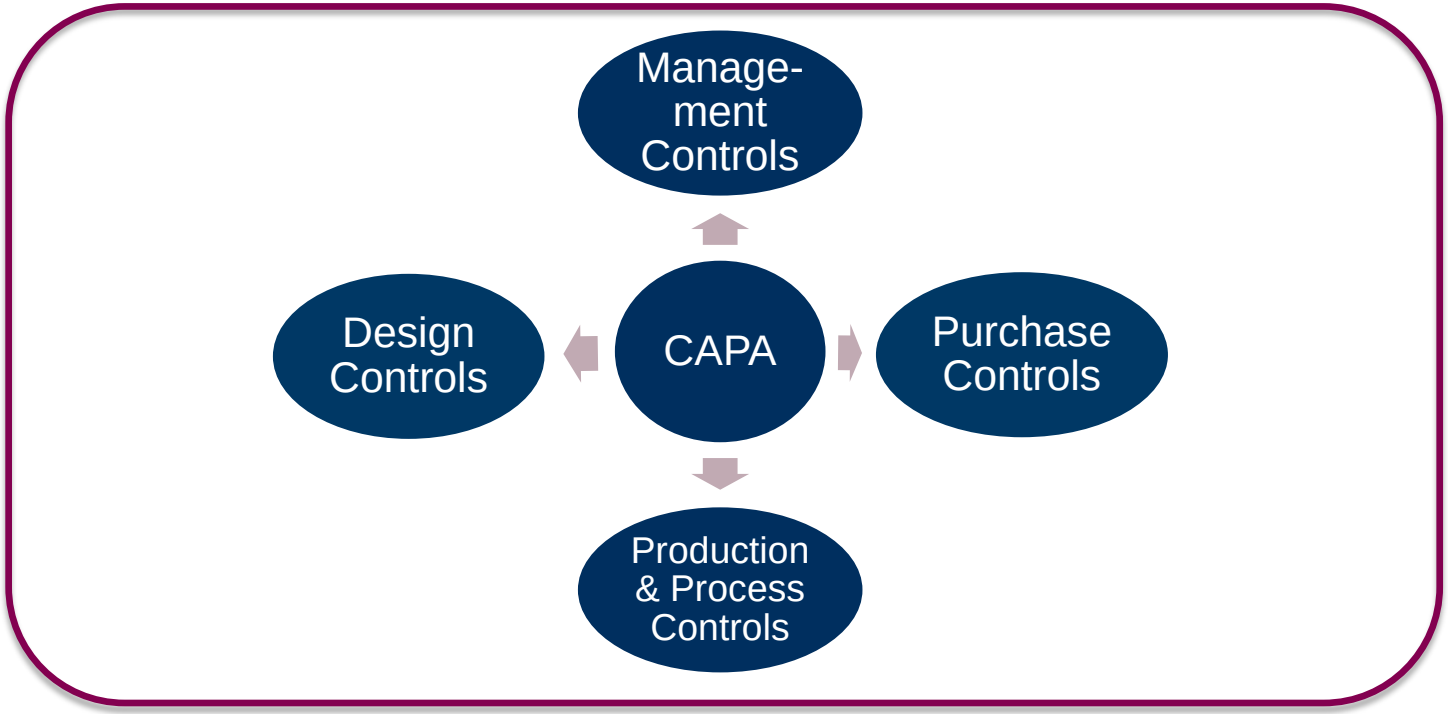
Global Market Trends of Device Strategies for Patient Centric Therapeutics

Li-Chun Tsou, Ph.D., MBA, **AstraZeneca - Global Operations – GTS Devices**

OMICS - 2015 Parenterals and Injectables International Conference, Chicago, USA 17-19 Aug 2015

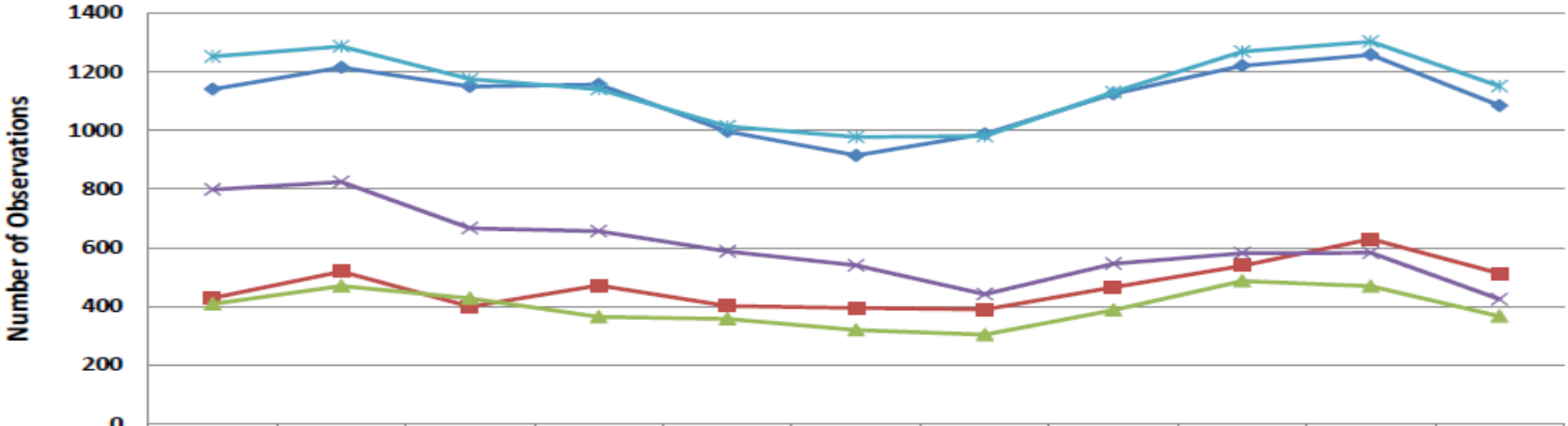
Device Strategy for Meeting Design Control Requirements

FDA – Quality System (QS) Regulations



FDA audits and inspections can be scheduled or unscheduled. The focus of area include the chart illustrated plus document controls.

FDA – 483 Warning Letter – 2003-2013



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
CAPA	1141	1215	1150	1157	997	915	988	1125	1221	1258	1085
DES	429	519	400	472	402	395	390	466	539	630	513
DOC	409	470	428	365	358	320	304	388	487	469	367
MGMT	799	825	667	657	588	540	442	546	582	583	425
P&PC	1252	1287	1175	1141	1014	978	981	1131	1269	1303	1151

Ref: 2013 Annual FDA Medical Device Quality System Data – 483 Observations and Warning Letter Citations, p.18,, UCM416501

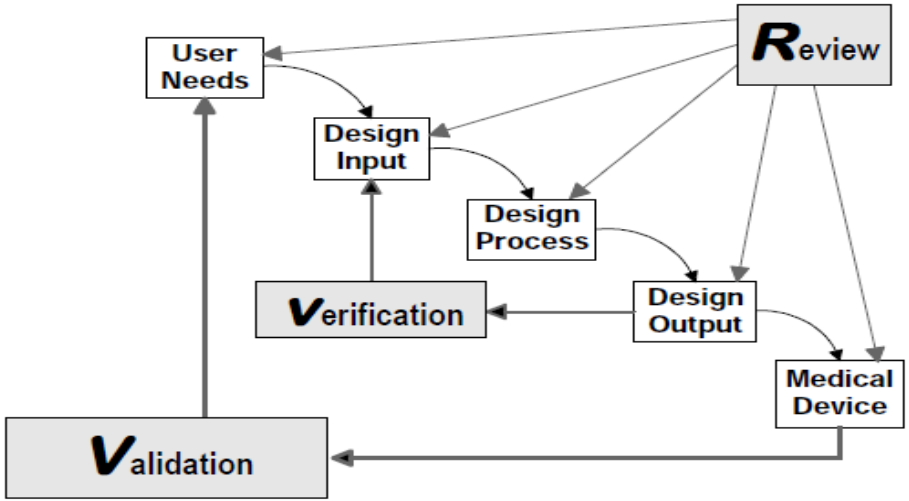
FDA – 483 Warning Letter - 2013

QS Subsystem	# of Observations	Percentage
P&PC	1,151	33%
CAPA	1,085	31%
MGMT	425	12%
DES	506	14%
DOC	367	10%
	Total: 3,534	

Ref: 2013 Annual FDA Medical Device Quality System Data – 483 Observations and Warning Letter Citations, p. 19, UCM416501, http://www.accessdata.fda.gov, CDRH, Office of Compliance, Julie.Stuart@fda.hhs.gov

Design Control Process

FDA Design control process enhances a new device's functional performance. An innovative injector for home use not only encourages patient to take control of their disease state but also improves their treatment adherence and therapy outcome.



Ref: "Application of Design Controls to Waterfall Design Process – Originated by Medical Device Bureau, Health Canada"
Design Control Guidance for Medical Device Manufacturers, Page.3, FDA –CDRH 11 Mar., 1997

Devices & Design Control

All injection devices follow Design Control Process. They look alike but may have different therapeutic indications and different patient populations. Therefore, Human Factor studies will be needed.

Ref: PharmaCircle, “Injection Devices - Reusable Injection Pens and Disposable Pens”, p.12, Updated on 19-Feb-2015

Typical Design Control Process_I

Design Planning

Collaborate with multiple functional groups to interact with regulatory affairs, marketing, clinical research, API and drug substance production are essential.

User Needs

Document User Needs through market research, focus group, and voice of patients.

Design Input

Conceptual input is important source of inputs but they do not equal to design input requirements. Design Input should be measurable properties.

Design Output

Design output can be diagram, drawing, specification, and procedures. Design output shall define the target value and acceptable tolerance range and limits.

Ref: Link closely to 820.50 and 820.130, “FDA Inspection Guides for Design Controls”, UCM 170251, http://www.fda.gov

Typical Design Control Process_II

Risk Assessment

Risk analysis should be addressed in the design plan. Risks should be considered throughout the design process and continued through the life cycle of the product.

Design Verification

Design verification activities include test, inspections, analyses, measurements, and demonstrations.

Design Validation

Design validation should demonstrate through objective evidences that the approved design met the predetermined user needs and intended uses by using initial production devices or the equivalents.

Design Review

Cross-functional group conducts Design Review throughout the key stages of product development.

Ref: Link closely to 820.100 and 820.120, “FDA Inspection Guides for Design Controls”, UCM 170251, http://www.fda.gov

Typical Design Control Process_III

Design Transfer

Design transfer should demonstrate that the approved design output was correctly translated into production specifications. These production specifications are documented in Device Master Record.

Design Change

Design change may include both the enhancement of the device and the improvement resulting from customer complaints. Post-production changes related to device design change must be assessed.

Design History File

Design history file contains document index of design control process. Design history file maintenance may include periodic review and update.

Ref: Link closely to 820.80 and 820.120, “FDA Inspection Guides for Design Controls”, UCM 170251, http://www.fda.gov

Types of Injectable Devices

Cost to correct any design errors is lower during early design phase.

Devices	Dosing	Frequency	Device Life	Device Type
TwinJects	Variable	Single Use	Disposable	Autoinjector
Symlin Pen	Variable	Multiple Use	Disposable	Pen
Enbrel	Fixed Dose	Single Use	Disposable	Autoinjector
Forteo Pen	Fixed Dose	Multiple Use	Disposable	Pen
SimpleJet	Fixed Dose	Multiple Use	Reusable	Autoinjector
Flex Pen	Variable	Mutiple Use	Reusable	Pen

Ref: PharmaCircle, “Reuseable Injection Pens and Disposable Injection Pens”, p. 12, 19-Feb-2015, http://www.pharmacircle.com

Regulatory Landscape for Combination Products

- **Japan** – PMDA uses new regulation for medical devices and combination products. Device Master Record and Design History File are constantly requested for authority review during new drug applications.
- **China** – SFDA catches up with US and EU regulatory requirements for medical devices and combination products. Functional tests are reviewed in details. Its dedicated lab conducted the testing to verify the claims.
- **US** – FDA has requested that human factor study to be conducted with the patient populations in the countries planned for product launch. For example, if a new products is submitted for US approval, the human factor studies should include the patient population study in US.
- **Brazil** – ANVISA has requested device test methods for functional performance evaluation on medical device and combination product.
- **EU** – EMEA regulatory submission requires a formal process validation conducted on three batches of full production scale of new products.

Ref: Emergo Group, "Japan Approval Process for Medical Devices" Updated on 17-Dec-2014, http://www.emergogroup.com

Design Control Process for Devices

- **Design Control Process Is Critical.**
- **Cross Collaboration Is Important.**
- **Risk Assessment Is Crucial.**

Device Strategy for Achieving Patient Centric Therapeutics

Competition on Diabetes Parenteral Devices

Sanofi Lyxumia is marketed in EU and Japan currently.

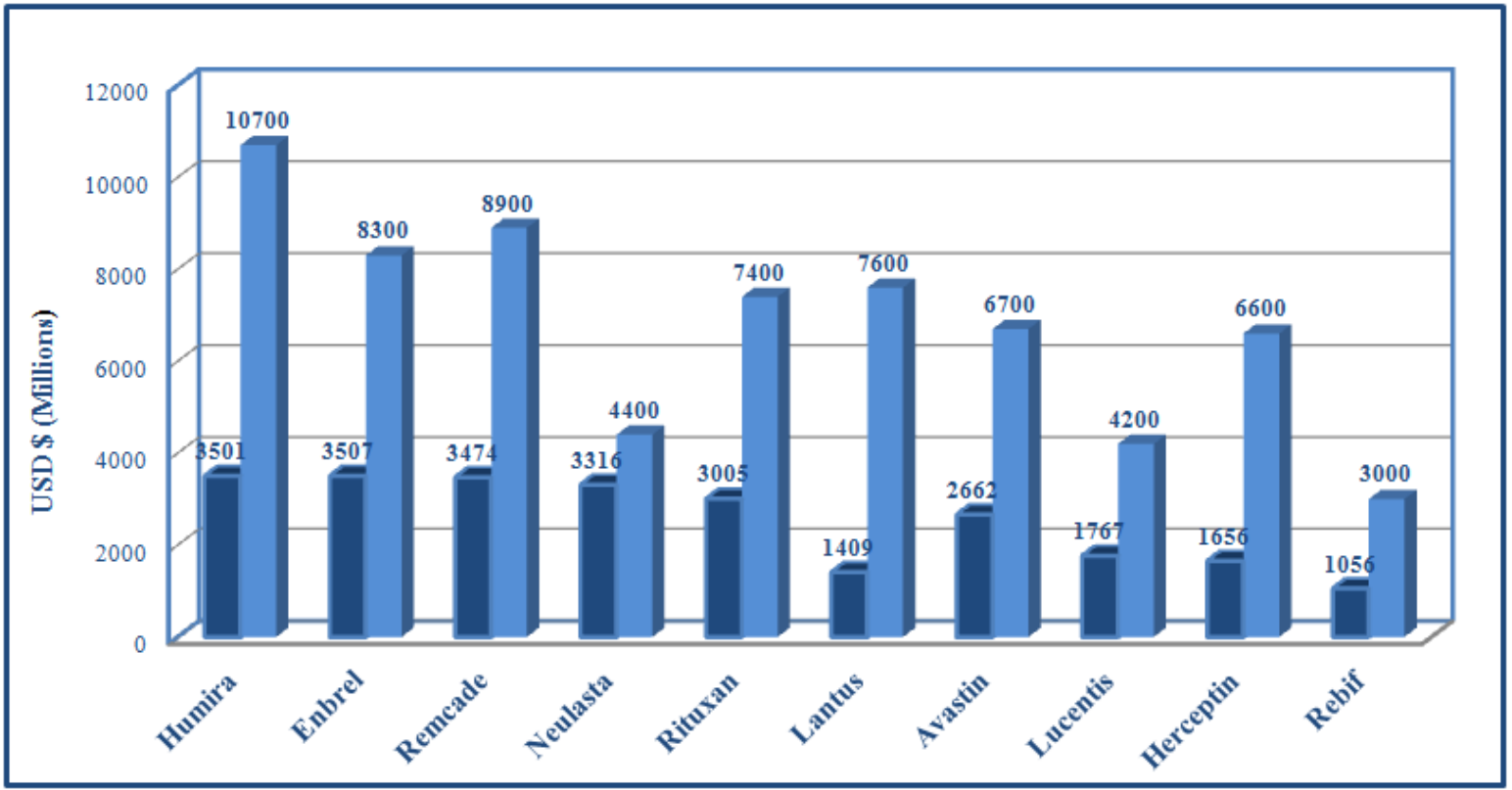
Intarcia takes a different approach using Exenatide in an implant for 12-month sustained release.

GSK Tanzeum is weekly dosing GLP-1 launched in US in Apr-2014. It required mixing and has gentler side effect.

Lilly Trulicity is weekly dosing GLP-1 using prefilled syringe based autoinjector. It launches in 4Q2014. KOLs consider that Trulicity is a strong competitor to Victoza to penentrate market.

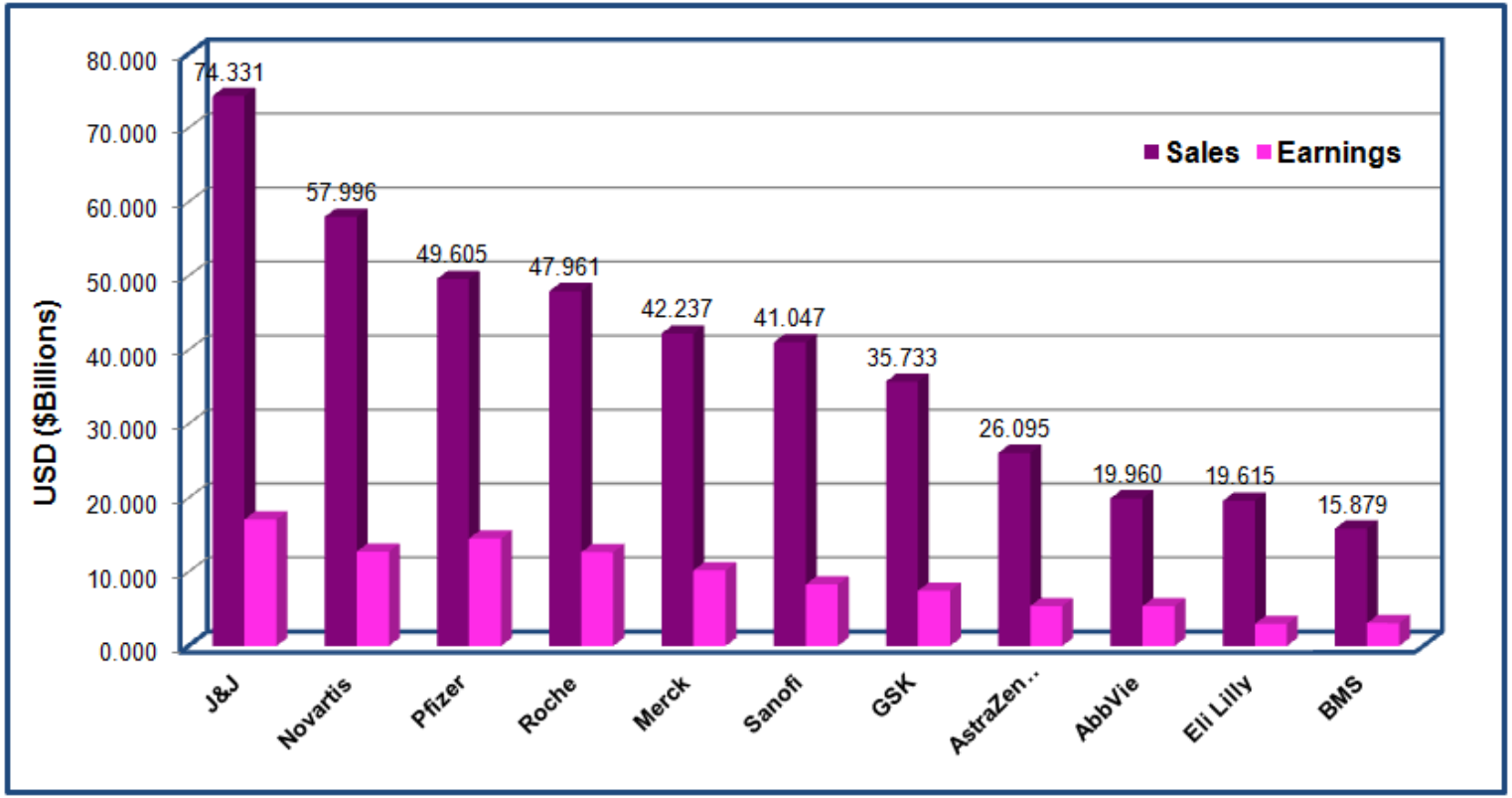
Novo Nordisk's Victoza is daily GLP-1. In its pipeline, a weekly dosing 'Semaglutide' and an oral GLP-1 drug are in development . Clinical trials are in progress.

Global Revenue Growth of Top 10 Biologics



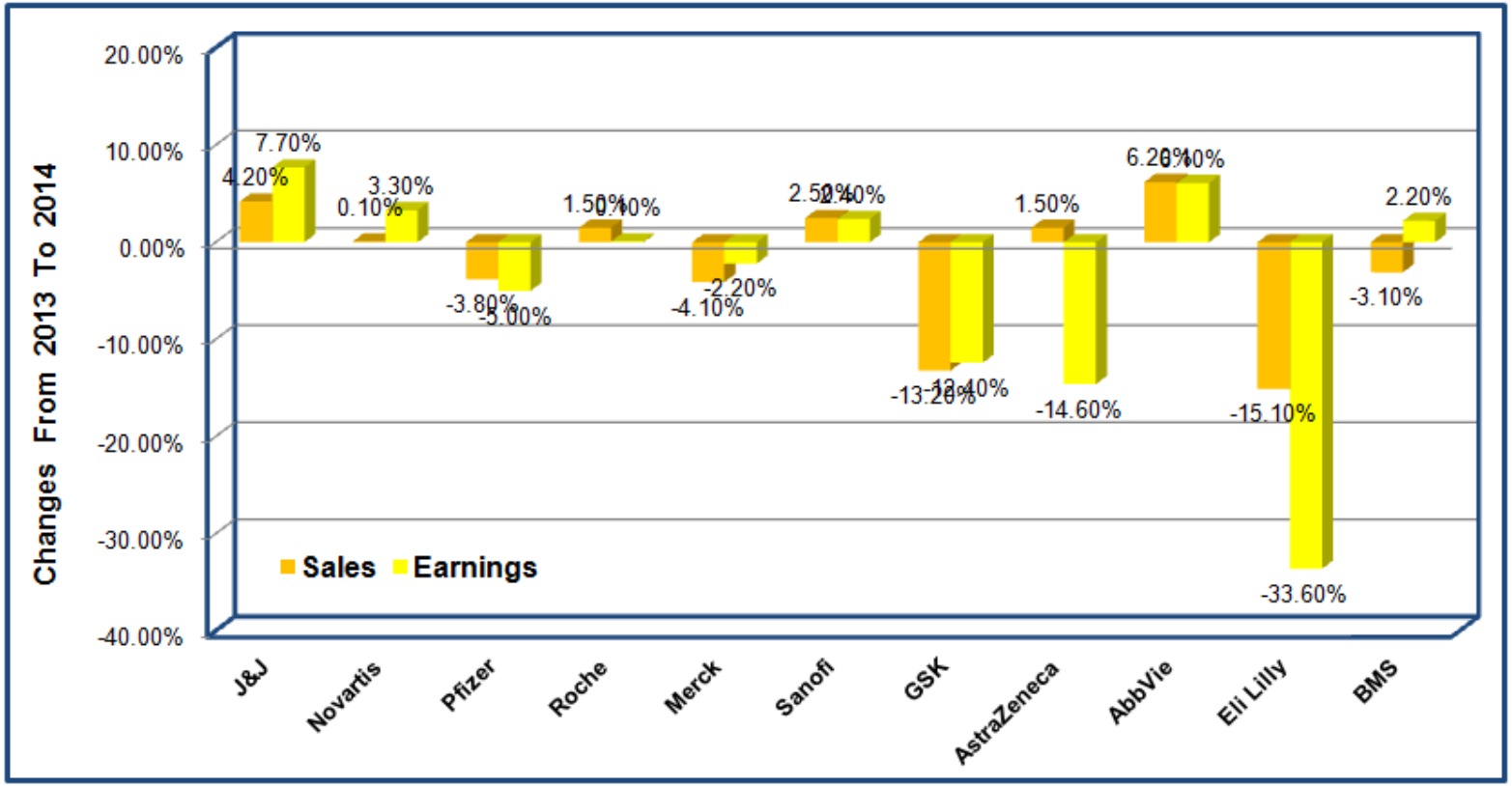
Ref: http://www.pmlive.com/top_pharma_list/Top_50_pharmaceutical_products_by_global_sales. High price tags have been observed in biologics e.g., Avastin is $4400 per month whereas Humira is about US$1650 for one weekly injection pen.

Global 2014 Pharma Sales and Earnings



Ref: "BioTech Boom" C&EN, Chemincal and Engineering News, p.25, http://www.cen.acs.org, In 2014, Biotech gains great profit margin whereas Pharmaceutical companies encountered sales and earnings pressures.

Global 2014 Pharma Sales and Earnings



Ref: "BioTech Boom" C&EN, Chemincal and Engineering News, p.25, http://www.cen.acs.org, Changes of Sales and Earnings from 2013 to 2014 of the top pharmaceutical Companies were summarized and compared.

Delivery Devices_Industry Benchmark

Autoinjector and pen devices have been marketed for many therapeutics. Product recall or device malfunction were documented and learned by all.

The interactions among device, user, and environment were studied through human factor engineering and shared globally.

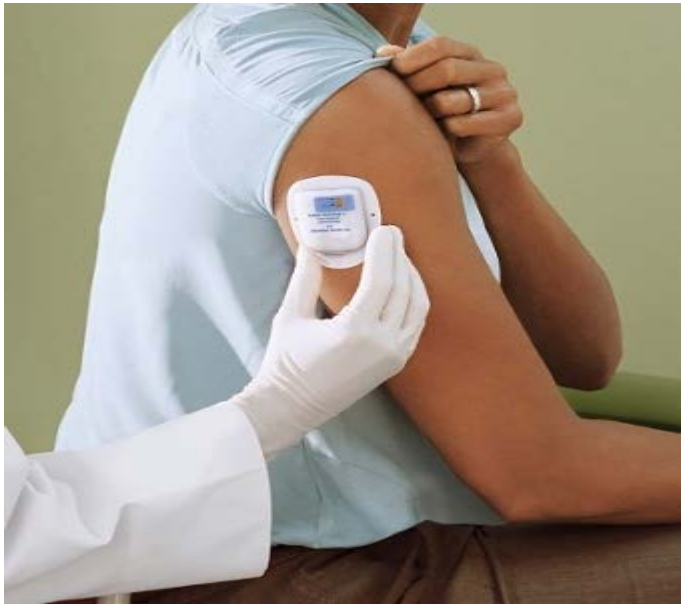
Ref: Frew A.J. , “What are the ‘ideal’ features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis to ensure the ease of use, portability, and accurate delivery of a life-saving drug?” Allergy, 2011; 66: 15–24.

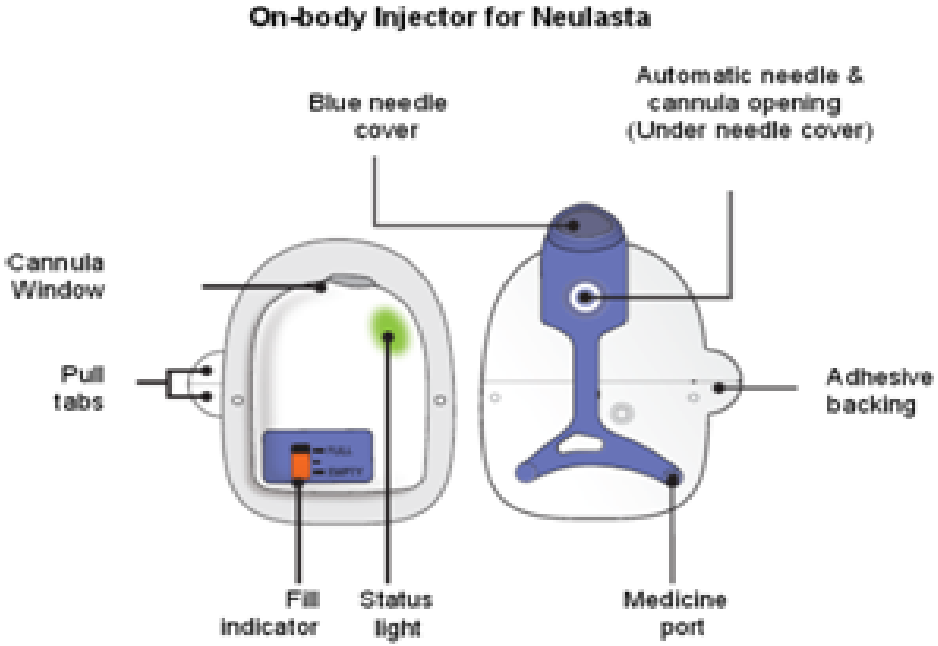
Case Study on Autoinjector Recalls

Autoinjector	Reason for Recall	FDA Date	Manufacturer
Enbrel SureClick Autoinjector	Syringe stalled due to insufficient siliconization; Cracked/broken Prefilled Syringe with sterility concern	01-28-2010	Amgen SHL
Simponi SmartJet Autoinjector	Recalled in US and Germany Market due to insufficient dose delivery	22-Feb-2011	J&J- Centocore & Janssen in Germany
Jext Ardrenaline Autoinjector	Approx. 1/2500 autoinjectors with manufacturing defect of needle bent causing needle to curl up	09-Dec-2013	ALK-Abello UK
Anapen Anaphylactic Injector	Recalled due to a potential problem with slow speed and delivery of adrenaline	24-May-2012	Lincoln Medical Limited Owen-Mumford

Ref: http://www.wsj.com/articles/SB10001424052748704900004576152482593092542 "Johnson & Johnson Recalled around 395 autoinjectors and injection devices from US and Germany due to a potential defect resulting insufficient dosing, 22-Feb-2011

Amgen Neulasta ON-Body Injector 02Mar2015





Amgen marketed new on-body injector for Neulasta to treat neutropenia. With Patient's ease of use at mind, the price is kept on par as the current autoinjector.

Micro-Pump, Patch Pump, and Bolus Injector

Ref: http://www.pharmacircle.com/technology_compare/ , “Subcutaneous and Transdermal Drug Delivery Technologies” 12-Mar-2015

Sandoz Biosimilar “Zarxio” received Approval

Sandoz received FDA approval on 06-Mar-2015 for Zarxio, a biosimilar Filgrastim. Zarxio was granted all indications approved in Amgen’s Neupogen.

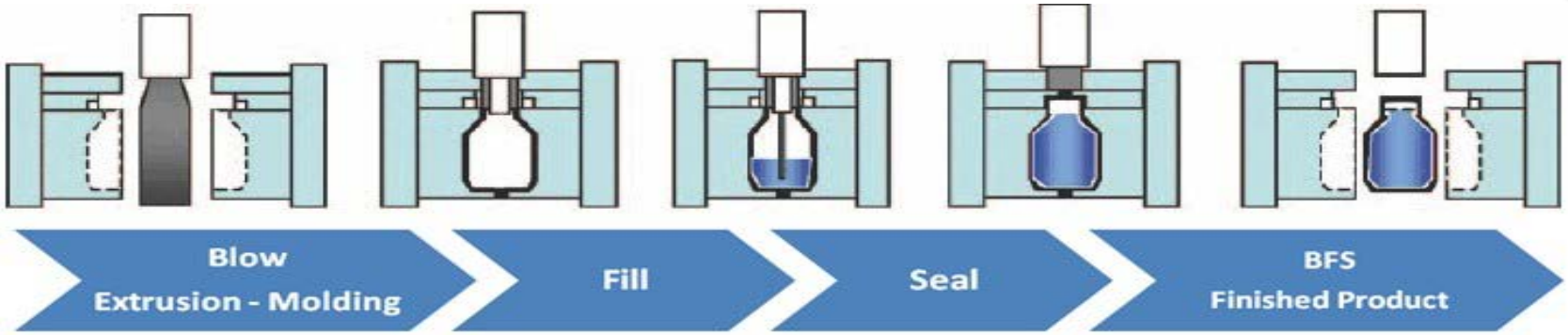
Zarxio is the first biosimilar approved for US by FDA. Sandoz has not disclosed its pricing strategy. Sandoz’s Zarzio has marketed in EU since 2009.

Oral Medication in Competing with Biologics

- **Celgene** has launched it oral psoriasis drug, Otezla, in UK on 25-Feb-2015. It was received the US trial results that Otezla is as effective as Enbrel.
- **Novo Nordisk** has positive Phase II trial results for its oral GLP-1 development. The research path has not been easy because digestive system is harsh to proteins and peptides. In order to meet bioavailability criteria, heavier dose is needed compared to subcutaneous injection dose.
- **Biogen** successfully marketed its new oral medication, Tecfidera, in treating multiple sclerosis.
- **Pfizer**'s oral medication, Xeljanz (Tofacitinib), reaches targets in Phase III psoriasis trial on 20-Mar-2015. It can also treat Rheumatoic Arthritis.
- **Gilead**'s Sovaldi is the first all-oral interferon-free hepatitis C treatment.
- **Oramed**'s oral insulin has the potential to create a new paradigm in treatment of diabetes.

Device Strategy for Manufacturing Biologics in Developing Countries

Blow-Fill-Seal Technology – Cost and Speed



Blow fill seal technology gains momentum lately.

Advantages in shape, cost, and speed attract design possibility.

Extractables, drug compatibility, and protein temperature sensitivity are the **focal points** of biologics manufacturing process.

Vaccines & Biologics for Developing Countries

Biologics and vaccines in developing countries are often sold at manufacturing cost. Blow-fill-seal technology provides an attractive option for a feasible product cost.

Price Transparency in Developing Countries

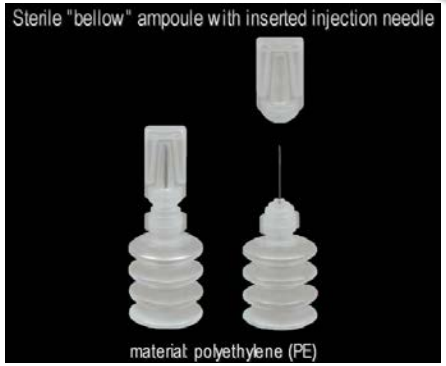
unite for children

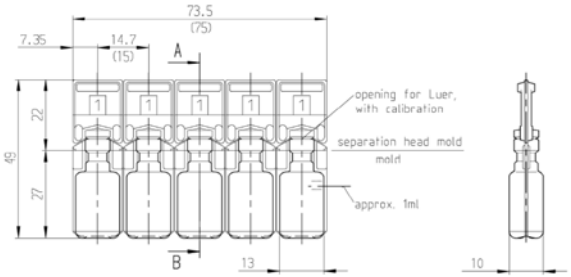
Average Price of Hep-B Vaccine in 2015 is USD $0.20/dose

Presentation	Supplier Name	HepB								
		2001	2002	2003	2004	2005	2006	2007	2008	2009
HepB vaccine in a single dose presentation	Crucell Switzerland AG	$0.5700	$0.5700	$0.5700-$0.6200				$0.2700	$0.2700	$0.2700
	LG Life Sciences Ltd.	$0.6800	$0.8100					$0.4000	$0.4000	$0.4000
	Serum Institute of India Ltd.									$0.2300
	Shantha Biotechnics Ltd.				$0.4100	$0.4100	$0.4100	$0.4100		
HepB vaccine in a two dose presentation	Crucell Switzerland AG	$0.5000	$0.5000	$0.5000				$0.2400	$0.2400	$0.2400
	LG Life Sciences Ltd.				$0.3700	$0.3600	$0.2400	$0.2400		
	Shantha Biotechnics Ltd.									
HepB vaccine in a six dose presentation	Merck & Co., Inc.	$0.5600	$0.5600	$0.5600	$0.6100	$0.6100-$0.6233	$0.6233			
	Shantha Biotechnics Ltd.									
HepB vaccine in a ten dose presentation	Crucell Switzerland AG	$0.3200	$0.3200-$0.3800	$0.3200	$0.3200	$0.3200-$0.3500	$0.3200-$0.3500	$0.2100	$0.2100	$0.2100
	Heber Biotec S.A				$0.4800	$0.4400	$0.2500-$0.3900	$0.2200-$0.2500	$0.2200	$0.2200
	LG Life Sciences Ltd.	$0.3100	$0.3100-$0.3800	$0.3100-$0.3200	$0.2700	$0.2500	$0.1850-$0.2400	$0.1850	$0.1800-$0.1850	$0.1750-$0.1850
	Panacea Biotec Ltd.							$0.2041	$0.2041	$0.2041
	Serum Institute of India Ltd.						$0.2100	$0.2100-$0.2190	$0.2100-$0.2290	$0.2100
	Shantha Biotechnics Ltd.		$0.4700	$0.4700	$0.2300	$0.2300	$0.2300	$0.2300-$0.2370	$0.2300-$0.2370	$0.2300-$0.2380

Ref: UNICEF and GAVI Alliance, "Vaccines and Biologics Pricing Transparency", https://www.unicef.org/supply/index_57476.html

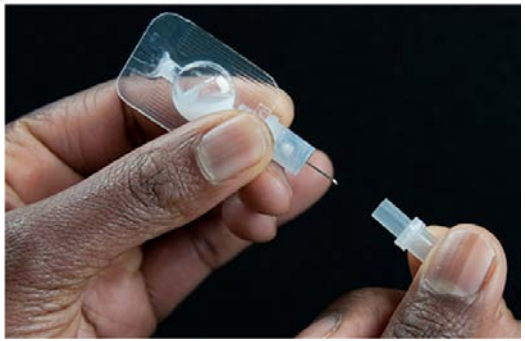
Pre-Filled Devices: Blow-Fill-Seal Technology

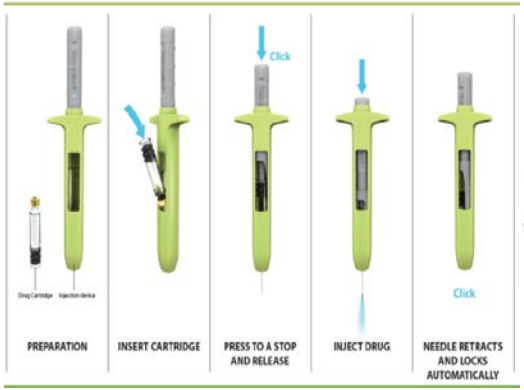




Examples of pre-filled syringes and stoppered vials manufactured by blow-fill-seal

Injectable Devices for Developing Countries

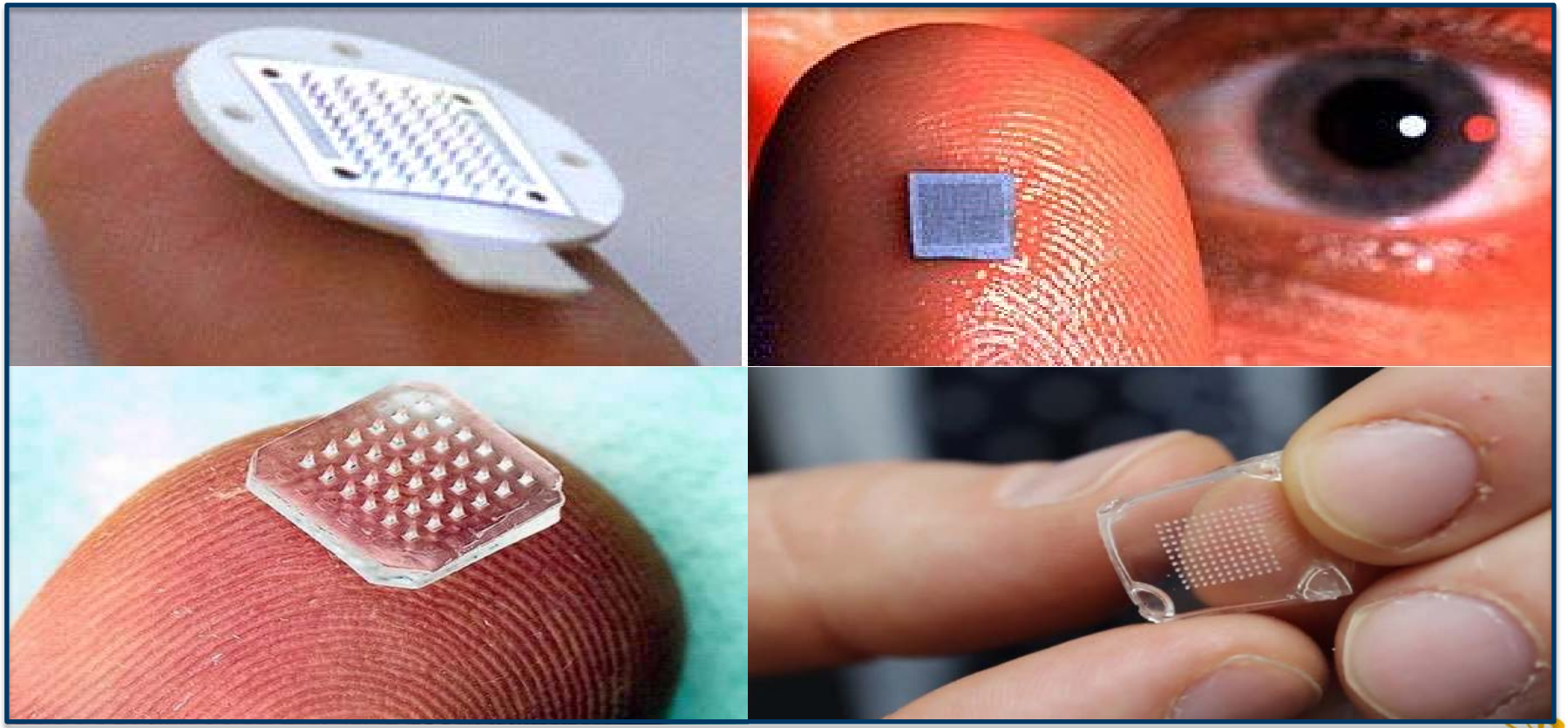




Examples of pre-filled syringes suitable for using in developing countries

Device Strategy for Leveraging Transdermal and Inhalation Delivery

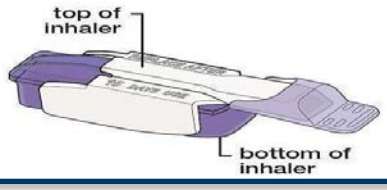
Micro-Needle Technology for Drug Delivery

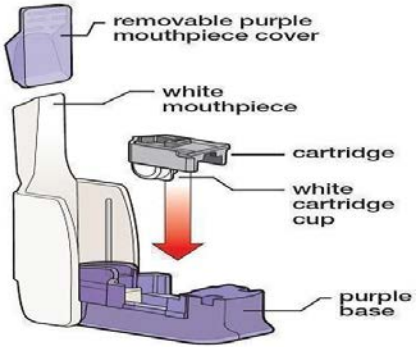


Micro-Needle technology has proceeded with clinical trial for vaccines and biologics development where COGS is estimated ~US$15.

Inhalation and Respiratory Delivery Devices

Afrezza –
Insulin Inhaler





Landmark can be load up to 200 doses.

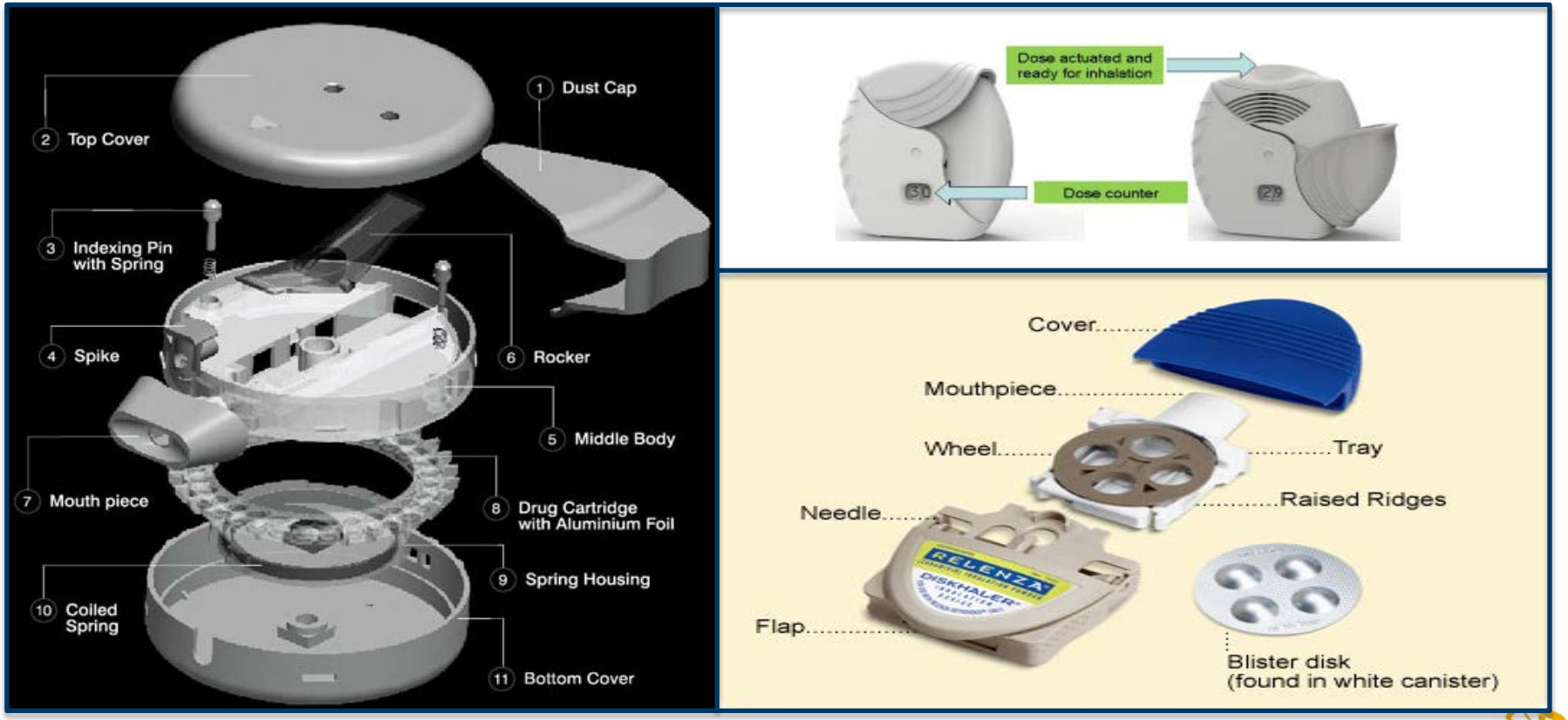
Insulair can be breath activated.

Close up of dose counter

Drug is in Cartridge & blisters.

Decision Resource “COPD 2015” indicates low COPD compliance due to the unmet needs in lacking patient-centric inhalation devices.

Inhalation and Respiratory Delivery Devices



Pharma Circle Review illustrates Dry Powder Inhaler with rotary blister package loaded with multiple doses for patient convenience.

Patient Centric Device Strategy

- Visualized Advantages and Constraints in Pre-Filled Syringes in Designing Cutting Edge Devices
- Adopted Global Design Control Process in Meeting Country Specific Regulatory Expectations
- Led Concurrent Engineering Commercialization Model in Achieving Successful New Product Launch

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