



4 November 2014

Square 1

The Business

Mitomycin-C and Ophthalmology

- Off label use of old oncologic agent
- First published use: 1963
- Glaucoma, refractive, corneal surgery

Mitomycin-C

- Interrupts healing, inhibits scarring
- Mechanism: Interruption of DNA synthesis
- Available in generic form
- On-label: Stomach and pancreatic cancer
- Off-label: Intraoperative use reduces scarring
- Reward: Extended efficacy

Intraoperative Mitomycin-C: Problems

- Currently ordered from outside pharmacy
- Unstable: Light shielding, refrigeration required
- Requires ordering of multiple doses
- Requires transfer with gown, gloves, eye-shield
- Extreme contact, vapor, aerosolization hazard
- Dosing irregularities
- Disposal hazards
- Waste of unused product



Mitosol[®]

(mitomycin for solution)

0.2 mg/vial

Kit for Ophthalmic Use

- Ophthalmic mitomycin-c kit
- Sterile, single use
- Lyophilized drug - Extended shelf life
- Closed mixing system - Safety
- Manufacturing controls, IFU
- Improved patient care, occupational safety

Mitosol™ Kit for Ophthalmic Use





Mitosol[®] vs. Compounding

	Compounding	Mitosol[®]
Assuredly Sterile	<i>No</i>	Yes
Manufacturing Controls	<i>No</i>	Yes
Directions for Use	<i>No</i>	Yes
Assured Potency	<i>No</i>	Yes
Assured Dosing	<i>No</i>	Yes
Shelf Life	<i>5 - 14 days</i>	24 months
"Black Box Warning" Removed	<i>No</i>	Yes
Room Temp Storage	<i>No</i>	Yes
Light Stable	<i>No</i>	Yes
Closed Transfer	<i>No</i>	Yes

Vendor Selection

Some Starting Points

- ISO-13485 certified, FDA registered
- cGMP compliant
- Previous FDA audit results
- Track record of supplier



Synergetics Part Number	Vendor	Vendor Part Number	Description	Current Approved Revision Level					
				Batch Record	BOM	Dwg	RCVG Instructions	Incoming Insp. Spec & Record	First Article Inspection Form
MOB.2	Synergetics	N/A	Finished Product (Box of 3 kits)	D	B	A	N/A	N/A	N/A
MOB0001	PerfecSeal	0900011	PETG Tray, Outer	N/A	N/A	B	C	C	N/A
MOB0002	PerfecSeal	0800010	Styrene Tray, Inner	N/A	N/A	B	C	C	N/A
MOB0003	Oliver	MOB0003	Tyvek Lid, Outer	N/A	N/A	A	C	B	N/A
MOB0004	Oliver	MOB0004	Tyvek Lid, Inner	N/A	N/A	B	C	C	N/A
MOB0005	Medimold	MOB0005	Pledget Container Base	N/A	N/A	4	B	Z	2
MOB0006	Medimold	MOB0006	Pledget Container Cover	N/A	N/A	4	B	Z	2
MOB0008	ICU Medical	CH-62	Clave Vial Adaptor w-Spike	N/A	N/A	N/A	D	B	N/A
MOB0009	ICU Medical	CH2000	Spiros Connector	N/A	N/A	N/A	C	B	N/A
MOB0010	Abbott/Solvay	1022864	Syringe, Pre-Filled (Sterile H ₂ O), 1ml	N/A	N/A	N/A	E	D	N/A
MOB0011	Kettenbach	30761	Instrument Wedge (Sugi Absorbent Swab)	N/A	N/A	N/A	C	B	N/A
MOB0012	Kettenbach	30661	Absorbent Strips, Halfmoon	N/A	N/A	N/A	C	B	N/A
MOB0013	Kettenbach	30663	Absorbent Strips, 6x4 mm	N/A	N/A	N/A	C	B	N/A
MOB0014	Kettenbach	30662	Absorbent Strips, 4x3 mm	N/A	N/A	N/A	C	B	N/A
MOB0018	Intas	200006290FL	Mitosol™ Drug Vial 0.2 mg	N/A	N/A	N/A	C	A	N/A
MOB0019	Kendall	DP5041B	Chemotherapy Waste Bag	N/A	N/A	N/A	C	B	N/A
MOB0020	Suburban Ind'l	MOB0020	Outside Carton, Printed	N/A	N/A	D	C	E	N/A
MOB0021	Cortegra	TBD	Instructions for Use	N/A	N/A	B	D	C	N/A
MOB0022	Cortegra	TBD	Package Insert	N/A	N/A	A	C	C	N/A
MOB0023	Kendall	5551100777	TB Syringe, Empty, 1ml	N/A	N/A	N/A	C	B	N/A
MOB0024	Medline	MDS090545	Alcohol Prep Pad, Sterile	N/A	N/A	N/A	C	B	N/A
MOB0026	Abbott/Solvay	1023574	Plunger Rod for MOB0010	N/A	N/A	N/A	B	A	N/A
MOB0033	Global Industrial	T9C239742	Plastic Pallet	N/A	N/A	A	-	A	N/A
55202650	Synergetics	N/A	Variable Info Label	N/A	N/A	B	N/A	N/A	N/A

Design Objectives in OEM Products

- *An integral part of your design history file*
- Define function of device/component
- Define specifications and their rationale
- Define vendors to be evaluated
- Define vendor/component selection criteria
- ***Document every step of this process!***

Example 1: Reconstitution Devices

- Function:
 - To reconstitute sterile, lyophilized agent
- Specifications
 - Needleless device = safety
 - Closed system = safety, sterility, simplicity
 - Affixes to prefilled syringe
- Define vendors to be evaluated
 - Self Designed: “Smart Rod”
 - West Pharma: “MixJect”
 - ICU Medical: “Spiros Connector”

Reconstitution Devices

- Vendor/component selection criteria
 - Conformance to the specifications
 - Simplicity of construction
 - Simplicity of assembly
 - Material compatibility, e.g. agent, sterility, etc.
 - ISO-13485, cGMP compliant, FDA registered
 - Total burdened cost

Make/Buy Decisions

Why Make?

- Control over entire process from start to finish
- Lower cost per unit
- Expansion of IP portfolio
- Accumulation of corporate assets

Why Buy?

- Potentially faster
- Lower development costs
- Fewer human and technical requirements



Make or Buy: Reconstitution Device

Vendor	Description	Cost	Tooling	Royalty	Assembly	TOTAL	Yr 1	Yr 2	Yr 3	TOTAL
						Units	60,000	100,000	150,000	310,000
Self- Designed	<i>Smart-Rod Syringe</i>	\$0.38	\$0.40	\$1.50	\$1.07	\$3.36	\$201,516	\$335,861	\$503,791	\$1,041,170
ICU Medical	<i>Spiros</i>	<i>\$1.75</i>	<i>\$0.00</i>	<i>\$0.00</i>	<i>\$0.00</i>					
	<i>Vial Adapter</i>	<i>\$1.50</i>	<i>\$0.00</i>	<i>\$0.00</i>	<i>\$0.00</i>					
	Total ICU Medical	\$3.25	\$0.00	\$0.00	\$0.00	\$3.25	\$195,000	\$325,000	\$487,500	\$1,007,500
West Pharma	<i>MixJect</i>	\$0.90	\$0.00	\$0.00	\$0.00	\$0.90	\$54,000	\$90,000	\$135,000	\$279,000

Assembly Assumptions

Wage + Benefits	\$16.00
Pieces/Hour	20
Hrs/Wk	40
Total Labor	\$857.60
Total Pieces	800
Assy Cost/Unit	\$1.07

Tooling Assumptions

Tool 1	\$43,100
Tool 2	\$16,875
Tool 3	\$64,680
Total Tooling	\$124,655

Decision

- ***Buy from West Pharmaceutical Services***
 1. Non-variable unit costs
 2. Lower up front costs (tooling)
 3. FDA approved for intended purpose

West Pharmaceutical Services

- Large NYSE listed pharma supply company
- Stoppers, caps, syringes, etc.
- Specialty delivery a developing strategic priority
- Reputation: Conservative, high quality, respected
- Mobius engages West for MixJect + Kitting

Prior to Pre-NDA Meeting

- Without warning, agreement cancelled
- Keeps Mobius' fees; claims ownership of kit
- Out critical component
- Out critical vendor
- Out substantial development fees

Final Decisions

- ***Buy from ICU Medical***
 1. Non-variable unit costs
 2. No tooling required
 3. FDA approved for intended purpose
 4. Far easier to assemble during kitting
- ***Move kitting to Synergetics***

Lessons: How to be Avoided

- Better research into nature of the vendor
- Understanding vendor' s strategic priorities
- LEAN manufacturing principles in action?
- Eat at home!

Example 2: Mitomycin-C

- Function:
 - Active pharmaceutical agent
- Specifications
 - Formulation identical to oncologic substance
 - 0.2 mg fill - 1:2 ratio with excipient
 - Sterile fill; vial seal able to withstand EtO cycle
- Define vendors to be evaluated
 - Bedford Labs - Div of Boehringer Ingelheim
 - Intas Pharma – Ahmedabad, India

Mitomycin-C

- Vendor/component selection criteria
 - Conformance to the specifications
 - Identical formulation
 - Ability to be packaged with a sterile kit
 - ISO-13485, cGMP compliant, FDA registered
 - Development costs and timeline
 - Development timeline
 - Unit cost
 - Total burdened cost

	India	USA
Development Costs	\$300,000.00	\$950,660.00
<i>Product and Process Development</i>		\$164,500.00
<i>Method Validation</i>		\$17,760.00
<i>Batch Development</i>		\$184,800.00
<i>Container/Closure Validation</i>		\$48,100.00
<i>Process Validation</i>		\$60,000.00
<i>Clinical Registration</i>		\$423,000.00
<i>Stability</i>		\$52,500.00
Development	\$300,000.00	\$950,660.00
Price/Vial	\$9.19	\$19.31
Year 1	\$609,464.52	\$1,475,486.67
<i>Cost of MMC/Kit</i>	<i>\$551,400.00</i>	<i>\$1,158,600.00</i>
<i>Development</i>	<i>\$58,064.52</i>	<i>\$316,886.67</i>
Year 2	\$1,015,774.19	\$2,406,330.00
<i>Cost of MMC/Kit</i>	<i>\$919,000.00</i>	<i>\$1,931,000.00</i>
<i>Development</i>	<i>\$96,774.19</i>	<i>\$475,330.00</i>
Year 3	\$1,523,661.29	\$3,356,496.77
<i>Cost of MMC/Kit</i>	<i>\$1,378,500.00</i>	<i>\$2,896,500.00</i>
<i>Development</i>	<i>\$145,161.29</i>	<i>\$459,996.77</i>
TOTAL	\$3,148,900.00	\$7,238,313.44
Year 1	Year 2	Year 3
60,000	100,000	150,000



Mitomycin: USA vs. India

	USA	India
Identical Formulation	Yes	Yes
Compatible w-Packaging	Yes	Yes
Development Cost	≈ M\$1	K\$300
Cost of Goods	\$19.31	\$9.19
Development Timeline	18 months	6 months
Supply Chain	Cleveland	India
Track Record	Yes: BMS, Self	No: SuperGen
OEM Experience	Yes: BMS, JNJ	Just starting
ISO, FDA Registration	Yes	No ISO, Yes FDA

Mitomycin: USA vs. India

	USA	India
Strategic Priority	No	Yes

Mitomycin: USA vs. India

	USA	India
cGMP Compliance	Questionable	Yes

What Next?

- Audit USA vendor
- Audit Indian vendor
- Audit Indian vendor supply chain, i.e. API
- References within industry
- Site visits, meetings with key personnel

The Winner

The Winner

- Intas Pharma
- 6 month timeline shortened to 90 days
- FDA audits in 2007 and 2011: Clean
- Development costs staged: K\$100 at approval

The Loser

- Bedford Laboratories
- FDA warning letter: 2008
- Health Canada rejection 2011
- Suspension: June 2011
- Cessation of contract business: August 2011
- Cessation of operations: November 2011
- FDA Consent Decree 2012

Take Home Message

Final Thoughts

- Documented understanding of requirements
- Documented decision tree
- Thorough research of vendor options
- 1:1 contact with decision makers
- Strategic priority
- Willingness to partner – no master/slave
- TOTAL cost of goods