



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.

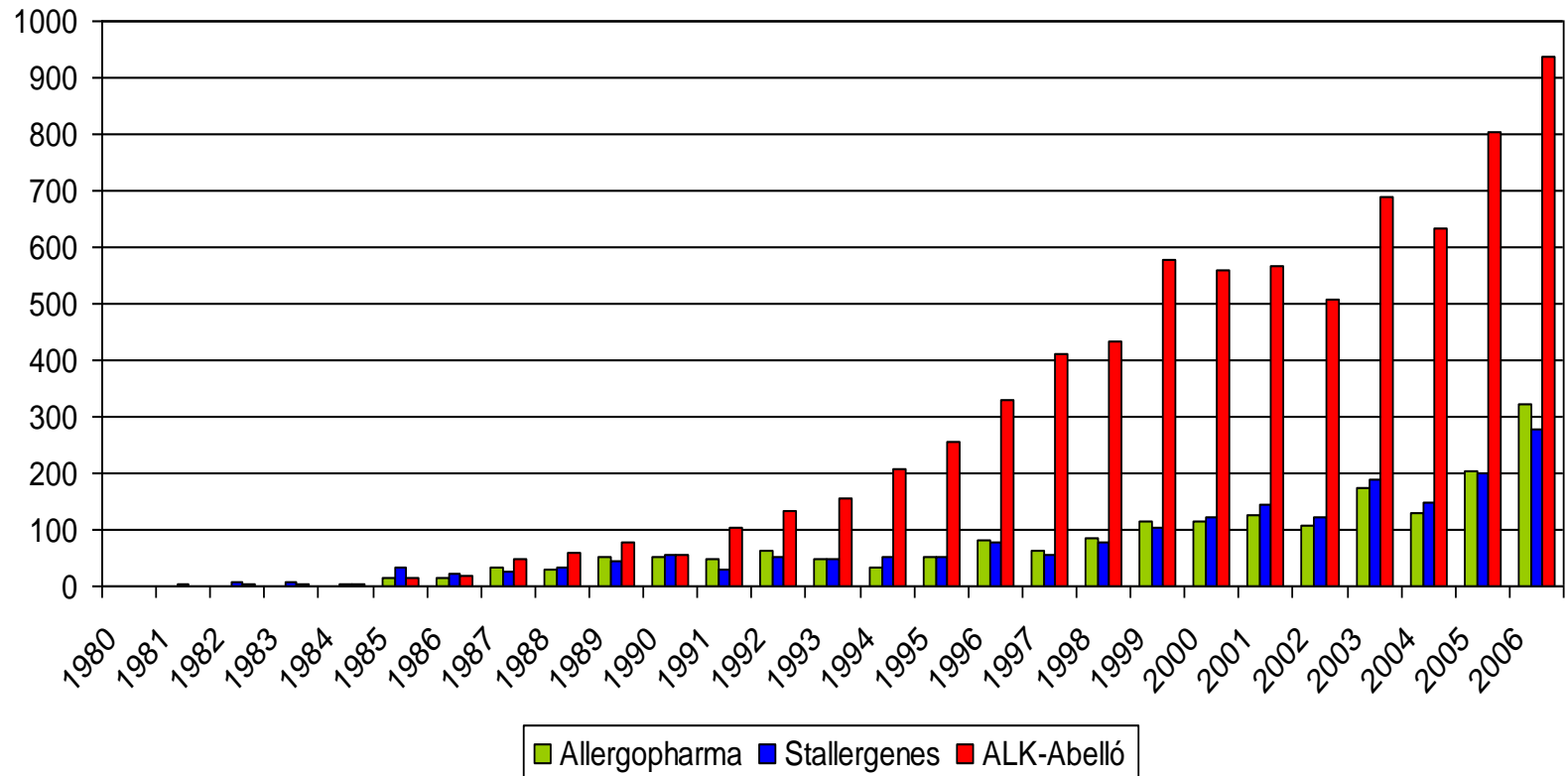
# Scientific production 2006: 32 articles

## *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

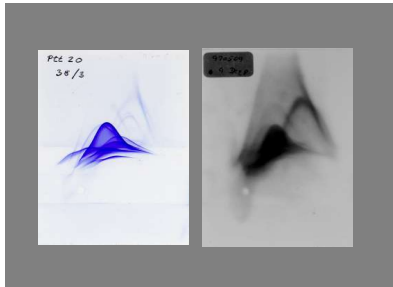
# ALK-Abelló: scientific impact

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”.

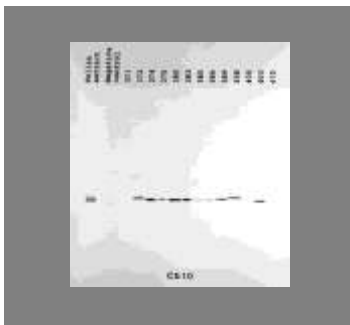
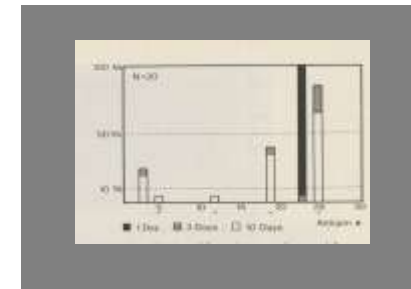
*Prog Allergy 25: 1-62, 1978.*

## ■ 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.

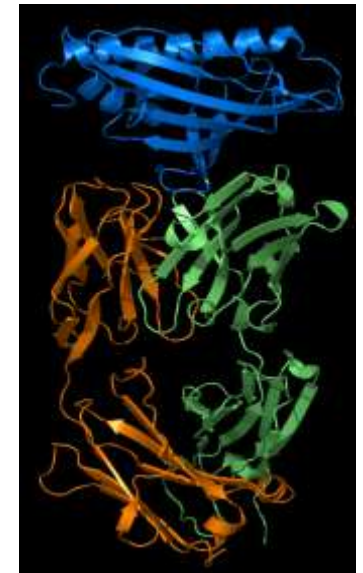
“X-ray and NMR structure of Bet v 1, the origin of birch pollen allergy”.  
*Nature Struct Biology* 3: 1040-1045, 1996.



## ■ 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			<b>Approved and launched</b>		
Tablet	Biological house dust mite allergen	Rhinitis/Asthma					
Tablet	Biological ragweed allergen	Rhinitis					
Tablet	Biological birch pollen allergen	Rhinitis					
	Recombinant allergy vaccines	Rhinitis/Asthma					

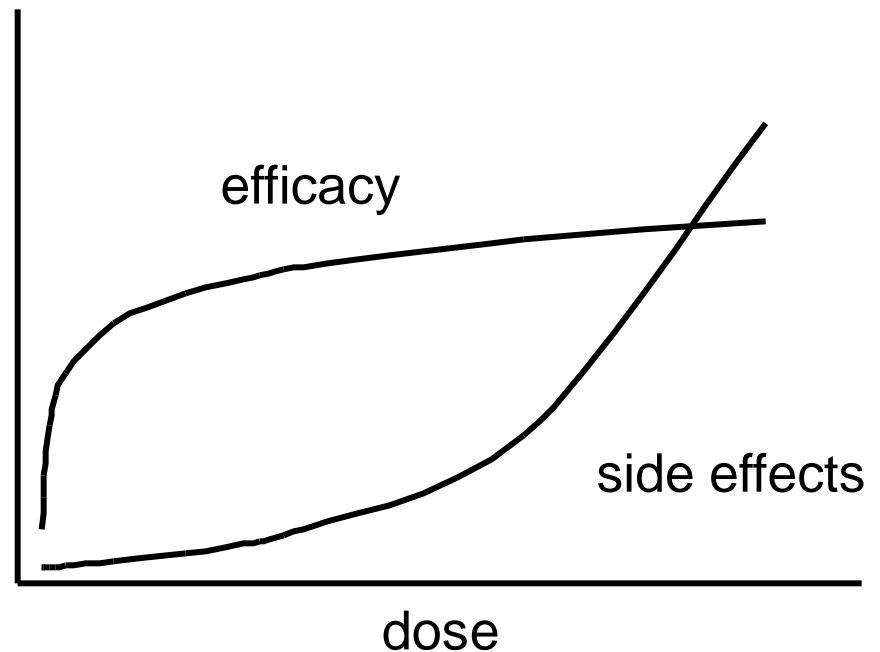
# Recombinant allergens

- 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

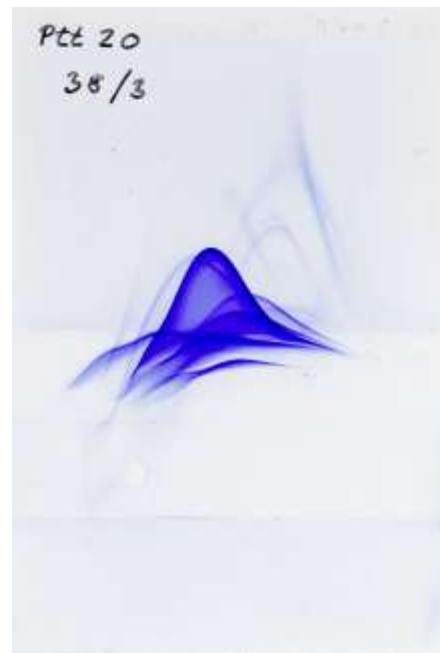


Optimal standardisation enables high dose treatment with minimal risk of side effects

The optimal dose represents a compromise between efficacy and safety

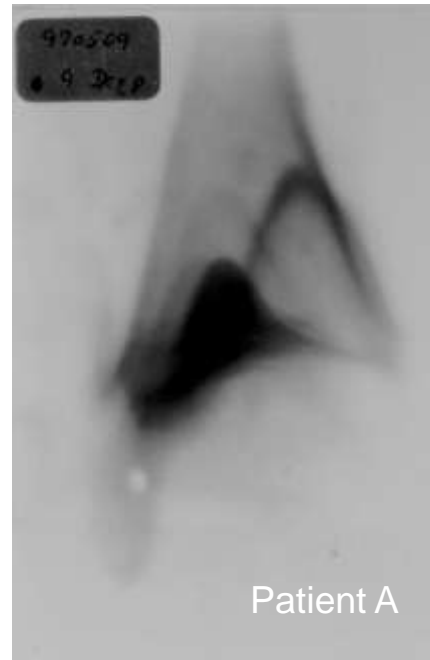
# Crossed (radio)-immuno-electrophoresis

## *Dermatophagoides pteronyssinus*



CIE

crossed immunoelectrophoresis

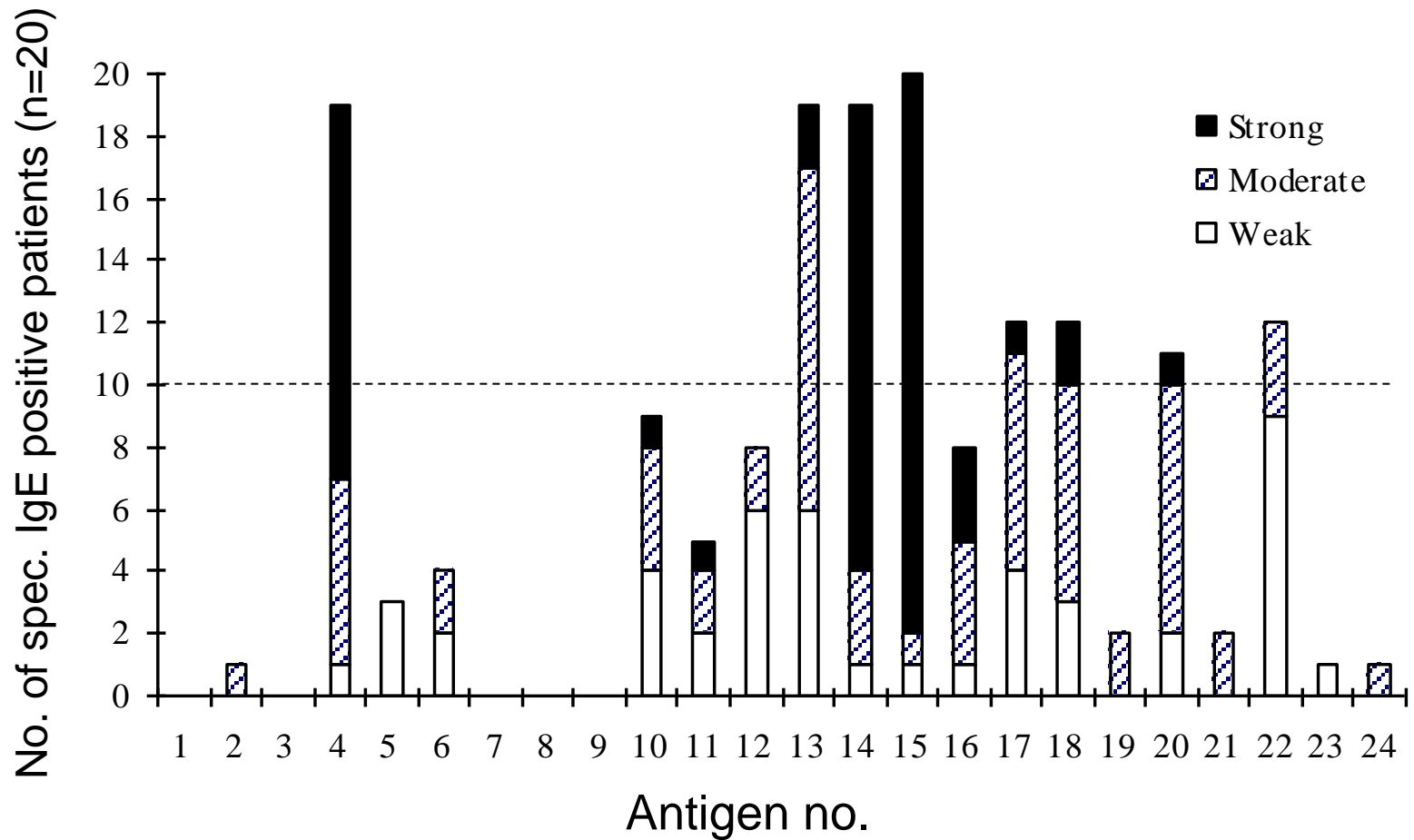


CRIE

crossed radio-immunoelectrophoresis

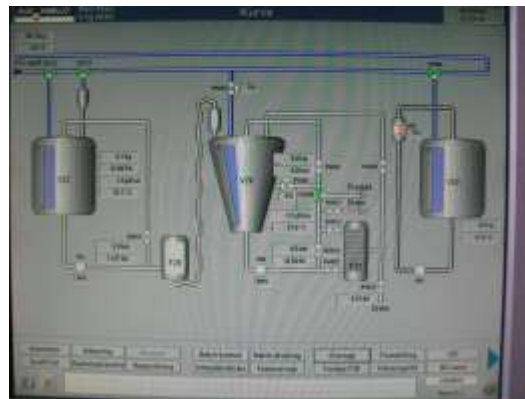
# Allergogram

## *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

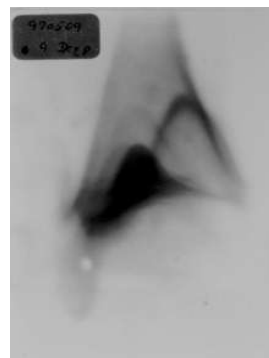


# Batch-to-batch standardisation

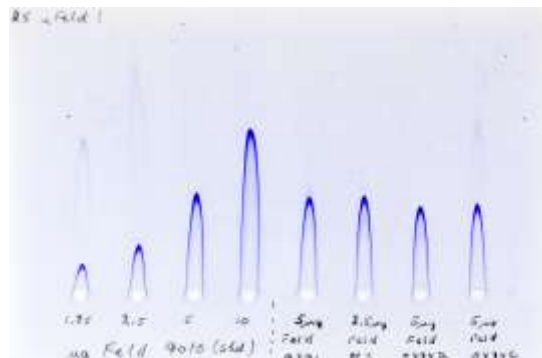
1. Complexity
2. Major allergen content
3. Total potency  
relative to internal standard



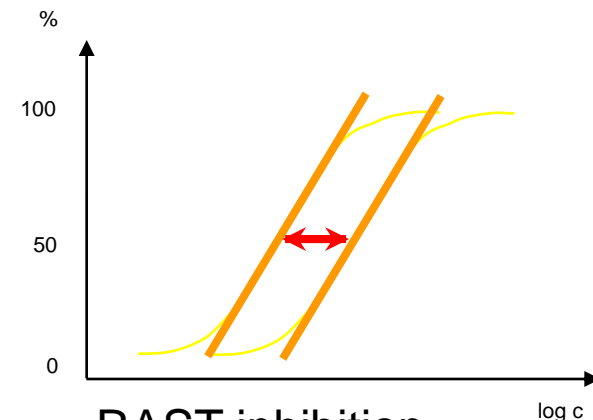
CIE  
and SDS-PAGE



CRIE

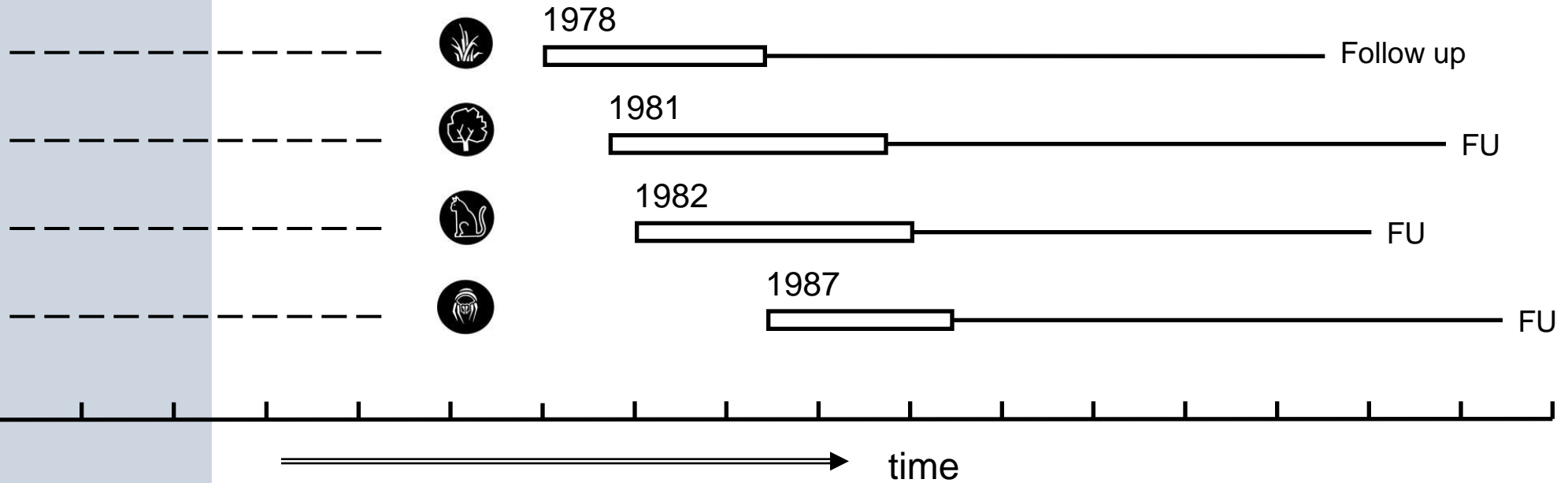


RIE  
or ELISA



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 $\mu\text{g}$

Allergen source	ref.	major allergen	dose in $\mu\text{g}$
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>