The 6th Annual
Dermatology Summit
an Advancing Innovation in Dermatology conference

Rare Dermatology

Orphan Disease Drug Development Opportunities & Challenges

Greg Licholai, MD

Yale University

6 January 2019

LUX ET VERITAS

Disclosures and affiliations

- Adjunct faculty at Yale University School of Management & Co-director Yale Center for Digital Health
- Chief Medical Officer & Medical Information Officer at PRA Health Sciences
- Former President and Chief Medical Officer at Castle Creek Pharmaceuticals

Today's themes

1. Rare dermatological diseases are underrepresented in drug development and pharmaceutical company sponsored trials
2. Mismatch exists despite significant success in R&D and investment in other areas of rare disease research
3. Only about one tenth of non-oncology rare dermatological conditions are being clinically investigated, mainly by academic centers
4. Substantive, important research into mechanism and novel approaches in dermatology is taking place mostly in academia

Introduction: Why should we care about dermatology rare diseases?

Rare diseases are not so rare

Significant dermatology unmet needs persist

Orphan model has been successful

Multiple high impact derm opportunities

How many people are affected by rare disease in the U.S.?

There are approximately **7,000** different types of rare diseases and disorders.

Approximately **30 million people** in the U.S. are living with a rare disease – That's equivalent to **1 in 10 Americans**.

80% of all rare disease patients are affected by approximately 350 rare diseases.

Source: RARE Diseases: Facts and Statistics. Global Genes. Retrieved from https://globalgenes.org/rare-diseases-facts-statistics/

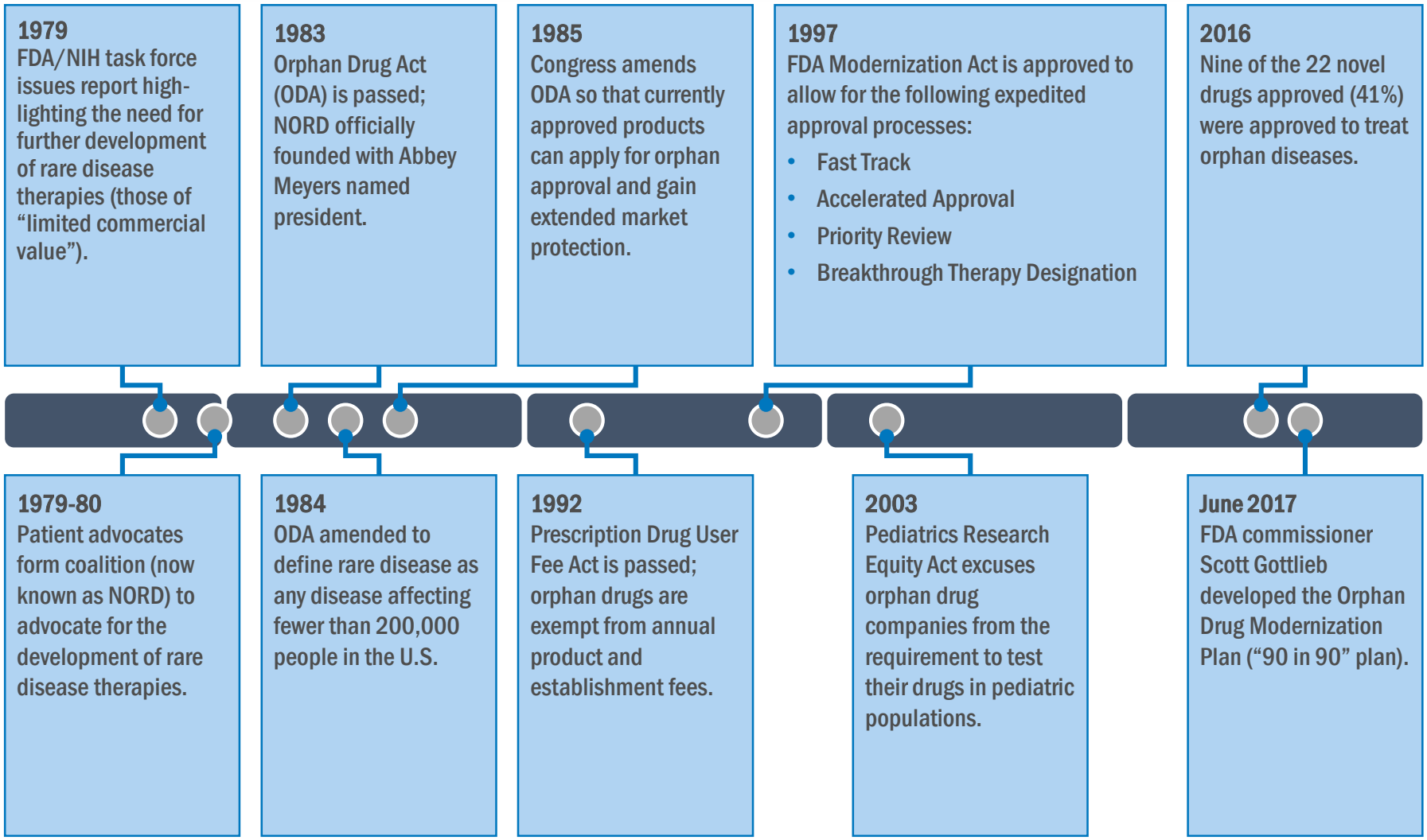
Some history and definitions

What led to the Orphan Drug Act (ODA)?

- Need for **financial incentives for pharmaceutical companies** to develop promising orphan drugs.
- Companies concerned about revenue generation compared to cost of orphan drug R&D due to small patient populations.
  - Average cost of drug research and development: $1 to 2 billion

Source: Regulatory Information: Orphan Drug Act. (2013). U.S. Food and Drug Administration

History of events in rare disease



Source: Major Milestones: Driving Progress on Behalf of Rare Disease Patients. NORD.
Public Law 99-91 - Aug. 15, 1985. An Act. To amend the orphan drug provisions of the Federal Food, Drug, and Cosmetic Act and related laws. Public Law 99-91, 99th Congress.

Incentives offered by Orphan Drug designation

- **7 years' market exclusivity**
- Tax credits for 50% of clinical trial costs
- PDUFA fee exemption
  - Requiring clinical data – $2,335,200
  - Not requiring clinical data – $1,167,600
  - Supplements requiring clinical data – $1,167,600
- Federal grants to help fund clinical trials
- Annual grant funding to defray the costs of qualified clinical testing expenses ($14 million total for 2008)

Source: Hyde R, Dobrovolny D. Orphan Drug Pricing and Payer Management in the United States: Are We Approaching the Tipping Point? *Am Health Drug Benefits.* 2010 Jan-Feb; 3(1): 15–23.

Growth drivers rare disease development

Pharma shift from “blockbusters” to “niche busters”

- Large pharma companies see many opportunities in orphan drug space
- Drivers of orphan drug R&D include:
  - Patent expirations of products for large patient populations
  - Global healthcare reform increasing competition
  - Growth of generic products
  - Increase in biosimilars
  - Increased clinical trial costs

Source: Kumar Kakkar A, Dahiya N. The evolving drug development landscape: from blockbusters to niche busters in the orphan drug space. Drug Dev Res. 2014 Jun;75(4):231-4. doi: 10.1002/ddr.21176.

Common wisdom*

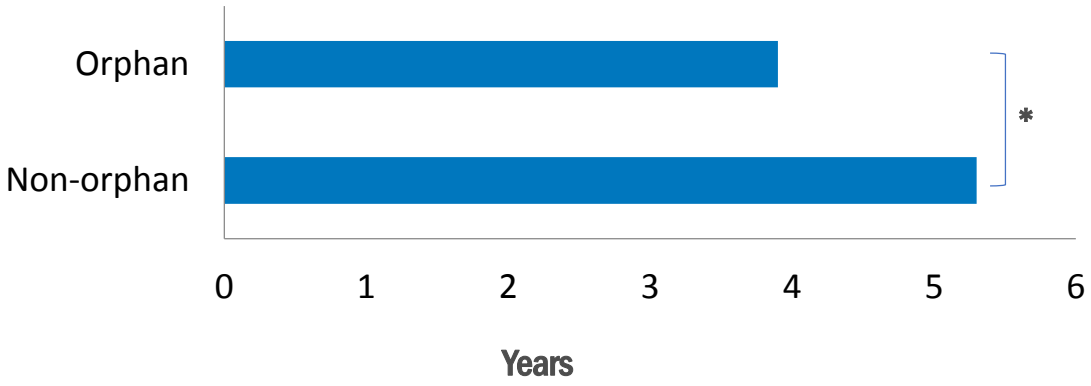
Orphan disease drug development is …

* among pharmaceutical executives

R&D driver: somewhat faster

Timelines

Phase II to launch clinical development time

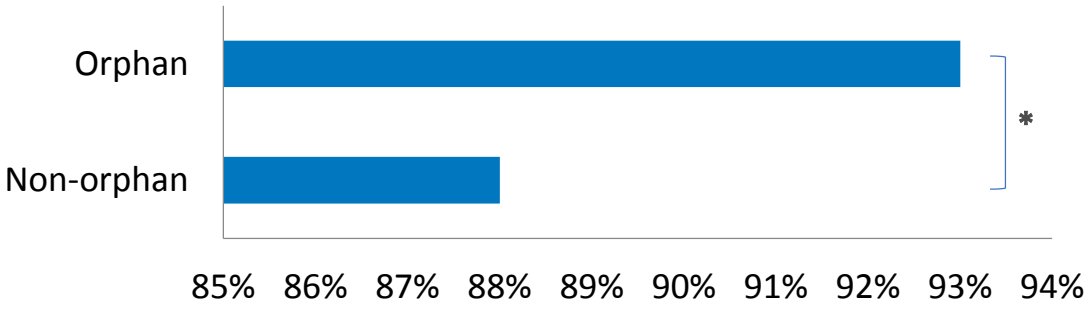


Costs

- Phase III development of orphan drugs cost about 25% less compared to non-orphan drugs.

Risk

Probability of regulatory success



Flexibility

- Protocol assistance guidance
- ODA allows for flexibility and exercise of scientific judgment in kinds and quantity of data required for a particular drug for an indication.

Source: Meekings, Kiran M.; Williams, Corey S.M.; Arrowsmith, John E. Orphan drug development: an economically viable strategy for biopharma R&D. (2012). Drug Discovery Today

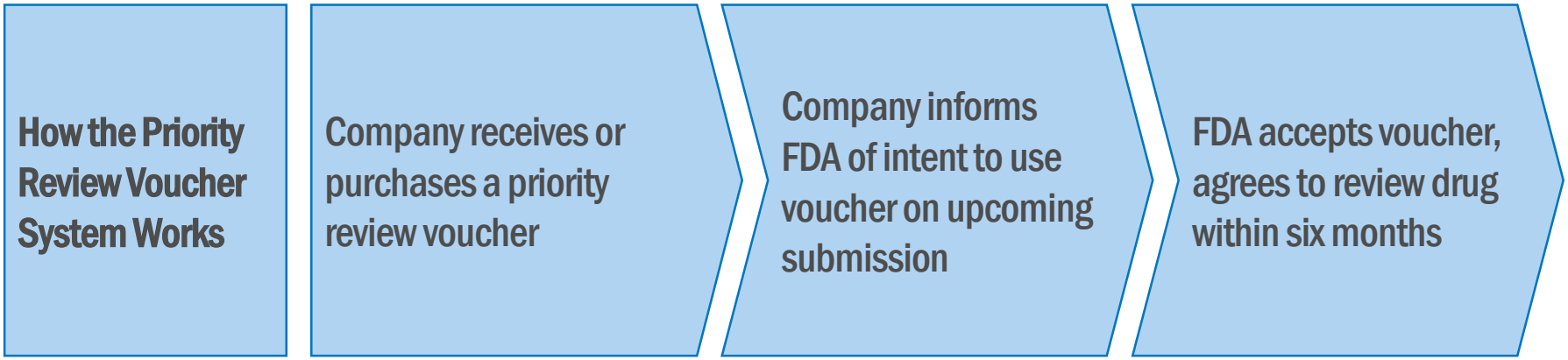
R&D drivers: somewhat less strict evidence

CDER NME/NBE Approvals 2009-2013			
	All	Rare	Common
≥2 adequate and well-controlled trials controlled trials	58%	33%	70%
1 Trial + Supporting Evidence	38%	60%	28%
Other	4%	7%	2%
Total approvals	159	52	107

Source: Pariser, Anne. (2014). *Rare Disease and Clinical Trials.* U.S. Food and Drug Administration.

Rare Pediatric Review Voucher

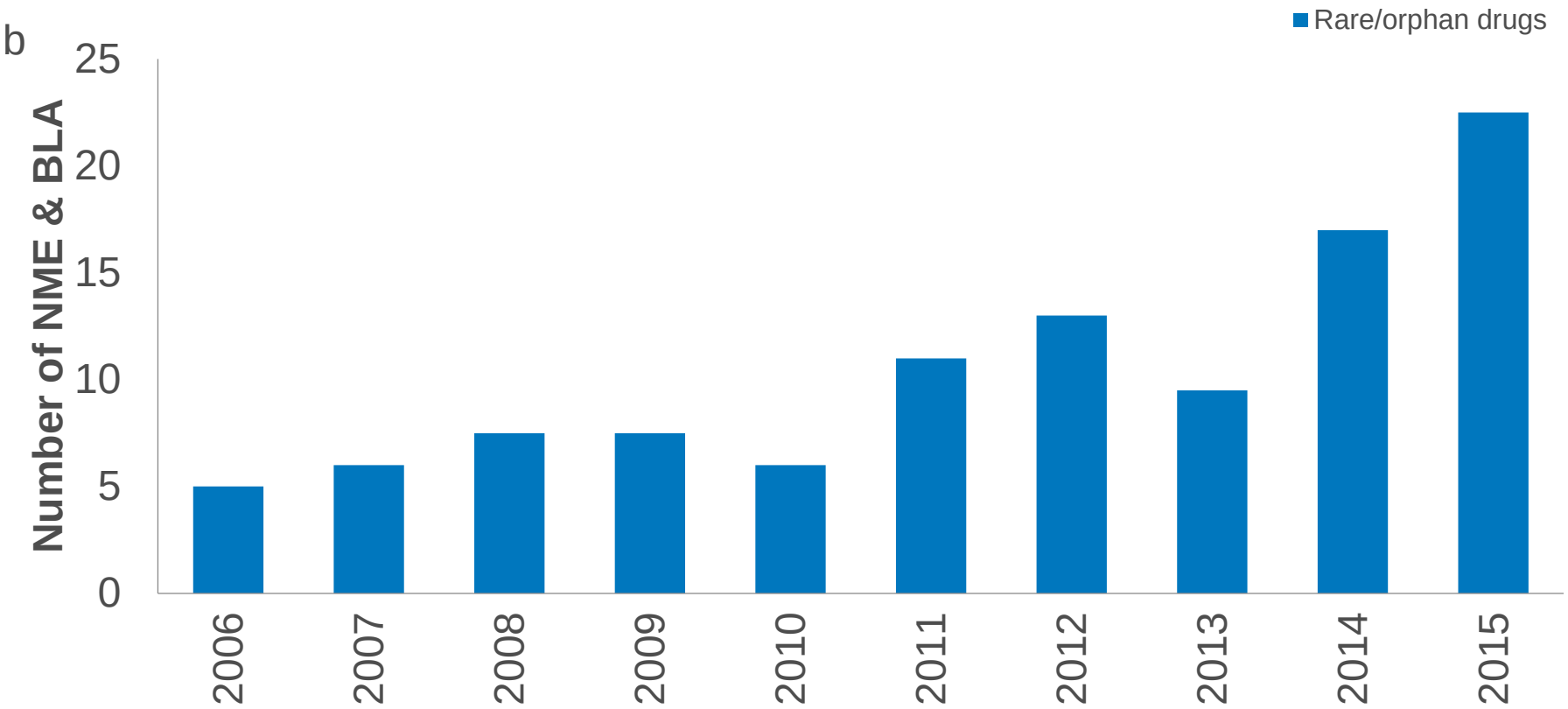
- Rare Pediatric Review Voucher
  - Voucher can be redeemed by recipient or sold to another company.
  - For example: BioMarin's voucher (first ever to be sold) was purchased for $67M.
  - In August 2015, AbbVie paid $350M for a voucher originally awarded to United Therapeutics.



Source: Gaffney, Alexander; Mezher, Michael; Brennan, Zachary. (2017). Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers. Regulatory Affairs Professionals Society.

Increase in rare disease approvals

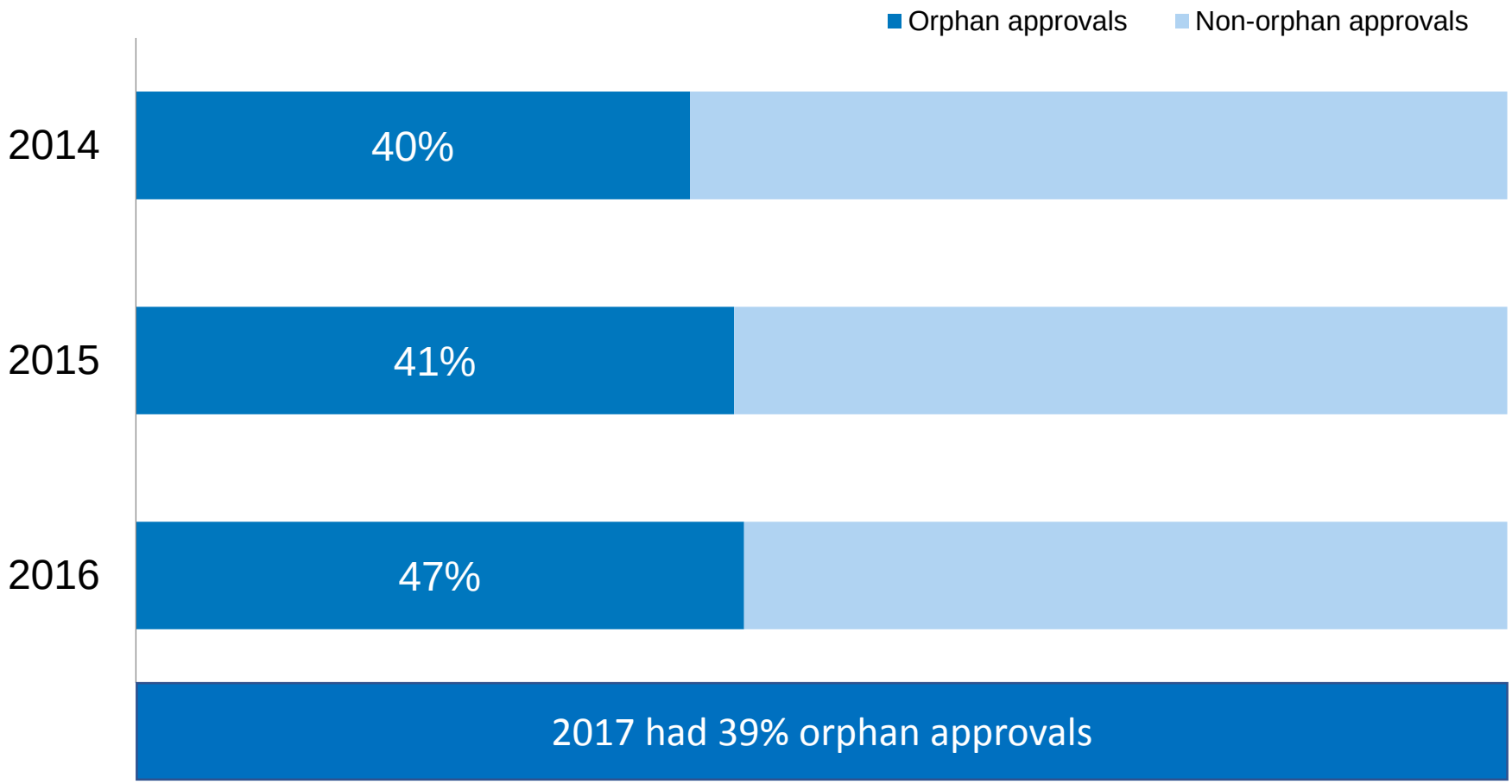
Number of new molecular entities (NMEs) and Biologics License Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) from 2006 to 2015



Source: Data are from the FDA website

Rare disease approvals are nearly half of all new drugs

- Before 1983, fewer than 10 treatments for rare diseases were approved.
- After 1983, FDA has approved **more than 500** orphan drugs.



Source: Medicines in Development for Rare Diseases: A Report on Orphan Drugs in the Pipeline. (2016). PhRMA.

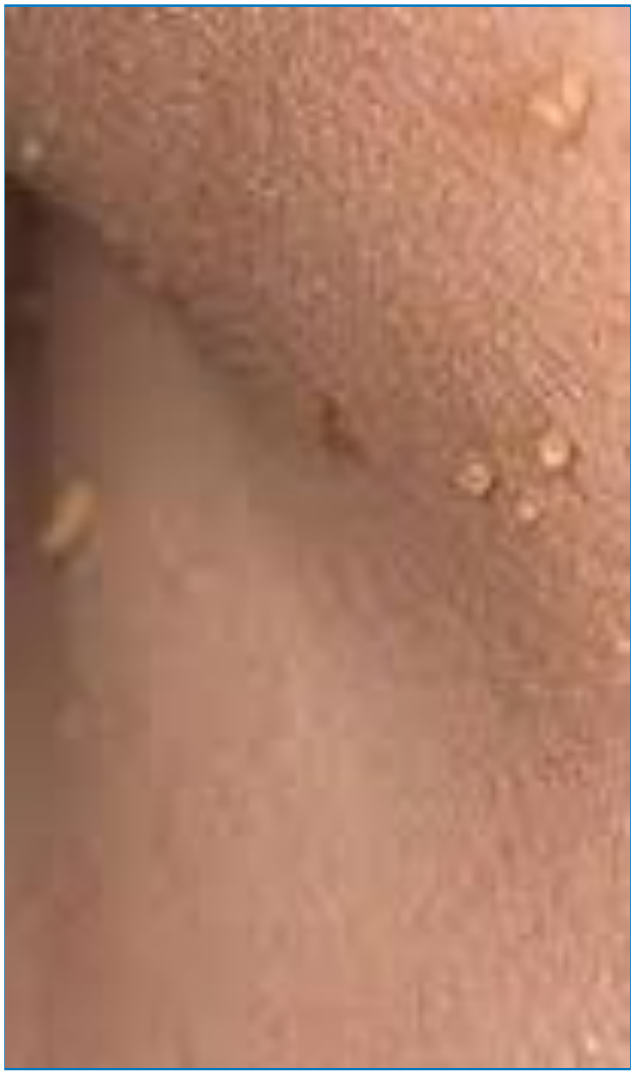
Rare dermatology development status

Long list of rare skin disease …

NIH's genetic and rare disease information center lists:

597

dermatologic diseases or genetic disorders with cutaneous manifestation



Source: NIH genetic and rare disease website; genodermatoses network website

… relatively few rare derm products in development …

There are over 560 medicines in development for all rare diseases but few in derm

Designation	Product	Status
Behcet's	Otezla (apremilast)	Phase III
Melanoma	Binimetinib	Phase III
Melanoma	Cavatak	Phase II
Melanoma	LN-144	Phase II
Erythropoietic porphyria	Scenesse (afamelanotide)	Phase III
Pernphiqus vulgaris	Rituxan (rituximab)	Phase II
Epidermolysis bullosa	Diacerin	Phase II/III
Congenital ichthyoses	PAT-001 (isotretinoin)	Phase I
Pachyonychia congenita	TD-101	Phase II
Diffuse systemic sclerosis	ARG 201	Phase II
Systemic sclerosis	Adempas (riociguat))	Phase II
Systemic sclerosis	Actemra (tocilizumab)	Phase III
Systemic sclerosis	Resunab (ajulemic acid)	Phase II

Source: Pharma medicines in development for rare disease (2016)

… and few orphan drugs approved in dermatology

Skin diseases with FDA approved therapies:

- Squamous Cell Carcinoma of Head and Neck: Erbitux (cetuximab)
- Melanoma: Taflinar (dabrafenib)
- Melanoma: Opdivo (nivolumab)
- Melanoma: Imlygic (tamilogene)
- Melanoma: Mekinist (trametinib)
- Erythema nodosum leprosum: Tholomid (Thalomid)
- Dermatofibrosarcoma protuberans: Gleevec (imatinib)
- Acne Rosacea: Metronidizole (Flagyl)
- Chronic granulomatous disease: Actimmune (interferon gamma-1b)
- Chronic Infantile Neurological Cutaneous Articular syndrome: Arcalyst (rilonacept) and Kineret (anakinra)
- Merkel cell carcinoma: Bavencio (avelumab)
- Behcet's disease: Humira (adalimumab)
- Pemphigus: Rituxan (Rituximab)

Source: Skin Diseases. Genetic and Rare Diseases Information Center (GARD); FDA website

Rare dermatology development challenges

FDA considerations in R&D for orphan drugs

Clinical development based on strict guidance and expectations

- Regulatory agencies approve drugs based on how patients ***feel***, ***function*** **or** ***survive***
- Requirements are based on clinical or surrogate evidence of substantial benefits that outweigh risks of therapy
- Treatments must be deemed to be **clinically meaningful**, which can be difficult to reach expert consensus

Need for consensus on relevant clinical endpoints

Challenges

- Adequate or relevant clinical **endpoints** have not been widely adopted for approval in rare diseases
- Substantial patient to patient **variability** with small populations lack statistical significance
- Regulators tend to rely on familiar scales and instruments
- Instruments not validated with accompanying clinical trials
- Regulators expect visual assessment, not photographic record

Regulatory standards

- Direct outcome measures of symptoms, functional status on survival (not signs cardinal signs of disease)
  - Examples: PFS, PGA, PRO, QoL, Complete wound closure

Clinical standards

- Based on clinical practice, expert assessment and practical approach to patients with rare diseases
  - Examples: EBDASI, IscorEB
- Assumption of clinical meaningfulness

Need for companion diagnostics and biological markers

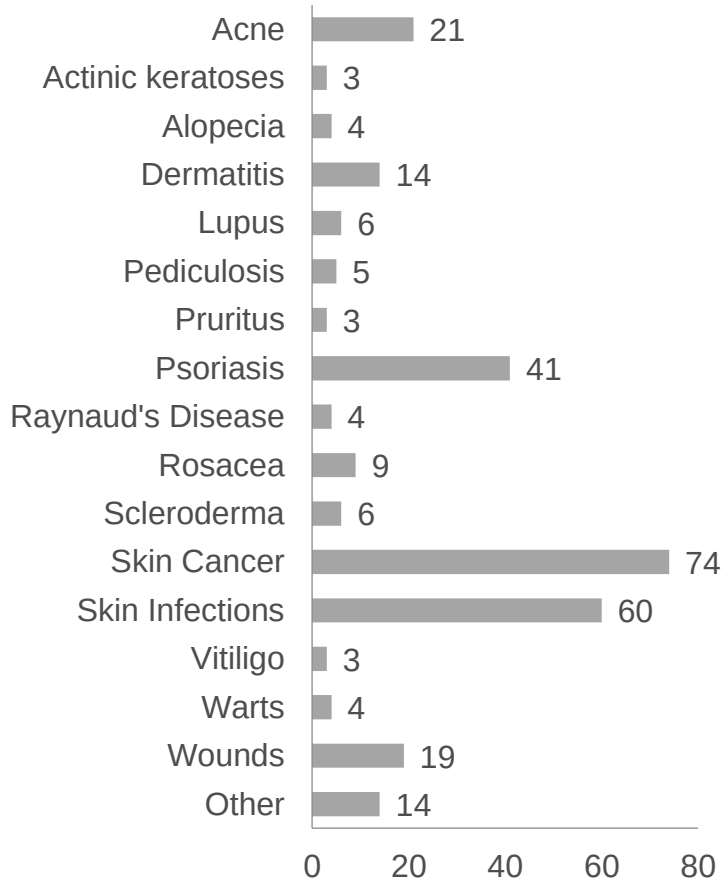
- Limited clinical use of **biological or laboratory markers** based on disease mechanism of action, including potential biomarkers that correlate to extent and progress of disease
- Need defined biomarkers to determine molecular targets and to develop optimal therapies; may help facilitate clinical trial design/measurements

Emerging landscape in dermatology rare diseases

Emerging landscape for targeted therapies in dermatology

- **Drivers changing dermatology drug development landscape**
  - Understanding underlying defects
  - Biological pathways
  - Identification of disease genes via NGS
- **Techniques for innovative medicine**
  - Gene modification strategies →siRNA, mRNA, gene transfer
  - Gene editing → TALENS, CRISPR/Cas9
  - Protein therapy
  - Cell therapy
- **Approaches**
  - Development of new therapies
  - Repurposing existing therapies

Medicines in development for skin diseases

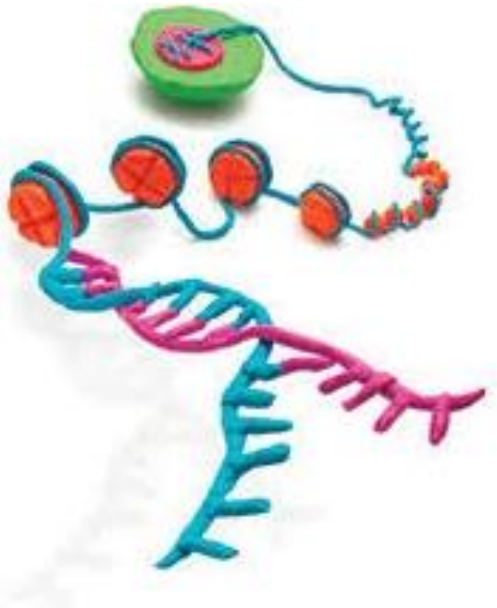


Source: Some medicines are listed in more than one category
Titeux M, Izmiryan A, Hovnanian A. The Molecular Revolution in Cutaneous Biology: Emerging Landscape in Genomic Dermatology: New Mechanistic Ideas, Gene Editing, and Therapeutic Breakthroughs. J Invest Dermatol. 2017 May;137(5):e123-e129. doi: 10.1016/j.jid.2016.08.038.
Biopharmaceutical Research Companies are Developing Nearly 300 Medicines to Treat Diseases of the Skin. Medicines for Development in Skin Diseases 2011 Report. PhRMA.

New therapeutic targets in dermatology…

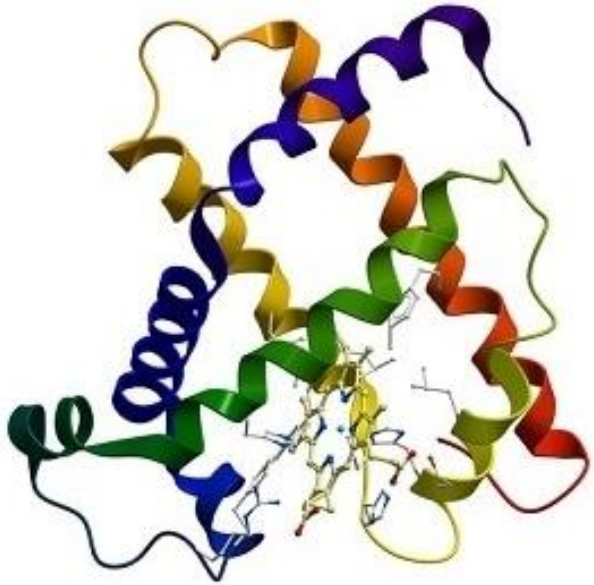
Functional genomics & epigenetics

Advanced ability to detect genetic disease signatures



Integrated proteomics

Better understanding of protein behavior, post-translational modifications, protein-protein modification, based on advanced techniques in mass spectrometry



Source: Titeux M, Izmiryan A, Hovnanian A. The Molecular Revolution in Cutaneous Biology: Emerging Landscape in Genomic Dermatology: New Mechanistic Ideas, Gene Editing, and Therapeutic Breakthroughs. *J Invest Dermatol*. 2017 May;137(5):e123-e129. doi: 10.1016/j.jid.2016.08.038.

…Leading to new therapies in early stage development

Gene Therapy	• Ex-vivo gene therapy for **JEB** and **RDEB** • Transplantation of **genetically modified epithelial sheets** made from autologous keratinocytes corrected with B3 chain of laminin 332 or COL7A1 cDNA	
Cell Therapies	• Mesenchymal stromal cells (MSC), induced pluripotent stem cells (iPSC), for **RDEB** • Bone marrow-derived transplantation, Mesenchymal stromal cells (MSC), induced pluripotent stem cells (iPSC), revertant cells for **dyskeratosis congenita**	
Biological Therapies	• Exon skipping, anti-sense for **RDEB** • siRNA intra-lesion injection for **pachyonychia congenita**	
Protein Replacement	• Recombinant ectodysplasin protein for **anhidrotic ectodermal dysplasia** • Recombinant type VII collagen for **RDEB** • Recombinant trans-glutaminase 1 for **lamellar Ichthyosis**	

Source: Titeux M, Izmiryan A, Hovnanian A. The Molecular Revolution in Cutaneous Biology: Emerging Landscape in Genomic Dermatology: New Mechanistic Ideas, Gene Editing, and Therapeutic Breakthroughs. J Invest Dermatol. 2017 May;137(5):e123-e129. doi: 10.1016/j.jid.2016.08.038.

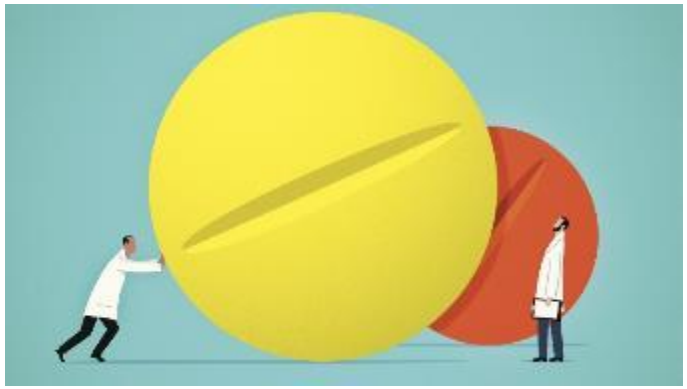
Considerations in drug pricing for orphan diseases

Value proposition must be clearly defined

- Burden of disease
- Clinical impact
- Cost effectiveness
- Medical solution

Three pricing models:

- **Value-added** pricing is based on replacement or enhancement of current treatments in the same category.
- **Cost plus** pricing based on its development costs and return on investment before new or generic drugs become available.
- **Comparable value** pricing compares the characteristics or benefits of drugs in different clinical categories.



Source: Philippidis, Alex. (2014). Genetic Engineering & Biotechnology News.

Summary

Where were we?

- Before ODA, fewer than 10 treatments for rare diseases were approved. Now FDA has approved more than 500 orphan drugs.

Where are we now?

- Incentives being created to drive R&D of orphan drugs: fast track, priority review, BTD, accelerated approval, tax credits, etc.

Where are we going?

- About 95% of rare diseases still lack FDA approved drug treatments.
- Need for more studies on natural history and underlying biological processes that may lead to new promising therapies in dermatology

Acknowledgements

- Afton Chavez, MD, Department of Dermatology, Alpert Medical School of Brown University
- Dedee F. Murrell, MA, BMBCh, MD, FACD, FRCP(Edin), Department of Dermatology, St George Hospital, Sydney and the University of New South Wales, Australia