Novel Drug-Device Combination Products

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Combination Products: a Perfect Marriage of Drug and Device
Novel combination products

Scope: Utilization of the Combination Product Regulatory pathway to commercialize unique medical innovations

• Opportunities to combine technologies, not just products
• Tools: Consider advances in a range of technologies as creating a set of tools, individually useful for designing unique capabilities into each component of a combination product (examples listed in next slides)
• Microchip-containing devices that control dosing from drug reservoirs integrated with the devices
• Implantable pump systems for drug delivery, generally using MEMS-based technologies also
• Systems that combine drug delivery and biosensing capabilities, linked to a microcontroller that evaluates the sensor data to determine dosing
Context: Realization of the advanced versions of drugs, biologics, and device products has depended on significant advances in a number of technologies that serve as tools.

- Application of materials science to regulate drug delivery (example: nanotechnology-based strategies to apply nanoparticles to treatment)
- Polymer chemistries ("Smart polymers") that react to environmental changes by releasing trapped therapeutic agents
- Micro-electromechanical systems (MEMS) or nano- (NEMS-may be implemented as nanoparticles) fabrication
- Real-time data management to fine-tune dose administration (amounts, timing) enabled by wireless devices and the Cloud
Norplant® Implant [Controlled Release Polymer]

- Non-erodible implantable system
  - Insert implant subcutaneously in the upper arm (office surgery)
- Met delivery goal: sustained delivery of the active agent, avoiding daily hormone surges
- Met safety goal: avoid first-pass metabolism through liver, as with oral contraceptives
- Long-acting, reversible contraceptive
- Six flexible silicone rods (2.5 mm × 43 mm)
- Dose/rod= 36 mg of levonorgestrel (progesterone analog)
- Long term controlled drug delivery for 5 yr or longer.
- Use where long-term controlled administration is required.
Norplant: Conclusions

- Norplant is 99% – 99.95% effective at preventing pregnancy
  - one of the most reliable forms of birth control.
- Explant procedure difficult (6.2% of cases): potential scarring
- Adverse events more objectionable than anticipated
- Don’t forget the market: Norplant® was groundbreaking and was pulled in 2002 after extensive litigation in the USA (50,000 lawsuits filed, cited as a factor in Wyeth decision).
  - A second generation, 2-rod version as well as the 6-rod product have been sold continuously ex-USA

DUROS® Implant [Osmotic Pump]

- Non-erodible implantable system.
  - Insert implant subcutaneously in the inner aspect of the upper arm.
- Sustained delivery of an active agent.
- Osmotically driven.
- Long term controlled drug delivery for 1-12 mo or longer.
  
- Use where long-term controlled administration is required.
  - Remove implant after 12 months; replace implant to continue therapy
- May be site-specific.
- Sterile; use radiation sterilization as final step.
  - Can terminally sterilize the device as a component and aseptically fill, if the drug is unstable to terminal sterilization.
DUROS® implant mechanism: Viadur™

- Reservoir contains drug in solution.
- Semi-permeable membrane allows water to enter device and contact osmotic tablets.
- Osmotic tablets swell when exposed to water.
- Tablet swelling exerts pressure against piston.
- Piston forces drug through diffusion moderator and results in drug release from the device.
DUROS® Implant Formulation Opportunities

• Device and mechanism accommodate aqueous and non-aqueous systems:
  – Provides option to avoid hydrolytic decomposition by using non-aqueous vehicles.

• SC site allows solution or suspension:
  – Particulate preparations are acceptable as long as physical form is stable for duration of implant.

• Due to small volume, adverse effects of excipients and vehicles are not as high risk as for standard preparations:
  – Example: DMSO, benzyl alcohol do not cause implant site irritation in small amounts.

• Control rate by altering properties of the semi-permeable membrane:
  – A range of dosage strengths of fixed duration can be produced.
Viadur™ DUROS® Implant
Constraints and Outcome

• Formulation must be very concentrated stable solution.
  – Formulation: 65 mg of leuprolide (free base) in 104 mg DMSO.

• Drug must be very potent.
  – 120 μg leuprolide acetate/day for 12 months.

• Drug must be stable at body temperature for extended periods.

• Pump/Drug interactions need to be managed and understood
  – Formulation must not occlude the semi-permeable membrane during use.


• Don’t forget the market: Viadur™ was groundbreaking and was pulled due to poor sales.
DUROS® Repurposed by Intarcia Therapeutics Inc

- The DUROS® device performed to technical expectations as the commercial product Viadur™, just need an alternative indication:

New Implantable Pump Could Cut Diabetes Treatments

Device Delivers Drug Continuously, Potentially Setting Stage for a Once-a-Year Treatment Option

Credits: WSJ Thursday 01Oct2014, B3; website: http://www.intarcia.com/

- ITCA 650: can hold a 1 yr. exenatide supply
  - “Two of the FREEDOM Phase 3 clinical trials are now successfully completed: FREEDOM-1 and the FREEDOM-1 HBL studies both met all their clinical endpoints.”
  - Duros® pump is licensed and exenatide is already marketed for Type 2 diabetes.
  - Implanted SC in abdomen.
Programmable Implantable Devices: Motivation

• Control time course.
• Control dose amount.
• Automate administration, chronic care (diabetes).
• Critical control in acute situations (cardiac intervention).
• >Safety (low therapeutic window products).
• >Efficacy
• >Convenience
• <Pain
Programmable Implantable Devices: Examples

• Reservoir-based: MicroCHIPS
  – Leuprolide (hormone therapy, chronic continuous)
  – PTH (hormone therapy, chronic pulsed)

• Piezoelectric pump-based: TumorFighter™
  – Chemotherapy, combination therapy

• Pump-based: Medtronic
  – Pain, Cancer (SynchroMed® Pump)
  – Diabetes (MiniMed 530G® Insulin Pump)

• Integrated systems
  – Artificial pancreas: sensing and delivery integrated with a controlling algorithm to automate dosing regimen
  – Diabetes (MiniMed 530G® Insulin Pump + Enlite® Sensor)
MicroCHIPS Technology Platform
**In Vitro** Leuprolide: Process Flow Description

- Precision dispensing of nanoliter volumes, using automated instrumentation.
- Multiple, sequential fills per reservoir (e.g. Fill – Lyo – Fill).
- Filled chips can be sealed containing a liquid or lyophilized then sealed.

Cross-sectional representation of a single reservoir from the multi-reservoir array.

Images of the reservoir filling operations, with a description of the process flow for filling and sealing operations.
**In Vivo Release of Leuprolide:**

Implantable Drug Delivery System

- Microchip containing drug
- Titanium case
- Antenna for wireless communication
- Electronics
- Battery

Scale: similar to commercial defibrillators.
Size can be reduced with custom electronics.

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**in vivo** Release – Leuprolide (Model Peptide)

NOTES:
- AUC approximates bioavailability-flat is better
- n=6 dogs
- Variability is typical of **in vivo** dosing (literature)
- Publication: *Nature Biotech*

**Comparison:**
Relative Standard Deviation for Leuprolide Depot Injection in Humans and Leuprolide MicroCHIPS Implant in Beagle Dogs

**Graph:**
- Average AUC (ng/mL*hours) vs. time post device implantation (weeks)
- Data points and error bars indicate variability over time.

**Bar Chart:**
- Comparison of relative standard deviation for different routes of administration:
  - MicroCHIPS SC Implant
  - SC Depot Injection
  - Human
  - Beagle Dogs
- Values: 0.0, 0.1, 0.3, 0.5
Leuprolide Feasibility Summary

Feasibility of chronic peptide delivery in vivo has been demonstrated.

• Highly concentrated (>100mg/mL) solutions of polypeptides were formulated that are stable at 37°C.
• In vitro release rate manipulated through:
  • reservoir geometry
  • formulation recipe
  • formulation physical state.
• Very small (100nL) volumes were processed.
• Reservoir-based devices were assembled into an in vivo package.
• Release mechanisms and electronics work for six months in vivo.
MicroCHIPS Clinical Trial: hPTH(1-34) Dosing from Implanted Device

• A hPTH(1-34) formulation and product assembly process were designed and proven to enable chronic pulsatile peptide release from the finished device upon command.
  • Bone growth requires intermittent release of hPTH(1-34)

• Eight osteoporotic postmenopausal women with osteopenia or osteoporosis were enrolled for the 4 months trial.

• Each device was wirelessly programmed after implantation to release escalating doses once daily for up to 20 days.

• Assess:
  • PK of hPTH(1–34) released from implantable devices in vivo in patients.
  • Compare PKs pre- and post-fibrous encapsulation of the device.
  • hPTH(1–34) bioactivity post-release.
  • Reliability and reproducibility of peptide release from the device.
**hPTH (1-34) In Vitro Release Data**

- Improved formulation results in a more pulsatile release profile.
- High concentrations of hPTH (1-34) (>100mg/mL) were formulated and lyophilized.
- Stability at 37°C was improved through formulation manipulation.
- Pulsatile *in vitro* release kinetics were achieved.

**Average % purity of the most concentrated fraction > 96%**

Feasibility of formulating hPTH (1-34) for delivery from a multi-reservoir array was demonstrated.
MicroCHIPS Clinical Performance

• PK (including reliability and reproducibility of peptide release from the device), safety, tolerability, and bioactivity (bioequivalence) of hPTH(1–34) were assessed.

  • PK: Device dosing produced similar PK to multiple injections and had lower coefficients of variation.
  • PK: Capsule formation did not significantly affect PK
  • Bioactivity (bioequivalence): Bone marker evaluation indicated that daily release from the device increased bone formation.
  • Safety: There were no toxic or adverse events due to the device or drug.
  • Tolerability: patients stated that the implant did not affect quality of life.

• **Summary conclusion:** data demonstrated the programmable implant delivered hPTH(1–34) at scheduled intervals, providing proof of concept that a polypeptide drug could be delivered safely for months using the MicroCHIPS device.
Medtronic: Implantable Programmable Pumps

SynchroMed® Infusion System

- Implantable, programmable drug delivery system
- Indications
  - pain (focus of example)
  - spasticity
  - cancer
- Commercially available since 1988

SynchroMed® II Programmable Pump
SynchroMed® System: Description

• Components:
  • Infusion pump
  • Intraspinal catheter
  • External programmer
• Implantation:
  • Pump placed abdominally SC.
  • Catheter inserted into intrathecal space of the spine, tunneled under the skin and connected to the pump.
• Maintenance:
  • Alert signals low reservoir volume.
  • Fill reservoir through port beneath skin (outpatient procedure).
Diabetes Therapy: The Debiotech Nanopump

- **Technology**: MEMS-based microfluidics enables a miniaturized insulin-delivery system.

- **Implementation**: The MEMS-based pump, mounted on a disposable skin patch, provides continuous insulin infusion SC at a rate that can be tightly controlled.

- **Benefits**:
  - Alternative to individual insulin injections, administered several times a day.
  - Size only *ca.* 25% of commercial pump.
  - Less obtrusive than commercially available pumps, can wear as skin patch.
  - Dosing regimen is patient-specific and patient-programmed.
Diabetes Therapy: The Nanopump

The MEMS Pumping Unit (left) and Reservoir (right):
- Incorporates a disposable insulin storage reservoir
- Programmed with a remote control
- Marketed as the JeweIPUMP™ for diabetes care

http://www.debiotech.com/newsite/file/others/Nanopump_article.pdf
MiniMed 530G® insulin pump

- Pump, worn on a belt, includes drug reservoir, battery, and user interface.
- Pump uses fast-acting insulin.
- Pump is refilled every two to three days with a reservoir that transfers insulin drawn from a vial.
- The insertion device inserts an infusion set.
- Pump mimics the pancreas, delivering pulsed insulin doses throughout the day through the infusion set.
- Programming delivers higher amounts of insulin for mealtimes, triggered by user before a meal or snack.

Accessed 05OCT2014.
**Diabetes Therapy: Continuous Glucose Monitoring Systems**

**Enlite® Sensor** (circled in red, right panel)

- Glucose sensor inserted under the skin (with insertion assist device) measures glucose levels.
- RF Transmitter sends glucose information from the sensor to a monitor.
- Monitor (may be built into the insulin pump or a stand-alone device) displays glucose levels; alerts user when glucose values exceed maximum or minimum limits.
- When used with the MiniMed 530G® system, Enlite® features a 93% hypoglycemic detection rate.
The “artificial pancreas” is the most commonly cited example of an integrated medical system that would serve unmet medical needs in type 1 and type 2 diabetics.
The Artificial Pancreas: System Design

Goal: significantly decrease diabetic complications using drug/biosensor/delivery device combinations

- External insulin pump.
- Implantable continuous glucose monitor (sample and sense).*
- Controlling software with dosing algorithms.*
  Designed to respond to specific signals or circumstances, transcending limits to dosing adjustment responsiveness of traditional drug administration.
- Wireless communication to allow reprogramming, data download, alerts.
- Power source.

* Greatest technical hurdles to commercialization.
The Artificial Pancreas: Approved Sep 2013

MiniMed 530G® with Enlite is the first diabetes management system in FDA's new class: "Artificial Pancreas Device System, Threshold Suspend."

Author's Conclusions

• The continuation phase results support and extend the findings of the study phase.
• Switching from optimized Multiple Daily Injections (MDI) to Sensor-Augmented Pump (SAP) therapy allows for rapid and safe A1C reductions.
• Glycemic benefits of SAP persist for at least 18 months.
• Maximal glycemic control is associated with more frequent wearing of the CGM sensor.

References:

Future 2005 Vision: Cloud Therapy?

Reference: WO2006010166 A3
2014 Actuality: Cloud Therapy

Reference: Wall St J 26Sep2014
Conclusions: Novel Combination Products for Controlled Drug Delivery

• The technology exists for implementing a range of types of device.
• Due to stringent regulatory requirements and the added complexity of gaining combination product approval, few examples of devices have received marketing approval.
• Barriers to widespread implementation of devices include:
  – Cost.
  – Invasiveness.
  – Limited indications that have attractive cost/benefit and risk/benefit.
  – Limited examples of drugs that are sufficiently potent and stable to contain in a device for long term use.
• Advances in intelligent drug delivery using biosensor feedback, potentially integrated with Cloud technology, could induce a quantum leap for personalized therapy prospects.
Selected References


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Linebaugh K (26Sep2014) *Wall St J*. “Citizen Hackers Tinker With Medical Devices.”
Websites

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http://www.fda.gov/oc/combination/

Intarcia http://www.intarcia.com/ (Home)

MicroCHIPS http://www.mchips.com/ (Home)

http://www.pharmaco-kinesis.com/media.php (Videos)

Medtronic
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THANKS-AND STAY IN TOUCH!