IsoMed® Constant Flow Infusion System

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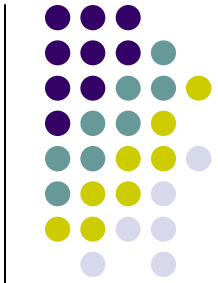
Outline

1. Problems Addressed by Device
2. Market and Competing Products
3. Device Description
4. Device Specifications
5. Refilling
6. Safety
7. Clinical Studies

Specific Problems



Colorectal liver cancer treatment

- Colorectal cancer is the third leading cause of death from cancer in the US. Every year 160,000 patients suffer from colon cancer. 40 to 50% will eventually develop liver metastases.
- 2/3 of liver metastases are unresectable ⇨ systemic chemotherapy is the most widely employed treatment ⇨ deliver medication to liver

⇨ Need a device to deliver medication on a continuous basis directly to the liver

El Deiry, 2006

Specific Problems

Chronic pain treatment

- 30 million patients suffer from chronic pain. 7 million of them cannot relieve their pain without opioids ⇨ need stable, long-term dosing treatment

⇨ Need an implantable drug delivery system to provide stable and long-term dose for patients

http://www.ninds.nih.gov/disorders/chronic_pain/chronic_pain.htm

Market for Infusion Pumps

Implantable infusion pumps (16%)

Other types of pumps (84%)

(Year 2000)

- Sale in 2000
  - $135 million with about 22,000 units of implantable infusion pumps sold
- Growing at a rapid rate
  - Due to increasing elderly population, growth in alternative site care, etc.
- Increase about 10% annually
- Should attract new entrants

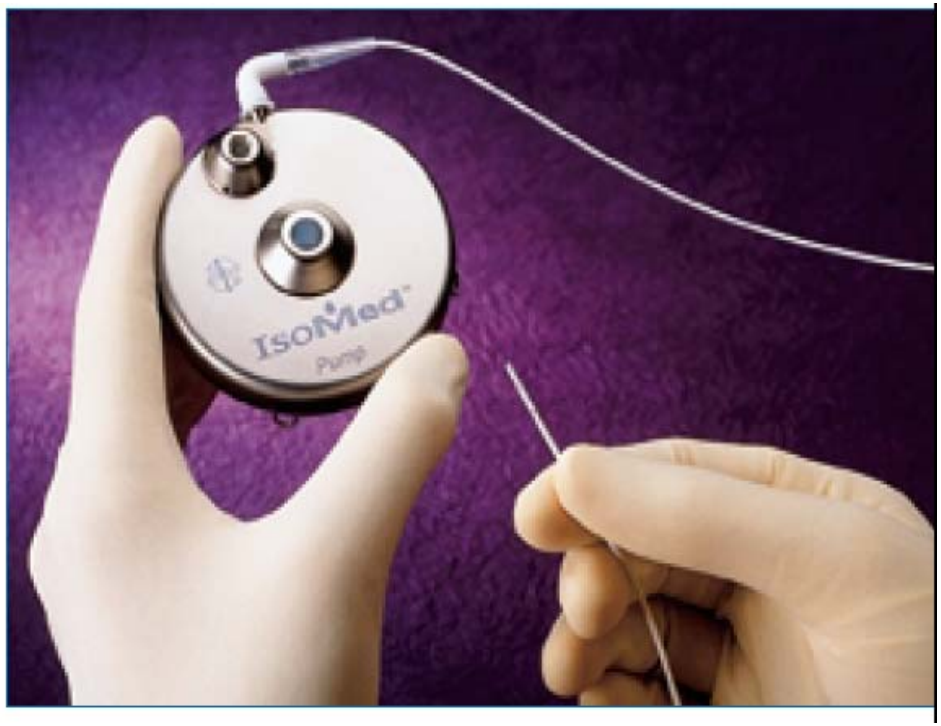
A report from Thompson Healthcare company (BBI Newsletter, 2000)

Competing Products & Market Share

- Medtronic with Constant Flow Infusion System: 45-50% market share
- Pfizer with Infusaid system: 35-40% market share
- Others: such as Codman (from Johnson & Johnson) with Codman Model 400 and 3000 Constant Flow Implantable Infusion Pump : 10-20% market share

A report from Thompson Healthcare company (BBI Newsletter, 2000)

IsoMed® Constant Flow Infusion System – History



- 1997-2000 1,200 units sold outside U.S.
- FDA approval in 2000
- Class II FDA Classification
- Other constant flow infusion system approved by FDA:
  - Codman Model 400 Constant Flow Implantable Infusion Pump
  - Codman Model 3000 Constant Flow Implantable Infusion Pump

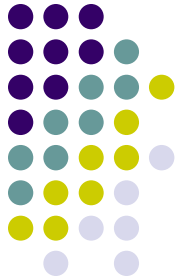
Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

IsoMed® Constant Flow Infusion System

Significant advantages

- Accurate constant flow drug pump
- Two-staged safety system designed to prevent inappropriate dosing
- Constant-flow drug delivery system with the widest range of refill intervals and the thinnest pump design

Device Price and Procedure Cost



IsoMed® Constant Flow Infusion System

- Pump & Catheter list price: $5,900.
- Total cost of procedure (hospitalization, physician fees, infusion system): $20,000-$25,000.

Codman Model 3000 Constant Flow Implantable Infusion Pump

- Pump & Catheter list price: $6,900
- Total cost of procedure: $20,000- $25,000

Operating Principles

- The system consists of a pump and catheter – both are implanted under the skin
- The pump is implanted in the abdominal area
- The catheter is tunneled under the skin to the site where medication is to be delivered

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

The system is approved for

- Continuous delivery of morphine into the intraspinal space for the treatment of chronic pain
- Continuous delivery of antispasticity medication into the intrathecal space for the management of severe spasticity
- Continuous delivery of chemotherapy drugs into a blood vessel for the treatment of certain types of cancer

Implant Procedure

- The pump is implanted during a surgical procedure
- Find the best position of the pump for the patient's comfort
- During the surgical procedure, a pocket under the skin to hold the pump will be formed
- Another incision where one end of the catheter will be placed

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

Site Specific Drug Delivery

Figure 1: Pump and catheter placement for intraspinal drug delivery

- Treatment of chronic pain or severe spasticity
- Area surrounds the spinal cord
- Intrathecal space & epidural space

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

Site Specific Drug Delivery

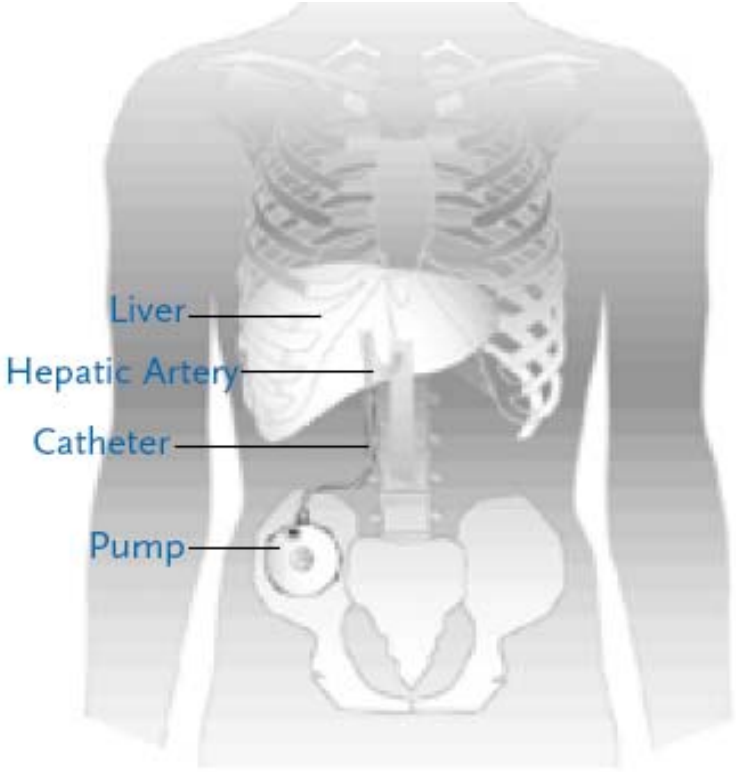
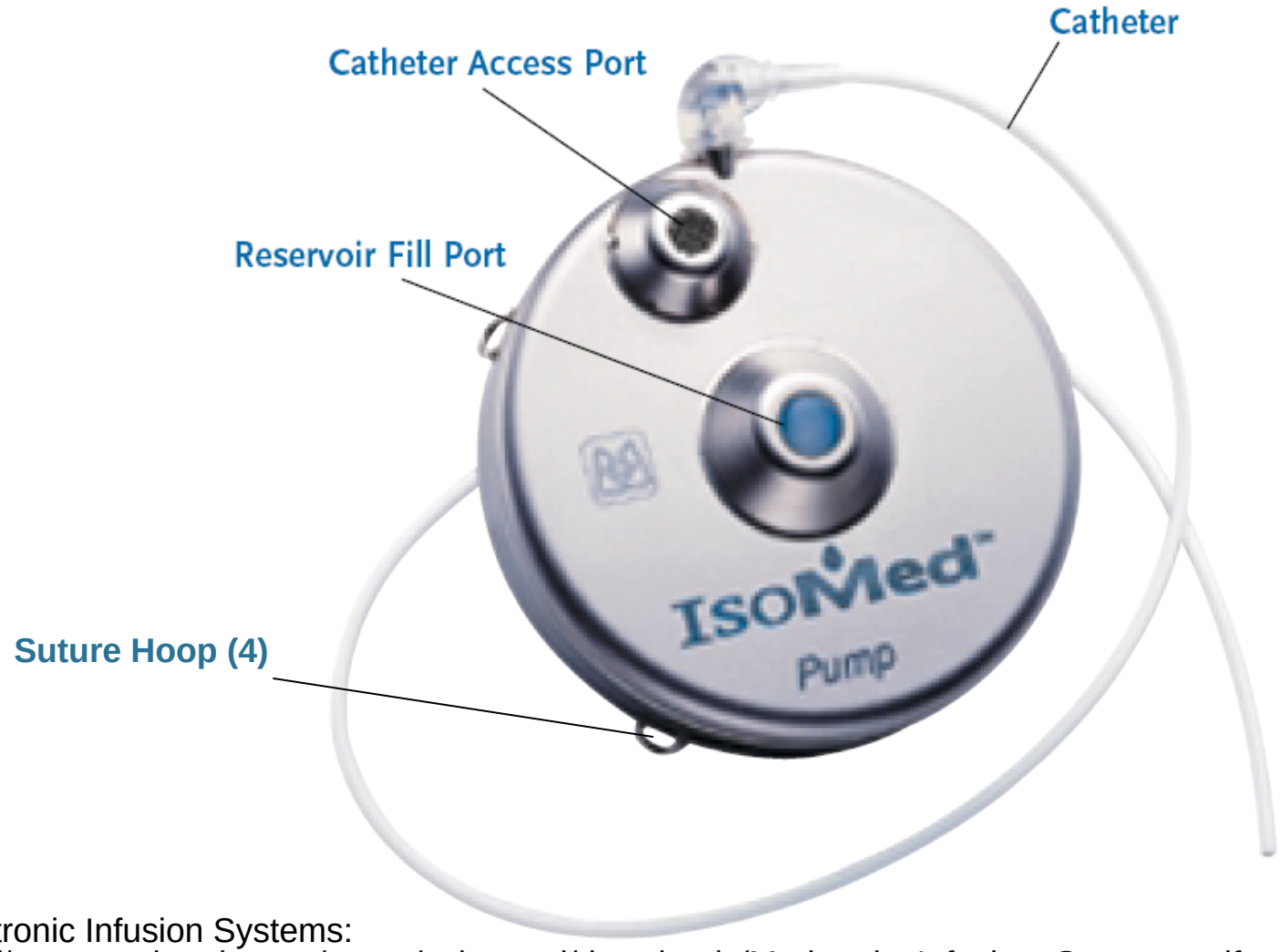


Figure 2: Pump and catheter placement for intravascular infusion of chemotherapy

- Chemotherapy for treatment of cancer
- Intravascular delivery
- Specific sites in the body through a vein or artery

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

IsoMed® Constant Flow Infusion System



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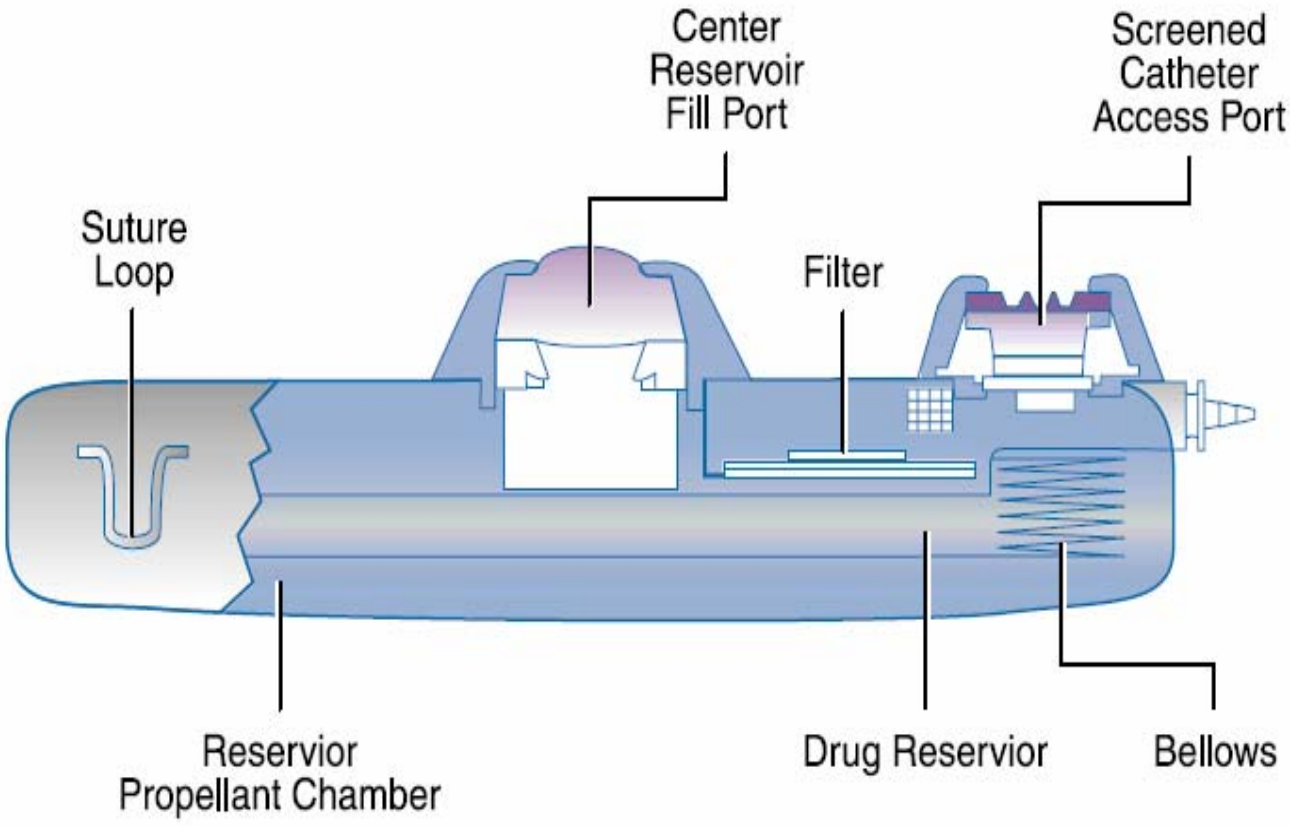
The Pump



IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Pump Reservoir

- Three Sizes
  - 20, 35, and 60mL
- Flow Rates Range
  - 0.3mL/day to 0.4mL/day
  - Length of Capillary Tubing Sets Flow
  - Longer Tube = Greater Resistance

$$R = \frac{8\eta\ell}{\pi r^4} \qquad FLOW = \frac{PRESSURE}{RESISTANCE}$$

Pump Specifications and Materials

		Model - Reservoir Size - Flow Rate		
	All Models	**8472-20-xx[1]**	**8472-35-xx[1]**	**8472-60-xx[1]**
External Properties				
Material	Titanium			
Thickness		17 mm (.67 in)	22 mm (.87 in.)	30 mm (1.2 in.)
Thickness including septum		24 mm (.95 in.)	29 mm (1.1 in.)	37 mm (1.5 in.)
Diameter	77 mm (3.0 in.)			
Weight (empty)		113 g (4.0 oz.)	116 g (4.1 oz.)	120 g (4.2 oz.)
Displacement volume		70 ml	101 ml	132 ml
Drug Reservoir				
Material	Titanium			
Usable capacity		20 ml	35 ml	60 ml
Dead space volume	3.5 ml			
Flow Rate				
Range		0.3 to 4.0 ml/day	0.3 to 4.0 ml/day	0.3 to 4.0 ml/day
Standard rates		0.5; 1.0; 1.5 ml/day	0.5; 1.0; 1.5 ml/day	0.5; 1.0; 1.5 ml/day

IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Pump Specifications and Materials

Internal Tubing	
Material	Titanium
Volume of fluid path between reservoir and catheter port	300 μl
Capillary Tubing	
Material	Glass
Length	Varies with flow rate 0.6 to 9.6 meters (1 to 31 feet)
Center Reservoir Fill Port	
Septum material	Silicone rubber
Puncture life	1000 punctures

IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Pump Specifications and Materials

Screened Side Catheter Access Port		
Material	Silicone rubber/ titanium	
Prime volume without catheter	0.15 ml	
Septum puncture life	500 punctures	
Pump Drive		
Pressure	2.10×10^5 pascal (2.10 bar)	Two Phase Gas-Liquid Propellant
Bacterial Retentive Filter		
Material	PVDF[2]	Polyvinylidene Difluoride
Pore size	0.22 micron	

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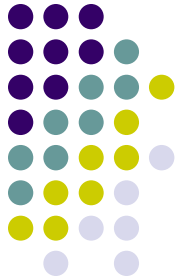
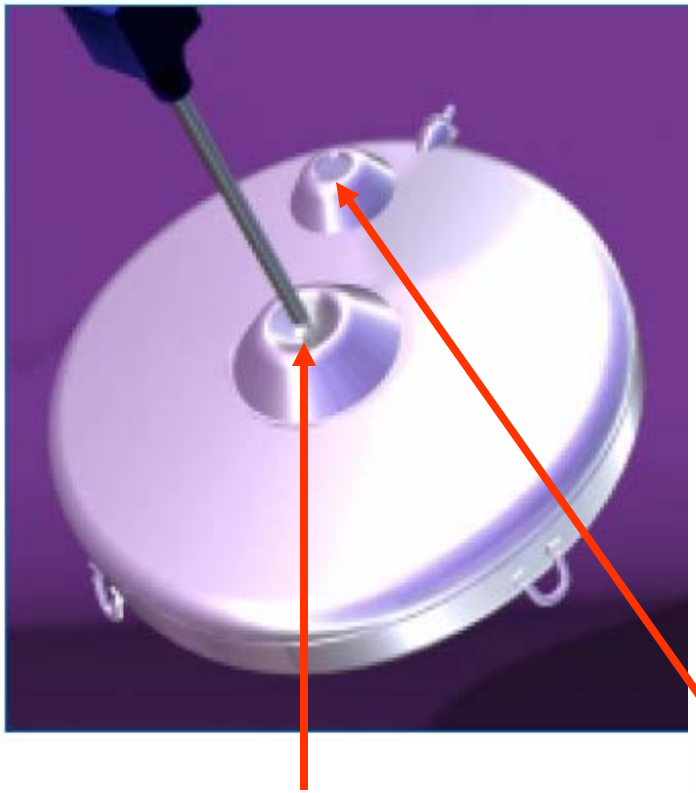
Percutaneous Access



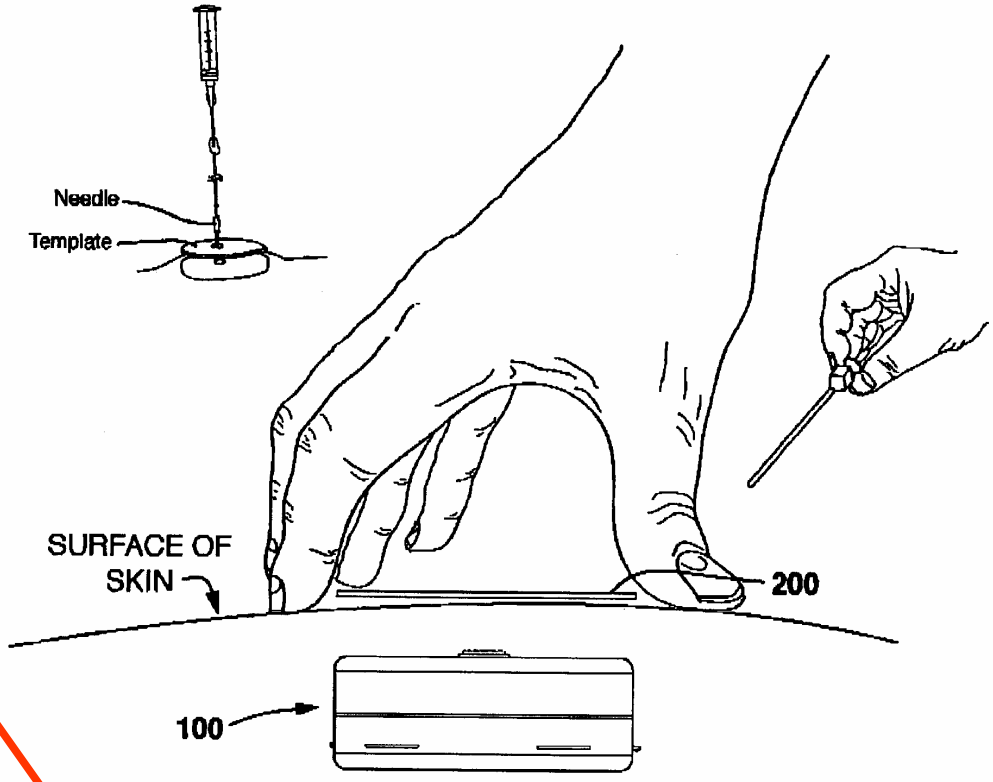
- 22 Gauge Non-Coring Needle Refills the Pump Reservoir
- 24 Gauge Non-Coring Needle or Smaller is Used to Access Cathater Port – Screen Prevents Unintentional Access to Catheter
- Note: The higher the gauge the smaller the needle diameter

FDA Publication Part 2 - Summary of Safety and Effectiveness http://www.fda.gov/cdrh/pdf/P990034b.pdf

Refilling The Reservoir



22 Gauge Non-Coring Needle

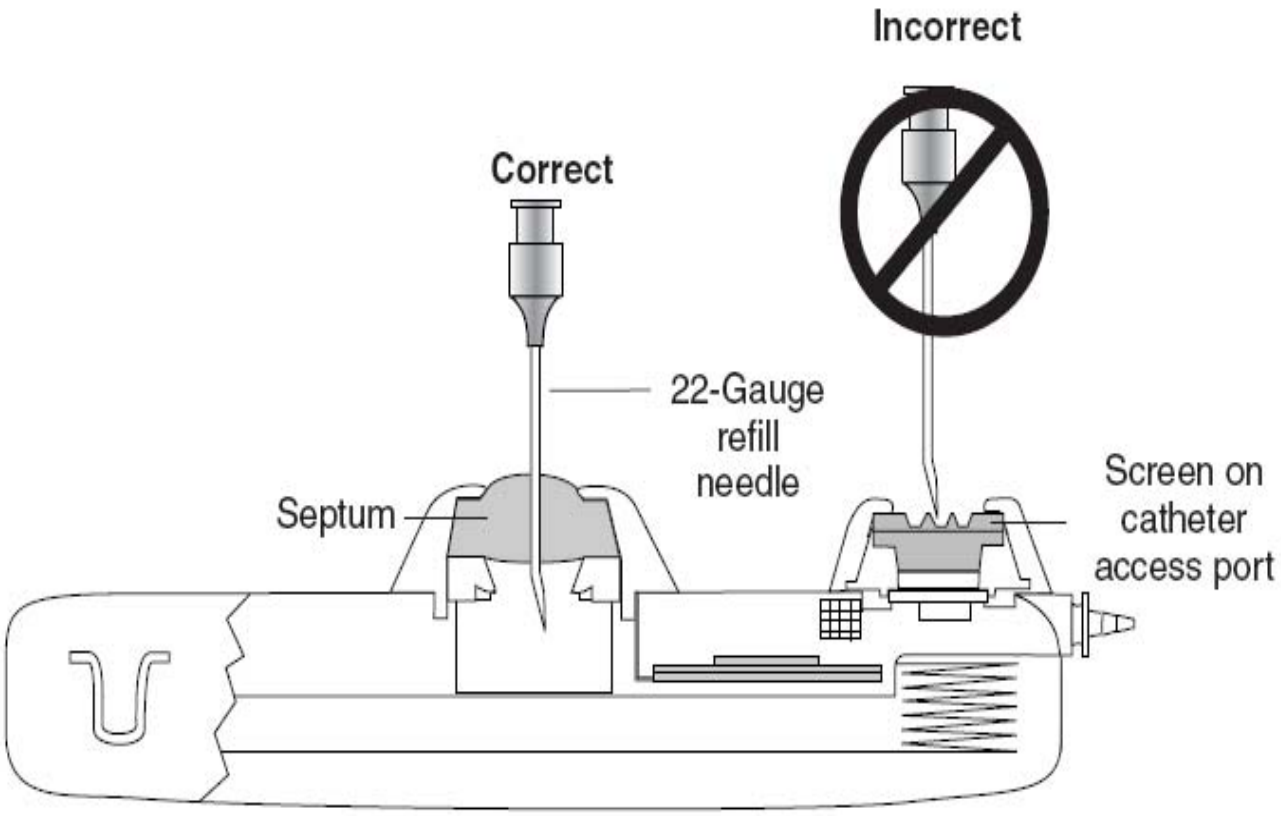


24 Gauge Non-Coring Needle (or smaller)

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

US Patent no: 7,044,932 Implantable drug pump access template

Refilling The Reservoir



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The Catheter

- Catheters that are approved are any one of the Medtronic intraspinal or intravascular catheters
- INTRASPINAL: InDura® Free-flow Intrathecal Catheter Model 8711
- INTRAVASCULAR: Any Medtronic Intravascular Catheter

Biocompatibility

- Materials in Contact with Body:
  - Titanium
  - Silicone Rubber
- Both Biocompatible in Previous Applications
- Device Passed Biocompatibility Testing

EMI Compatibility

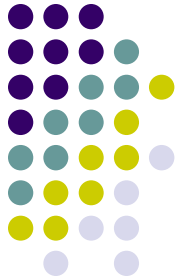
- No Ferromagnetic Components
- Within acceptable specific absorbance rate (SAR) and heating in 1.5T MRI
- Small effect on MRI image quality

Stability of FDA Approved Drugs

Drug	Indication	Drug stability
Morphine	Chronic pain (cancer pain or nonmalignant pain)	90 days
Floxuridine (FUDR)	Cancer	27 days

Medtronic Infusion Systems:
http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf

Potential Adverse Effects



- Return of Symptoms on Pump Failure
- Catheter Complication due to Kinks, Pressure Exertion, Breakage/Disconnection, Blockage, and Dislodgement
- Drug Complications and Side Effects
- Infection

Clinical Data

- Two studies in the US and one in Europe
- Purpose of studies was to determine accuracy, effectiveness, and safety of the device

Example Clinical Data: Intraspinal Study in the US – Serious Adverse Events

Table 2. Serious[a] Adverse Events (N = 110 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Unable to withdraw /inject into catheter access port	1	0.02	1	0.9%
PROCEDURE-RELATED[b]				
Implant				
Pocket hematoma/seroma	27	0.46	24	21.8%
CSF leak/accumulation	6	0.10	6	5.5%
Catheter cut/kink/dislodgement	4	0.07	4	3.6%
Pocket skin erosion/ wound dehiscence	4	0.07	4	3.6%
Pocket inflammation/ infection	3	0.05	3	2.7%
Explant				
CSF leak	2	0.03	2	1.8%

[a] Events that resulted in invasive intervention, death/disability, or hospitalization/prolonged hospitalization.

[b] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

IsoMed Technical Publication: http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Example Clinical Data: Intraspinal Study in the US – NonSerious Adverse Events

Table 3. Non-Serious Adverse Events (N = 110 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Dull needle in refill kit	1	0.02	1	0.9%
PROCEDURE-RELATED[a]				
Post-surgical pain/discomfort	15	0.25	15	13.6%
CSF leak	3	0.05	3	2.7%
Pocket inflammation	3	0.05	3	2.7%
Lumbar infection/inflammation	3	0.05	3	2.7%
Fill/refill error	2	0.03	2	1.8%

[a] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

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Accuracy and Reliability

- Puncture life of refill septum is at least 1000
- Flow rate is confirmed to ± 10% at 37°C of labeled flow rate
- Accuracy over all temperature ranges 35-39°C, pressures (0.85-1.05 bar), and fill (full or nearly empty) was ± 29% of the labeled flow rate

IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Accuracy and Reliability

Table 6. Intrathecal Study Results

Measure	Results	Experience	Number of Patients
Average clinically measured flow rate accuracy	99%	541 pump refills	106
Serious adverse event-free survival at 3 months[a]	100%	289.7 months	110

[a] Related to IsoMed pump and accessories.

Table 7. Intravascular Study Results

Measure	Results	Experience	Number of Patients
Average clinically measured flow rate accuracy	91%	419 pump refills	67
Average clinically measured flow rate accuracy adjusted for drug viscosity/arterial pressure	101%	419 pump refills	67
Serious adverse event-free survival at 3 months[a]	100%	169.4 months	79

[a] Related to IsoMed pump and accessories.

IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Pooled Results

Table 9. Pooled Study Results

Measure	Results	Experience	Number of Patients
Average clinically measured flow rate accuracy	100%	960 pump refills	173
Serious adverse event-free survival at 3 months[a]	100%	459.1 months	189

[a] Related to IsoMed pump and accessories.

IsoMed Technical Publication:
http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf

Future Direction

- Include Telemetry and Monitoring
- Address the Problem of Hematoma/Seratoma by Exploring Alternative Implantation Sites and Materials
- Explore Alternative Catheters and Materials to Reduce Catheter Complications

References

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- Medtronic Infusion Systems: http://www.medtronic.com/neuro/colorectal/downloads/Medtronic_Infusion_Systems.pdf
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- FDA Publications on the Device: http://www.fda.gov/cdrh/pdf/p990034.html
- IsoMed Technical Publication: http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_techmanual.pdf
- IsoMed Spec Sheet: http://www.medtronic.com/neuro/hai/physician/pdfs/isomed_specsheet.pdf

Thank You!

- **Professor Sonek**
- **Classmates**

Have a good Summer!!!