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Science, Policy and Potential of Cell and Gene Therapies

4 December 2019, 12:00-1:30pm
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Avalere Health | An Inovalon Company

"Colman's made their money by the mustard left on the plate"

The traditional model for many medicines is the same as for English Mustard – that lethally hot stuff...

Everyone was treated, and the benefit was critically important to a subset. This applies from vaccines to statins, and even for a baby aspirin

The good news is that prescribing became a form of insurance where the costs were leveraged across a broad population and with affordable costs per dose, especially as generics were issued after a predictable time, most people got access

As such the return on Investment of a blockbuster was based on number of patients rather than cost of drug

Biologics are breaking this model, cell and gene therapy most of all

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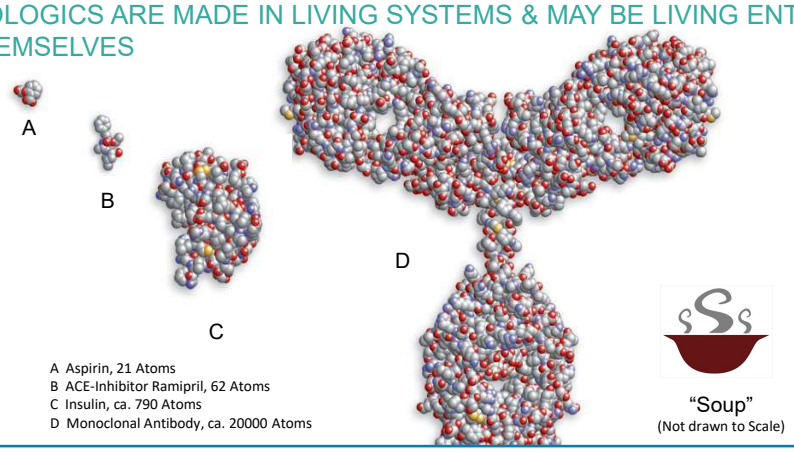
Drugs are usually small, Biologics can be big, Cells are huge

BIOLOGICS ARE MADE IN LIVING SYSTEMS & MAY BE LIVING ENTITIES THEMSELVES



A Aspirin, 21 Atoms
B ACE-Inhibitor Ramipril, 62 Atoms
C Insulin, ca. 790 Atoms
D Monoclonal Antibody, ca. 20000 Atoms

Complexity is a challenge, but specificity determines the economics – historically most therapies targeted a disease not a person

Derived from a slide presented by Brockmeyer Biopharma GmbH
Source: VFA 2010

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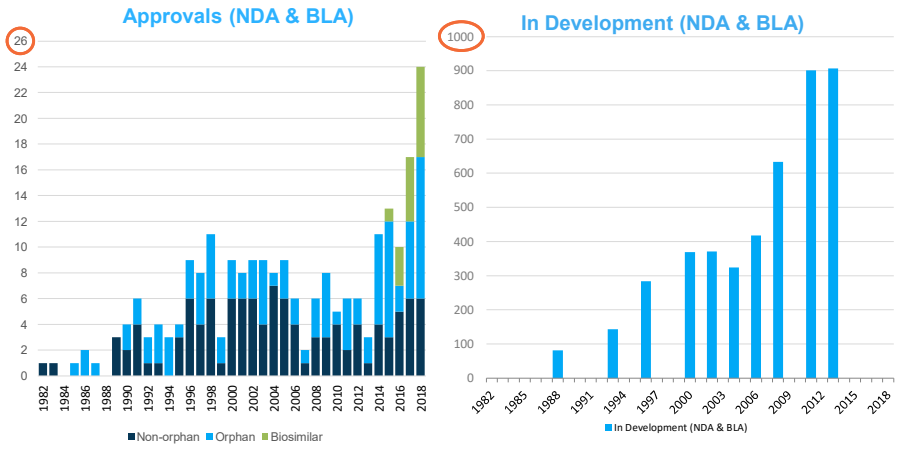
Biologics are an increasing part of the US pipeline



The expansion of specialty continues increasing – this adds to their visibility and cost, C&GT even more so

1. FDA. "Drug and Biologic Approval Reports." Not including vaccines and blood products. Link. (accessed November 2019).
2. PhRMA. "Biotechnology Research Promises to Bolster the Future of Medicine with More Than 900 Medicines and Vaccines in Development." (2013). Link.

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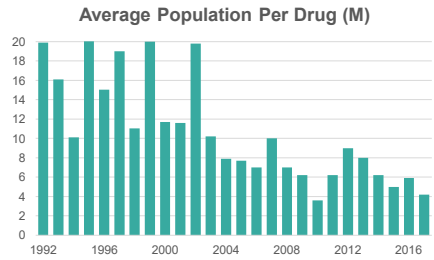
Major Shift from Blockbuster to Specialty to Individuals

EVER MORE DRUGS FOR EVER SMALLER POPULATIONS



"To the individual patient, of course, the improvements are profound. But, as measured against GDP, everyone knows the rate of spending is unsustainable" - Dr. Gottlieb[1]

"Without competition, payers, meaning citizens, will pay more, but we believe an even worse result is that barriers to biosimilars will delay or kill the promise of personalized medicine.

If cheaply mass-produced biosimilars fail in the US, how can we afford to mass-customize tailored treatments?"[2]

Bruce Pyenson, FSA
Principal & Consulting Actuary
Milliman

As we see narrower indications and populations, with R&D per product unchanged, access becomes critical

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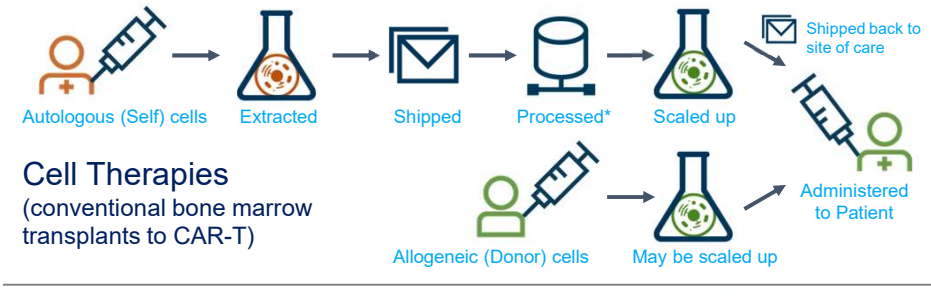
1 BioCentury *A Pathway to Biopharma 3.0* 3Sep18 – quotes from the FDA Commissioner Scott Gottlieb
2 BioCentury *Is Personalized Medicine Doomed Worldwide if Biosimilars Fail in the U.S.?* Here

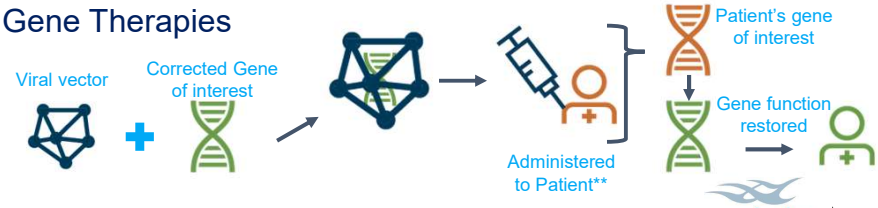
Cell and Gene Therapies (CAGT) in Outline

MANY MECHANISMS, EACH DIRECTED TO RESTORING GENETIC FUNCTION



Cell Therapies
(conventional bone marrow transplants to CAR-T)

Gene Therapies



CAR-T: Chimeric Antigen Receptor T-Cells
* May or may not be genetically modified; ** Directly or through stem cell-based delivery
Cell icon adapted from https://www.shutterstock.com/image-vector/cell-icons-670596565
Sources: https://stemcells.nih.gov/info/2001report/chapter11.htm, https://www.asgct.org/education/different-approaches

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Multiple Regulatory Pathways Are Available for the Approval of Medicines in the US

THE SPONSOR ELECTS THE PATHWAY TO PURSUE, BUT USUALLY DOES SO SUBJECT TO THE ADVICE OF FDA THROUGHOUT DEVELOPMENT

STATUTE	PATHWAY
U.S. Food Drug & Cosmetic Act	New Drug Application (NDA) - 505(b)(1) and 505(b)(2)[1] 510k and PMA[2]
	Generic Drugs Abbreviated NDA (505(j) or ANDA)
U.S Public Health Service Act	Biologic License Application (BLA) or "Standalone" 351(a)
	Biosimilar BLA (351(k))[3] (Can Be Interchangeable)

Cell and Gene Therapies are biologics licensed by the Center for Biologic Evaluation and Research (CBER) at FDA

1. Hatch Waxman 1984 created the 505(b)(2) and 505(j) pathways
2. BPCIA: Biologics Price Competition and Innovation Act is part of the Patient Protection and Affordable Care Act of 2010

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FDA-Approved[1] CAR-T and Gene Therapies

KYMRIAH (tisagenlecleucel)
- Genetically-modified autologous CAR-T
- Patients up to 25 with B-cell precursor ALL; adult patients with r/r large B-cell lymphoma(including DLBCL)
- Approved August 30, 2017
- $373,000 - $475,000[2]

YESCARTA (axicabtagene ciloleucel)
- Genetically modified autologous CAR-T
- Adult patients with r/r/ large B-cell lymphoma (including DLBCL)
- Approved October 18, 2017
- $373,000[2]

LUXTURNA
- AAV vector-based gene therapy for retinal dystrophy
- Subretinal injection into each eye
- Approved December 19, 2017
- $425,000 per eye[3]

ZOLGENSMA (onasemnogene abeparvovec-xioi)
- AAV vector-based gene therapy for patients under 2 with SMA
- Intravenous infusion
- Approved May 24, 2019
- $2,125,000[4]

ALL: acute lymphoblasticleukemia; r/r/: relapsed or refractory; DLBCL: diffuse large B-Cell Lymphoma; AAV: adeno-associated virus; SMA: spinal muscular atrophy
1 Full list of FDA-approved CAGT available at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
2 Source: https://khn.org/news/staggering-prices-slow-insurers-coverage-of-car-t-cancer-therapy/
3 Source: https://www.biopharmadive.com/news/nice-luxturna-gene-therapy-recommendation-novartis-discount/562211/
4 Source: https://www.npr.org/sections/health-shots/2019/05/24/725404168/at-2-125-million-new-gene-therapy-is-the-most-expensive-drug-ever

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Regenerative Medicine Advanced Therapy (RMAT) designation

The 21st Century Cures Act[1] created the (RMAT) designation if:

- The drug is a regenerative medicine therapy, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, except for those regulated solely under Section 361 of the Public Health Service Act and part 1271 of Title 21, Code of Federal Regulations;
- The drug is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; AND
- Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition

Designation enables access to expedited approval pathways (priority review, accelerated approval, etc.)

FDA has over 800 active INDs on file for Cell and Gene Therapies[2]
High touch and resource intensive for FDA too

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1. 21st Century Cures Act here
2. *Statement from Scott Gottlieb on new policies to advance development of safe and effective cell and gene therapies* 15Jan19 here

FDA has Many Levers to Accelerate Review Beyond Standard/Priority Reviews

1	2	3
Fast Track	**Breakthrough Therapy**	**Regenerative Medicine Advanced Therapy (RMAT)**
• Facilitate development and review of drugs to treat serious conditions, fill unmet medical need • Includes diseases with no available therapies • Requested by company	• Expedite development and review of drugs with preliminary clinical evidence demonstrating "substantial" improvement over available therapy • Endpoints include irreversible morbidity or mortality (IMM)	• 21st Century Cures Act § 3033 designates includes cell and gene therapies as RMAT eligible if: • Intended to treat, modify, reverse, or cure serious or life-threatening disease or condition, and if • Preliminary evidence suggests it can address unmet medical needs thereof • Designation enables access to expedited approval pathways (priority review, accelerated approval, etc.)

**Based on FDA's interpretation of Section 3033
Sources: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation, 21st Century Cures Act Section 3033.

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Cell and Gene Therapy Pipeline with Expedited Designation

Manufacturer	Name and Therapeutic Area	FDA Expedited Program
Prevail Therapeutics	PR001 – Parkinson's disease	FDA Fast Track Designation
National Cancer Institute	CD22-CAR – Lymphoma (CAR-T therapy)	FDA Breakthrough Designation
UniQure	AMT-130 – Huntington's Disease	FDA Fast Track Designation
Abeona Therapeutics	ABO202 – Infantile Batten Disease	FDA Fast Track Designation
Fibrocell Technologies	FCX-007 – Epidermolysis Bullosa Dystrophica, Recessive	FDA RMAT Designation
Orchard Therapeutics	OTL-103 – Wiskott-Aldich Syndrome	FDA RMAT Designation
Magenta Therapeutics	MGTA-456 – Inherited Metabolic Disorders	FDA RMAT Designation

FDA expects they will receive over 200 INDs per year for Cell and Gene Therapies by 2020 and approve10-20 per year by 2025

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1.Statement from Scott Gottlieb on new policies to advance development of safe and effective cell and gene therapies 15Jan19 here

We Look Forward to Your Questions

Avalere is a vibrant community of innovative thinkers dedicated to solving the challenges of the healthcare system. We deliver a comprehensive perspective, compelling substance, and creative solutions to help you make better business decisions. As an Inovalon company, we prize insights and strategies driven by robust data to achieve meaningful results.

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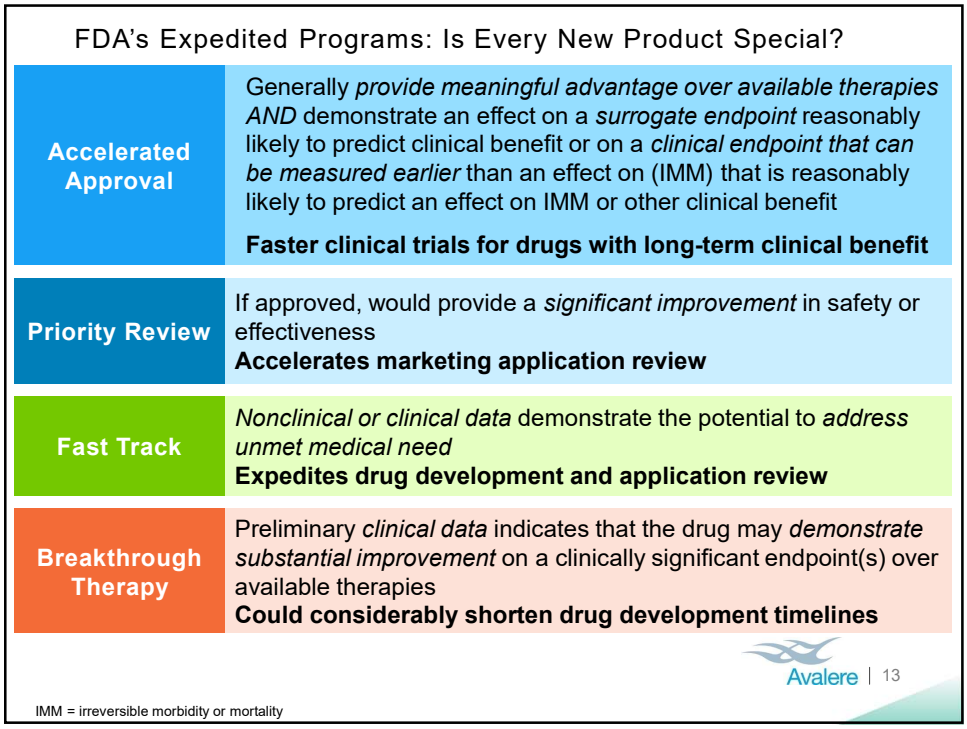
FDA's Expedited Programs: Is Every New Product Special?
Accelerated Approval
Generally provide meaningful advantage over available therapies AND demonstrate an effect on a surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit
Faster clinical trials for drugs with long-term clinical benefit
Priority Review
If approved, would provide a significant improvement in safety or effectiveness
Accelerates marketing application review
Fast Track
Nonclinical or clinical data demonstrate the potential to address unmet medical need
Expedites drug development and application review
Breakthrough Therapy
Preliminary clinical data indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
Could considerably shorten drug development timelines
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IMM = irreversible morbidity or mortality