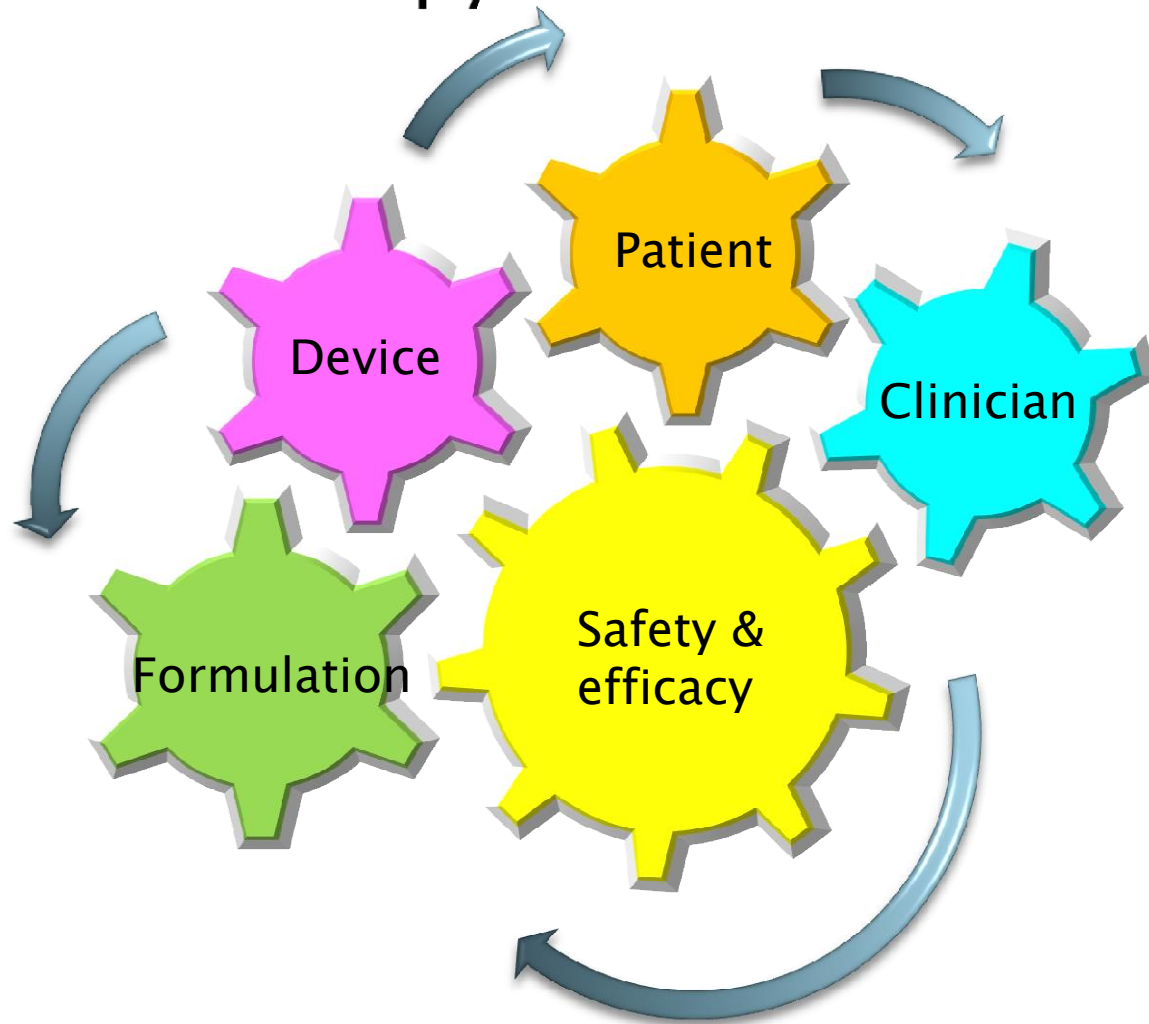# THE IMPORTANT FACTOR
for better clinical outcomes
WITH INHALER THERAPY

Important factors for better clinical outcomes with inhaler therapy
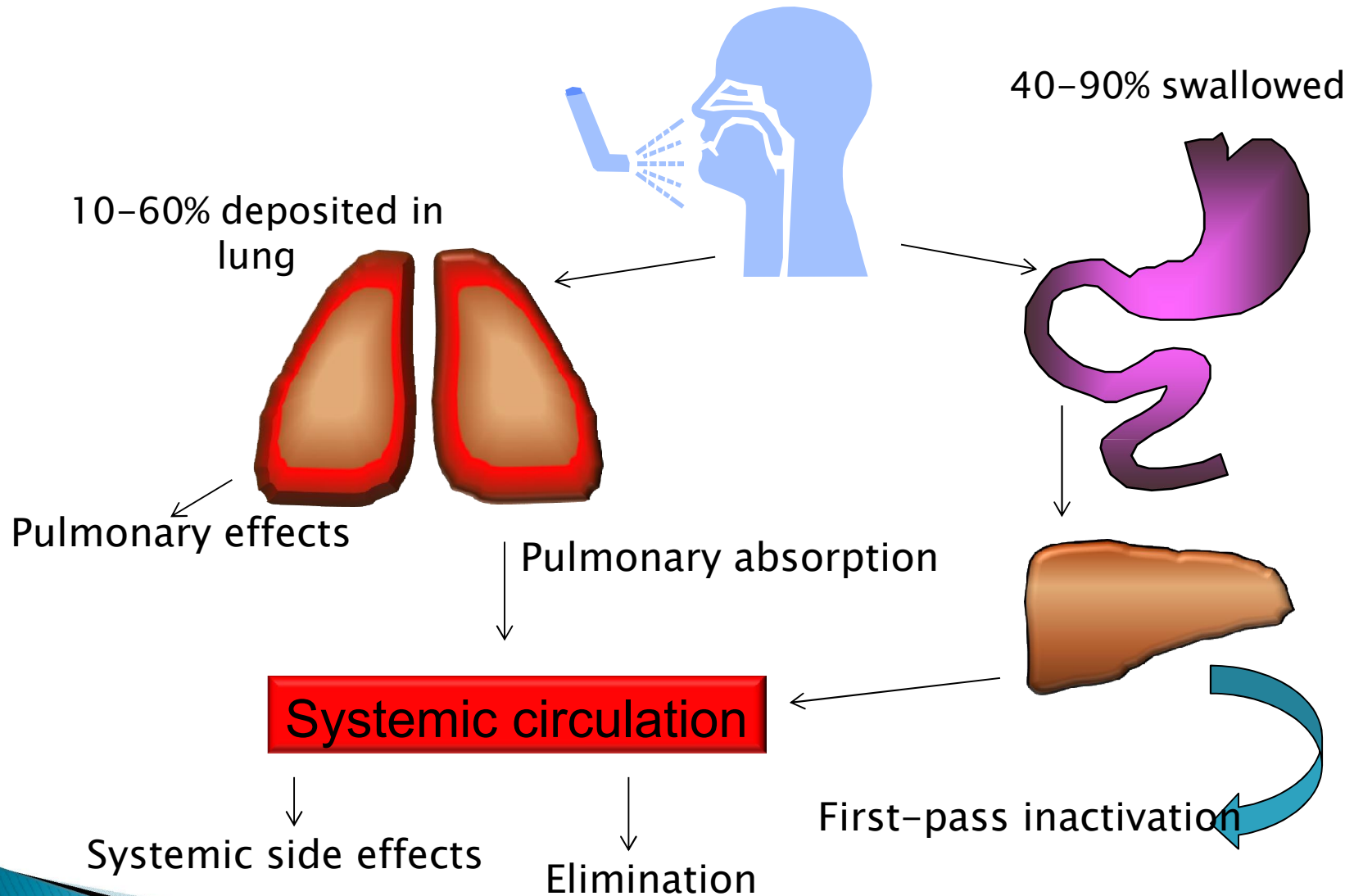
1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297–1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308–1331

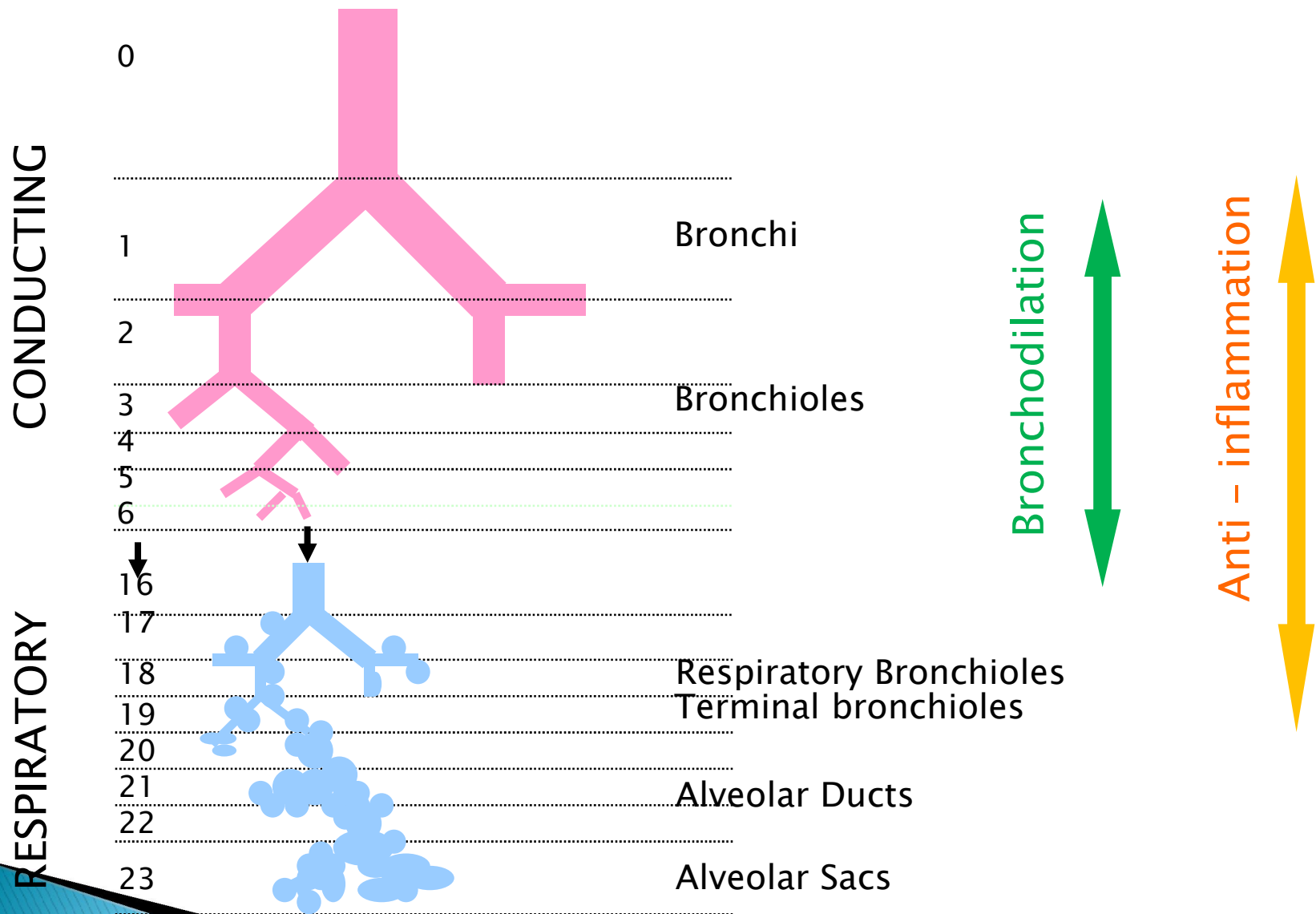# Overview of pulmonary aerosol delivery

Pharmacokinetics of inhaled therapy

40-90% swallowed

10-60% deposited in lung

Pulmonary effects

Pulmonary absorption

Systemic circulation

Systemic side effects

Elimination

First-pass inactivation

Defining the Airway Targets – Airways Anatomy

Adapted from Lee SL et al., AAPS J. 2009 ;11(3):414–23.

Hypothesis from available data
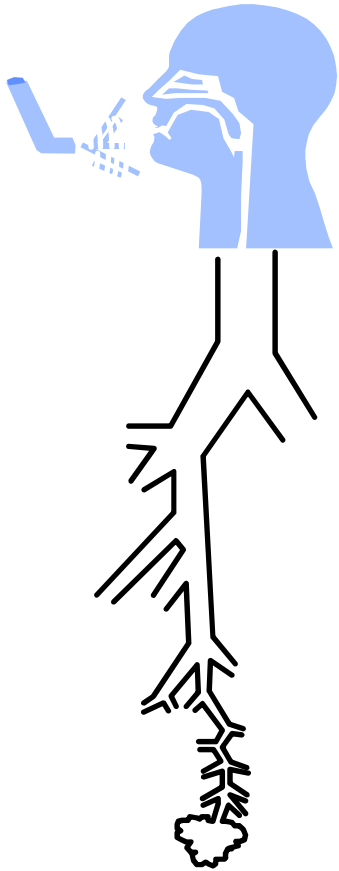
Particle size (microns)	Regional deposition	Efficacy	Safety
>5	Mouth/oesophageal region	No clinical effect	Local side effects
1–5	Upper/central airways	Clinical effect	Subsequent absorption from lung
<1	Peripheral airways/alveoli	Clinical effect	Subsequent absorption from lung

Fine particle dose – emitted dose containing particles <5μm
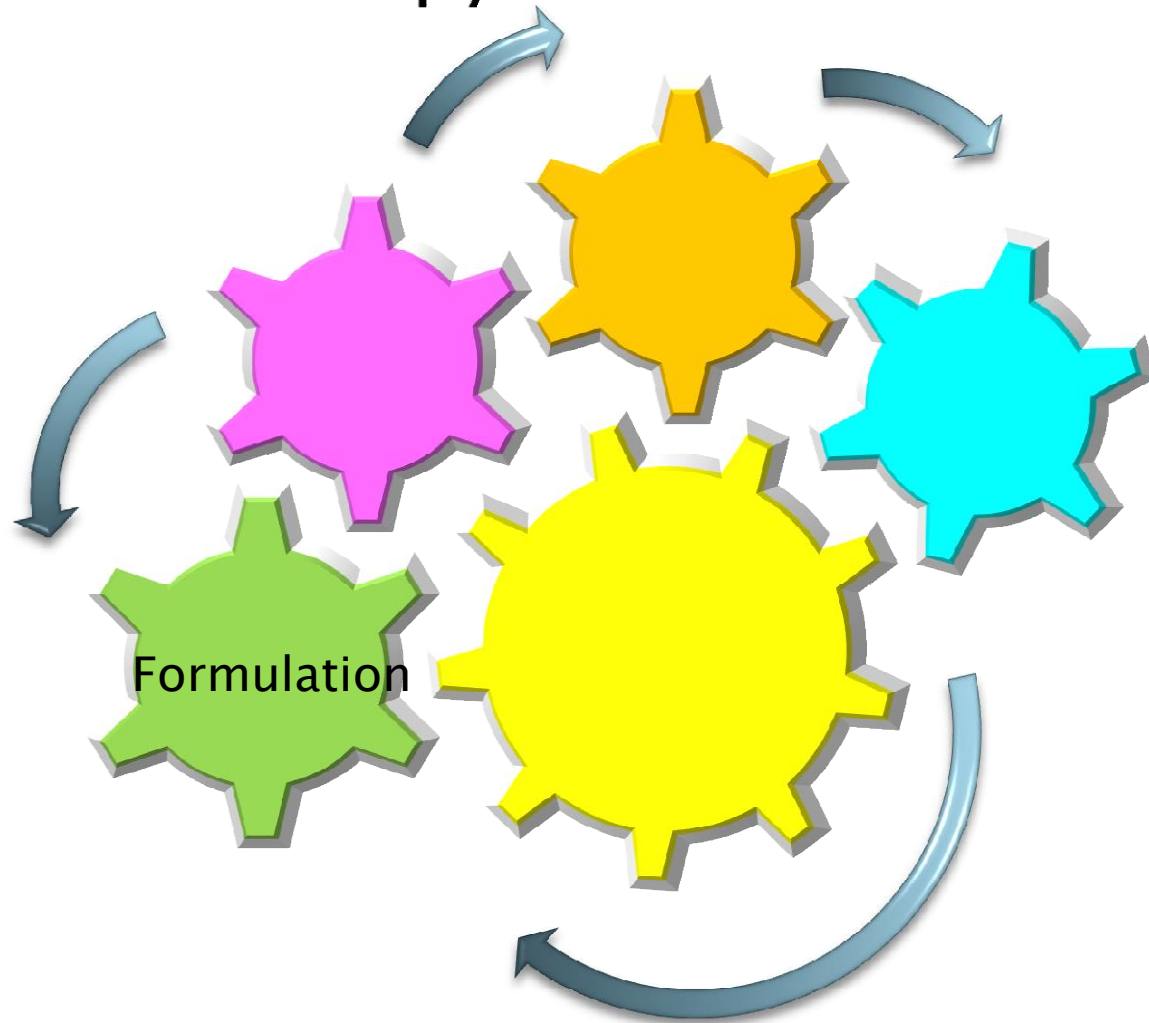
Adapted from Laube et al., Eur Respi J 2011:37:1308–1331
Chrystyn Allergy 1999; 54(s49): 82–87.

Important factors for better clinical outcomes with inhaler therapy

Formulation

1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297–1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308–1331

Bioequivalence of inhaler therapy

What Bioequivalence means in Drug Development ?

- Bioequivalence means "the absence of a significant difference in the **rate and extent** to which the **active ingredient** or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the **site of drug action** when administered at the same molar dose under similar conditions"

1. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.1

Bioequivalence: oral

API + Excipients → Dissolution testing → Human PK study

API=active pharmaceutical ingredient
PK=pharmacokinetic

Daley-Yates et al., Expert Opin Drug Deliv. 2011 :8(10):1297-

Bioequivalence: inhaled
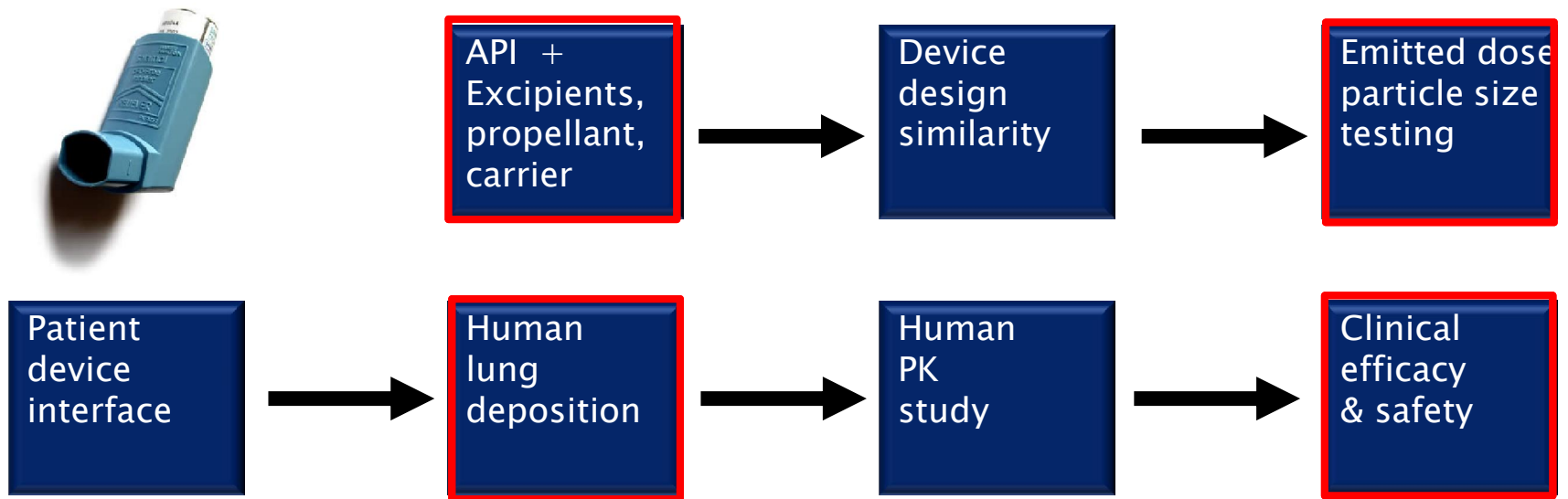
API=active pharmaceutical ingredient
PK=pharmacokinetic

Daley-Yates et al., Expert Opin Drug Deliv. 2011 :8(10):1297-308

Metered Dose Inhaler

Metered dose
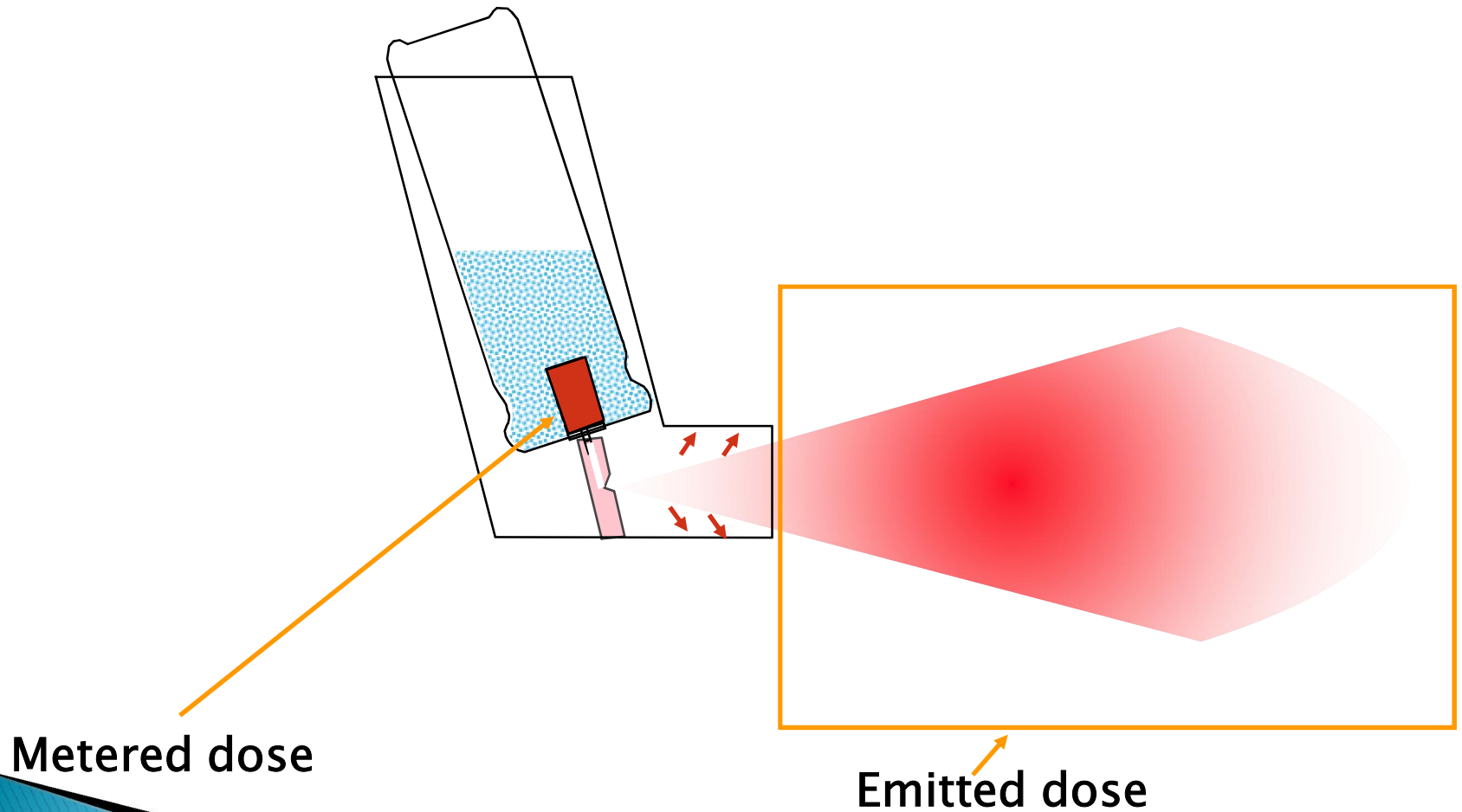
Emitted dose

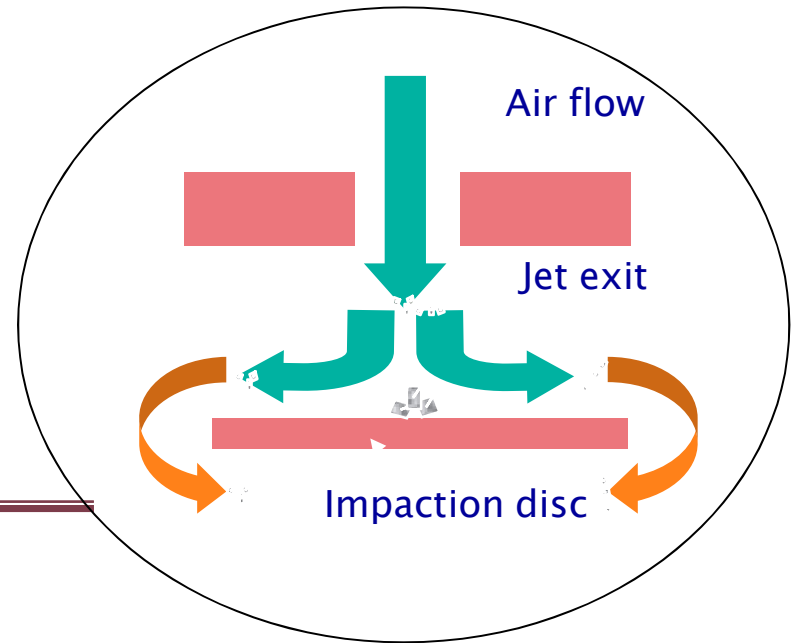# In-Vitro Assessment of Particle size of emitted dose

Andersen Cascade Impactor
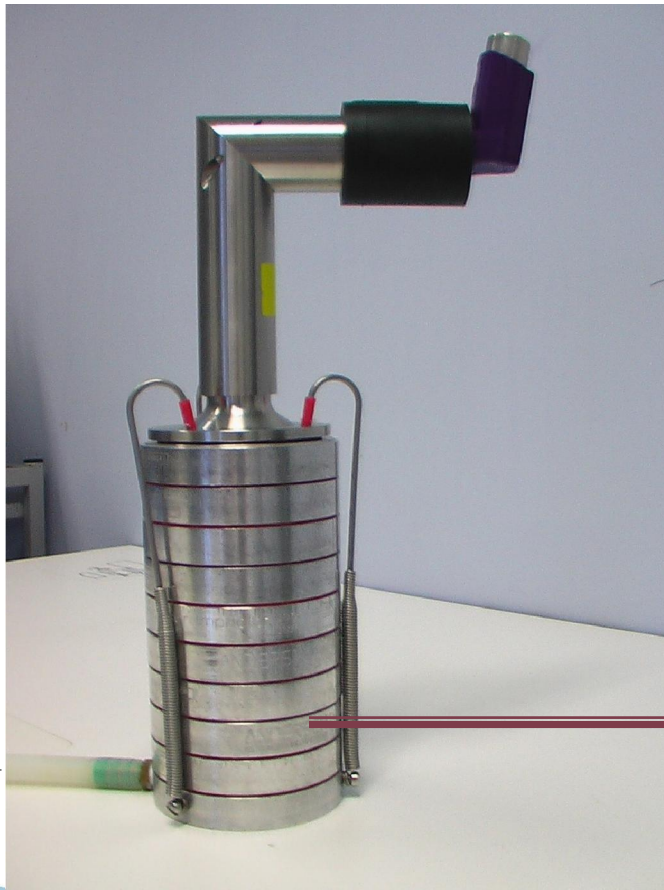
Pump

Air flow

Jet exit

Impaction disc

Excipients

Bronchial asthma showing reduction in FEV1 after inhalation of Qvar.

Nobata K, Fujimura M, Myou S, Ishiura Y, Mizuguchi M, Nishi K, Nakao S.

Department of Internal Medicine, Ishikawa Prefectural Central Hospital, Kanazawa, Japan. k-nobata@yg7.so-net.ne.jp

Abstract

The administration of Qvar (a hydrofluoroalkane-134a beclomethasone dipropionate; HFA-BDP) is highly useful for the treatment of patients with asthma. However, we found in a case of bronchial asthma that replacing the prior inhaled corticosteroids with Qvar resulted in temporary dyspnea and reduction in forced expiratory volume in 1 second (FEV1). Qvar contains beclomethasone dipropionate combined with absolute ethanol and an alternative to fluorocarbon. The patient had complicated alcohol-induced asthma. FE

Qvar contains beclomethasone dipropionate combined with absolute ethanol.

The patient had complicated alcohol-induced asthma. FEV1 decreased markedly and immediately after Qvar inhalation

Summary

▸ Establishing bioequivalence of inhaled drugs is a multi-step process.

▸ *In vitro* testing useful for – quality control, product specifications, dose uniformity, release and stability on storage.

▸ *In vivo,* Clinical studies reported the efficacy and safety

▸ A weight-of-evidence approach to bioequivalence with reliance on data rather than a abridged approaches that rely on assumptions may be more acceptable.

Important factors for better clinical outcomes with inhaler therapy
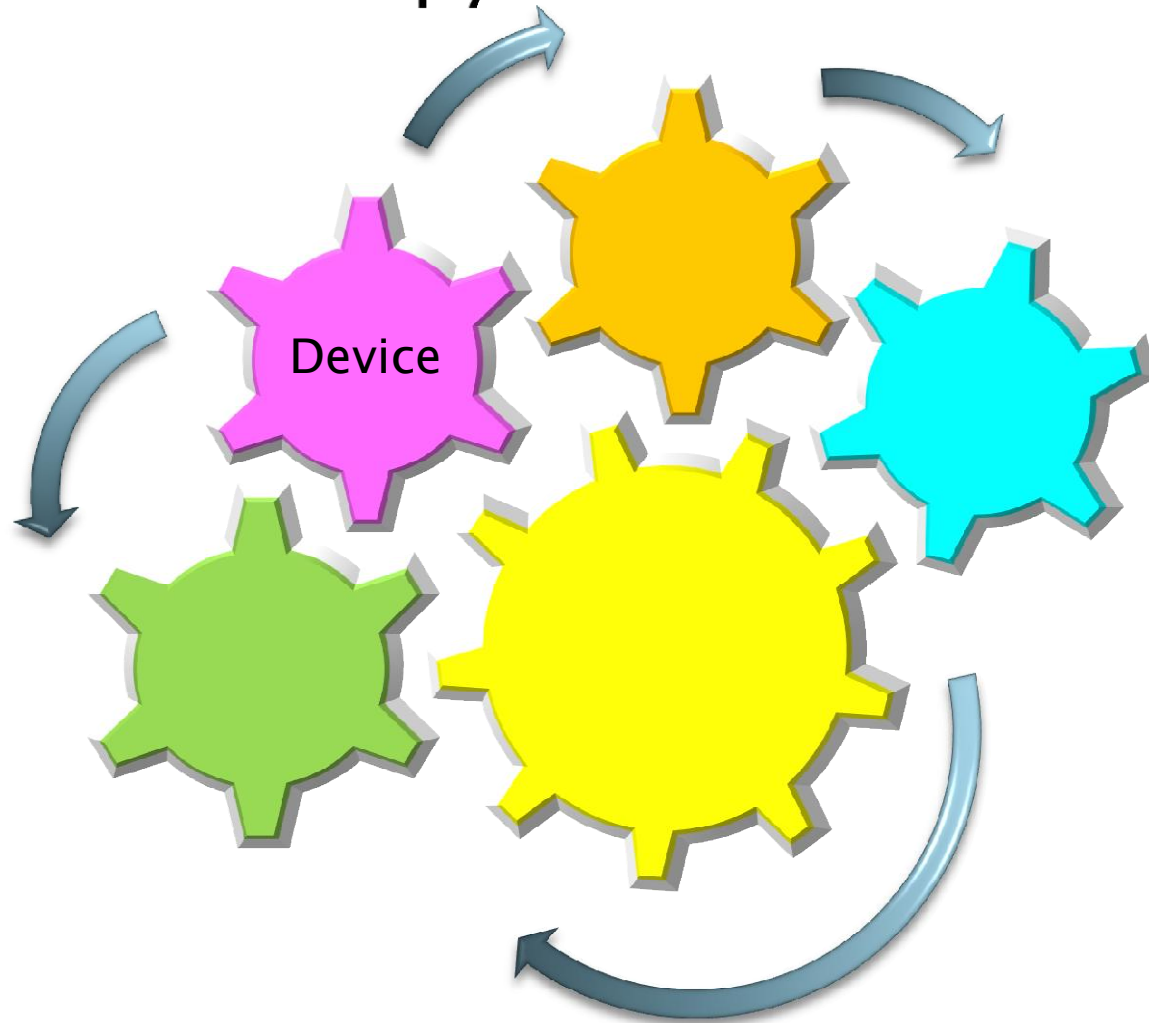
Device

1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297-1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308-1331

Effect of inspiratory flow rate on % Dose delivered

Adapted from J Aerosol Med 12:75, 1999

DPI Device Resistance

Assi and Chrystyn. *J Pharm & Pharmacology 2000;52:58*
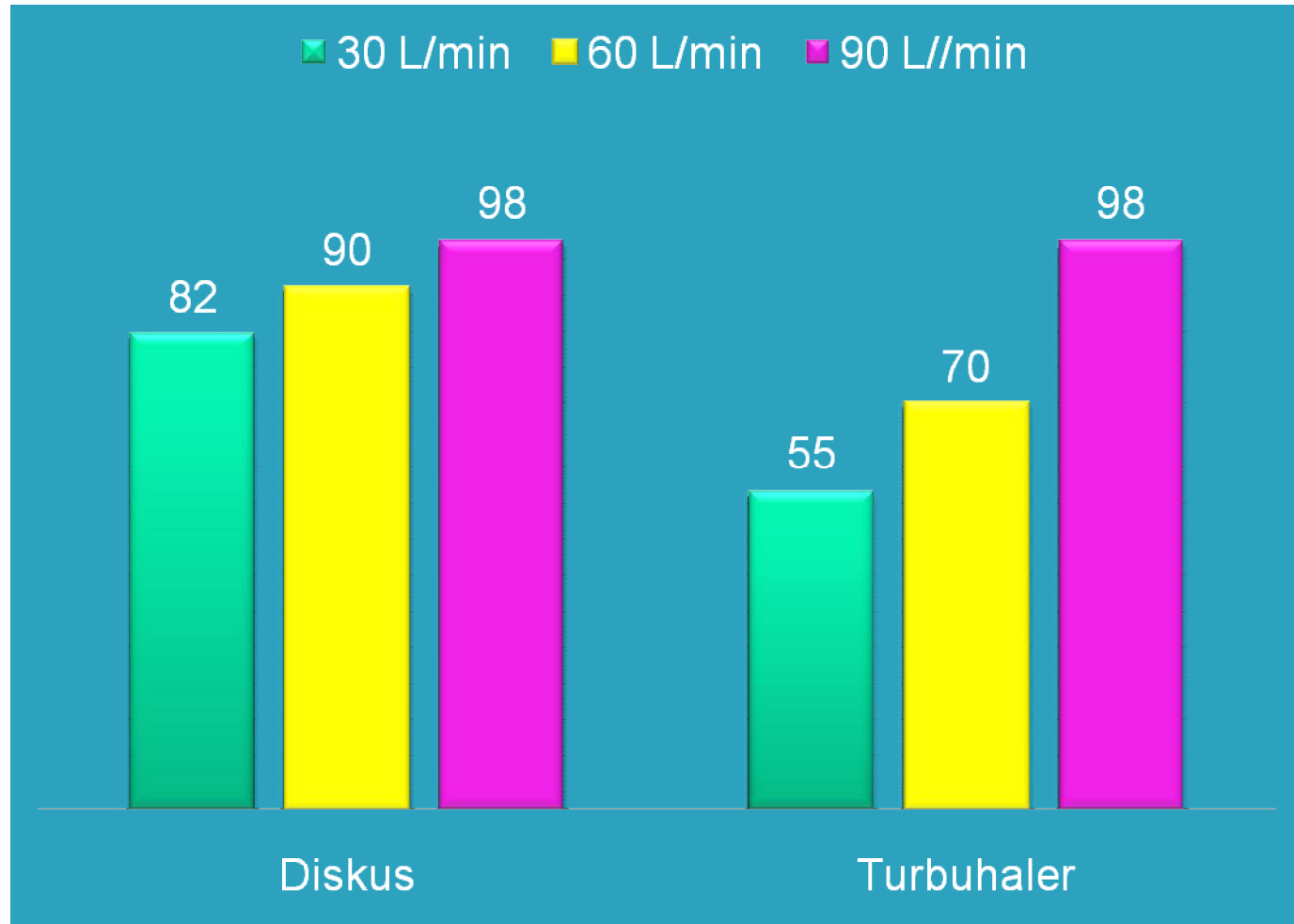
Handling of Inhaler Devices in "Real Life" Pulmonary Practice

> Critical Errors
> n = 300

Male (n , %)	140 (46.7)
Age (mean, SD yr)	48.1 +/- 16.9
No formal education (n, %)	77 (25.7)
High School or higher (n, %)	223 (74.3)
Diagnosis (n %)	
Asthma	219 (73)
COPD	55 (18.3)
Other	26 (8.7)
Prior device-handling education (n, %)	294 (98)

Khassaeneh et al Resp Care 2008 Vol 53 pg 324–329

Results

Device	Essential Step	Critical Error (n , %)
MDI (n = 193)	Remove mouthpiece cover	6 (3.1)
	Shake device vigorously before use	82 (42.5)
	Trigger and simultaneously breathe in	130 (67.4)
Accuhaler (n = 103)	Open the device	0
	Slide the lever until it clicks	7 (6.8)
	Breathe in rapidly and deeply	4 (3.9)
Turbuhaler (n = 146)	Unscrew and lift off the cover	2 (1.4)
	Hold the inhaler upright with the grip downwards	37 (25.3)
	Turn the grip until it clicks	35 (24)
	Breathe in rapidly and deeply	20 (13.7)

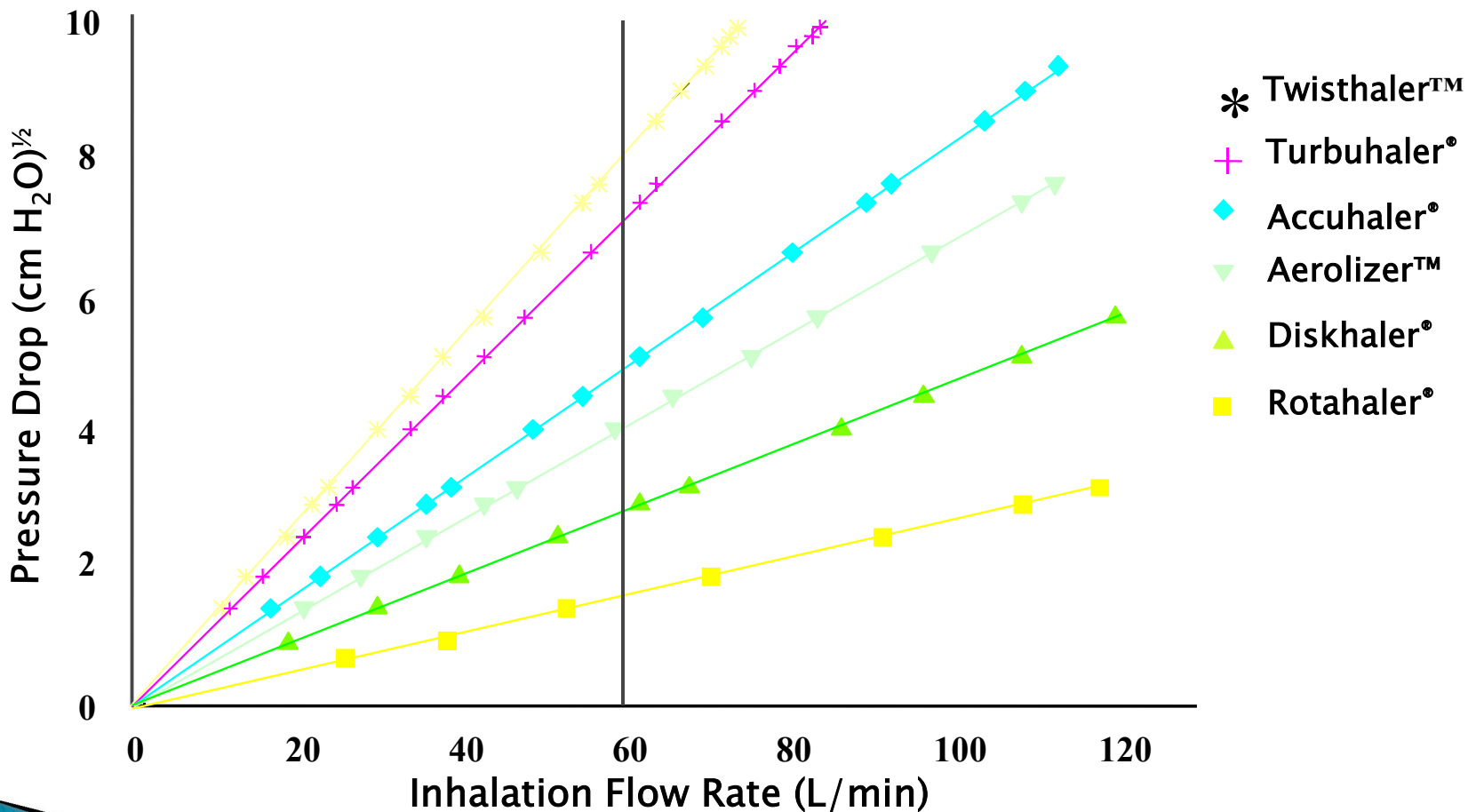# Important factors for better clinical outcomes with inhaler therapy

Safety & efficacy

1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297-1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308-1331

1 year GOAL study : TOTAL CONTROL achieved with sustained treatment

% of patients

Legend:
- FP Phase II
- FP Phase I
- SAL/FP Phase II
- SAL/FP Phase I

Steroid naïve (S1): 40%, 50%
Low dose ICS (S2): 28%, 44%
Moderate dose ICS (S3): 16%, 29%

Bateman E. et al, Am J Respir Crit Care Med 2004 ; 170 : 836–844
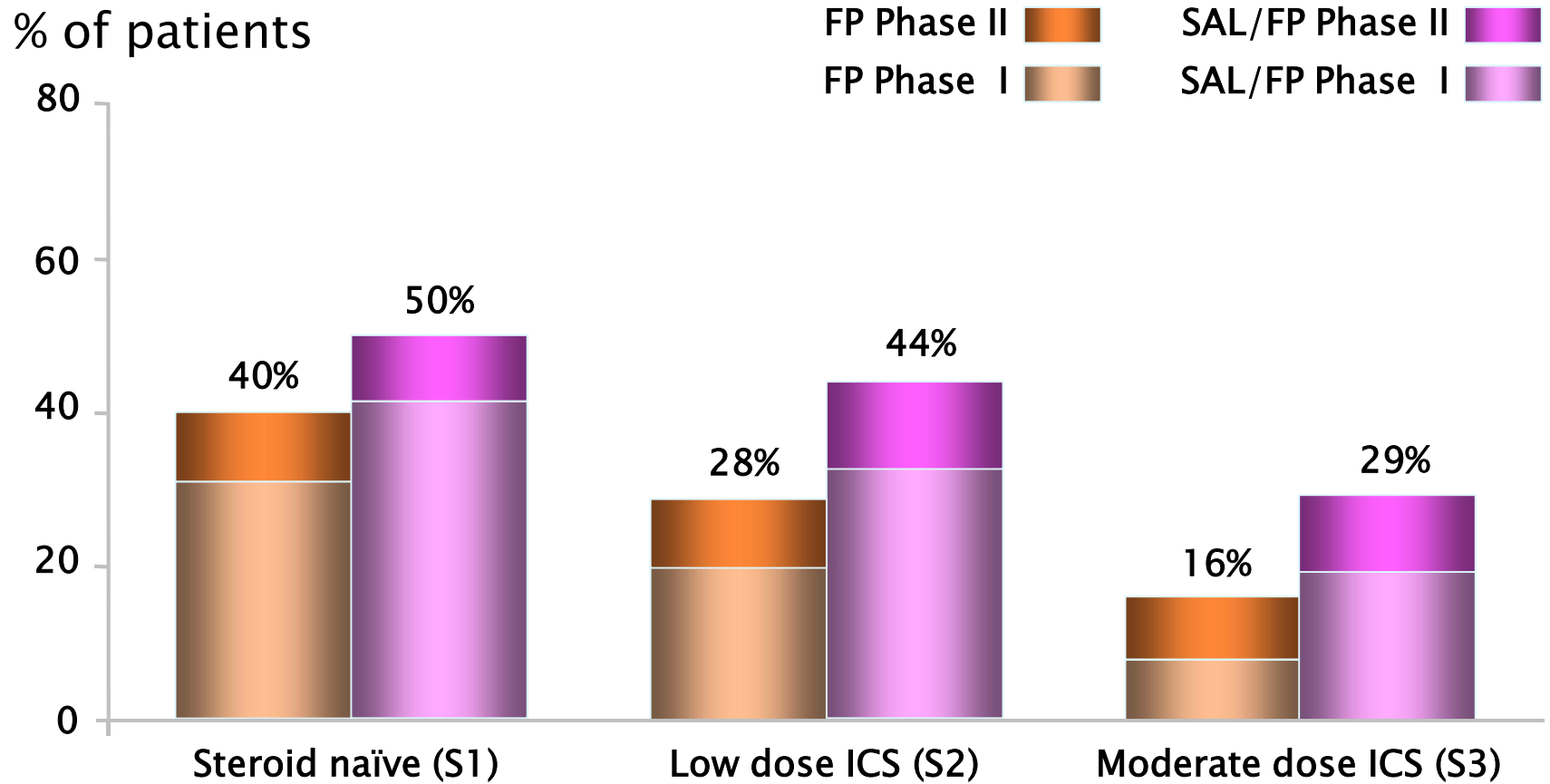
3 years TORCH study : Rate of exacerbations

25% reduction

Mean rate of exacerbations /year

	1.13	0.97*	0.93*	0.85*†‡
n=	1524	1521	1534	1533

Placebo | Salmeterol | Fluticasone propionate | Salmeterol / Fluticasone propionate combination

Treatment

*p < 0.001 vs. placebo; †p = 0.002 vs. salmeterol; ‡p = 0.024 vs. fluticasone propionate

Exacerbation: a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these.

Calverley et al. NEJM 2007;356:775–89

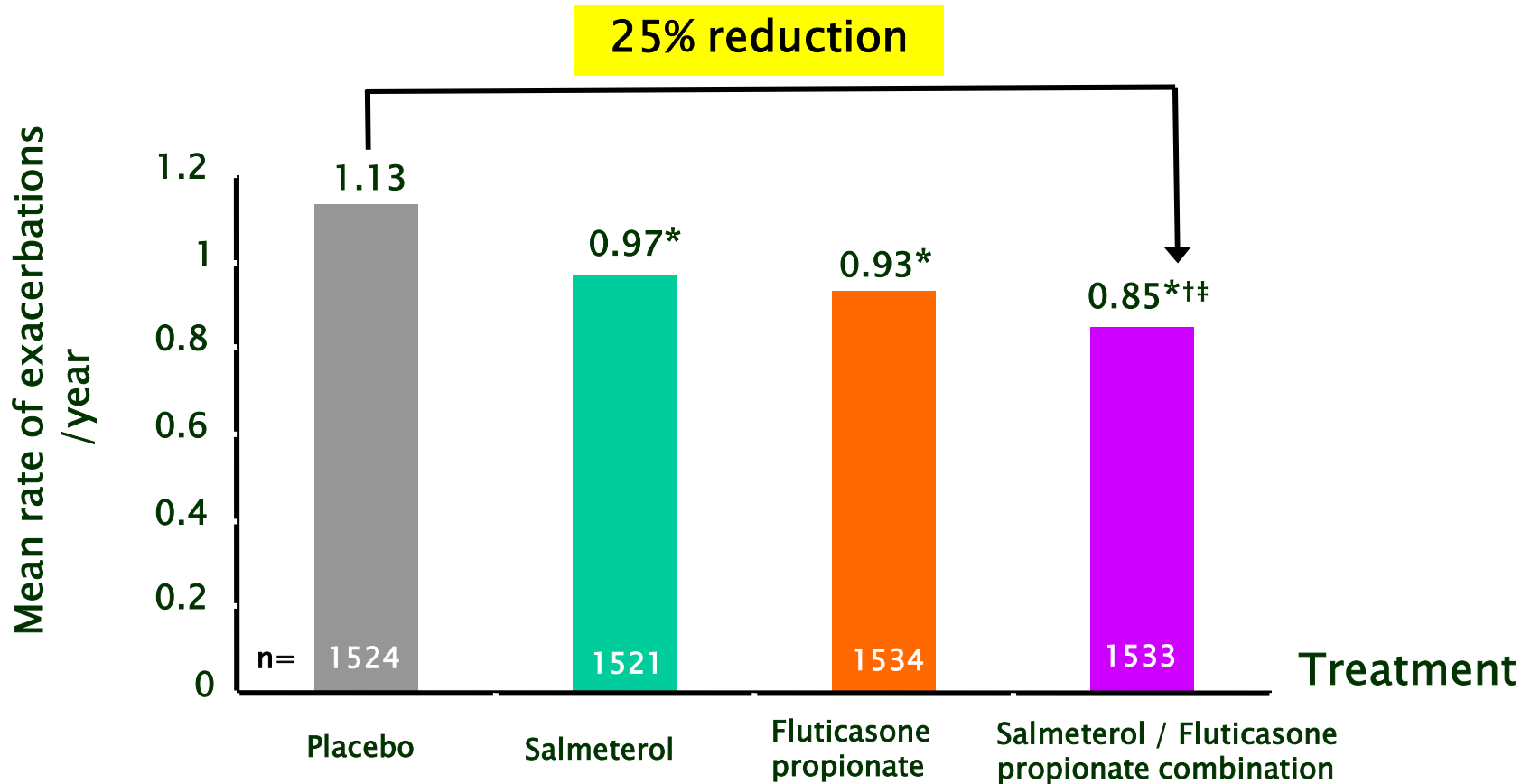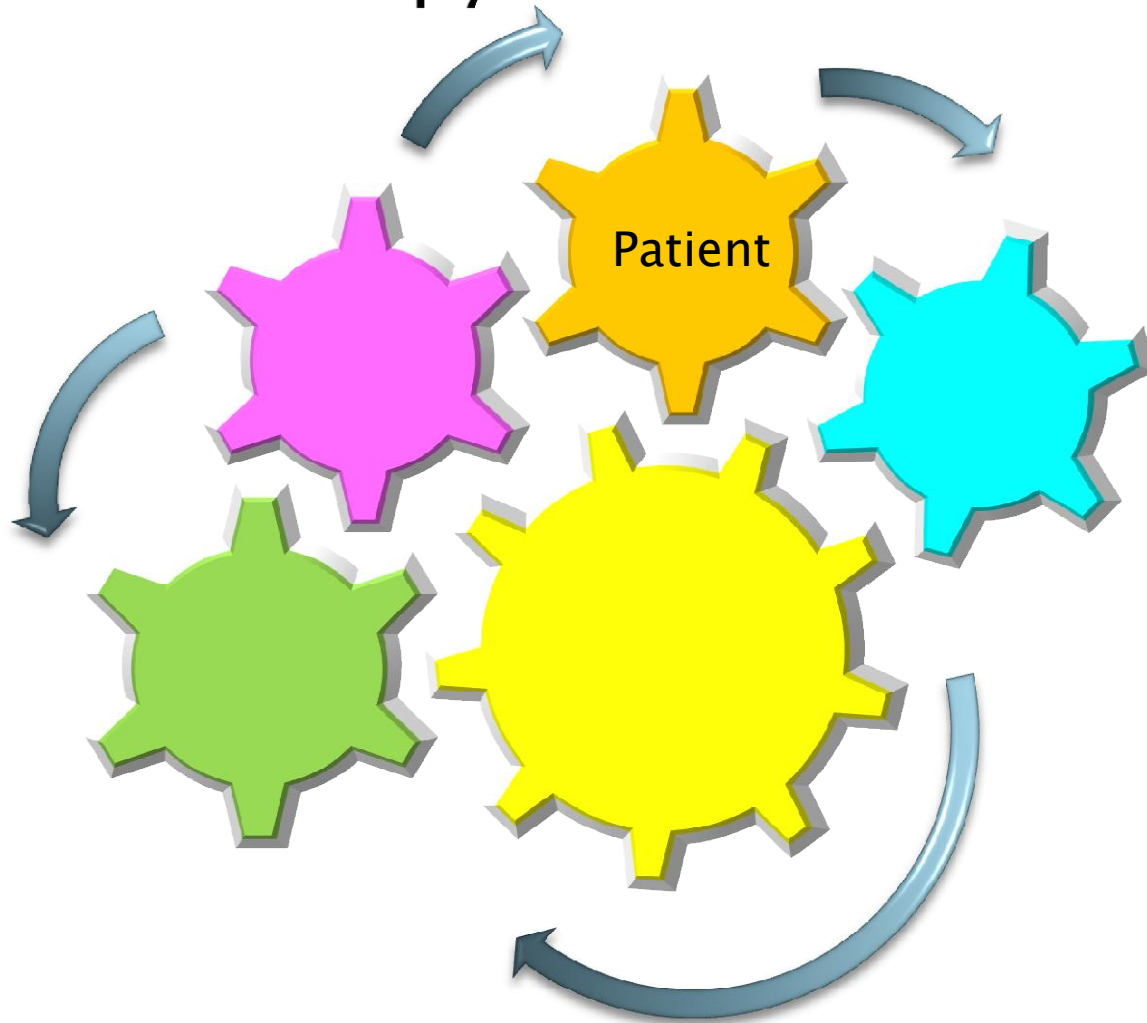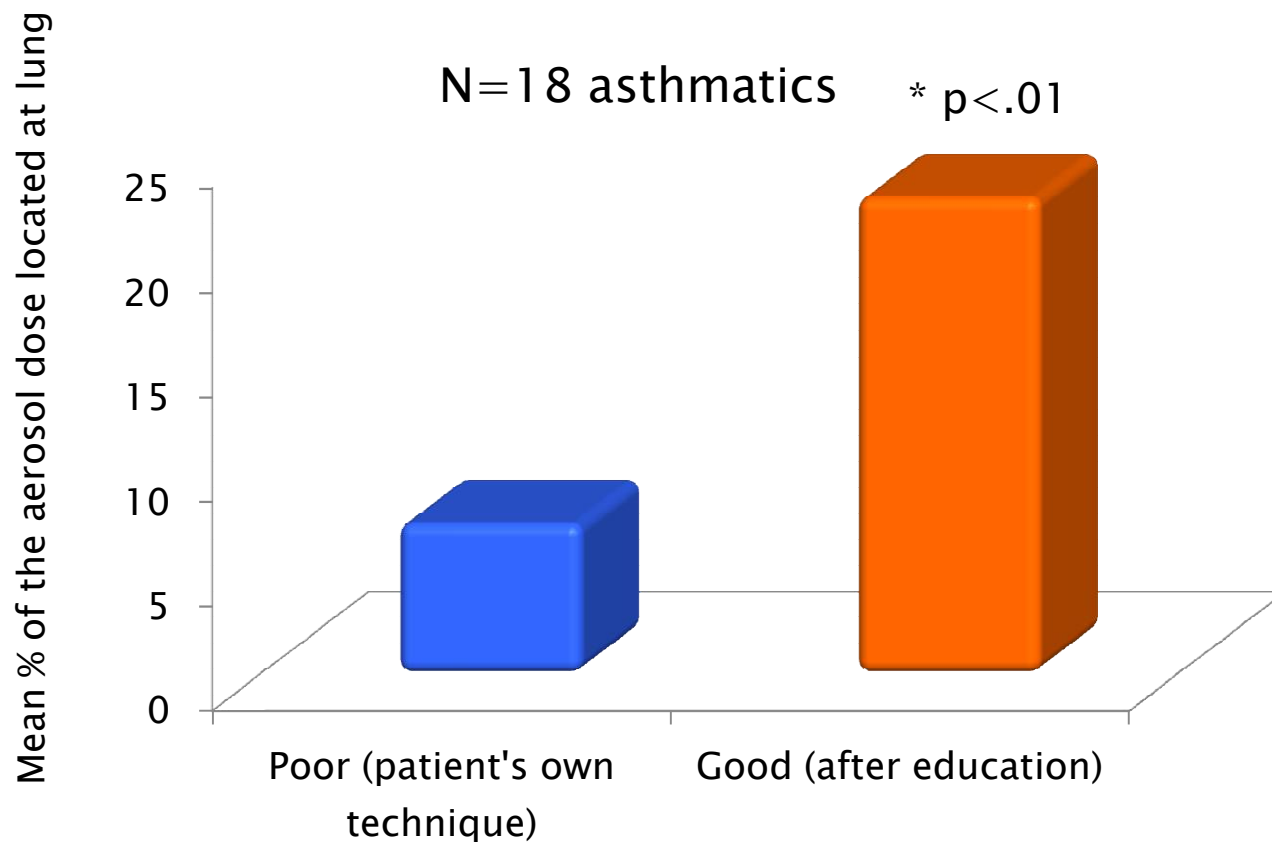# Important factors for better clinical outcomes with inhaler therapy

Patient

1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297-1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308-1331

Co-ordination with pMDIs and lung deposition

Newman at al Thorax1991;46:712-716

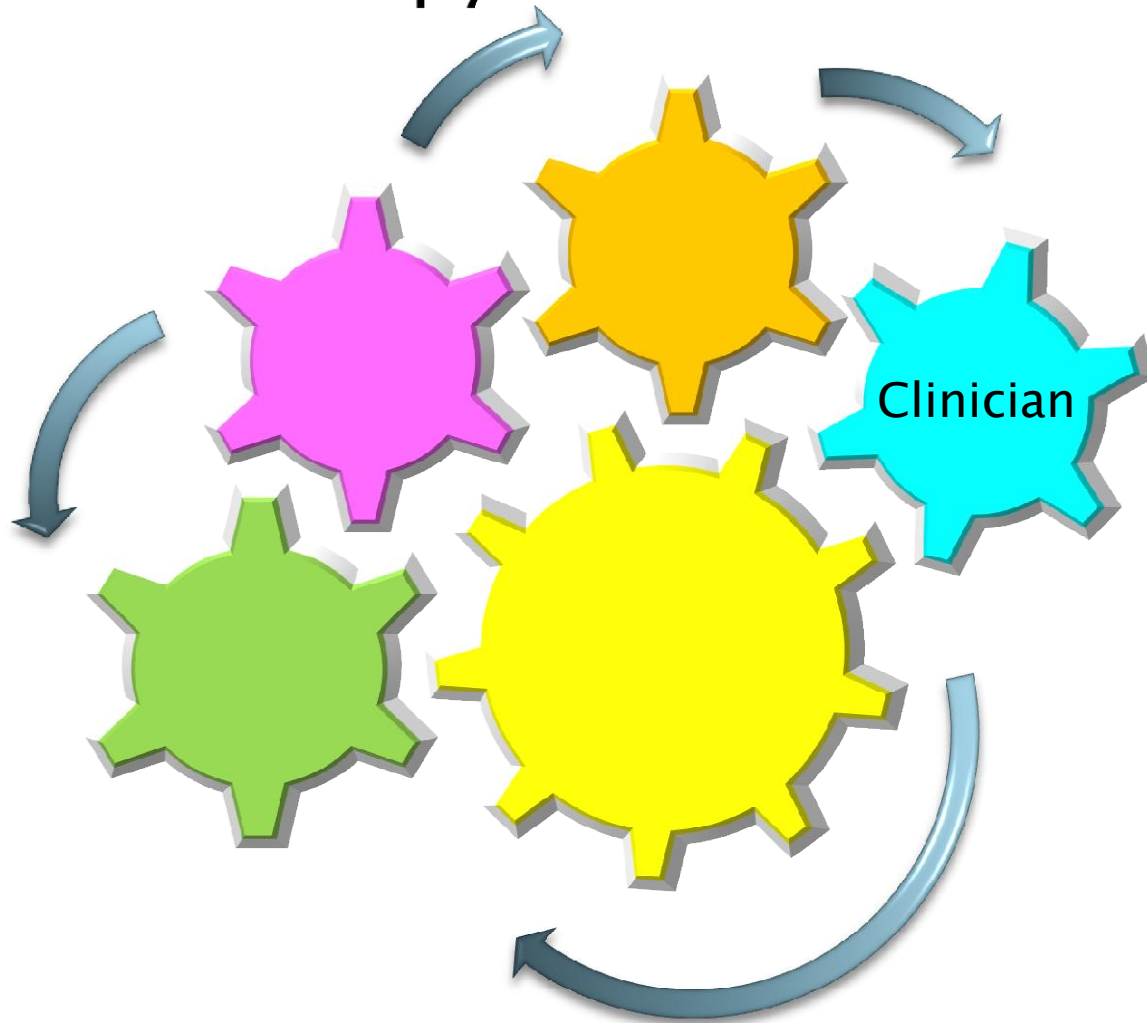# Important factors for better clinical outcomes with inhaler therapy

Clinician

1. *Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297-1308*
2. *Modified from Laube et al., Eur Respir J 2011; 37: 1308-1331*
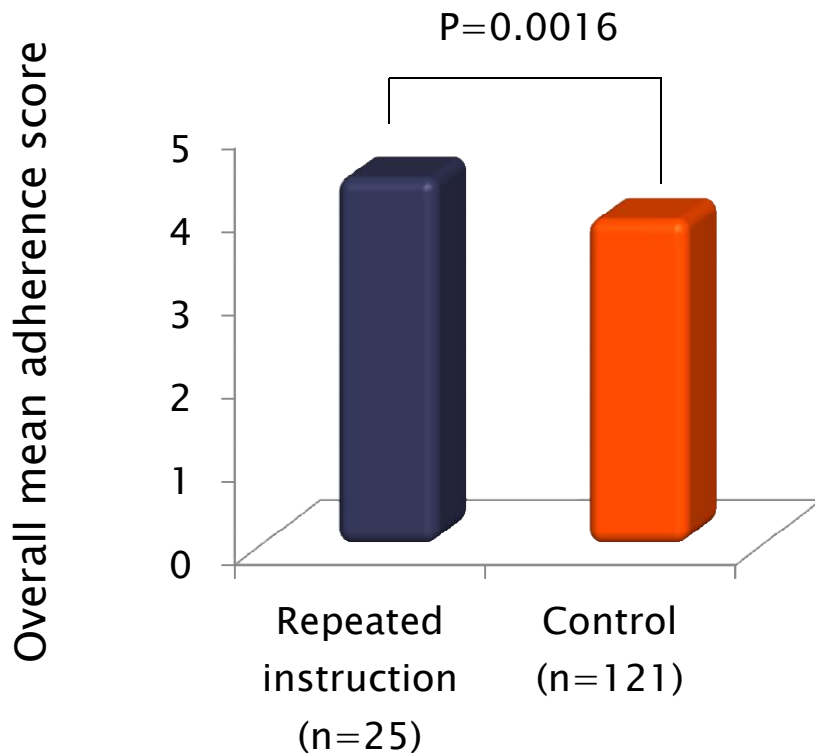
Percentage of patients making
at least one critical error
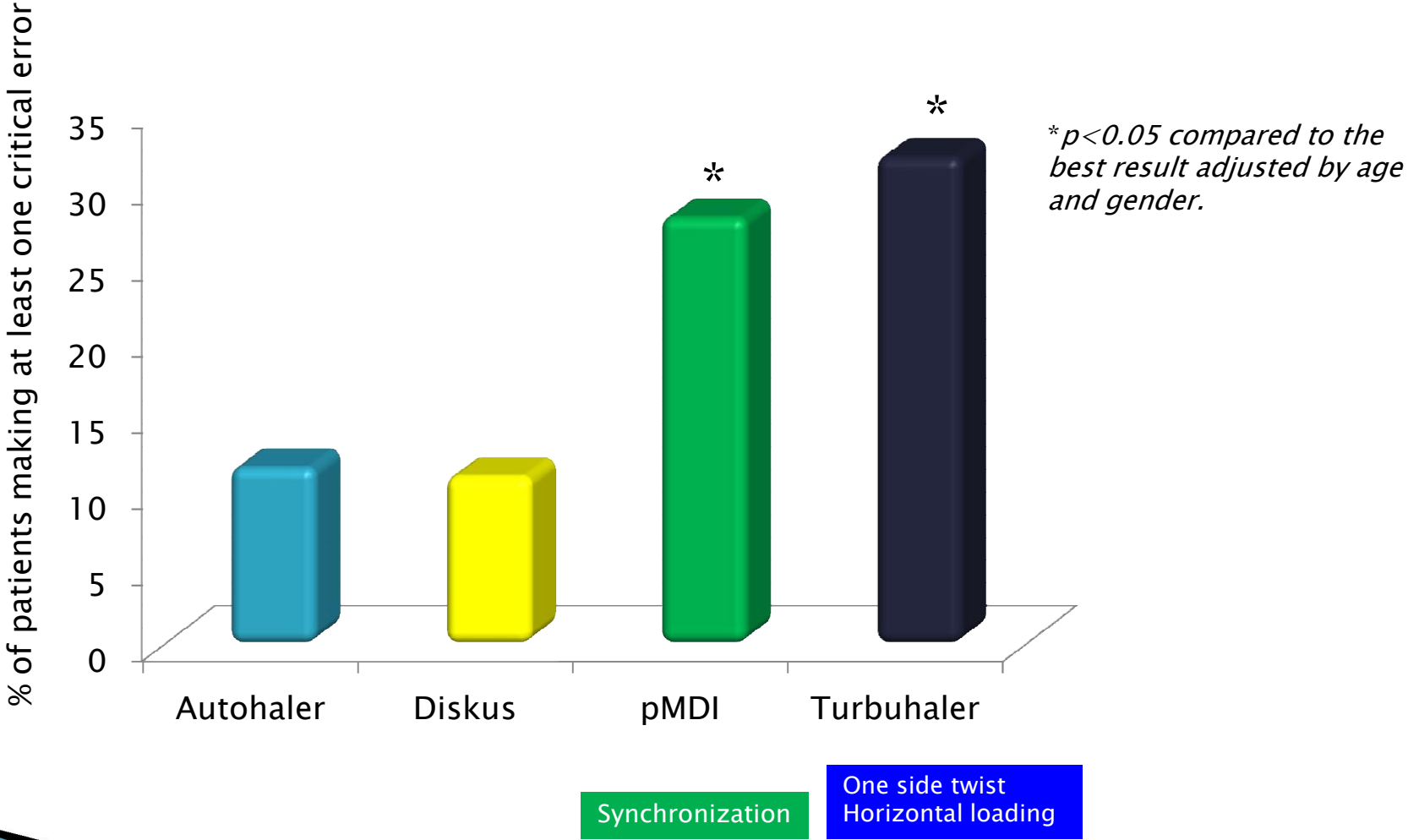
*p<0.05 compared to the best result adjusted by age and gender.

Legend: Synchronization | One side twist Horizontal loading

Molimard et al, J Aerosol Med 2003: 16: 249–254

Repeated Instruction on Inhalation Technique Improves Adherence to the Therapeutic Regimen in Asthma

	r	p
Frequency of asthma exacerbation	–.19	.021
Frequency of emergency room visits (per year)	–.19	.042
SGRQ scores		
Total	–.22	.024
Symptoms	–.21	.022
Activities	–.10	.27
Impacts	–.20	.035

[Correlation between the overall mean adherence score and asthma-related outcomes in asthmatic patients]

*SGRQ= St George's Respiratory Questionnaire

Takemura etc, Journal of Asthma 2010: 47(2):202-208

Repeated Instruction on Inhalation Technique Improves Adherence to the Therapeutic Regimen in COPD patients

P=0.032

Overall mean adherence score

| Repeated instruction (n=22) | Control (n=33) |
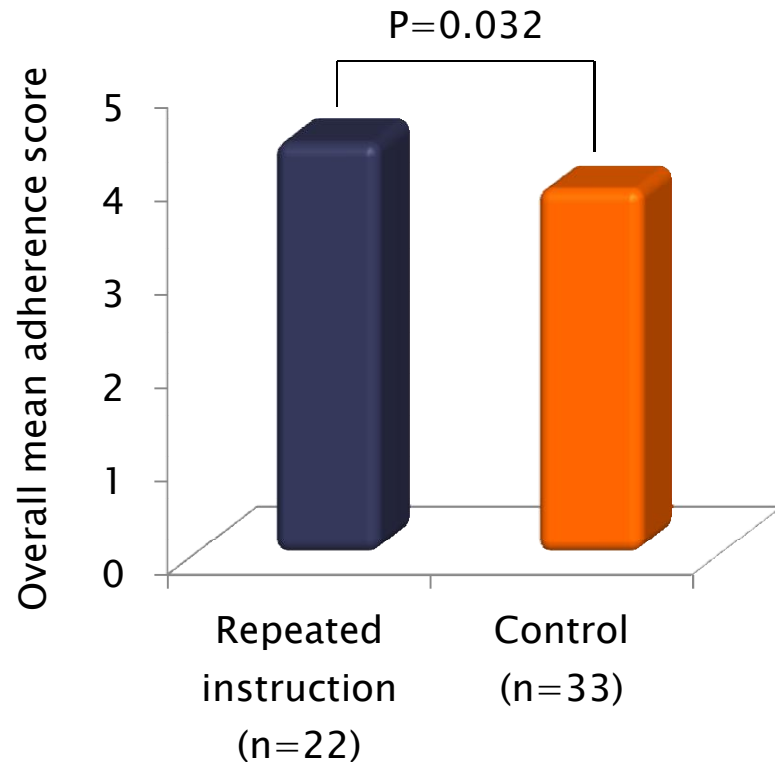
SGRQ scores	r	p
Total	−.35	.023
Symptoms	−.43	.002
Activities	−.17	.21
Impacts	−.35	.011

[Correlation between the overall mean adherence score and SGRQ*]

*SGRQ= St George's Respiratory Questionnaire

Takemura etc, International Journal of COPD 2011:6 97–104

Important factors for better clinical outcomes with inhaler therapy

- ➤ Easy to use
- ➤ Low resistance flow

Device

Patient

- ➤ Knowledge
- ➤ Good technique
- ➤ Compliance

Clinician

- ➤ Select appropriate device
- ➤ Give instruction
- ➤ Check device technique
- ➤ Assess control

Formulation

Safety & efficacy

- ➤ Bioequivalent in API, excipient ex.Alcohol
- ➤ Lung deposit

- ➤ High efficacy Ex. Gain control, reduce exacerbation
- ➤ Low side effect

1. Modified from Daley-Yates et al., Expert Opin. Drug Deliv. 2011: 8(10):1297-1308
2. Modified from Laube et al., Eur Respir J 2011; 37: 1308-1331