Dermatology Therapeutics Area
Working Group

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Overview

- Background
- Identified Areas of Therapeutic Need with Committee Recommendations
Pediatric Dermatology

Background

- High Demand
- Small Workforce
- Ambulatory-Based
- Medical > Procedural
- Limited Evidence-Basis
- Few FDA-Approved Treatments
Skin-Related Disease in Children

- Up to 30% of pediatric primary care visits
- ER/hospital consultation > direct hospital admissions
- Limited OR utilization
- The majority without FDA-approved treatment
Workforce

- Society for Pediatric Dermatology (www.pedsderm.net)
  - 1,000 members
  - 45 states
  - 37 countries

<table>
<thead>
<tr>
<th>Year</th>
<th># (%) Completing a Fellowship</th>
<th># (%) Passing the Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>24 (25)</td>
<td>90 (96)</td>
</tr>
<tr>
<td>2006</td>
<td>3 (10)</td>
<td>41 (93)</td>
</tr>
<tr>
<td>2008</td>
<td>18 (58)</td>
<td>31 (91)</td>
</tr>
<tr>
<td>2010*</td>
<td>24 (63)</td>
<td>33 (91)</td>
</tr>
<tr>
<td>2012</td>
<td>43 candidates (95)</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>~200 (80)</td>
<td>~235 (94%)**</td>
</tr>
</tbody>
</table>

*Last year for grandfather eligibility
**~60% qualified by meeting grandfather criteria.
# Workforce Shortage: Comparative Supply

<table>
<thead>
<tr>
<th>US Specialty</th>
<th>Per Capita Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologists</td>
<td>30,000 people</td>
</tr>
<tr>
<td>Pediatricians</td>
<td>1,500 people &lt;18</td>
</tr>
<tr>
<td>Pediatric Rheumatologists</td>
<td>240,000 people &lt;18</td>
</tr>
<tr>
<td>Pediatric Dermatologists</td>
<td>385,000 people &lt;18</td>
</tr>
</tbody>
</table>
Workforce Shortage: Comparative Density

Rheumatologists

0:1:150,000

Dermatologists

0:1:114,000

Pediatric Subspecialist-to-Child Ratio
Workforce Shortage: Medicaid Access

Acceptance Rate

Acceptance of a New Pediatric Medicaid Patient by All Dermatologists

Average overall market size-weighted acceptance rate: 19%

"When I grow up, I want to go into medicine and help people who can pay out of pocket."
Thank You

- BPCA
- NICHD
- FDA
Dermatology Therapeutic Area Working Group Members

- Rosemary Addy, M.H.S.
- Carl C. Baker, M.D., Ph.D.
- Kimberley W. Benner, Pharm.D.
- Katherine Berezny, M.P.H.
- Julie Block, CEO, National Eczema Association
- Jeffrey Blumer, M.D., Ph.D.
- Denise Cook, M.D.
- Beth Drolet, M.D.
- Linda Duffy, Ph.D., M.P.H.
- Beth Durmowicz, M.D
- Lawrence Eichenfield, M.D.
- Roselyn Epps, M.D.
- Jacqueline Francis, M.D., M.P.H.
- Norma Gavin, Ph.D.
- Adelaide Hebert, M.D.
- Maria K. Hordinsky, M.D.
- Thomas Hultsch, M.D., Ph.D.
- Wendla Kutz, M.S.N., C.N.S.
- Marie Ann Leyko, Ph.D.
- Anne Lucky, M.D.
- Martha Nguyen, J.D.
- Ian M. Paul, M.D., M.Sc.
- Hanna Phan, Pharm.D.
- Denise J. Pica-Branco, Ph.D.
- Merrily Poth, M.D.
- Hari Cheryl Sachs, M.D.
- Alex Silver
- Gina Simone
- Donna Snyder
- Perdita Taylor-Zapata, M.D.
- Katerina Tsilou, M.D.
- Surendra K. Varma, M.D
- Kelly Wade, M.D., Ph.D.
- Jonathan K. Wilkin, M.D.
- Teri Woo, Ph.D., R.N.
- Lynne P. Yao, M.D.
- Anne Zajicek, M.D., Pharm.D.
Identified Areas of Therapeutic Need

- Atopic Dermatitis
- Hemangioma of Infancy
- Epidermolysis Bullosa & Other Genodermatoses
- Pediatric Dermatology Drug Development
Atopic Dermatitis

Subcommittee Members

- Larry Eichenfield, M.D.
- Adelaide Hebert, M.D.
- Julie Block
- Hanna Phan, Pharm.D.
- Kimberly Benner, Pharm.D.
**Atopic Dermatitis - Clinical Features**

- Chronic, recurrent, inflammatory skin disease characterized by widespread redness, edema, scaling, crusting.
- Severe itch often interrupting sleep for multiple family members.
- Lifelong tendency towards dry skin, occupational skin disease, skin infections, eye problems, disrupted family and social relationships, and work/school absenteeism.
AD is a phenotype, representing a group of conditions caused by genetic and environmental factors responsible for:

- Skin barrier defects
- Increased susceptibility to bacterial, viral, fungal skin infections
- Immune dysfunction
Atopic Dermatitis - Epidemiology

- Onset < 2 years in 80%
- 8-15% childhood prevalence
  - 60% - mild, spontaneous improvement over ~10 yr
  - 35% - persistent with a range of associated problems
  - 5% - severe lifelong disease
- 300% rise in prevalence over the past 30 yr
- Strong genetic link with other allergic conditions
  - food allergy (15-30%)
  - asthma (50%)
  - allergic rhinoconjunctivitis (66%)
  - eosinophilic esophagitis/gastroenteritis
Atopic Dermatitis - Non-Allergic Comorbidities

- Sleep deprivation
- Neuropsychiatric
  - ADHD
  - anxiety, depression
  - autism
- Poor growth*
- Osteopenia*
- Cataracts*

* Possibly corticosteroid-related
Atopic Dermatitis-Therapeutic Issues

- Early therapeutic intervention and disease control may favorably impact progression and comorbidities.
- Poor adherence is a common cause of treatment failure.
- Obstacles to adherence
  - No well-defined standard-of-care
  - Conflicting recommendations
  - Medication phobia
  - Labeling/access restrictions
  - Topical treatment is time-consuming, complex and difficult to master.
Atopic Dermatitis - Principles of First-Line Treatment

- Skin care education
  - Avoid complex topical products
  - Bathing
  - Emollient
- Control itch and skin infection
- Topical Rx
  - Corticosteroids
  - Calcineurin inhibitors
# Pediatric Indication

**FDA-Approved Topical Corticosteroids**

<table>
<thead>
<tr>
<th>Product</th>
<th>Age group</th>
<th>Frequency of Application</th>
<th>Duration of Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>clobetasol propionate 0.05% foam</td>
<td>&gt; 12 yr</td>
<td>2 times daily</td>
<td>2 wk</td>
</tr>
<tr>
<td>fluocinolone acetonide 0.01% scalp oil</td>
<td>&gt; 12 yr</td>
<td>2 times daily</td>
<td>2 wk</td>
</tr>
<tr>
<td>mometasone 0.1% cream/ointment</td>
<td>&gt; 2 yr</td>
<td>1 time daily</td>
<td>3 wk</td>
</tr>
<tr>
<td>fluticasone 0.05% lotion</td>
<td>&gt; 1 yr</td>
<td>1-2 times daily</td>
<td>4 wk</td>
</tr>
<tr>
<td>aclometasone 0.05% cream/ointment</td>
<td>&gt; 1 yr</td>
<td>2-3 times daily</td>
<td>2 wk</td>
</tr>
<tr>
<td>prednicarbate 0.1% cream/ointment</td>
<td>&gt; 1 yr</td>
<td>1-2 times daily</td>
<td>3 wk</td>
</tr>
<tr>
<td>fluticasone 0.05% cream</td>
<td>&gt; 1 yr</td>
<td>1-2 times daily</td>
<td>4 wk</td>
</tr>
<tr>
<td>desonide 0.05% foam/gel</td>
<td>&gt; 3 mo</td>
<td>2-3 times daily</td>
<td>4 wk</td>
</tr>
<tr>
<td>hydrocortisone butyrate 0.1% cream</td>
<td>&gt; 3 mo</td>
<td>2-4 times daily</td>
<td>4 wk</td>
</tr>
<tr>
<td>fluocinolone acetonide 0.01% body oil</td>
<td>&gt; 3 mo</td>
<td>3-4 times daily</td>
<td>2 wk</td>
</tr>
</tbody>
</table>
**FDA-Approved Topical Calcineurin Inhibitors (TCI)**

<table>
<thead>
<tr>
<th>Product</th>
<th>Age group</th>
<th>Frequency of Application</th>
<th>Duration of Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>pimecrolimus cream 1%</td>
<td>≥ 2 yr</td>
<td>2 times daily</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>tacrolimus ointment 0.03%</td>
<td>≥ 2 yr</td>
<td>2 times daily</td>
<td>&gt;1 yr</td>
</tr>
<tr>
<td>tacrolimus ointment 0.1%</td>
<td>≥ 18 yr</td>
<td>2 times daily</td>
<td>&gt;1 yr</td>
</tr>
</tbody>
</table>

**Indication:** "second-line therapy for the short-term and non-continuous chronic treatment of AD in non-immunocompromised adults and children [≥2 years of age] who have failed to respond adequately to other topical prescription treatments for [AD], or when those treatments are not advisable"
# Pimecrolimus Cream Enrollment Clinical Trials Reviewed at Approval Nov. 2001

<table>
<thead>
<tr>
<th>Phase 3 Controlled Studies/Pivotal</th>
<th>Duration of Exposure</th>
<th># Exposed subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric (2-17 years)</td>
<td>26 wk</td>
<td>130</td>
</tr>
<tr>
<td>Pediatric (2-17 years)</td>
<td>26 wk</td>
<td>137</td>
</tr>
<tr>
<td>Infants (&lt;2 years)</td>
<td>26 wk</td>
<td>123</td>
</tr>
<tr>
<td>Controlled Supportive Safety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants (&lt;2 years)</td>
<td>6 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>204</td>
</tr>
<tr>
<td>Pediatric (2-17 years)</td>
<td>1 yr</td>
<td>474</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>1 yr</td>
<td>328</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1,396</td>
</tr>
<tr>
<td>Infants (&lt;2 years)</td>
<td>6 mo – 1 yr</td>
<td>327</td>
</tr>
<tr>
<td>Children (2-17 years)</td>
<td>6 mo – 1 yr</td>
<td>741</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>1 yr</td>
<td>328</td>
</tr>
</tbody>
</table>

TCI Labelling Change

- Q4 2003 TCI Rx: 11% to infants <2 yr
- Oct. 2003 FDA PAC for product registry protocol review; AERS malignancy reports shifted focus of the meeting
- Jan. 2006 boxed warning based on a theoretical risk of malignancy

Outcomes

- Abrupt decrease in Rx (esp. infants)
  - Caregiver phobia
  - Provider hesitation
  - Third-party payor restriction
- Epidemiological/clinical studies without TCI/lymphoma link
- Mandated post-marketing surveillance studies in process

## Pimecrolimus Cream Enrollment - All Clinical Trials as of May 2010

<table>
<thead>
<tr>
<th>Age</th>
<th>Duration of Exposure</th>
<th># Subjects Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (&lt;2 years)</td>
<td>≤6 yr</td>
<td>~10,000</td>
</tr>
<tr>
<td>Children (2-17 years)</td>
<td>≤10 yr&lt;sup&gt;c&lt;/sup&gt;</td>
<td>~21,000</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>≤3 yr</td>
<td>~16,000</td>
</tr>
<tr>
<td>Other Age Ranges:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 months</td>
<td>≤26 wk</td>
<td>~350</td>
</tr>
<tr>
<td>3 months-17 years</td>
<td>≤27 wk</td>
<td>~100</td>
</tr>
<tr>
<td>1-4 years</td>
<td>≤12 wk</td>
<td>~75</td>
</tr>
<tr>
<td>≥2 years</td>
<td>≤18 wk</td>
<td>~5,600</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>≤12 wk</td>
<td>~2,200</td>
</tr>
<tr>
<td>Unspecified</td>
<td>≤3 yr</td>
<td>~450</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>&gt;55,000</td>
</tr>
</tbody>
</table>
Committee Recommendations

- Reevaluate the evidence
- Revise labeling to reflect safety and efficacy of pimecrolimus cream in infants \( \geq 3 \) months
- Remove the boxed warning if the evidence is lacking.
Severe Atopic Dermatitis—Beyond Topical Therapy

- No FDA-approved systemic therapy
- Off-label, level 3 evidence-based Rx: immunosuppressive and cytostatic agents (cyclosporine, azathioprine, mycophenolate mofetil, methotrexate); immunomodulators (IVIG, IFN-gamma)
- Few adult-only trials of new chemical entities (anti-IL-4, oral phosphodiesterase inhibitors)
Severe Atopic Dermatitis- Existing Resources

- International core outcomes consortium: Harmonizing Outcome Measures for Eczema (HOME)

- US multicenter research network: Pediatric Dermatology Research Alliance (PeDRA)- Inflammatory Skin Diseases Group unfunded comparative study of cyclosporine, azathioprine, mycophenolate mofetil and MTX (NCT01447381)
Committee Recommendations

- Provide funding to expand clinical trials of systemic therapies for severe AD initiated by PeDRA.
- Encourage drug comparison efficacy studies, rather than placebo-controlled trials.
- Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications and new chemical entities.
- Develop and validate standardized outcomes measures for pediatric AD across the age spectrum.
Genodermatoses

Subcommittee Members

- Anne Lucky, M.D.
- Adelaide Hebert, M.D.
- Elena Pope, M.D.
- Megha Tollefson, M.D.
- Wynnis Tom, M.D.
Epidermolysis bullosa (EB) is a rare, inherited condition of skin fragility and blistering, significant early morbidity and mortality.

- Herlitz-Junctional EB (JEB-H): usually fatal in the first months or years of life
- Recessive Dystrophic EB (RDEB): crippling skin and systemic morbidities; shortened life span.
- EB simplex (EB Dowling-Meara): increased neonatal morbidity and mortality
Genodermatoses

- Comorbidities
  - Poor wound healing
  - Impaired nutrition and failure to thrive
  - Secondary infection
  - Chronic itch and pain
  - Anemia
  - Osteoporosis, pathologic fractures
  - Loss of hand function
  - Isolation from peers and society

- The costs of managing EB are high
- Optimal care is via tertiary centers that support a coordinated team.
- No FDA-approved therapeutic agents are available for any subtype or age group.
Genodermatoses

- 15 genes have been identified to cause various forms of EB.

- Recent therapeutic strides applicable to patients with severe forms of EB:
  - Methodology for gene replacement
  - Protein replacement
  - Biologic therapy
Committee Recommendations

- Provide funding to expand the EB Clinical Research Consortium national registry/database
  - Centralize genetic testing results
  - Identify potential subjects for clinical trials

- Registry expansion should occur in parallel with clinical studies to allow maximum progress.
Committee Recommendations

- Support studies to test and validate outcome measures.
- Initiate therapeutic trials in adults.
- Define inclusion criteria for children with severe EB subtypes to enable early enrollment in the same trials.
- Develop parameters to maximize safety for the youngest age groups.
- Encourage fast-track FDA approval for EB drugs.
Hemangioma of Infancy

Subcommittee Members

- Beth Drolet, M.D.
- Kelly Wade, M.D.
- Elena Pope, M.D.
- Megha Tollefson, M.D.
Hemangioma of Infancy

- The most common tumor of childhood
- ~ 80,000 infants/yr in the US
- Complications necessitating treatment (~12%): disfigurement, ulceration/pain, visual impairment, airway obstruction, congestive heart failure
- No FDA-approved treatments; 1 industry-sponsored, phase II/III international multicenter, PCDB trial
- Existing research network (HIG; Hemangioma Investigator Group)
Hemangioma of Infancy: Treatment Options

- X-irradiation
- Non-intervention
- Corticosteroids
- IFN-α
- Vincristine
- Excision
- Lasers
- β-blockers

β-blocker Treatment for Hemangioma of Infancy

- Index case failed high dose IV corticosteroids
- Treatment complicated by hypertrophic cardiomyopathy
- Incidental rapid improvement
- Open-label treatment of 10 additional cases
- Published as a short communication (400 words)
- 268 publications as of 11/25/12

**β-blocker Treatment for Hemangioma of Infancy**

- Off-label oral and topical beta blockers have rapidly been adopted as first line therapy.
- **Propranolol suspension**
  - 30,000 more Rx 2011 vs. 2007, *including complicated HOI*
  - Pierre-Fabre sponsored phase II/III multicenter, PCDB trial: propranolol in an optimized suspension; (planned FDA submission 1/07/13); *this protocol excludes complicated HOI*.
- **Propranolol gel: Pierre Fabre (proof of concept)**
- **Timolol ophthalmic (0.5% or 0.1% GFS)**
  - 4-10X more potent than propranolol
  - AEs (4% of children on intraocular timolol for glaucoma): bradycardia, hypoglycemia, and wheezing
  - Anticipated Rx for 10% HOI = 80 fold increase compared to infantile glaucoma
Oral β-blocker Clinical Needs

- Additional safety/efficacy information
- Propranolol (generic suspension, nadolol? atenolol?)
- Validation for consensus-derived guidelines*
  - Monitoring
  - Dose escalation
  - Initiation < 2 mo
  - Use in pre-term infants
  - Use in PHACE/LUMBAR syndrome
  - Duration of treatment
  - Discontinuation

*Drolet B et al. Pediatrics, in press
Topical β-blocker Clinical Needs

- Propranolol gel, ophthalmic preparations: timolol, ?betaxolol)
- Safety/efficacy/PK
- Oral/topical comparative data
- Dosing
- Indications
  - Ulceration
  - Periorbital lesions
  - Premature infants, especially <2 mo old
Committee Recommendations

- If Pierre Fabre oral propanolol receives FDA approval for *uncomplicated* HOI, there remains a desperate need for additional studies to evaluate safety/efficacy of oral propranolol for *complicated cases*.

- Utilize expertise within PTN, NICHD, HIG and industry to design & perform
  - Standardized safety reporting protocol to track likely AEs for infants enrolled in β-blocker studies
  - Phase I/II studies of percutaneous application of timolol maleate ophthalmic solution
Pediatric Dermatology Drug Development Issues

Subcommittee Members

- Elaine Siegfried, M.D.
- Jon Wilkin, M.D.
- Larry Eichenfield, M.D.
- Roselyn Epps, M.D.
- Maria Hordinsky, M.D.
- Surendra Varma, M.D.
- Teri Moser Woo, R.N., Ph.D.
Many skin-related conditions are:
- common
- costly in economic terms
- chronic
- cause significant morbidity
- carry substantial comorbidity risks
- generate emotional distress
- markedly impair quality of life for the affected child and family
“Quality-of-life illnesses are disorders that are regarded as unimportant to those who don’t have them.”

-Ray Slavin, M.D.

“Skin disease won’t kill you, but it can ruin your life.”

-Elaine Siegfried, M.D.
The unmet need is high for safe/effective treatments for children with chronic and severe pediatric dermatologic diseases.
Major obstacles hinder new drug development for pediatric skin diseases

- Product labeling that overemphasizes *theoretical* risks of new treatments compared to *well-established* risks of poorly controlled, chronic disease
- Underappreciated risks of AEs from widespread off-label use of drugs that lack evidence-based treatments
- No well-defined risk parameters or guidelines for development of new drugs in children with non-lethal, but life-altering disorders
Pediatric Dermatology
Drug Development Issues-
Goals

- To state the need for well-defined regulatory clinical development pathways to inform, facilitate and incentivize new treatments for severe and chronic pediatric skin diseases.

- To generate an official request to seek input from experts in order to draft a guidance document for FDA review and modification per the Current Good Guidance Document Practices.

- To offer initial suggestions for inclusion into a Level 1 Guidance Document for New Drug Development in Pediatric Dermatology.
Pediatric Dermatology
Drug Development Issues-
Guidance Document Suggestions

- Develop optimal packaging to assist in delivery of appropriate amounts of topical medication
- Determine optimal topical dosing quantities
- Do not postpone early phase drug trials in infants and children until after efficacy is determined in adults.
- Do not exclude drugs that have not achieved proven efficacy in adults as presumably ineffective in children.
- Do not place higher priority on theoretical risks of new drugs than established morbidity, and impact on QOL for pediatric skin disease.
Pediatric Dermatology
Drug Development Issues-Guidance Document Suggestions

- Determine age limits for initial trials based on the drug and the disease, e.g.
  - Include premature infants with a newly detected HOI in trials for of a topical beta-blocker.
  - Include children as young as age 2 with severe AD in trials involving systemic immunosuppressant medications.

- Apply adverse event data for drugs that have been studied for other pediatric indications to further study of skin disease in children.
Be aware of the Harmonizing Outcome Measures for Eczema (HOME) project ([http://www.homeforeczema.org](http://www.homeforeczema.org)): experts working together to agree on core set of outcome measures for use in all AD clinical trials.

HOME III will be held 4/6/13 in San Diego, CA. Representatives from the EMEA will be participating. Similar FDA participation would be optimal.
Incorporate input from parents of affected children in clinical trials protocol design via surveys seeking parental opinion on
- tolerable washout periods
- acceptable duration for placebo exposure
- achievable frequency of study visits
- tolerable number of phlebotomies and skin biopsies
- worthwhile outcomes

 Require use of microtainer technology for routine hematology and chemistry assays.
Support the Pediatric Dermatology Research Alliance (PeDRA), a currently unfunded network to facilitate design and conduct of clinical trials, share resources and garner sufficient cohorts to study pediatric skin diseases.

- Hemangioma Investigator Group (HIG)
- Epidermolysis Bullosa Clinical Research Consortium (EBCRC)
- Pediatric Inflammatory Skin Diseases Group (PISDG)
Pediatric Dermatology
Drug Development Issues-
Committee Recommendations

- Recognize new drug development as a significant unmet need for children with severe and chronic skin disease.
- Appreciate the importance of an FDA-issued guidance document relevant to new drug development for children with severe and chronic, but non-life threatening skin diseases.
The committee is aware that 21CFR10.115 specifically encourages submission of subjects and drafts to the FDA for consideration and modification towards creating guidance documents.

Apply background information provided towards developing a level 1 guidance document for new drug development for the top 3 identified areas of need: hemangioma of infancy, epidermolysis bullosa and atopic dermatitis as a first priority.
Provide additional support to convene a working group of experts to create an initial draft for review and modification by FDA.

The ideal working group would include participants with expertise in

- Clinical care of children with skin disease
- Drug development for skin disease
- Pediatric drug development
- Guidance document design