



Characteristics of products for specific allergy management

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Introduction to ALK-Abelló

- Pharmaceutical company devoted to specific allergy
- Founded in 1923
- 1400 employees worldwide
- Turnover of 200 M EUR
- 32% of global marketshare
- World leader within specific allergy management



Headquarters, Horsholm, Denmark

ALK-Abelló: global presence



□ Distributors

★ Research

● Production

■ Subsidiaries in France, the Netherlands, Italy, Spain, Sweden (Nordic), Switzerland, Germany, UK, USA, Austria.
Sales offices in China, Finland, Norway and Denmark.

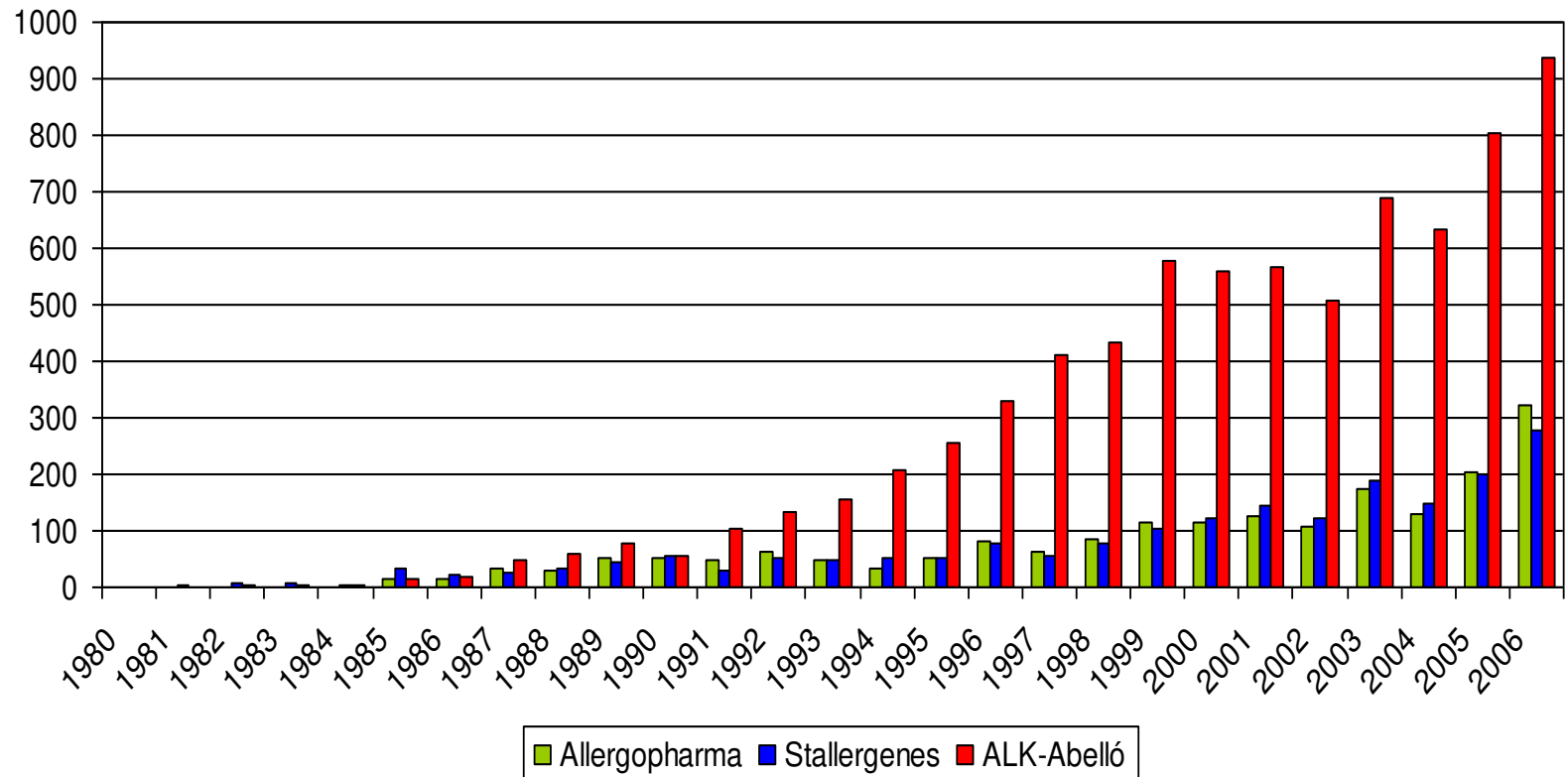
Scientific production 2006: 32 articles

Alutard SQ

- Frew *et al.* J Allergy Clin Immunol 117: 319, 2006.
The worlds largest immunotherapy trial with 400 patients
- Niggemann *et al.* Allergy 61: 855, 2006.
5 year follow up data on the Preventive Allergy Treatment study
- Wang *et al.* Allergy 61: 191, 2006.
First immunotherapy study in China with standardised extracts
- Werfel *et al.* Allergy 61: 202, 2006.
First immunotherapy study showing effect on atopic dermatitis
- Blumberga *et al.* Allergy 61: 843, 2006.
Reduction in steroid use in asthma patients after immunotherapy
- Quercia *et al.* Allergy Asthma Proc 27: 151, 2006.
Improved safety of bee immunotherapy using alum formulation

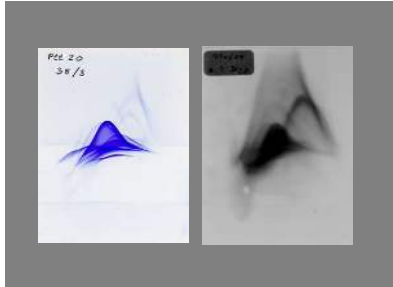
ALK-Abelló: scientific impact

Citations in each year



Ref.: ISI Web of Science (10.03.2007) search with
"Allergopharma", "Stallergenes" or "ALK" in address field

30 years of allergen research



■ Extracts

Løwenstein H.

“Quantitative immunoelectrophoretic methods as a tool for the analysis and isolation of allergens”.

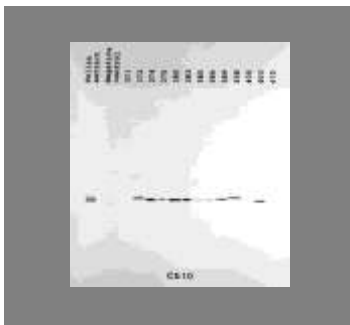
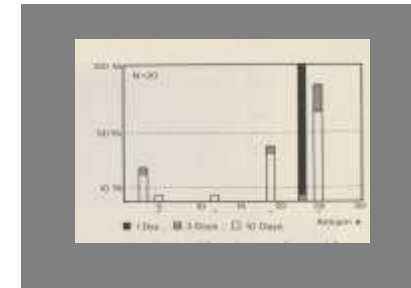
Prog Allergy 25: 1-62, 1978.

■ Purified single allergens

Ipsen H and Løwenstein H.

“Isolation and immunochemical characterization of the major allergen of birch pollen (*Betula verrucosa*)”.

J Allergy Clin Immunol 72: 150-159, 1983.



■ Isoallergens

Larsen JN, Strømman P, and Ipsen H.

“PCR based cloning and sequencing of isogenes encoding the tree pollen major allergen Car b I from *Carpinus betulus*, (hornbeam)”

Mol Immunol 29: 703-711, 1992.

30 years of allergen research

■ Recombinant allergens

Gajhede M, Osmark P, Poulsen FM, Ipsen H, Larsen JN, van Neerven RJJ, Schou C, Løwenstein H, and Spangfort MD.

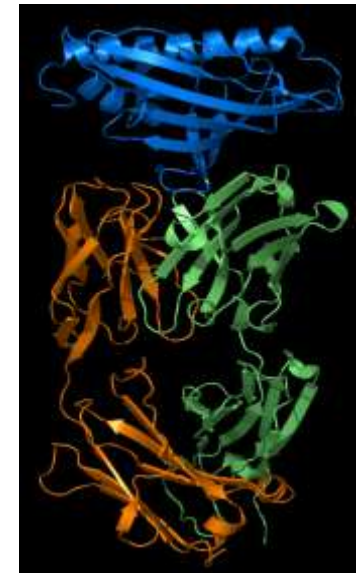
“X-ray and NMR structure of Bet v 1, the origin of birch pollen allergy”.
Nature Struct Biology 3: 1040-1045, 1996.



■ Allergen-Antibody complex

Mirza O, Henriksen A, Ipsen H, Larsen JN, Wissenbach M, Spangfort, MD, and Gajhede M.

“Dominant epitopes and allergic cross-reactivity: Complex formation between a Fab fragment of a monoclonal murine IgG antibody and the major allergen from birch pollen Bet v 1”.
J. Immunology 165, 331-338, 2000.



ALK-Abelló product portfolio

SCIT



Subcutaneous immunotherapy (SCIT)
Injections under the skin
~ 50% of the sales

SLIT



Sublingual immunotherapy (SLIT)
Under the tongue
~ 26% of the sales

TABLETS



Tablet-based allergy immunotherapy
Under the tongue
No sales figures yet

OTHER



Allergy Diagnosis: Skin prick tests
Emergency treatment for allergic shock
(adrenaline pen)
~ 24 % of the sales

R&D Pipeline

Product specifications			Research	Preclinical	Status		
Product type	Active ingredient	Indication			Phase I	Phase II	Phase III
GRAZAX®	Biological grass pollen allergen	Rhinitis			Approved and launched		
Tablet	Biological house dust mite allergen	Rhinitis/Asthma					
Tablet	Biological ragweed allergen	Rhinitis					
Tablet	Biological birch pollen allergen	Rhinitis					
	Recombinant allergy vaccines	Rhinitis/Asthma					

Recombinant allergens

- Portfolio of exclusive recombinant IP rights from 40 Licensed or Owned patent families relating to
 - ▶ Recombinant allergens
 - ▶ Mutated allergens
 - ▶ Expression systems

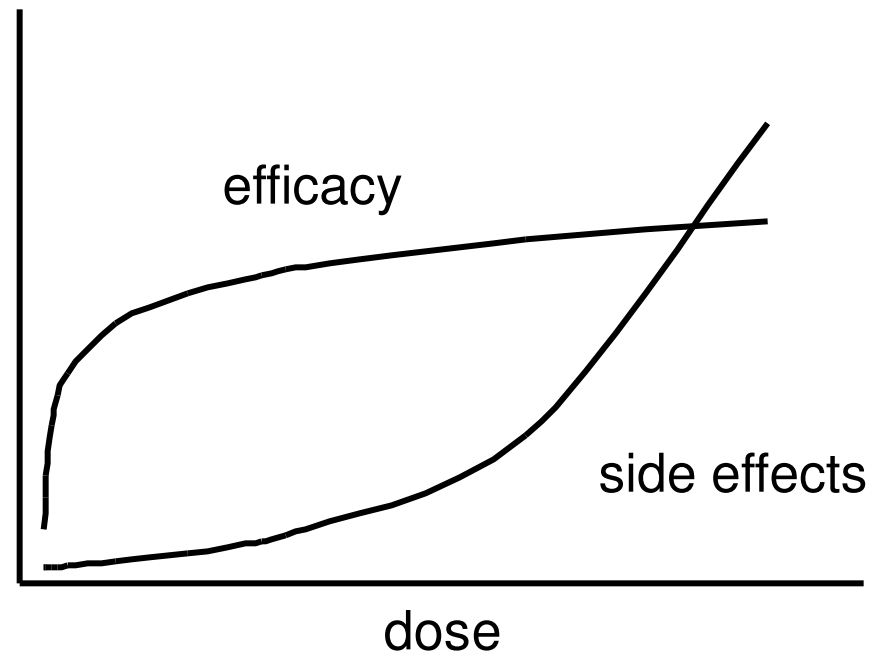
- Includes more than 60 issued US-patents, amongst which 43 relates to grass-, house dust mite-, and ragweed allergens

- Fifty-seven published articles in peer reviewed journals between 1992 and 2005
 - ▶ ~ 5 publications on recombinant allergens per year

Standardisation of allergen vaccines

■ Optimal standardisation ensures

- ▶ Reproducibility
- ▶ Safety
- ▶ Efficacy
- ▶ Simplicity
- ▶ Accuracy
- ▶ Precision

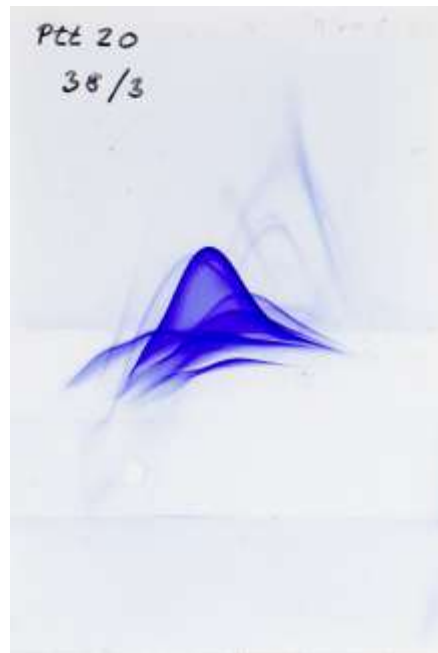


Optimal standardisation enables high dose treatment with minimal risk of side effects

The optimal dose represents a compromise between efficacy and safety

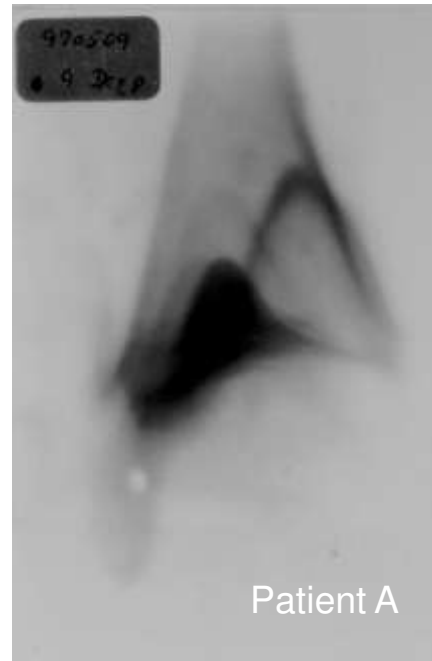
Crossed (radio)-immuno-electrophoresis

Dermatophagoides pteronyssinus



CIE

crossed immunoelectrophoresis

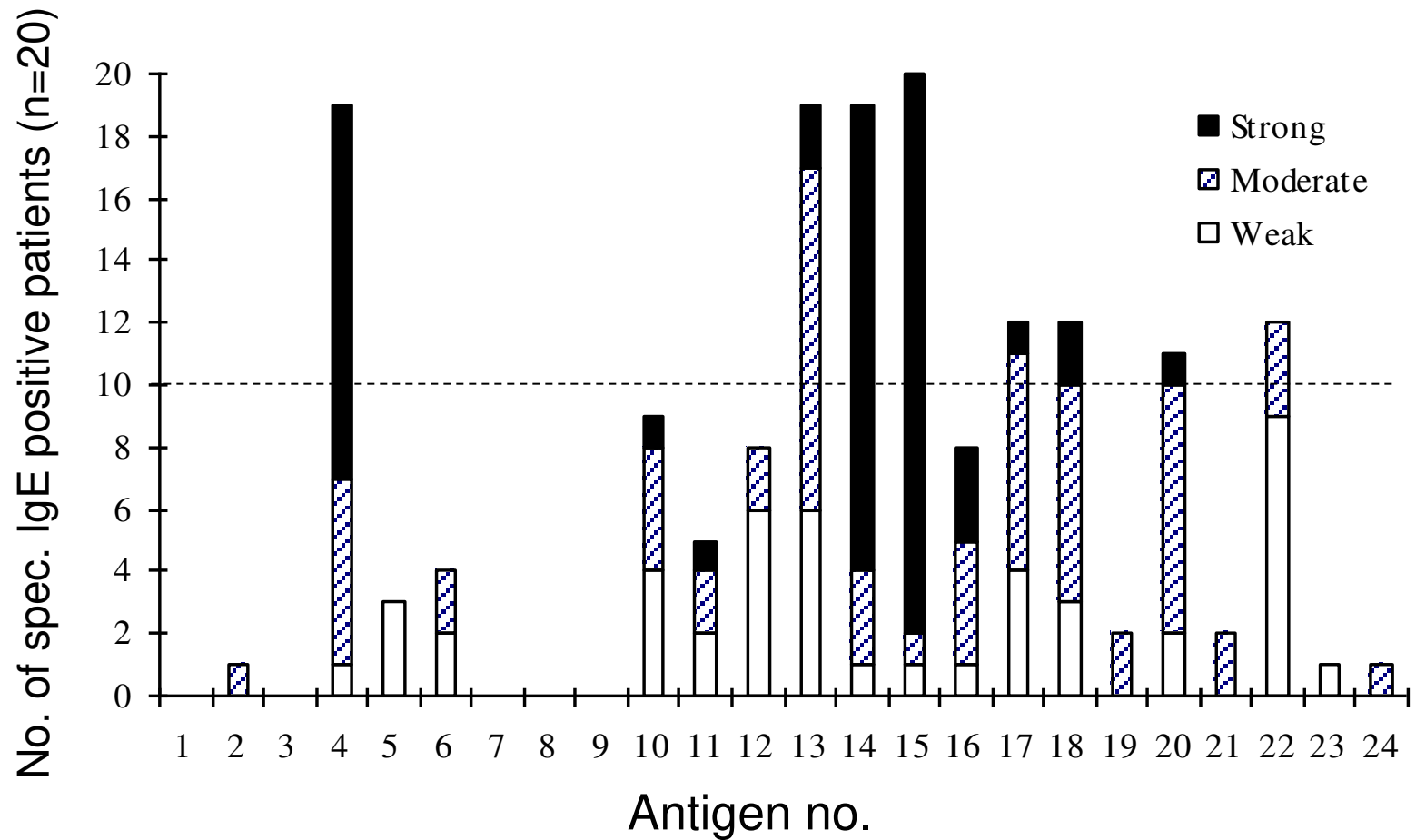


CRIE

crossed radio-immunoelectrophoresis

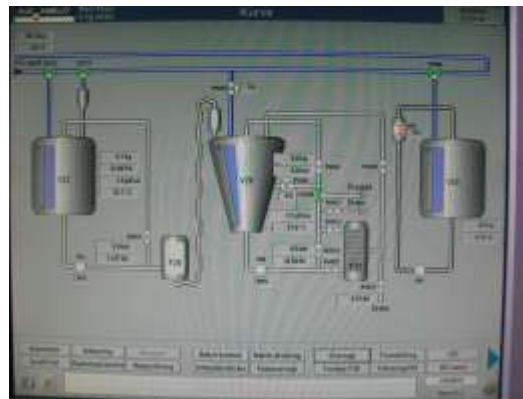
Allergogram

Dermatophagoides pteronyssinus



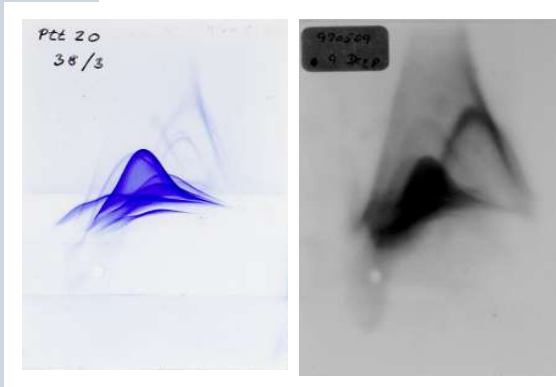
Standardisation

- Selection of raw material
- Preparation of extract
- Characterisation of extract
- Selection of in house reference preparation (IHRP)
- Biological testing of IHRP
- Batch-to-batch standardisation
- Formulation of vaccine

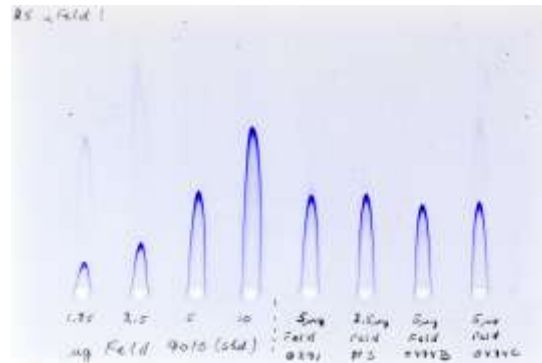


Batch-to-batch standardisation

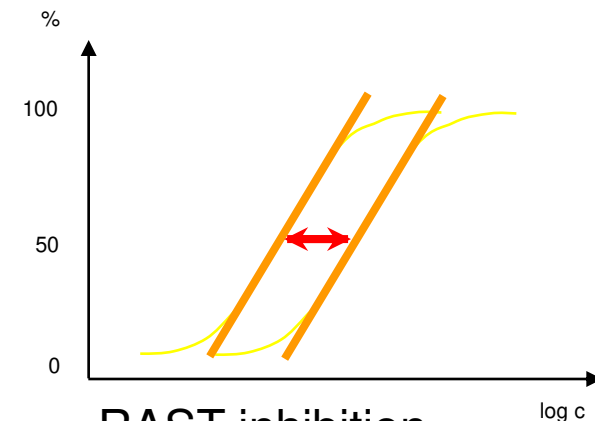
1. Complexity
2. Major allergen content
3. Total potency
relative to internal standard



CIE
and SDS-PAGE

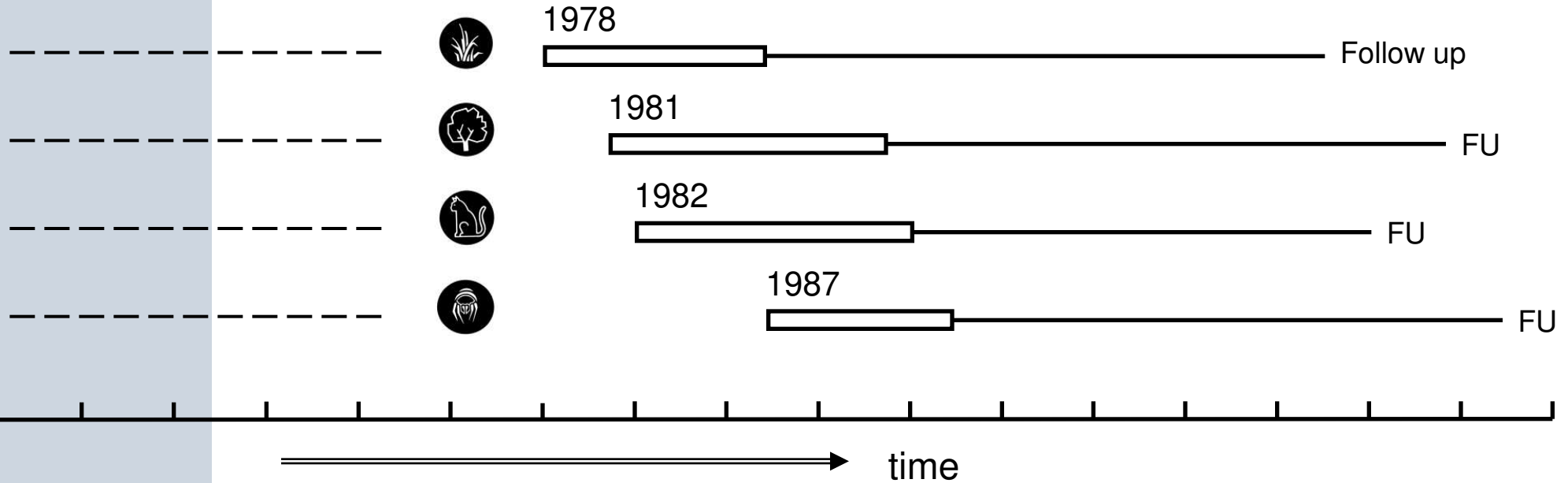


RIE
or ELISA



RAST inhibition
or related methods

Recommended clinical maintenance dose



Clinical experience

Definition of 100,000 SQ

Verification of clinical maintenance dose

→ μg

Standardization based on individual major allergens

Recommended clinical maintenance dose

References



Mosbech H, Østerballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. *Allergy* 43:523-529, 1988.



Nüchel Petersen B, Janniche H, Munch EP, Wihl JÅ, Böwadt H, Ipsen H, Løwenstein H: Immunotherapy with partially purified and standardized tree pollen extracts. I. Clinical results from a three-year double-blind study of patients treated with pollen extracts either of birch or combinations of alder, birch and hazel. *Allergy* 43:353-362, 1988.



Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow K, Sundin B, Løwenstein H. Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. *J Allergy Clin Immunol* 87:955-964, 1991.



Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: clinical efficacy and side effects. *J Allergy Clin Immunol* 91:709-722, 1993.

Recommended maintenance doses in μg

Allergen source	ref.	major allergen	dose in μg
Cat	1 - 4		
<i>Felis domesticus</i>		Fel d 1	14.6
House dust mite	5, 6		
<i>Der. pteronyssinus</i>		Der p 1	9.8
<i>Der. farinae</i>		Der f 1	13.8
Short Ragweed	7		
<i>Ambrosia artemisiifolia</i>		Amb a 1	10.0
Grasses	8, 9		
<i>Dactylis glomerata</i>		Dac g 5	12.0
<i>Festuca pratense</i>		Fes p 5	18.6
<i>Lolium perenne</i>		Lol p 5	12.5
<i>Phleum pratense</i>		Phl p 5	20.2
Tree	10		
<i>Betula verrucosa</i>		Bet v 1	13.0

Documenting Alutard SQ

- 65 peer reviewed international publications
- 23 peer reviewed randomized controlled studies published on clinical outcome
 - ▶ **Early effect**
 - reduction in symptoms(60%)/need for medication(70%)
 - ▶ **Progressive effect**
 - reduction in symptoms/need for medication
 - reduction in hyperresponsiveness/late phase response
 - ▶ **Persistent effect**
 - long-term reduced symptoms/need for medication
 - long-term reduced hyperresponsiveness/late phase response
 - ▶ **Preventive effect**
 - prevention of new sensitivities and exacerbation of disease (rhinitis into asthma)
 - ▶ **Immunological effect**
 - immunomodulation

Standardisation is not standardised

- Each manufacturer has own standard and standardisation principles
- Allergen extracts from different manufacturers differ in composition and cannot be compared
- No common units or measures
- Regulatory requirements are not optimal



- Each product should prove useful in dbpc clinical trials
- Ask your agent for clinical documentation and standardisation procedure

ALK-Abelló Research, Denmark



<http://www.alk-abello.com>