Aeroallergen Immunotherapy Selection Guide

This document is to be used in conjunction with the Aeroallergen Immunotherapy Guide. It has been updated by the ASCIA Immunotherapy Working Party and extracted into this separate Guide.

ASCIA Immunotherapy Working Party members are listed on the ASCIA website www.allergy.org.au/members/committees#wpim

ASCIA resources are based on published literature and expert review.

ASCIA health professional document references are at www.allergy.org.au/hp/papers

Abbreviations

AIT	Allergen immunotherapy	IT	Immunotherapy
DF	Dermatophagoides farinae	sIgE	Allergen specific IgE
DP	Dermatophagoides pteronyssinus	SCIT	Subcutaneous immunotherapy
HDM	House dust mite	SLIT	Sublingual immunotherapy
IgE	Immunoglobulin E	SPT	Skin prick test
IgG	Immunoglobulin G		

Contents

Aeroallergens

AIT is indicated in the management of allergic disease (allergic rhinitis, asthma, eczema) when there is evidence of allergen-specific IgE and when the disease is thought to be caused or aggravated by exposure to the specific allergen.

AIT is considered to work through induction of allergen-specific tolerance (immune regulation). Therefore, rational therapy requires identification of the allergen/s most relevant to the disease process. This relies on knowledge of the disease process, detailed history taking, and appropriate allergy testing:

- Selection of relevant aeroallergens for immunotherapy requires detailed knowledge of allergen exposure as it is determined by local botany and aerobiology. Prevalence and distribution of plant species according to geographical location or region is the first consideration, but pollination is influenced by climate, weather, seasonality, as well as diurnal patterns.
- The patient history should assess symptom variability by season and weather as well as indoor/outdoor, day/night, home/work, normal environment/holiday, animal exposure/pet ownership, occupation etc.
- To consider an allergen relevant to the disease process, symptomatic exacerbation should correlate with allergen exposure.

The effectiveness of immunotherapy depends on inclusion of relevant allergens in adequate concentrations to achieve tolerance. Omission of relevant allergens may reduce efficacy of immunotherapy. However, since the total concentration of allergen available in commercial mixtures is limited and since efficacy of immunotherapy is known to be dose-dependent, inclusion of numerous or unnecessary allergen extracts may reduce efficacy by dilution of the important allergen components.

It is also unclear as to whether immunotherapy targeting multiple allergens, even if all allergens were presented at optimal strength, would be as clinically effective as single AIT. Some studies have indicated that single AIT can be effective even in those who are poly-sensitised, but it has not been shown whether multiple allergens would be more or less effective in these patients.

In many cases the clinical pattern suggests particular responsible allergens and when these are confirmed by allergy testing there may be little difficulty in prescribing immunotherapy. Common examples include:

Clinical pattern	**AIT (IT)**
Seasonal rhinoconjunctivitis (hay fever) worse outdoors, similar pattern each year, correlating with spring grass pollination *with* sensitisation to ryegrass.	IT with ryegrass pollen extract.
Perennial rhinoconjunctivitis and/or asthma with predominantly indoor symptoms, often worse in mornings and evenings *with* sensitisation to HDM.	IT with HDM allergen extract (after excluding chronic rhinosinusitis).
Perennial rhinoconjunctivitis and/or asthma with exacerbation on exposure to animals e.g. cats *with* sensitisation to cat.	IT with cat allergen extract.

However, difficulties occur with multiple pollen sensitisation, sensitisation to moulds, sensitisation to multiple allergen groups, and determining significance of equivocal allergy test results.

Cross-reactivity within allergen groups creates further complexity as it may be unclear whether an allergic sensitisation is primary or a result of cross reactivity. It should only be necessary to include primary allergens in immunotherapy for optimal results. For grass pollen a single test such as one skin prick test (SPT) or blood-IgE test will not necessarily reveal the primary

sensitising grass pollen. Choice of grass may depend on geographical location and timing of symptoms, as well as comparative response to grasses of different subfamilies (represented by Bahia, Bermuda and Ryegrass).

Numerous randomised controlled trials and meta-analyses including Cochrane reviews attest to the efficacy of AIT. However it is not known whether the general principle of AIT is applicable to any and all allergens. In theory if immunological mechanisms of allergy are consistent in all allergic disease, and if the quality of the allergen extract is sufficient in terms of the presence of the major allergenic proteins in sufficient quantities, then any allergen should provide effective immunotherapy.

Allergens for which level 1 evidence is available include the following:

- Pollens: grasses (timothy, Pooideae mixes), birch, mountain cedar, cypress, olive, parietaria, ragweed).
- Mites: Dermatophagoides pteronyssinus (DP).
- Moulds: Alternaria.
- Animals: Cat.

Other allergens in common use may have small trials or cohort descriptions as evidence for efficacy, but some allergens have little or no supporting evidence for efficacy.

Aerobiology

Allergens may be encountered predominantly:

- Indoors (mites, animal dander).
- Outdoors (pollens).
- Both indoors and outdoors (moulds).

Mites and animal danders are encountered predominantly in domestic homes but significant exposures can occur in other public places (e.g. buses, schools). Allergens may be carried by pollen grains or fragments, fungal spores or fragments, or allergenic protein on skin scales or dust particles.

Any airborne protein can potentially induce an allergic reaction. However, in general only particles smaller than 5um can be inhaled into the lungs triggering asthma. Pollen grains are usually larger than this, but submicronic respirable starch granules laden with allergen can be released, particularly following rainstorms.

Plant pollens may be dispersed by wind (anemophilous) or insects (entomophilous):

- Insect pollinated plants are usually not allergenic, since these pollens are large, heavy and sticky.
- Although often incriminated by patients, flowering plants are mostly entomophilous, therefore less likely to be significant causes of respiratory allergic symptoms.
- Anemophilous (wind pollinated) plants produce vast quantities of light airborne pollen, but tend to have insignificant appearing inflorescences (flowers) and often go unnoticed.
- Some plants are amphiphilous (pollination occurs by wind and insects).

Cross-reactivity of allergens

Allergen cross-reactivity occurs when an immune response (humoral and/or cellular), arising primarily and specifically in response to one allergen also reacts with another structurally similar antigen, to which the immune system might never have been exposed. Closely related plants are likely to have structurally similar allergens but cross-reactivity can also occur in phylogenetically distant plants.

Conversely plants which are closely related are non-identical and may have distinct epitopes and hence may be partially but not fully cross-reactive. Homologous allergenic proteins that are widely distributed across distinct plant groups are referred to as pan-allergens. An example is the birch pollen allergen Bet v1, a pathogenesis-related protein (PRP), also present as Aln g1 in alder pollen and as Mal d1 in apple (food).

Patients often have multiple sensitisations (poly-sensitised). This might be due to multiple primary sensitisation or to cross-reactivity. If it is certain that exposure has not occurred, then cross-reactivity is the only possibility.

It is important to remember that each allergenic species has multiple allergenic proteins which have multiple epitopes, some of which may be pan-allergens, some of which may have cross-reactive epitopes and others may have unique epitopes. Therefore, people may show different patterns of cross-reactivity.

Cross-reactivity can be proven if all IgE antibodies to an allergen can be pre-absorbed by another primary allergen in ELISA inhibition studies. Cross-reactivity can be present in some patients and not others (e.g. olive tree pollen s-IgE is fully absorbed by ryegrass pollen in some people, reflecting IgE to shared allergens such as profilin, but not in others). The presence of mono-sensitisation to olive tree pollen proves that it has unique epitopes (frequently of the allergen oleosin; Ole 1), not cross-reactive with ryegrass.

The implications of cross-reactivity for immunotherapy are that not all cross-reactive allergens need to be included in the immunotherapy prescription. It is recommended where possible to target primary sensitising allergens if known (e.g. patients in southern Australia are likely to be primarily sensitised to ryegrass with cross-reactivity to Paspalum, and therefore should be treated with ryegrass as it is unlikely that additional benefit will be conferred by the addition of Paspalum extract. However, patients from northern Australia are likely to be primarily sensitised to Paspalum with cross-reactivity to ryegrass and the reverse is likely to be the case).

It is often difficult to determine whether two separate sensitisations are independent or caused by cross-reactivity. If multiple sensitisations are present, including some to which exposure has not occurred or is minimal, this may be due to pan-allergens.

Native plants

Native Australian and New Zealand plants fall into grass, weed and tree groups:

- Native grasses are not thought to be important allergens.
- The major native pollinating weed is saltbush, in the chenopodium family.
- Several trees are anemophilous and can cause pollinosis, but are seldom dominant or important allergens. A few native tree pollens are available for allergy testing (mainly because these are introduced species in the USA), and are available for immunotherapy only as aqueous extracts. Other allergenic native trees may be cross-reactive with European/USA trees for the purpose of allergy testing (e.g. native callitris is cross-reactive with cypress but the effectiveness of immunotherapy with cross-reactive rather than primary allergen extracts has not been established.

Grass Pollen

- Grass pollens are the most common allergenic pollens implicated in seasonal allergic rhinitis.
- Grasses of allergenic importance are usually weedy, wild or agricultural plants rather than lawn grasses, with the exception of Bermuda grass.
- Pollination seasons are generally distinct in temperate regions (southern Australia and New Zealand) but less so in northern or subtropical regions.

- Representative grasses from the family Poaceae and allergenically relevant subfamilies are shown in table 1.
- Grasses in the Pooideae subfamily are almost completely cross-reactive with each other. Panicoideae (bahia, johnson) show some cross-reactivity with Pooideae but have clinically relevant non cross-reactive epitopes. Bermuda grass has significant distinct (non cross-reactive) allergenicity.
- Major panicoideae bahia (Paspalum) and johnson (Sorghum) are partially cross-reactive but independent sensitisation has been documented.
- Those in rural agricultural areas may be exposed and sensitised to cereal crops but these are highly cross-reactive with wild grasses (wheat, barley, oats and rye with Pooideae, maize with Panicoideae).
- Canola is a highly visible cropping plant but is entomophilous and not thought to be an important allergen; it produces volatile organic compounds (VOCs) which might cause respiratory irritation in some people.
- Ryegrass (or Timothy grass in Europe) is often taken to be representative of the Pooideae group. It is not known whether mixtures of different Pooideae grasses (three grasses, five grasses) available commercially have any advantage over a single representative pollen extract for immunotherapy. It is generally thought that where there is significant sensitisation to incompletely cross-reactive grasses (bahia, bermuda, johnson, cereal crops), the additional extracts should be used for immunotherapy, but there is little evidence for this. Addition of more partially cross-reactive extracts reduces the concentration of each.

Grass pollens are extremely frequent aeroallergens used in immunotherapy. The choice of immunotherapy extracts for treatment of seasonal allergic rhinitis will be made almost daily in allergy practice. The question of whether it is necessary to include all available sensitisations to achieve optimal results is unresolved. It is likely that best results will be achieved by including all primary independent sensitisations. Decisions may be aided on the following grounds:

- SPT reactivity - include strongest sensitisations.
- Seasonal pattern:
  - Spring only: ryegrass.
  - Prolonged season through summer: bermuda, bahia.
- Geographical location:
  - Northern regions: primary sensitisation more likely to bahia, bermuda, johnson.
  - Southern regions: primary sensitisation more likely to ryegrass.

In many cases immunotherapy with an extract of ryegrass pollen (or a mixture of three or five grasses closely related to ryegrass in the Pooideae family), will provide optimal results for grass pollen immunotherapy, but addition of bermuda, bahia or johnson can be considered depending on sensitisation, location and seasonal pattern.

Table 1: Grasses - All family Pooaceae

Subfamily	Common representative	Latin	Available immunotherapeutics	Generic therapeutics
Pooideae	Rye	*Lolium perenne*	individual pollens (SCIT, SLIT) 3 grasses (SCIT, SLIT) 5 grasses (SCIT, SLIT, SLIT tablet)	12 grasses (pooideae+ bermuda) 5 grasses/4 cereals (pooideae+ maize)
	Timothy	*Phleum pratense*		
	Sweet vernal	*Anthoxantum odoratum*		
	Meadow/Kentucky	*Poa pratensis*		
	Cocksfoot	*Dactylis glomerata*		
	Wintergrass	*Poa annua*		
	Wild oats	*avena fatua*	not available	
Panicoideae	Bahia	*Paspalum spp.*	Paspalum notatum	
	Johnson	*Sorghum halepense*	Johnson	
Chloridoideae	Bermuda	*Cynodon dactylon*	Bermuda	

Weed Pollen

- Weeds are prolific and widespread.
- Weed pollen allergens are only minimally cross-reactive with grasses.
- The independent contribution of weed pollens to allergic rhinitis and the necessity for inclusion of weed pollen extracts is often unclear in individual patients.
- Weed pollen sensitisation is proven to cause respiratory allergy because of seasonal differentiation and occasional patients with weed mono-sensitisation who are symptomatic.
- The majority of patients who are sensitised to weed pollens will be co-sensitised to grasses.
- Inclusion of weed pollen extracts in immunotherapy may be indicated if sensitisation is strong, exposure is likely to be heavy, and symptoms correlate with weed pollination season (where it is distinct from grass pollen season).

Table 2: Common allergenic weeds (minimal cross-reactivity between families)

Family	Subfamily	Species name	Common name	Available test/immunotherapy
Plantaginaceae		Plantago lanceolata	English plantain	Plantain
Asteraceae		Multiple;	Capeweed, Daisy	compositae mix
		Ambrosia artemisifolia	Ragweed	Ragweed
		Parthenium hysterophorus	Parthenium	no
Amaranthaceae	Chenopodioideae	Chenopodium spp.	Saltbush	chenopodiaceae mix (European species)
Urticaceae		Parietaria judaica	Wall pellitory	Wall pellitory
Boraginaceae		Echium plantagineum	Paterson's Curse/ Salvation Jane	no

Tree Pollen

- Many trees are anemophilous and trees may pollinate heavily in local areas.
- Trees generally pollinate for shorter periods than grasses, and mostly overlap with grass pollination seasons but some pollinate well before or after spring.
- Introduced (exotic) trees are the most important sources of allergenic pollen in developed areas.
  - Oleaceae can be important allergens, including olive trees in South Australia and some other parts, as well as ash and privet in some areas.
  - Birch, cypress and elm are also significant allergens to a minority of individuals in some areas (e.g. birch in the South Island of New Zealand).
  - Some trees are suspected or proven to be allergens but testing is not routinely available, e.g. white cedar/Chinaberry (Melia azaderach), a common street tree.
- Of the Australian native trees, casuarina is anemophilous and thought to be a significant allergen in rare cases but is no longer available for allergy testing or therapy.
- Callistemon (bottlebrush), melaleuca, eucalyptus and Acacia longifolia (golden wattle) are available for allergy testing and for therapy as aqueous extracts (Hollister Stier).
  - Sensitisation to eucalyptus or melaleuca is very rare, whereas positive SPT to acacia and callistemon are more common. However, the clinical significance of these allergens is questionable.
  - Callitris spp. (white cypress, Murray pine) are native conifers related to cypress. The pollen is allergenic but largely cross-reactive with commercial cypress pollen extracts.

Table 3: Trees

Common tree name	Latin name	Pollination season	Test available	Immunotherapy available
Olive	Olea europa	mid-late spring	Olive (olea europaea)(H-S) Olive (olea europea)(S)	Alustal, Staloral, aqueous
Ash	Fraxinus spp.	early spring	Ash, White (Fraxinus Americana)(H-S) Ash (Fraxinus excelsior)(S)	Alustal, Staloral, aqueous
Plane	Platanus acerifolia	early spring	Sycamore, American (Platanus occidentalis) (H-S) Plane (Platanus vulgaris) (S)	Alustal, Staloral, aqueous
Birch	Betula pendula	early spring	Birch mix (PRW)(H-S) Birch (Betula alba)(S)	Alustal, Staloral, aqueous
Cypress	Cupressus spp.	late winter/early spring	Cypress (Cupressus arizonica)(H-S) Cypress (Cupressus sempervirens)(S)	Alustal, Staloral, aqueous
Chinese Elm	Ulmus parvifolia	late summer/early autumn	Elm, Chinese (Ulmus parvifolia)(H-S)	aqueous only

As there are pollens that can't be tested, patients may present with seasonal symptoms, but negative allergy tests.

Moulds

- The term “mould” refers to a subset of fungi which produce hyphae and spores (as opposed to mushrooms and other solid fruiting bodies).
- Spores and hyphal fragments can become airborne and respirable.
- Outdoor airborne mould spores can be facilitated either by dry windy conditions (e.g. alternaria, cladosporium, epicoccum) or by increased humidity or rainfall.
- Indoor mould spore exposure is related to dampness, humidity and poor ventilation.
- The mould most important for respiratory allergic disease is Alternaria alternata, with both high prevalence indoors and outdoors, and high sensitisation rates.
  - Alternaria levels in outdoor air have been shown to be greatest in spring, summer and autumn and lowest in winter. Therefore, there is seasonal variability, generally extending beyond pollen seasons.
  - Importantly, Alternaria is abundant in dry inland areas as well as coastal areas. It is present in indoor air and in house dust samples.
  - Alternaria sensitisation is considered important for respiratory allergy; it has been implicated in asthma exacerbations by direct challenge studies.
- Other moulds of potential allergenic significance detected at substantial levels in Australia include (genus names) Cladosporium, Stemphyllium, Epicoccum, Aureobasidium (Pullularia), Penicillium, Phoma, and Helminthosporium.
  - Cladosporium is also an abundant atmospheric mould with similar characteristics and some cross-reactivity to Alternaria.
  - Penicillium, Aspergillus and Helminthosporium are mostly found indoors or in damper environments.
- Moulds are widespread and regional differences in prevalence have not been systematically studied.
- Moulds prevalent in Australia (and presumably New Zealand) are similar to those in other countries.
- Mould immunotherapy can be considered in allergic rhinitis or asthma where sensitisation is strong and disease activity correlates with exposure (e.g. seasonal symptoms in the absence of pollen allergy, or extending beyond pollen seasons, or symptoms indoors with proven mould exposure).
- Evidence for effectiveness of immunotherapy with mould extracts is positive (mostly limited to alternaria), but not as robust or extensive as for pollens and mites. A significant issue is the variability of allergen content in mould extracts from different manufacturers.
- It is recommended to use the same brand of extract for immunotherapy as used for SPT where possible.
- Chronic allergic fungal (mould) sinusitis with eosinophilic inflammation and allergic sensitisation to homologous moulds may benefit from mould immunotherapy, but evidence is of poor quality.

Dust mites

- The predominant house dust mite (HDM) species in Australasia is Dermatophagoides pteronyssinus (DP) but Dermatophagoides farinae (DF) may also be found.
- HDM are prevalent in humid coastal areas of Australia and all of New Zealand, but are low or absent in dry central Australia, although the prevalence can increase by using evaporative air conditioning.

- Houses with poor ventilation and temperature maintained above 20^{o}C tend to have higher HDM levels.
- HDM allergens tend to be large particles which settle, therefore becoming airborne only in disturbed air.
- Blomia tropicalis is a significant allergen in the far northern parts of Australia and is only partly cross-reactive with DP.
- HDM allergy is associated with perennial allergic rhinitis and asthma, as well as atopic eczema.
- Measures to reduce HDM exposure are of limited effectiveness.
- HDM Immunotherapy is indicated for HDM induced allergic rhinitis, allergic asthma and possibly eczema.
- Symptoms are usually perennial. However, in the absence of deliberate provocation testing (which is not routinely available), it is often difficult to determine whether HDM exposure is relevant to disease exacerbation, because:
  - Eczema and asthma are often endogenous or multifactorial.
  - Perennial rhinitis can be caused by factors other than HDM such as chronic sinusitis, or it may be idiopathic.
  - HDM levels cannot routinely be measured.
  - Variability in HDM exposure is difficult to characterise, therefore difficult to correlate with symptom variation.
- It has been shown that lower-level HDM sensitisation (SPT <6mm) is less likely to be associated with positive symptoms on challenge with HDM allergen, therefore immunotherapy would be questionable in those with marginal sensitisation unless evidence for symptom exacerbation related to HDM exposure is available.
- Indications for HDM immunotherapy are therefore clearest:
  - In those with strong sensitisation (larger SPT size, higher IgE level).
  - In those whose history is highly suggestive of disease activation with dust mite exposure.
  - Where there is a positive provocation test (when available).
- The majority of patients are sensitised to both DP and DF, whereas a smaller proportion are mono-sensitised, usually to DP.
  - Dual sensitisation may be due to cross-reactivity or separate exposure.
  - It is not clear whether HDM immunotherapy requires both DP and DF for optimum efficacy but combined extracts are commonly used in Australia.
  - DP monotherapy predominates in NZ.
  - Blomia tropicalis should be added in patients from tropical areas if sensitisation is significant.

Animal allergens

- Cat is very commonly allergenic and dog less frequently so.
- Other animal allergens including horse and rabbit are available for SPT and immunotherapy.
- Choice of extract for immunotherapy depends on major **unavoidable** exposure and test results.
- Animal extracts tend to be less reliable for diagnosis than pollens and dust mite, and the content of major allergens is highly variable between manufacturers.

- It is probably more important in the management of animal allergy that the source of extract used for SPT matches that used for therapy (e.g. in some cases a blood test for s-IgE to dog is positive and the patient has symptoms on exposure, but SPT is negative. This patient is unlikely to respond to immunotherapy using that brand of extract).
- A small number of trials indicate efficacy of SCIT and SLIT with cat, whereas the few trials of dog immunotherapy are either of poor quality or show immunological but not clinical efficacy.
- There are no clinical trials to support efficacy of immunotherapy to other animals.
- Mixed animal immunotherapy has not been subjected to clinical trial with animal provocation outcome measures.
- Immunotherapy for cat allergy is considered to be standard therapy.
- Immunotherapy for dog and horse allergy is also undertaken by most allergy specialists.

Allergen selection criteria

The choice of allergen/s depends on many criteria:

- Allergen/s shown to be relevant to patient exposure.
- Allergen/s shown to be positive on SPT or blood s-IgE testing.
- Allergen/s commercially available in a form suitable for immunotherapy.
- Allergen/s demonstrated to be of consistent and optimal quality.
- Allergen/s demonstrated to be effective for immunotherapy in randomised clinical trials.
- Allergen/s for immunotherapy matching allergens used for SPT.

It is important to consider the following:

- Clinical relevance of the allergen.
- Allergen extracts available.
- Major allergen or multiple allergens.
- Occasionally a challenge (deliberate exposure), may provide further evidence of the relevance of the allergen to the symptoms.

With regard to multiple AIT, many questions remain:

- Where allergens are shown to be cross-reactive, is it necessary to include all allergens or just a prototype species?
- Where there are multiple non cross-reactive pollens do all need to be included?
- In a patient sensitised to multiple allergens, should the allergen be included in the mixture in proportion to the size of the SPT or level of sIgE, exposure, symptom severity, or should all relevant allergens be included in equal proportions?
- Is it necessary to include all allergens of different groups to which the patient is sensitised (e.g. moulds in a patient predominantly pollen-allergic)?
- Is it possible to determine the dominant allergens to which the patient is exposed?
- Are some allergen species inherently more pathogenic than others, out of proportion to the SPT size? (e.g. plantain - sensitisation frequent, clinical importance uncertain).
- What level of sensitisation is significant in perennial allergens such as HDM?

These questions become more critical where SLIT is contemplated, when the range of available allergens is limited. Although allergen mixtures can be obtained, it is currently recommended that not more than two SLIT allergen preparations should be used.

Mixing allergens

Some allergen extracts, particularly moulds, cockroach and HDM, contain proteases which may degrade proteins over time and studies have shown reduced recovery of pollen proteins when mixed with these allergens. However, studies vary and the formulation of the allergen (glycerinated, aluminium hydroxide precipitated) as well as storage conditions may influence this effect. Therefore, aside from the issue of the reduction of concentration of individual allergens that results from mixing allergens in commercial preparations, it is not recommended to mix allergens from different groups because of protease activity and potential allergen degradation.

The following groups should in general be administered separately:

- Pollens (grass, tree and weed pollens may be mixed in the same preparation where indicated).
- Moulds (where available, it is common practice to mix different moulds in the same preparation although this has not been validated).
- Mites (different HDM species may be combined).
- Animals (different animal extracts are commonly combined; this has not been validated but animal dander extracts are not known to contain high protease levels).

Mixtures of pollen and HDM or pollen and mould are not recommended.

In theory mixtures of pollen and animal dander should be reasonably stable.

Mixing of non cross-reactive allergens in some commercially available products (Alustal, Staloral) results in a reduction in the final concentration of each allergen (e.g. a 1:1 mixture of ryegrass and ragweed will result in only 50% of the final concentration of each in the extract). This may not be the case for specialist formulated aqueous preparations where a full strength of both separate allergens can be included in the extract by reducing the proportion of diluent.

IMPORTANT NOTE: Different brands of extracts, or aqueous and alum absorbed extracts should never be mixed in the same bottle due to unknown risk of compatibility, stability and risk of administration.