Rare Dermatology
Orphan Disease Drug Development Opportunities & Challenges

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Disclosures and affiliations

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• 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 dermat 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.

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

1979 FDA/NIH task force issues report highlighting the need for further development of rare disease therapies (those of “limited commercial value”).

1979-80 Patient advocates form coalition (now known as NORD) to advocate for the development of rare disease therapies.

1983 Orphan Drug Act (ODA) is passed; NORD officially founded with Abbey Meyers named president.

1984 ODA amended to define rare disease as any disease affecting fewer than 200,000 people in the U.S.

1985 Congress amends ODA so that currently approved products can apply for orphan approval and gain extended market protection.

1997 FDA Modernization Act is approved to allow for the following expedited approval processes:
- Fast Track
- Accelerated Approval
- Priority Review
- Breakthrough Therapy Designation

2016 Nine of the 22 novel drugs approved (41%) were approved to treat orphan diseases.

1983 Orphan Drug Act (ODA) is passed; NORD officially founded with Abbey Meyers named president.

1984 ODA amended to define rare disease as any disease affecting fewer than 200,000 people in the U.S.

1992 Prescription Drug User Fee Act is passed; orphan drugs are exempt from annual product and establishment fees.

2003 Pediatrics Research Equity Act excuses orphan drug companies from the requirement to test their drugs in pediatric populations.

June 2017 FDA commissioner Scott Gottlieb developed the Orphan Drug Modernization Plan (“90 in 90” plan).

Source: Major Milestones: Driving Progress on Behalf of Rare Disease Patients. NORD.

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)

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:
  o Patent expirations of products for large patient populations
  o Global healthcare reform increasing competition
  o Growth of generic products
  o Increase in biosimilars
  o Increased clinical trial costs

Orphan disease drug development is …

Faster

Cheaper

Easier

* among pharmaceutical executives
**R&D driver: somewhat faster**

### Timelines

**Phase II to launch clinical development time**

- **Orphan**
- **Non-orphan**

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<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Orphan</td>
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<tr>
<td>Non-orphan</td>
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### Costs

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

### Risk

**Probability of regulatory success**

- **Orphan**
- **Non-orphan**

<table>
<thead>
<tr>
<th>Probability</th>
<th>85%</th>
<th>86%</th>
<th>87%</th>
<th>88%</th>
<th>89%</th>
<th>90%</th>
<th>91%</th>
<th>92%</th>
<th>93%</th>
<th>94%</th>
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<tbody>
<tr>
<td>Orphan</td>
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<tr>
<td>Non-orphan</td>
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### 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.

### CDER NME/NBE Approvals 2009-2013

<table>
<thead>
<tr>
<th>Requirement</th>
<th>All</th>
<th>Rare</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 adequate and well-controlled trialsandez controlled trials</td>
<td>58%</td>
<td>33%</td>
<td>70%</td>
</tr>
<tr>
<td>1 Trial + Supporting Evidence</td>
<td>38%</td>
<td>60%</td>
<td>28%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Total approvals</td>
<td>159</td>
<td>52</td>
<td>107</td>
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</tbody>
</table>

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

**How the Priority Review Voucher System Works**

1. Company receives or purchases a priority review voucher
2. Company informs FDA of intent to use voucher on upcoming submission
3. FDA accepts voucher, agrees to review drug within six months

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.

2014: 40% orphan approvals
2015: 41% orphan approvals
2016: 47% orphan approvals

2017 had 39% orphan approvals

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

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

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

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**Medicines in development for skin diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Count</th>
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<tbody>
<tr>
<td>Acne</td>
<td>21</td>
</tr>
<tr>
<td>Actinic keratoses</td>
<td>3</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>14</td>
</tr>
<tr>
<td>Lupus</td>
<td>6</td>
</tr>
<tr>
<td>Pediculosis</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>41</td>
</tr>
<tr>
<td>Raynaud’s Disease</td>
<td>4</td>
</tr>
<tr>
<td>Rosacea</td>
<td>9</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>6</td>
</tr>
<tr>
<td>Skin Cancer</td>
<td>74</td>
</tr>
<tr>
<td>Skin Infections</td>
<td>60</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>3</td>
</tr>
<tr>
<td>Warts</td>
<td>4</td>
</tr>
<tr>
<td>Wounds</td>
<td>19</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
</tr>
</tbody>
</table>

Source: Some medicines are listed in more than one category

Biopharmaceutical Research Companies are Developing Nearly 300 Medicines to Treat Diseases of the Skin. Medicines for Development in Skin Diseases 2011 Report. PhRMA.
<table>
<thead>
<tr>
<th>New therapeutic targets in dermatology…</th>
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<tbody>
<tr>
<td><strong>Functional genomics &amp; epigenetics</strong></td>
</tr>
<tr>
<td>Advanced ability to detect genetic disease signatures</td>
</tr>
<tr>
<td><strong>Integrated proteomics</strong></td>
</tr>
<tr>
<td>Better understanding of protein behavior, post-translational modifications, protein-protein modification, based on advanced techniques in mass spectrometry</td>
</tr>
</tbody>
</table>

...Leading to new therapies in early stage development

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

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.

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
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