Role of Excipients in New Dosage Forms and Regulatory Implications

Multiple stakeholders; **one objective.**

- International Pharmaceutical Excipients Council
- Collaborative solutions for excipient industry stakeholders

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Overview and Agenda

- Overview of combination products (drug delivery devices) regulatory pathways and drivers
- Requirements for polymers and plastics used in medical devices
- Regulatory review of novel excipients in combination products
- Opportunities for additional discussion and development of strategy

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Background

- Life cycle management of drugs is driving invention of new formulations for already approved drugs
  - Extend patents
  - Protection of intellectual property
  - Use of regulatory schemes that allow companies to make modest changes to already approved drugs
  - Patient compliance

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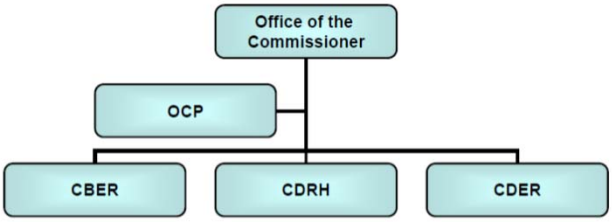
Background

- Mandated by the Medical Device User Fee and Modernization of 2002 (MDUFMA)
- Office established December 24, 2002



- Office of the Commissioner, Office of Special Medical Programs (OSMP)

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Illustrative Examples

- Approval of Neupro® Rotigotine transdermal system), a skin patch designed to treat symptoms of early Parkinson's disease
- Daytrana® (methylphenidate transdermal system) patch for treating Attention Deficit Hyperactivity Disorder (ADHD) in children six to 12 years of age
- FDA Approves Inhaled Insulin Combination Product for Treatment of Diabetes (Exubera®, an inhaled powder form of recombinant human insulin (rDNA))
- TissuGlu® Surgical Adhesive (TissuGlu) is a urethane-based, liquid surgical adhesive which is activated upon contact with tissue fluid. TissuGlu is applied by a hand-held applicator containing the adhesive.

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Combination Products

- Combination Product (21 CFR 3.2(e)):
  - a product comprised of two or more regulated components that are physically, chemically or otherwise combined or mixed as a single entity;
  - two or more separate products packaged together (e.g., drug and device products); or
  - A product packaged separately but intended for use only with an approved, individually specified product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product, the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.
  - (Similar to 3rd bullet but both products investigational include components that are regulated under different types of regulatory authorities, and by different FDA Centers
- These products raise regulatory, policy, and review management challenges

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Combination Product Examples

- Bandage with antimicrobial coating
- Bandage packaged with tube of antibiotic ointment
- Pre-filled delivery device, e.g., syringe or inhaler that contains drug or biologic (EpiPen, Advair)
- Antimicrobial coated catheter
- Drug-eluting stent (Taxus, Xience)
- Antibody-drug conjugates (Mylotarg)
- Light source and photo-activated drug (Photofrin)

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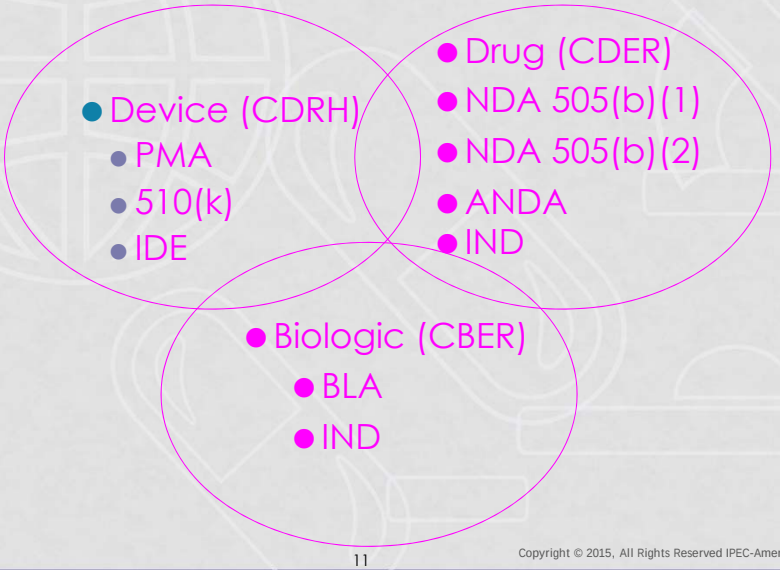
Not Combination Products

- Drug-drug, device-device, or biologic-biologic combinations
- Most concomitant use of drugs, devices and biologics
- General drug or biologic delivery devices (e.g., unfilled syringe or infusion pump) not intended for use with an individually specified drug or biologic product

Regulatory Pathway for Combination Products

- Primary jurisdiction - OCP classifies based on:
  - Primary mode of action of the product, and,
  - Article responsible for the primary mode of action then assigns review to the most appropriate center
- Multidisciplinary considerations when a drug is involved
  - regardless of 'regulatory jurisdiction'
- Regulation of the combination product as a drug raises new issues for excipients
  - Polymers (plastic) used commonly as raw materials in devices may be evaluated as an excipient in drug delivery systems

Assignment/Jurisdiction



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Assignment / Jurisdiction

- Mode of Action (MOA) – "the means by which a product achieves its intended therapeutic effect or action" – drug, device, biologic definitions (21 CFR 3.2(k))
- PMOA – "the single mode of action of a combination product that provides the most important therapeutic action … The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects…" (21 CFR 3.2(m))

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Assignment Algorithm

- If unable to determine the PMOA with reasonable certainty, then consider…
- FIRST: Consistency (Tier 1)
  - Assign the product to the Center that regulates other combination products that present similar questions of safety and effectiveness
- SECOND: Safety and Effectiveness (Tier 2)
  - When FIRST does not apply, assign the product to the Center with the most expertise related to the most significant safety and effectiveness questions

(21 CFR 3.4)

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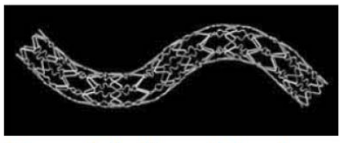
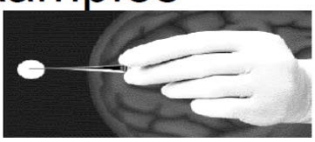
PMOA Examples



Drug Eluting Stent

- PMOA – stent opens artery (device)
- Secondary MOA – drug prevents inflammation and restenosis
- Assigned to CDRH



Drug Eluting Disk

- PMOA – chemotherapy for brain tumor (drug)
- Secondary MOA – local delivery of drug by the device
- Assigned to CDER [20]

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Algorithm Assignment example

- Contact lens coated with glaucoma drug – CDER
  - MOA: Lens corrects vision
  - MOA: Drug treats glaucoma
  - Device and drug have independent modes of action – Algorithm:
    - First of its kind product: Tier 2 = CDER
      - In this hypothetical example, the most significant safety and effectiveness questions are related to the characterization, manufacturing, and clinical performance of the drug component, while the safety and effectiveness questions raised by the vision-correcting contact lens are considered more routine.
    - Other products like this: Tier 1 = CDER

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Polymeric Materials used in Medical Devices

- Polyvinyl chloride
- Polycaprolactone
- Polyethylene terephthalate
- Polyglycolic acid
- Polylactic acid
- Poly (tetrafluoroethylene)
- Polymethylmethacrylate
- Silicone
- Ultrahigh molecular weight polyethylene
- **Thermoplastic polyurethanes (TPU)**

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TPU Device Applications

Cardiovascular
- Cardiac assist pump bladders, tubing, housing, coatings
- Heart pacemaker connectors, coatings, lead insulators
- Cardiac stents
- Blood Bags
- Blood oxygenating tubing,
- conduits
- Percutaneous shunts

Wound Care
- Skin dressing and tapes
- Suture materials
- Wound dressings

Other
- Transdermal drug delivery patches
- Surgical drapes
- Connectors
- Closures
- Fittings
- Endotracheal tubes
- Reconstructive surgery materials

Orthopedics
- Orthopedic splints
- Bone adhesives

Urology
- Catheters
- Hemodialysis tubing, membranes

Drug or Device?

- Drug –
  - (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
  - (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
  - (C) articles (other than food)intended to affect the structure or any function of the body of man or other animals; and
  - (D) articles intended for use as a component of any articles specified in clause (A),(B), or (C). . . .
  - New Excipient-
    - Inactive ingredient intentionally added to therapeutic and diagnostic products that:
      - Are not expected to exert therapeutic effects at intended dosage; and
      - Are not fully qualified by existing safety data to the proposed level of exposure, duration of exposure or route of administration

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Drug or Device?

- "device" –
- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
  - recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Regulatory Overview For Devices

- Agency makes clearance or approval decision for a medical device supplied in its finished form
- Agency does not clear or approve individual raw materials that are used in fabrication of medical devices
- Biocompatibility of final device depends on materials, processing of materials, manufacturing methods, sterilization process and manufacturing residuals present in final device
- Device raw materials are not required to be manufactured under GMP
- Supplier may provide some level of biocompatibility data, ISO 9001 (or equivalent) quality systems and have notification of change policies

ISO Risk Based Framework for Biocompatibility Studies

Device categorization by nature of body contact (see 5.2)			Biologic effect							
Category	Contact	Contact duration (see 5.3) A – limited (≤ 24 h) B- prolonged (>24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Surface device	Intact skin	A	X	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X	O	O		O	
		C	X	X	X	O	X	X	O	
	Breached or compromised surface	A	X	X	X	O				
		B	X	X	X	O	O		O	
		C	X	X	X	O	X	X	O	
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X	O			X
		C	X	X	O	X	X	X	O	X
	Tissue/bone/dentin*	A	X	X	X	O				
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X		O^		X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X	O				
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

ISO 10993 - Seven key principles

- Selection of materials - material characterization, formulation of each component material (adhesives, impurities and constituents associated with processing)
  - Should not either directly or through release of material constituents:
    - Produce adverse local or systemic effects
    - Be carcinogenic; or
    - Produce adverse reproductive and developmental effects
  - Device master files with proprietary/confidential information
- Relevance of materials used in manufacture, including leachables and degradation to the overall toxicological evaluation
- Toxicology testing based on bioavailability of material (nature, degree, duration, frequency, conditions of exposure)
- *Invitro and invivo* tests should be conducted in accordance with GLP
- Full experimental data to enable independent conclusion
- Evaluation of toxicological effects with changes to chemical composition, manufacturing process, physical configuration or intended use
- Overall safety assessment should be made in conjunction with other non-clinical tests, clinical studies and post market experiences

FDA's Regulatory Policy – Combination Products

- Consideration given to the **potential interaction** (desired or undesired) between the device and the drug/biological constituents
- Impact of **leachables/extractables** of the device materials into the drug/biologic substance or final combination product
- Changes in **stability** of the drug constituent when delivered by the device or when used as a coating on the device;
- Drug **adhesion/absorption** to the device materials that could change the delivered dose
- Presence of inactive **breakdown products** or manufacturing residues from device manufacture that may affect safety, or device actions that could change the drug performance characteristics at the time of use;
- Changes in the stability or activity of a drug constituent when used together with an energy emitting device

GMP Requirements for Combination Products

- Maintenance of 2 separate manufacturing systems (21 CFR Parts 210/211 for drugs/biologics and 21 CFR Part 820 for devices) not required
- For single entity and co-packaged combination products, there are 2 options:
  - Option 1: Demonstrate compliance with all GMP parts included in combination products
  - Option 2; Implement streamlined approach demonstrating compliance with either drug or device CGMP requirements
  - For combination products including biologics, cGMP for biological products in parts 600 – 680 apply
  - For combination products including any HCT/Ps, Part 1271 including current good tissue practice and donor eligibility requirements apply

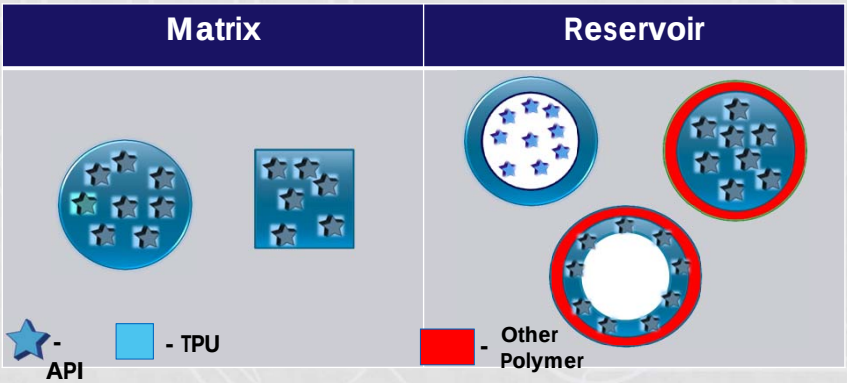
Where TPU Excipients Are Used

- Intravaginal Rings
  - Contraception
  - HIV prevention
  - Glycerin
- Vaginal Pessaries
- Subcutaneous Implants
  - Opioids
  - Antipsychotic
- Bladder Implants
  - Bladder Cancer
- Ocular Implants
- Osmotic Pumps
  - Insulin
- Sensor Devices

Photo courtesy of ViroPan, Inc.

Photo courtesy of Axxia Pharmaceuticals, LLC.

Flexible Delivery System Design



Regulatory Requirements for Excipients in Drug Delivery Systems

- **Regulatory expectations for Novel excipients**
  - Full characterization in connection with the product
  - Safety justification following data as outlined in the FDA Guidance for Industry: *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - Address the safety of the polymer and components of the polymer in accordance with this guidance

Example of Records for Implants Currently in the FDA IID

Inactive Ingredient	Route	Dosage Form	CAS #	UNII	Max. Potency	Unit
DIMETHYLSILOXANE/ METHYLVINYLSILOXANE COPOLYMER	IMPLANTATION	PELLET, IMPLANT		Pending	**142**	MG
DIMETHYLSILOXANE/ METHYLVINYLSILOXANE COPOLYMER	IMPLANTATION	ROD		Pending	**142**	MG
POLYGLACTIN	IMPLANTATION	PELLET, IMPLANT	26780507	Pending	25.2	MG
SILASTIC BRAND MEDICAL GRADE TUBING	IMPLANTATION	PELLET, IMPLANT		N/A		
SILASTIC BRAND MEDICAL GRADE TUBING	IMPLANTATION	ROD		N/A	**13**	MG
SILASTIC MEDICAL ADHESIVE,SILICONE TYPE A	IMPLANTATION	PELLET, IMPLANT		Pending	13	MG
ETHYLENE VINYL ACETATE COPOLYMER	IMPLANTATION	ROD		Pending	61	MG
CELLULOSE, MICROCRYSTALLINE	INTRAVITREAL	IMPLANT	9004346	OP1R32D61U	1.66	MG
MAGNESIUM STEARATE	INTRAVITREAL	IMPLANT	557040	70097M6I30	0.0048	MG
POLYVINYL ALCOHOL	INTRAVITREAL	IMPLANT	9002895	532B59J990	0.119	MG

What does the potency value mean from a precedence standpoint?

In this case, the tubing is the excipient. No max potency recorded

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Example of Records for Implants Currently in the FDA IID

Inactive Ingredient	Route	Dosage Form	CAS #	UNII	Max. Potency	Unit
METHYL PYRROLIDONE	PERIODONTAL	DRUG DELIVERY SYSTEM		JR9CE63FPM		
POLYLACTIDE	PERIODONTAL	DRUG DELIVERY SYSTEM	26680104	459TN2L5F5		
CARBOXYMETHYLCELLULOSE SODIUM	SUBCUTANEOUS	IMPLANT	9004324	K679OBS311	16	MG
DIMETHYL SULFOXIDE	SUBCUTANEOUS	IMPLANT	67685	YOW8V9698H	104	MG
MAGNESIUM STEARATE	SUBCUTANEOUS	IMPLANT	557040	70097M6I30	0.5	MG
POVIDONES	SUBCUTANEOUS	IMPLANT		FZ989GH94E	6	MG
SODIUM CHLORIDE	SUBCUTANEOUS	IMPLANT	7647145	451W47IQ8X	77	MG
STEARIC ACID	SUBCUTANEOUS	IMPLANT	57114	4ELV7Z65AP	1.04	MG
POLYGLACTIN	SUBCUTANEOUS	PELLET, IMPLANT	26780507	Pending	25.2	MG
ETHYLENE VINYL ACETATE COPOLYMER	SUBCUTANEOUS	ROD		Pending	61	MG

What does the potency value mean from a precedence standpoint?

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Example of Records for Implants Currently in the FDA IID

Inactive Ingredient	Route	Dosage Form	CAS #	UNII	Max. Potency	Unit
BARIUM SULFATE	VAGINAL	DRUG DELIVERY SYSTEM	7727437	25BB7EKE2E	5.9	MG
POLY(DIMETHYLSILOXANE/METHYLVINYLSILOXANE/METHYLHYDROGENSILOXANE) DIMETHYLVINYL OR DIMETHYLHYDROXY OR TRIMETHYL ENDBLOCKED	VAGINAL	DRUG DELIVERY SYSTEM		Pending	9980	MG
ETHYLENE-VINYL ACETATE COPOLYMER (28% VINYL ACETATE)	VAGINAL	INSERT		8ILA5X28VS	1677	MG
ETHYLENE-VINYL ACETATE COPOLYMER (9% VINYLACETATE)	VAGINAL	INSERT	24937788	4OKC630HS6	197	MG
LACTOSE MONOHYDRATE	VAGINAL	INSERT	64044515	EWQ57Q8I5X	760.5	MG
MAGNESIUM STEARATE	VAGINAL	INSERT	557040	70097M6I30	23	MG
POVIDONES	VAGINAL	INSERT		FZ989GH94E	49	MG
STANNOUS 2-ETHYLHEXANOATE	VAGINAL	INSERT	301100	519A78R12Y	0.07	MG
STARCH, PREGELATINIZED CORN	VAGINAL	INSERT	9005258	O8232NY3SJ	210	MG
TETRAPROPYL ORTHOSILICATE	VAGINAL	INSERT	682019	4PE821G3GH	0.35	MG
HYDROGEL POLYMER	VAGINAL	INSERT, EXTENDED RELEASE		N/A	236	MG
POLYESTER	VAGINAL	INSERT, EXTENDED RELEASE		N/A		
POLYURETHANE	VAGINAL	SPONGE	9009545	Pending		
HIGH DENSITY POLYETHYLENE	INTRAUTERINE	INTRAUTERINE DEVICE	9002884	UG00KM4WR7		
POLYETHYLENE LOW DENSITY CONTAINING BARIUM SULFATE (20-24%)	INTRAUTERINE	INTRAUTERINE DEVICE		N/A	150	MG

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Regulatory Issues and Opportunities

- Emerging area of drug delivery devices
  - Implant materials like discs, rods, tubes being evaluated as excipients
  - Polymeric materials generally have long term precedence of use in devices
  - Materials with long history of use in devices are not necessarily "novel chemistries"
- Needs careful consideration of how these excipients are evaluated, what data is captured and how precedence is established
- Requires collaboration from both industry and regulators
  - IPEC
  - FDA Office of Combination Products
  - Combination Products Council and/or other Industry Organizations

Thank You!

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