a recess.

First plunger 137 is movably fitted into a first stepped through-hole 111 which leads to an outlet 108 able to be fitted with an adapter 151 while second plunger 197 is movably fitted into a second stepped hole 171 which also leads to outlet 108. Loader 101 can
be operated in a similar way to loader 1 except that with loader 101 spacers can be loaded by
 depressing plunger 167 instead of by loading individual spacers by hand through a spacer inlet
opening.

Figures 9 and 10 show a third embodiment of a loader 201 in accordance with the present invention. For the sake of brevity, many features have a function similar to that of the first and second embodiment of the present invention will not be described for this embodiment. For the sake of clarity of illustration, the hidden portions of plungers have been drawn with solid lines in figure 9 and the plungers omitted totally from figure 10. In this embodiment, the loader is provided with a first, seed dispensing means such as a plunger 237 and a second, spacer-dispensing means such as a plunger 297 and first and second magazine receiving recesses 223, resp. 283. First magazine receiving recess 223 is adapted to receive and retain a seed magazine 53, while second magazine receiving recess 283 is adapted to receive and retain a spacer magazine 53A. As mentioned before, in order to avoid confusion, seed magazines 53 and spacer magazines 53A can have different shapes or sizes or colours. First plunger 237 is in a first stepped through hole 211 which leads to the top of the first arm 275 of a Y-shaped channel 277, while second plunger 297 is in a second stepped hole 271 which leads to the top of the second arm 279 of the Y-shaped channel 277. The two arms 275, 279 of the Y-shaped channel meet at the top of the vertical leg 281 of the Y-shaped channel 277. The arms 275, 279 are desirably wider at the top and taper towards their intersection with leg 281. Arm 275 act as a seed-transporting path while arm 279 acts as a spacer-transporting path. Leg 281 extends down to an opening 208 in the bottom surface 285 of the loader. In order to prevent seeds 65 and spacers 65A from becoming jammed in the leg 281, the dimensions of leg 281 is desirably selected so that it is sufficiently narrow to preclude seeds and spacers from passing each other (or to begin passing each other). A removable blocking device such as a pin 287 is insertable in a hole 289 which extends from the rear surface of the loader towards the front of the loader and which intersects leg 281. When inserted into hole 289, this pin 287 prevents seeds and spacers in the leg 281 from passing. It is further contemplated that pin 287 may be a valve-type member that is spring biased to block leg 281. Upon overcoming a spring bias, pin 287 would provide an opening in fluid communication with leg 281 so as to allow a plug of seeds and spacers to pass. The front surface of loader 201 has a transparent portion 291, desirably made of radiation shielding material such as leaded acrylic, which allows an operator to see the contents of leg 281 while being shielded from radiation emitted by seeds in leg 281. This transparent portion 291 can be made quickly
and easily removable in order to facilitate cleaning of the pathways, clearing foreign material or clearing any jammed seeds or spacers. In the event of a seed needing to be removed this rapid disassembly means that the operator is exposed to radiation from the seed for only a short time and therefore receives only a small dose of radiation. When forming a plug of seeds and spacers, the pin 287 is placed in the blocking position and the seeds and spacers dropped onto the pin 287, so that they gradually fill up the leg 281. The transparent portion 291 can be provided with graduation marks to aid checking the number of seeds and spacers in the device. The transparent portion 291 allows the operator to check the progress of the plug construction and, if the operator is interrupted when building a plug, it allows him to check on his return the status of the plug under construction. Non-standard arrangements of seeds and spacers, e.g. seeds separated by a variable number of spacers can also be validated visibly through transparent portion 291 before being loaded into a needle.

Loader 201 can be operated in a similar way to loader 101.

In a further embodiment of the invention, shown schematically in figure 11, a single plunger 337 is used to alternatingly load a spacer 65A and a seed 65. Plunger 337 is connected to a piston 351 which has two extensions 353, 355 which are aligned with the arms 375, 379 of a Y-shaped channel 377 which forms the seed and spacer transporting path. Extension 353 is shorter than extension 355. This means than when plunger 337 is depressed then extension 355 will pass through the magazine (not shown) in first magazine receiving port 359 before extension 353 passes through the magazine (not shown) in second magazine receiving port 357. Plunger 337 is provided with 3 recesses 361'-361''' that can co-operate with a spring-loaded indexing pin 363 on the inside of the hole 311 in which it is supported. The first recess 361'is aligned with the indexing pin 363 when neither extension is in line with the magazine receiving ports 357, 359. Second recess 361'' is aligned with the indexing pin 363 when extension 355 has passed through the level of the magazine receiving ports 357, 359. Third recess 361''' is aligned with the indexing pin 363 when extension 353 has passed through the level of the magazine receiving ports 357, 359. An operator can load magazines onto this loader after raising plunger 337 until the first recess 361'is aligned with the indexing pin 363. Let us assume that the first magazine contains seeds and second magazine contains spacers. The operator can then eject a seed 65 from the first magazine by lowering plunger 337 until second recess 361'' is aligned with the indexing pin 363. A spacer 65' can then be ejected by depressing plunger 337 until third recess 361''' is aligned with the indexing pin
363. If it is desired to eject a further spacer before ejecting a further seed then the plunger is lifted up until second recess 361’’ is aligned with the indexing pin 363 and then depressed again. If it is desired to load a seed then the plunger is lifted until first recess 361’ is aligned with the indexing pin 363 and then lowered again until second recess 361’’ is aligned with the indexing pin 363.

Alternatively, an automated seed and spacer loading device may be used to form a stranded product according to the order from the customer in step 10 of Figure 1. Figure 15 depicts an automated seed and spacer loading device 500 based on the loader described in commonly-assigned United States Patent No. 6,730,013, the contents of which are hereby incorporated by reference as if having been fully disclosed herein. Loading device 500 produces a stranded braid incorporating a linear series of seeds and spacers in the order desired. The stranded braid may then be inserted into a needle assembly and provided to the end user.

Loading device 500 includes a seed push rod 510 for forcing individual seeds from a seed magazine holder 534 through the escapement mechanism 532 and into a hub needle 530 which supports and extends into the center of a hollow braid 532. Servo motors control the actuation of push rod 510. A tensioning piston 512 keeps the braided material mechanically taught to the Hub Needle while the braid 532 material is being loaded with Seeds and Spacers. A vibratory bowl feeder 514 feeds bulk Spacers to the Vibratory Feed Track 516 which in turn feeds seeds to 532 escapement mechanism in a single line. Escapement 532 includes a pneumatic escapement piston 536 to operate the mechanism which alternately feeds the seeds and spacers into the hub needle so as to be inserted into the center of braid 532.

Loading device 500 further includes spacer eject/reset button 518 for releasing spacers that are incorrectly fed into the escapement mechanism. Such spacers are ejected past the spacer ejector plate 522 which covers a spacer ejector hole and which is activated by the spacer eject/reset button 518. A hub needle release button 520 is provided to activate release of the hub needle 530 when loading is complete.

Once properly loaded, device 500 is automatic in operation. The operator loads the device with a magazine of seeds, bulk spacers into the vibrating bowl, and a hub
needle with braided material. After device 500 is loaded with the key three components a start button is pushed and the device automatically loads the seeds and spacers into the braided material. The machine also supplies the correct tension and spacing during the loading operation through the braided material tensioning piston. Device 500 is reset to the start position through a reset switch that is depressed by the operator once the strand is complete. This machine is typically set to load 10 Seeds and 11 spacers per strand through its programmable logic controller 540. Programmable logic controller 540 may be programmed to provide for the loading of any combination of seeds and spacers.

The pre-plugged needles are shown in FIG. 12. A sealed outer bag 410 will contain a number of inner bags 412, for example, three. Each inner bag 412 may in turn contain a plurality of needles 416. Outer bag 410 is the primary sterility barrier for its components and its contents will be sterile when received as material for use in the instant invention. Outer bag 410 will be delivered in a box 418 with appropriate packaging to keep the contents from compromising the sterility barrier.

The needles 416 are desirably standard 18 gauge Brachytherapy implant style needle. The needle is plugged at one end with a bio-absorbable material. This is the plug that allows retention of components after loading. The needle plugging material is a mechanical barrier that is positioned at the free tip of the needle. During the implant process, the plugging material and loaded components are deposited into the patient.

There is a tubular plastic shield 420 for each needle 416 to ensure safety for both shipping and use. Plastic shield 420 is mechanically fit onto needle 416, with the top of the shield 420a fitting snugly onto the bevel of the needle luer fitting 422. The bottom 424 of the tubular plastic needle shield 420 contains a plug 425 to provide assurance that loaded components will not fall out of the needle. It also protects the loaded needle from external debris. This plug is soft rubber-like material that is twist fit into the needle shield.

There is a stylet 426 for each needle 416. The stylets 426 are packaged with their needles 416 in the inner package 412, as shown in Figure 12. After loading seed and spacer components into the needle, the stylet will be inserted through the luer fitting into the needle and advanced until the tip of the stylet reaches the components within the needle. An
elastomeric or deformable guard 430 is placed over a stylet 426 and fits within the luer fitting on the needle to ensure that the stylet is not advanced during the shipping process.

The inner bag 412 is a plastic and Tyvek material with an adhesive backed sealing fold on the top of the bag. The needles 426 are loaded into inner bag 412, with the bag initially unsealed. Once needle loading is done, and the loaded needles 416 are placed back into the inner bag, the adhesive backed fold 415 will be used to seal the inner bag. This sealed inner bag will then be removed from the aseptic assembly area for packaging and shipping to the end user.

The outer bag 410 is the sterilized package. It is made from plastic and Tyvek material and contains a number of unsealed inner bags. After introduction into the aseptic assembly area, the outer bag will be disposed.

Aseptic technique must be used when sterile pre-plugged needle packaging is used. Bag 410 is sprayed with isopropyl alcohol and transferred into the aseptic assembly area. Unsealed bag 412 is then removed from bag 410.

Needles and stylets are then removed from bag 412. A tubular plastic needle shield 420 is on each needle 416. The shield plug placed over the free end 424 of the needle shield 420, and the rubber guard 430 positioned over the needle stylet are then removed. Each needle 416 may then be placed onto a seeds loading device.

Each needle 416 is filled, to prescription, with sterile seeds and spacers and then can be removed from the loading device used. A stylet 426 may then be placed into the needle 416 and advanced until the contained components are advanced into the lowest portion of the needle and sealed against the needle plugging media. The stylet 426 is then withdrawn approximately one half of an inch from the loaded needle. The rubber guard 430 is then positioned on the stylet slightly above the luer fitting on the needle.

The stylet 426 will be reinserted approximately one half of an inch back into the needle. This sets the angular tip 426 of the rubber guard into the bevel of the luer fitting on the needle. The loaded needle is then labelled and inserted back into bag 412.
Once all of the needles are loaded, they are put back in bag 412, and the adhesive backing of the bag will be exposed and the adhesive fold 415 will be positioned over the front of bag 412 to ensure a new sterility barrier. Finally, the sealed bag(s) 412 will be removed from the aseptic assembly area and placed into a shipping container 418.

The shipping container should be made of shielded material, preferably shielded returnable stainless steel box. This shield box with pre-loaded needles is shipped from the seeds manufacture’s packaging facility to the end user with sterile packaging for immediate clinical use.

The shipping box 418 may be returned by the physician to the manufacturer for re-labelling and reuse.

The invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed, since these embodiments are intended as illustration of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.
What is claimed is:

1. A method for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, comprising the steps of:
   a) receiving order from an end user with device order and a needle-loading pattern, specifying the type and number of seeds;
   b) supplying sterile seeds, spacers and sterile pre-plugged needles;
   c) loading the pre-plugged needles with the sterile seeds according to the prescribed needle-loading pattern in a aseptic environment;
   d) enclosing the pre-loaded needles in a shielded steel box; and
   e) shipping the box to the end user.

2. A method for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, comprising the steps of:
   a) receiving order from an end user with device order and a needle-loading pattern, specifying the type and number of seeds;
   b) supplying sterile seeds, spacers and sterile pre-plugged needles;
   c) loading the pre-plugged needles with the sterile seeds according to the prescribed needle-loading pattern in a aseptic environment, using an automated seeds loading device;
   d) enclosing the pre-loaded needles in a shielded steel box; and
   e) shipping the box to the end user.

3. A method of claim 1, further comprising the steps of:
   f) taking the preloaded needles out of the sterile packaging and using the needles for implant; and
   g) returning the shielded box to the seeds manufacturer for reuse.

4. A system for providing preloaded needle service by a seeds manufacturer without the need of third-party vendors, comprising the steps of:
   a) a computer system to receive device order and needle-loading pattern, including the number and type of seeds, from the end user and to track order fulfilling information;
b) a plurality of sterile seeds, spacers and sterile pre-plugged needles according to the order taken by the computer;

c) an automated seeds loading device loading to sterile seeds and/or spacers into the sterile pre-plugged needles according to the order taken by the computer; and

d) a shielded box for shipping the preloaded needles to the end user.
PACKAGES WITH FIXED NUMBER OF NEEDLES IN EACH

FIG. 12

8-PRE-PLUGGED NEEDLES 416

FIG. 13

BAG 414
LEFT OPEN (NOT SEALED)
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7  A61N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7  A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>column 2, line 42 - line 46 column 3, line 30 - line 40</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
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  *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document or which is special use
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search: 9 November 2004

Date of mailing of the international search report: 18/11/2004

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk, Tel. (+31–70) 340-3043, Tx. 31 651 epo nl, Fax: (+31–70) 340-3016

Authorized officer: Rodríguez Cossio, J
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<td>A</td>
<td>WO 00/61229 A (MUELLER JOHN; MEDI PHYSICS INC (US); SHANKS CHARLES E (US)) 19 October 2000 (2000-10-19) abstract</td>
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</tr>
<tr>
<td>A, P</td>
<td>US 6 730 013 B1 (HELLE KEVIN ET AL) 4 May 2004 (2004-05-04) cited in the application the whole document</td>
<td>1, 2, 4</td>
</tr>
</tbody>
</table>
| A        | US 1 576 535 A (JOSEPH MUIR) 16 March 1926 (1926-03-16) | }
**INTERNATIONAL SEARCH REPORT**

**Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **☒** Claims Nos.: 3
   - because they relate to subject matter not required to be searched by this Authority, namely:
     - Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. **☐** Claims Nos.;
   - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. **☐** Claims Nos.;
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest.
- **☐** No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
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<tr>
<td>US 6530875 B1</td>
<td>11-03-2003</td>
<td>AU 9693601 A</td>
<td>06-05-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 0234325 A1</td>
<td>02-05-2002</td>
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<td>US 2003171639 A1</td>
<td>11-09-2003</td>
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<td>BR 0115340 A</td>
<td>26-08-2003</td>
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<td>CA 2428591 A1</td>
<td>23-05-2003</td>
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<td>EP 1335773 A2</td>
<td>20-08-2003</td>
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<td>JP 2004526474 T</td>
<td>02-09-2004</td>
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<td></td>
<td>WO 0240078 A2</td>
<td>23-05-2002</td>
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<td>CA 2426550 A1</td>
<td>20-06-2002</td>
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<td>EP 1346372 A1</td>
<td>24-09-2003</td>
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<td>WO 0249043 A1</td>
<td>20-06-2002</td>
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<td>EP 1169087 A1</td>
<td>09-01-2002</td>
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<td>WO 0061229 A1</td>
<td>19-10-2000</td>
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<td>US 6730013 B1</td>
<td>04-05-2004</td>
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<td>EP 1169087 A1</td>
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<td>19-10-2000</td>
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<td>06-05-2002</td>
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<td>WO 0234325 A1</td>
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