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Summary of recommendations for the design of clinical trials and the registration of drugs used in the treatment of asthma ☆

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Summary With new drugs being introduced to treat asthma it is timely to review criteria that can be used to assess efficacy in clinical trials. Anti-asthma drugs are classified into symptoms-modifying, symptom preventers and disease modifying agents. Attention is drawn to the types of experimental evidence required in preclinical studies to support further clinical development of a new therapy. Clinical trials demand careful selection of patients to maximise the strength of the efficacy signal according to the type of trial being designed. While provocation tests are useful in suggesting efficacy, negative tests do not necessarily indicate lack of anti-asthma activity. Therapeutic trial designs need to take account of duration of treatment, dose–response relationships and confirmatory trials. Outcome measures include symptoms, lung function, reduction in concomitant medication, exacerbations, quality of life and measures of inflammation. Interpretation of results need to

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include the clinical relevance of any changes as well as statistical significance. Special consideration needs to be given to the evaluation of drugs for acute severe asthma, asthma in children and older people, co-morbidity such as rhinitis, and inhaler devices. As with all drugs introduced into practice, careful attention needs to be paid to both short- and long-term safety.

Introduction

Asthma is a chronic inflammatory disorder of the airways resulting in airway re-modelling with increased responsiveness to exogenous and endogenous stimuli and variable airflow limitation.[1,2] In its typical form, asthma has its onset in early childhood and presents with symptoms of wheezing, breathlessness and cough, occurring either spontaneously or in response to external stimuli. The disease has a varying natural history, ranging from a transient disease of childhood through to persistent severe disease throughout life.

In childhood, asthma is frequently associated with atopy (the predisposition to develop immunoglobulin-E against specific allergens) and is associated with other features of atopy, including eczema, rhinitis and sinusitis. Late onset asthma may occur in association with sensitisation to occupational exposures involving either IgE or non-IgE mechanisms or in the absence of any known stimulus (intrinsic or cryptogenic asthma).

It is conceivable that, in the future, asthma may not be defined as a single disease entity but will be recognised as a number of distinct conditions of differing aetiology, sharing a similar pattern of symptoms.

International treatment guidelines have been established for the management of the condition. In the development of new treatments specific aspects need to be considered and these include:

- the present classification of drugs used for the management of asthma.
- disease severity and the impact of this in clinical trials.
- appropriate trial design and duration.
- appropriate use of endpoints and their duration (including exacerbations).
- evaluation of efficacy and clinical validity.
- special populations, including children and elderly.
- evaluation of safety.

The aim of present international treatment guidelines is to control asthma by reducing underlying lung inflammation, improving symptoms and preventing exacerbations.

Objectives and nomenclature

The objectives of drug development in asthma can be divided into four categories:

(i) Prevention of asthma in individuals at risk.
(ii) Prevention of symptoms, exacerbations and further complications including morbidity and mortality.
(iii) Treatment of symptoms and exacerbations.
(iv) Cure of the disease, defined as the absence of symptoms, exacerbations, and variable airflow limitations one year after stopping treatment.

Only objectives (ii) and (iii) are currently attainable, but advances in our knowledge of the aetiopathogenesis of the disorder, together with novel therapeutic approaches (pharmacogenetics, therapeutic vaccination, immunomodulatory agents) may allow studies addressing (i) and (iv) in the future.

Anti-asthma drugs may be classified in the following categories:

- Symptom-modifying ('relievers', e.g. bronchodilators).
  These products act by relaxing smooth muscle and thus improving airflow through the conducting airways.[3] Registration of this class of drug requires demonstration of a beneficial effect on objective measures of airflow (e.g. FEV_1, PEFR), and on symptoms, with no detectable adverse effect on the inflammatory process or progress of the disease.
- Symptom preventers ('controllers').
  These products prevent or reduce symptoms of asthma, generally by their effect on the airway inflammatory process.[3] Registration of this class of drug requires demonstration of benefit in symptomatology, disease control, lung function, exacerbations and/or quality of life, supported by evidence of relevant pharmacological effects on the inflammatory process in vivo.
- Disease-modifying agents.
  Currently no products are available with a demonstrable effect on the progress or severity

of asthma or for prevention in patients at risk of the disease. Registration of products that would affect the progress of asthma would require long-term studies, demonstrating a change in the severity rating of the disease in a significant number of patients. Registration of drug products to prevent asthma developing would require long-term studies in patients identified as at high risk of developing asthma (predominantly children). Sensitive and accurate prognostic tools and a placebo group would be important elements in registering this type of drug product.

- Structure-modifying agents.
  Currently there are no products that demonstrate a effect on the structural changes seen in chronic asthma ('airway remodelling') and the progress or severity of disease. Registration would require direct evidence of structural effects (from bronchial biopsy or imaging techniques) together with evidence of associated benefit (improvement in lung function or symptoms, reduction in use of other medications) and a prolonged absence or reduction of objective signs and symptoms of disease. The development programme should also demonstrate that there is no long-term decline in lung function or increase in bronchial hyper-responsiveness (BHR).

Preclinical studies

In vitro and in vivo studies should be conducted to provide some scientific rationale for use of an experimental asthma drug in human studies. Guidance on the preclinical safety testing, including tests for reproductive toxicity, genotoxicity and carcinogenicity and advice on the design of toxicokinetic studies are available in reports from the International Conference on the Harmonisation of Technical Requirements for Pharmaceuticals (ICH) (www.ifpma.org).

In vitro tests are of use in high throughput testing and in ascertaining the biological responses of compounds, however, in vivo studies are generally more informative. Although there is no animal model that reproduces the chronic relapsing and remitting features of human asthma, animal models can display some pathological features of the asthmatic process.[4] Presently, there are no animal models with which to assess potential disease-modifying drugs. In the future genetically modified animals may provide more representative models of human asthma.

Clinical trials

Diagnosis and inclusion criteria

Diagnosis

It is necessary to ensure that a patient population for a trial is homogenous. Diagnosis should be based on age, history, symptoms and signs, airway observations over time and current treatment and control.

In the GINA guidelines,[3] asthma severity is divided into intermittent, mild persistent, moderate persistent and severe persistent. The classification of severity is complicated by the fact that many patients are treated with anti-inflammatory agents such as inhaled corticosteroids, and, because of the risks associated with discontinuation, the judgment of the level of severity of asthma is often made in the presence of inhaled corticosteroid therapy.

Exacerbations have been defined as episodes of worsening of asthma with a predetermined increase in symptoms and a fall in PEFR. A severe exacerbation is usually defined as one that requires oral corticosteroids as judged by the clinical investigator, or an episode in which morning PEFR falls by more than 30% from mean baseline PEFR on at least 2 consecutive days.[5]

Airway observations include variability in airflow limitation, and an increase in FEV_1 following inhalation of a short-acting β-agonist of at least 12% of the baseline value is a commonly used measure.[6] In the presence of severe airflow obstruction, such as a baseline FEV_1 of less than 1 l, an increase of 200 ml is considered significant. Peak expiratory flow rate (PEFR) may also be used, requiring an increase of at least 60 l/min to confirm a diagnosis of asthma. In monitoring lung function, FEV_1 compared with PEFR is a robust measurement being highly repeatable. Measurements such as the ratio of residual volume to total lung capacity (RV/TLC), slow vital capacity (SVC) and trapped gas volume measurements could be helpful as supportive data in understanding the nature and extent of the disease.

Inclusion criteria

In Phases II and III trials, a broad range of patients should be included based on baseline lung function, e.g. baseline FEV_1 between 45% and 85% of predicted. Additional randomisation criteria such as the requirement for a minimal level of symptoms at run-in and the absence of a recent exacerbation for 6 weeks prior to enrolment will secure sufficient scope for improvement. Level of severity may

be stratified, for example by taking into account the degree of symptoms, or baseline FEV_1 or the amount of corticosteroid therapy. Co-morbidities such as rhinitis, simusitis and gastro-oesophageal reflux occur in association with asthma and should be recorded because these may confound the treatment effect. Atopy, defined by positive skin prick tests to common aero-allergens and the measurement of serum IgE, may be important when certain specific agents are being tested. The inclusion or exclusion of smokers needs to be considered.

Provocation tests in humans

Most provocation tests are done early in the development of new anti-asthma compounds as proof-of-concept studies for decision-making purposes.

Such testing requires rigorous and distinct experimental protocols for each of the various bronchoconstrictor stimulae[7] as well as standardised methodologies for data analysis.[8]

Antigen challenges

Bronchial allergen challenges: Following allergen inhalation, in asthmatics with specific sensitisation to that allergen, IgE-mediated cells rapidly release histamine, prostaglandins and leukotrienes leading to bronchoconstriction. This early asthmatic response (EAR) (20% fall in FEV_1 from baseline) gradually improves over the next 2 h.[9] In approximately 50% of subjects, a late asthmatic response (LAR) is seen 2–4 h after challenge and may last up to 24 h. Traditionally, a decrease in FEV_1 of $>15\%$ from baseline between 4 and 12 h after challenge is considered diagnostic of LAR. Although most of the currently available anti-asthma drugs show beneficial effects on the LAR, there is considerable debate as to what predicts the development of the LAR and the relevance of this model to clinical asthma is questioned.[10]

Nasal allergen challenges: Reproducible nasal symptoms and cellular recruitment are induced in nasal secretions[11] which make them suitable for a cross-over study. The advantages of the nasal allergen challenge model compared to the bronchial challenge model are that the nasal challenge model is safer, easier to perform, and easier to repeat, and nasal mucosa is easily accessible for repeated measurements. The disadvantage is that nasal challenge is not a direct assessment of bronchial reactivity, but a surrogate.

Exercise challenges

The degree of protection afforded by a drug against exercise-induced bronchoconstriction may be used to assess therapeutic benefit in patients with mild asthma who have minimal symptoms and near-normal airway function. Although the pathogenesis of exercise-induced bronchoconstriction is incompletely understood, airway cooling and drying are thought to release inflammatory mediators leading to airway smooth muscle constriction.

Non-specific challenges

BHR is a characteristic feature of asthma that is sensitive to reliever and controller drugs. BHR can be measured by inhalation challenge testing with methacholine, histamine, leukotrienes, bradykinin, or adenosine monophosphate (AMP) as well as after exposure to non-pharmacologic stimuli such as hyperventilation with cold dry air, SO_2, and inhalation of hypertonic or hypotonic aerosols.

Negative and positive predictive values

In allergic asthma, dissociation between airway inflammation, airway function and airway hyperresponsiveness has been reported[12] suggesting that the effects of therapy should not be assessed by a single provocation test. If adequately powered, measurements of airway function, airway inflammation and BHR can be done before and after antigen challenge in a single clinical study. At the end of the study, changes from baseline can be compared between treatment groups (placebo or active comparator). A negative provocation test is not necessarily indicative of a lack of activity. On the other hand, positive results in such tests probably indicate a good chance of positive outcome in confirmatory therapeutic efficacy studies since the compound has shown beneficial effects under difficult conditions.

Therapeutic trial design

Classically, pivotal trials should be randomised, parallel group, double blind and controlled. In Western Europe most asthmatics with moderate or severe disease are treated with inhaled corticosteroids and this treatment should not be withdrawn. This problem can be addressed by the use of an add-on design. Trials with comparators are recommended as part of the registration dossier in Europe. Comparison to reference therapies is needed for pharmacoeconomic purposes. The choice of comparator depends on the treatment goal for the drug and the target claims. Classical comparators, such as inhaled corticosteroids for anti-inflammatory controller therapy, are advocated.

Duration

The duration of asthma trials depends on the treatment strategy and should be tailored to the outcome and intended labelling, as below:

- studies in acute severe asthma may require a study duration of only a day or days,
- for regular, or as needed, use of bronchodilators, short term trials (6–12 weeks) may be used,
- for controller therapies, trials lasting at least 3 months are necessary,
- for a study of exacerbations, trials should be extended to a minimum of 6 months,
- therapies that target the underlying structural changes or the course of the disease, will need longer-term trials of at least a year and consideration should be given to a follow-up period after drug withdrawal to ascertain persistence of effect,
- disease-modifying drugs impacting the natural history of the disease may require several years of study.

Dose: response trials—Phase II

The general principles of "dose response information to support drug registration" are contained in ICH E4 (www.ifpma.org). Design and interpretation of these studies can be enhanced by information on mechanism of action, drug affinity to the target and drug metabolism and pharmacokinetics.

Administration of a drug by the inhaled route, as frequently used for asthma, brings an additional level of complexity. Drug effectiveness for inhaled medication is largely a measure of topical activity while safety relates to both local and systemic drug effects. Dose–response relationships, particularly for inhaled drugs, may be complicated by asthma severity (which influences the site and extent of drug deposition) and disease variability. Lack of differentiation between doses may reflect the large inter-subject variability of the inhaled dose delivered (as reflected in plasma concentrations), sensitivity to end points,[13] and duration of the study (influence of onset of action and time to maximal response). It is prudent to choose the therapeutic doses of an investigational drug in Phase II dose ranging using the same end points to be used in the Phase III trials.

Confirmatory trials—Phase III

- Equivalence or non-inferiority design:
  Equivalence studies test the clinical hypothesis that agents (usually a new and a standard therapy) differ to an extent that is clinically unimportant. Non-inferiority trials test the hypothesis that the new agent is at least not inferior to the standard treatment by a prespecified amount. In equivalence or non-inferiority trials similar weight is given to the per-protocol and the intent-to-treat analysis. Equivalence trials usually require that the 95% confidence interval for the difference between treatments be within some a priori clinically important treatment boundary. Equivalence or non-inferiority trials are generally necessary for the assessment of a new delivery device for the same inhaled drug, but may also be used to compare 2 drug therapies of the same class (ICH E10, www.ifpma.org).
- Cross-over design:
  In general, cross-over designs should not be used for confirmatory asthma trials, due to the variability of the disorder. However, they may be used to understand better the mechanisms of a treatment or to investigate the heterogeneity of responses to treatment.
- Add-on versus monotherapy design:
  The ideal evaluation of a new drug for asthma would be a monotherapy trial, however, in practice it is difficult to recruit any but the mildest asthmatics who are not already receiving maintenance therapy, e.g. inhaled corticosteroids. Thus, either the current therapy has to be withdrawn and substituted by the test agent or an add-on design must be adopted. In an add-on study patients are randomised to receive the test agent or placebo in addition to their current anti-asthma therapy. It is desirable to recruit patients who are all on the same maintenance therapy, e.g. low dose inhaled corticosteroids, or at least to stratify for different treatment regimens.
- Withdrawal (sparing effect) design:
  The withdrawal of a controller drug, usually oral or inhaled corticosteroids, under the cover of the test therapy or placebo, is helpful but may pose difficulties in recruitment. In particular, the run-in period during which the minimum effective dose should be established is usually too short and most withdrawal studies have shown that the minimum effective dose was not reached. Steroid sparing may also be used as a secondary endpoint to support key efficacy claims but does not necessarily lead to a claim itself. Add-on and corticosteroid-sparing components can be combined into a single trial.
- Effectiveness design:
  Real life, pragmatic or effectiveness trials should not be used for confirmatory efficacy but may provide useful supportive data and are helpful in confirming the safety profile. In these trials, broader cohorts of asthma patients are treated in

the absence of disease-related exclusion criteria. In pivotal trials, the selection of patients usually excludes "outliers" who may represent a large part of a population of asthmatics, e.g. tobacco smokers. Co-morbidities (e.g. rhinosinusitis) and health economics can also be taken into account in effectiveness studies.

Outcome measures

End-points used to determine drug effectiveness have been influenced by knowledge of the pathogenesis of asthma and mechanisms of action of current therapies. Bronchodilator-induced improvements in endpoints such as FEV_1 and PEFR correlate well with improved asthma symptoms and therefore objective measures of lung function became the standard both in clinical practice and regulatory assessment.[14] With the hypothesis that pulmonary inflammation causes asthma and with the advent of new mechanism-based drugs, interest has focused on asthma exacerbations and patient-centred measures as important endpoints for testing new therapies. For many drugs, co-primary endpoints combining lung function and patient-centred outcomes should be used in confirmatory efficacy studies. The minimal important changes for many asthma clinical trial assessments have been established.[15]

Symptoms

Patients recognise a number of symptoms including cough, wheeze, chest tightness and dyspnoea. In clinical trials patients self-report their symptoms on diary cards. With increasing focus on asthma control this reporting system is being supplemented by other patient-centred outcome measures, especially composite scores of asthma control.[16] Symptom scores or composite endpoints require clinical validation to be acceptable for registration.

Lung function

There is a variety of methods used to measure lung function including spirometry measures (FEV_1 and FVC) and PEFR. FEV_1 has several advantages, being robust, repeatable, standardised, easy to perform and reflecting airway calibre. PEFR is easier to perform, and enables an objective measure to be made by the patients themselves at frequent intervals, however is a less reliable measurement than FEV_1 because it is not observed in the clinic. In more severe disease the peripheral airways, including the alveoli, may become involved and FEV_1 better reflects airflow in the more distal generations of the bronchi than PEFR but is still not an adequate assessment of the peripheral airways. Neither FEV_1 nor PEFR are sensitive to obstruction in the lung periphery and other measures of lung function, such as the ratio between residual volume and total lung capacity, a SVC or inspiratory capacity, may be useful in assessment of this "silent" area of the lung in asthma.

Reduction in concomitant medication

In clinical trials the use of a concomitant medication, usually a short-acting inhaled bronchodilator (prescribed for immediate relief of symptoms), is an additional useful outcome measure. Reduction in use of such medication will confirm an improvement in lung function and symptoms. Similarly, reduction in inhaled or oral corticosteroid usage, when trial medication is added to the treatment regimen, is also used as an outcome measure. Establishment of a baseline corticosteroid dose, inherent variability of the disease and clinical relevance of observed reductions are challenges with this outcome measure.

Exacerbations

The definition of exacerbations in asthma combines the occurrence of symptoms, impairment in airflow, and medication needs. Frequency, duration and severity need to be considered. Changes in concomitant medication will reduce the relevance of exacerbation measurements.

Quality-of-life

Quality-of-life (QoL) measurements may be in the context of general health, or asthma specific. General health measures such as the SF-36 are standardised, but they may not be responsive enough to identify small but clinically important changes in asthmatic patients' quality of life.[17] Asthma-specific questionnaires are available for adults, adolescents and children and the degree of change considered to be of minimal clinical relevance has been identified.[18]

Measurements of inflammation and airways pathology

Surrogate endpoints using biomarkers to demonstrate disease progression would greatly facilitate the development of disease-modifying drugs. More comprehensive and sophisticated analyses involving genomics or proteomics may offer this in the future.

Evaluation and analysis

Interpretation of results cannot rely on statistical significance alone but needs to include the clinical relevance of any changes, taking account of expert

clinical opinion, in the context of adequately powered prospective studies.

The use of surrogates and non-clinical markers of disease activity is to be encouraged particularly in early drug development and to characterise the pharmacodynamic activity in relation to clinical efficacy parameters. Care needs to be taken not to over-interpret findings (e.g. anti-inflammatory effects based on isolated findings) and conclusions need to be made in the context of the population, study design and surrogate/disease marker.

Published systematic reviews of asthma treatments, which included meta-analyses, have been criticised.[19] The use of meta-analyses for the evaluation of therapies for regulatory submissions is considered in a draft guideline (www.emea.eu.int). This states the accepted regulatory purposes for meta-analysis, several which could be utilised in the development of an asthma therapy. Ideally, the meta-analysis should be prospectively planned as part of the clinical development programme. The meta-analysis protocol details the key aspects to be undertaken very much in the same way as a study-related protocol. Retrospective meta-analyses may be acceptable but only when stringent prerequisites can be fulfilled. The meta-analyses need to be assessed with regard to both the clinical significance and robustness of the findings.

Special situations

Acute severe asthma

Acute severe asthma may be life-threatening. It may develop over days or rapidly over minutes. Patients are usually in varying degrees of distress with dyspnoea and chest tightness, and may have difficulty in speaking full sentences. Peak flow measurements are severely reduced, usually by more than 50%. Significant hypoxaemia is present, with either hypocapnia, or during severe episodes, hypercapnia.

These patients should be treated in hospital. Standard therapy for these episodes consists of oxygen therapy, rapid-acting bronchodilators and corticosteroids. There are few published trials on the optimal timing and dosing of corticosteroids, and some recent studies indicate that the recommended doses of intravenous hydrocortisone are unnecessarily high.

Studying newer agents in the treatment of acute severe asthma is not easy. It is difficult to use alternative treatments in a situation that is potentially life-threatening. In this regard, studies of newer agents may need to be performed in addition to standard therapy where endpoints are either spirometry, need for additional standard therapy, or clinical outcomes. The sample sizes required for adequate power may be large, making these difficult, expensive, time-consuming, and not routine. However, there is a medical need for new therapies in acute severe asthma and additionally, adequate trials of existing therapies along with analytical work, such as endpoint validation and severity definitions, are required.

Paediatric asthma

Children exhibit important age-related differences in anatomy, physiology, pathology, development and drug metabolism from adults, as well as in social and emotional factors. Therefore, pharmacodynamics and kinetics should be addressed separately in paediatrics.

The pathology of asthma is often less progressed in children, with a smaller degree of airway remodelling, that may be reflected in differing responses to treatment. Paediatric asthma is generally less severe than in adults, with intermittent and mild persistent disease characterising the majority of patients. Therefore, response to treatment may differ from the response observed in adult patients with longer standing chronic disease and should be studied separately.

Lung function is normal (or can be normalised by therapy) in between symptomatic episodes in the majority of paediatric asthma. Therefore, study inclusion may often rely upon the documentation of bronchial reactivity, using the number of episodes of bronchoconstriction for example as an endpoint.

Treatment and outcome measures need to be appropriate to the age of the child, using the ICH classification of paediatric age ranges (www.ifpma.org). Techniques for evaluating lung function in infants and young children should use effort independent methods validated in these age-groups. Questionnaires and diary cards may need to be completed by parents/carers and will require separate validation for infants, pre-school, and schoolchildren.

Asthma in the elderly

There are several problems with respect to both diagnosis and management that make asthma in the elderly of special consideration. A major problem in this age group is the certainty of the diagnosis, particularly in differentiating it from chronic

obstructive pulmonary disease (COPD) and other conditions such as congestive cardiac failure, endobronchial neoplasm or pulmonary fibrosis. Diagnosis can be defined as significant reversibility to inhaled bronchodilator β-adrenergic agonist, taken as an increase in FEV_1 of 15% or of 200 ml, whichever is greater, the latter particularly in the presence of significant baseline airflow obstruction.

Satisfactory control of symptoms is not usually adequately achieved in this group of patients. Self-monitoring of peak flows and symptoms is usually not a problem, although incoordination due to arthritis, muscle weakness, neurological problems or deteriorating cognitive and mental ability may lead to poor usage of inhalers. Many elderly patients with moderate to severe airways obstruction are prescribed home nebulisers for administration of β-agonist bronchodilators. Glucocorticoid therapy is of proven benefit, but the potential for systemic side-effects may be more prevalent in the elderly. Use of oral corticosteroid therapy may also be associated with greater probability of glucose intolerance, systemic hypertension, cataracts and osteoporosis, which are all more common in the elderly. Oral therapy has special considerations since there may be changes in metabolism of drugs due to ageing or concomitant disease processes, and potential for interactions with other drugs taken. This highlights the need to consider the inclusion of elderly patients in therapeutic trials of new therapies.

Co-morbidity

Epidemiological studies have shown that at least 60–70% of asthmatics also experience rhinitis and 20–30% of patients with allergic rhinitis also have asthma. Asthma can also co-exist with COPD. The airflow obstruction of COPD may either be totally non-reversible or partially reversible with an anticholinergic or β-adrenoceptor bronchodilator. Other co-morbidities that impact upon asthma are gastro-oesophageal reflux and chronic sinusitis. Asthma is also susceptible to the influence of sex hormones, particularly progesterone which might, in part, explain why chronic severe asthma is more frequent in adult women whereas, in children, asthma predominates in males. Usually patients with co-morbidity are excluded from clinical studies. However, real patients have such co-morbidities and trials are needed in this area. These may be done in late-stage development or during effectiveness studies.

Inhaler devices

Inhalation therapy is widely used for the treatment of asthma. An ideal device should deliver a reproducible, pre-determined dose of drug to the lung and should have minimal deposition of drug other than in the lung so that minimal systemic effects occur.[3] The CPMP is close to publishing guidance on the pharmaceutical requirements for both dry powder inhalers and metered dose inhalers. Similarly, the European Committee for standardisation (CEN) has drafted procedures for the evaluation of nebulizing systems and their components.

The most commonly prescribed inhalation devices include pressurised MDIs with or without spacers, dry-powder inhalers, and nebulisers. There are large differences in design and performance between the various devices. The characteristics of each individual drug + device combination should be carefully assessed by both in vitro and in vivo methods. This should require clinical testing, depending on the acceptability and robustness of the surrogate in vivo methods.

Lung dose from inhaled drug delivery is important to establish, as it determines the efficacy and risks of treatment. Such information may be obtained from animal models, pharmacokinetic studies and from imaging techniques. Gamma scintigraphy, which provides only 2-D imaging, may be use to estimate lung deposition. However, potentially more robust 3-D techniques include single photon emission computed tomography (SPECT) and positron emission tomography (PET). 3-D imaging assesses more accurately regional deposition patterns in the lung. Further validation of these imaging techniques is required.

The standard in determining clinical efficacy and bioequivalence between delivery systems remains the chronic dosing clinical trial. Pharmacodynamic studies such as challenge studies may be an alternative for particular classes of molecules such as beta agonists. Well-powered and adequately designed clinical trials to show non-inferiority or equivalence should normally be performed. Clinical trials also help in providing data to guide the prescribers on substitution of different devices containing the same drug.[20]

It is not generally possible to extrapolate directly from data in adults to children. Data should be generated to show that the device can be used by children and that the inspiratory flow rate needed is achievable by the targeted age group.

Safety

Core safety assessments required during preclinical and clinical development include:

- in vitro genotoxicity/mutagenicity,
- animal fertility and embryotoxicity studies,
- acute and chronic animal toxicology (the latter in two different mammalian species),
- recording of sought and volunteered adverse reactions during clinical studies,
- routine physiological and laboratory screening, e.g. electrocardiography (ECG), serum haematology and biochemistry.

Additional assessments may be indicated, based on the findings from preclinical research or on the known pharmacology and toxicology of the drug class. There are some special aspects of asthma therapy which necessitate specific safety assessments:

Patient population: asthma is particularly prevalent in younger people, so potential drug effects on growth, development, maturation, and fertility are important. In elderly patients adverse effects related to concomitant disease (e.g. impaired hepatorenal function) or its treatment (potential drug interactions) are important.

Inhaled therapeutics: specific preclinical inhalation toxicology studies are mandatory. All inhaled medications have the potential to cause bronchospasm; this is often related to non-drug components. The potential for inducing bronchospasm should be evaluated during patient studies, measuring expiratory flows before and 5 min after drug administration. A drop of 15% in FEV_1 or 20% in PEFR is taken as a positive test. Patients receiving inhaled proteins in clinical trials should be monitored for symptoms suggesting an immune-modulated pneumonitis/alveolitis (cough, fever, dyspnoea) that would mandate appropriate investigation (lung imaging, measurement of gas transfer factor).

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