EVALUATION AND APPLICATION OF A PK APPROACH TO THE ESTIMATION OF LUNG DEPOSITION OF INHALED ANTI-ASTHMATIC DRUGS

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THEMES OF THIS PRESENTATION

- PART 1

RATIONALE OF A PK MODEL TO TEST BIOEQUIVALENCE OF DRUG FORMULATIONS ADMINISTERED BY INHALATION

- PART 2

RESULTS OF THE ELPEN ROLENIUM BIOEQUIVALENCE STUDY

LIMITS OF CLINICAL STUDIES – A CLASSIC EXAMPLE

(DOCKHORN ET AL. J. ALLERGY CLIN. IMMUNOL. 1995, 96, 50 – 56)

- Equivalence test of 2 salbutamol inhalation formulations
- Study design – Randomized, single dose, double blind, double dummy, 6 periods, cross-over
- Treatments – 1 / 2 / 3 puffs product 1 ; 1 / 2 puffs product 2; placebo
- Endpoints – FEV_1
- Patients – Moderate asthma, $Beta_2$ responders
- Results – “There were no statistically significant differences between any of the 5 treatments …”
- The 2 formulations were considered equivalent even if the system was unable to distinguish the effect determined by double doses of salbutamol !!!!!!!

A REASON OF FAILURE : TYPICAL SIGMOIDAL DOSE RESPONSE CURVE OF A BETA-AGONIST IN VITRO

Billington and Hall *Respiratory Research* 2011, **12**:89
http://respiratory-research.com/content/12/1/89

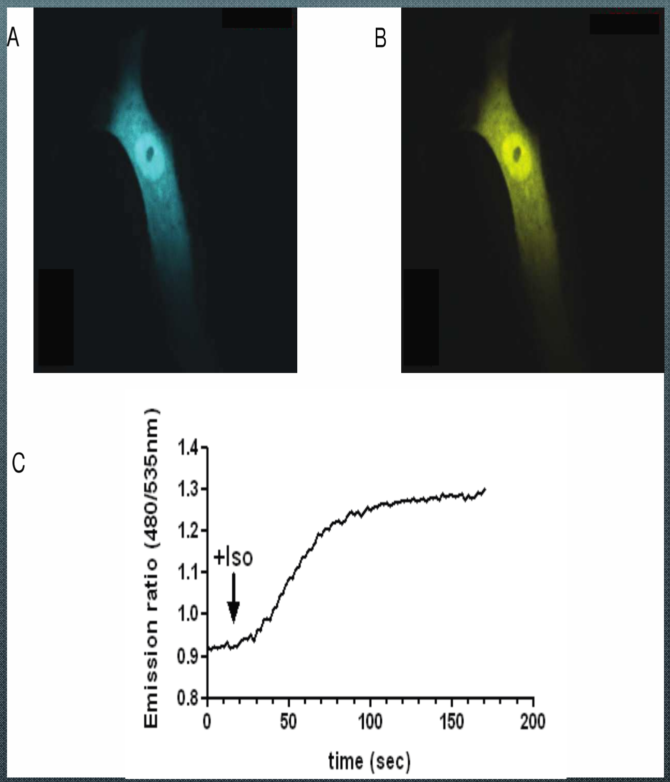


Figure 1 Isoproterenol-induced changes in cyclic AMP activity in a single hASM cell imaged via confocal microscopy using the altered emission profile of CFP-Epac(dDEP,CD)-VENUS as a readout. CFP-Epac(dDEP,CD)-VENUS expression 48 hours post-transfection is shown in panel A (CFP excited with 440 nm and 480 nm CFP emission fluorescence recorded). Panel B shows uncorrected FRET in the same cell under basal conditions (CFP excited with 440 nm and 535 nm FRET emission fluorescence recorded). Panel C is a representative trace of the altered emission ratio (essentially a change in FRET) in real time in response to 10 μM isoproterenol (+ Iso).

CLINICAL STUDIES OR PK STUDIES ?? PRO & CONTRA

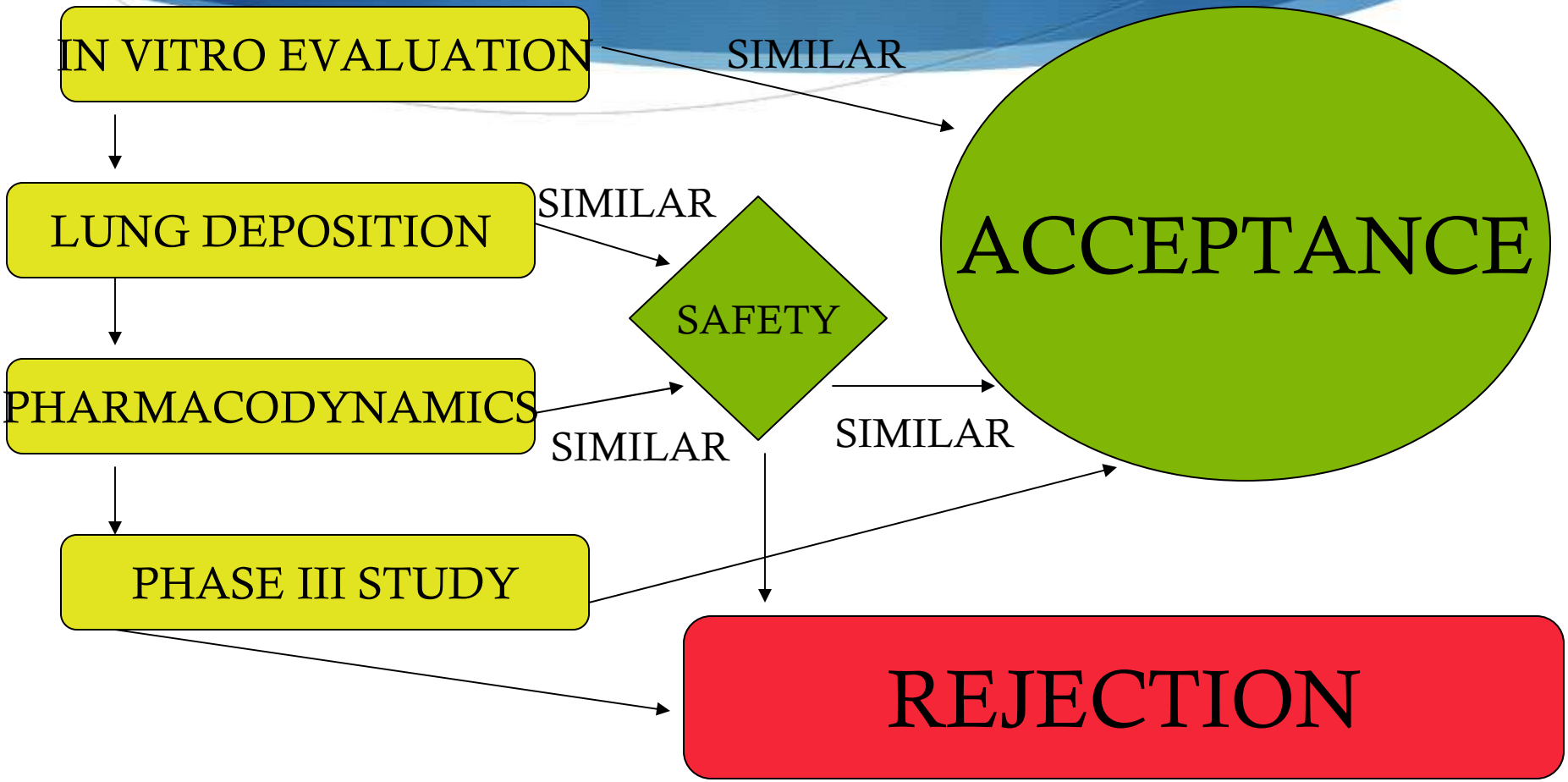
- **CLINICAL STUDIES – A LOT OF MINUS**
- Outside of linear dose response ranges modest sensitivity of the assay
- Big difficulties to exclude placebo effects
- High costs due to long observation periods
- Risk of biases due to investigator and patient factor, need of complex blinding methods

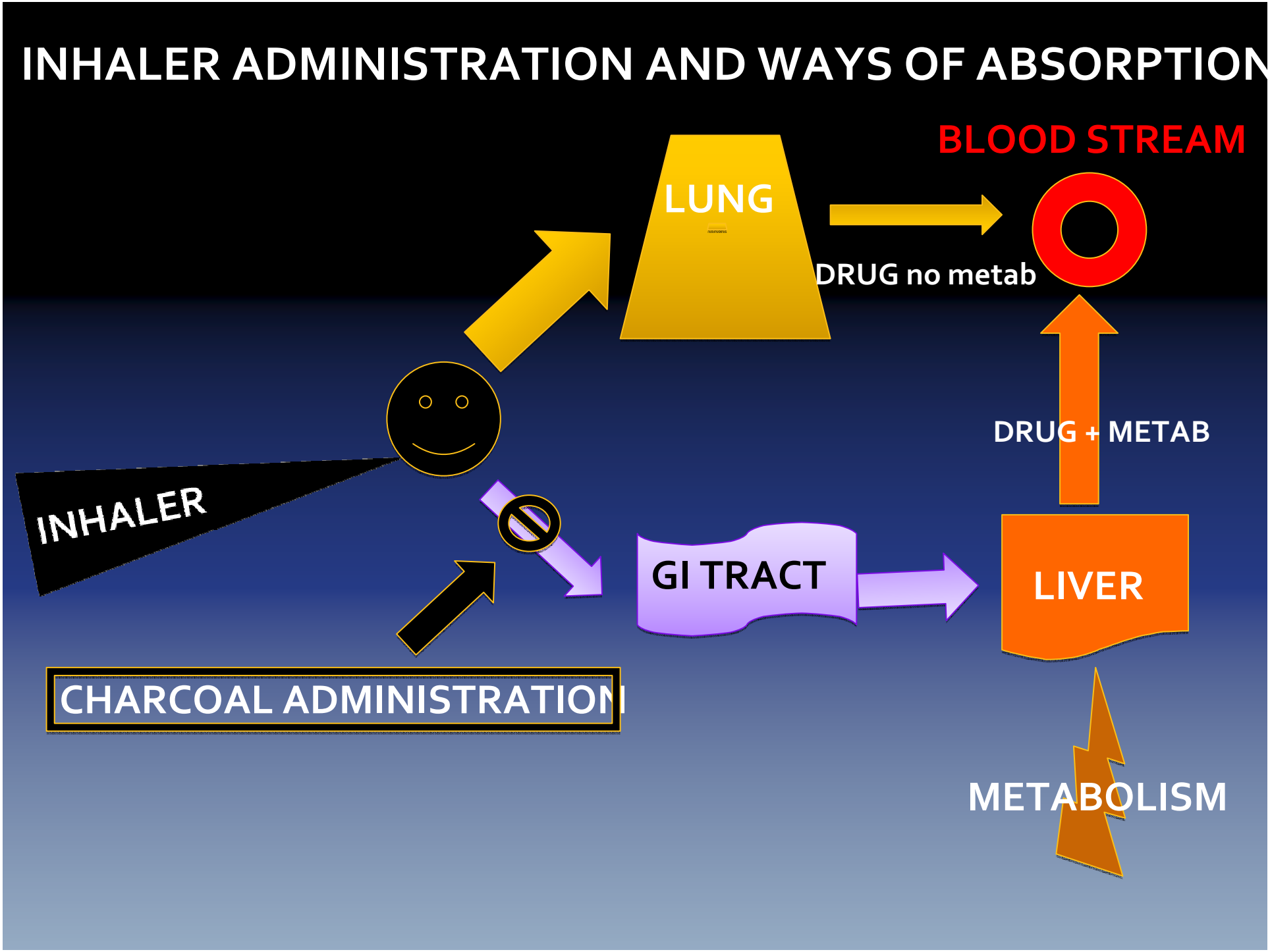
- **PK STUDIES – VERY EFFECTIVE, VERY SENSITIVE**
- No risk of placebo effects
- Results adequate and optimal for statistic analyses
- No influence of investigator or patients on the results, objective data
- In the specific case of inhaler bioequivalence PK tests are very sensitive detecting differences between formulations otherwise undetectable in clinical studies

NEW EMEA RULES ON INHALER TESTING 2009

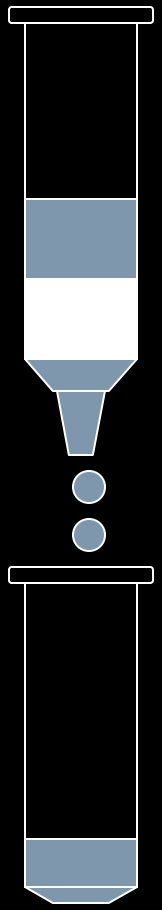
- Doc. Ref. CPMP/EWP/4151/00 Rev. 1
- **GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS**
- **Date for coming into effect : 1-8-2009**

NEW RULES OF BIOEQUIVALENCE ACCORDING TO CPMP/EWP/4151/00 FLOW-CHART



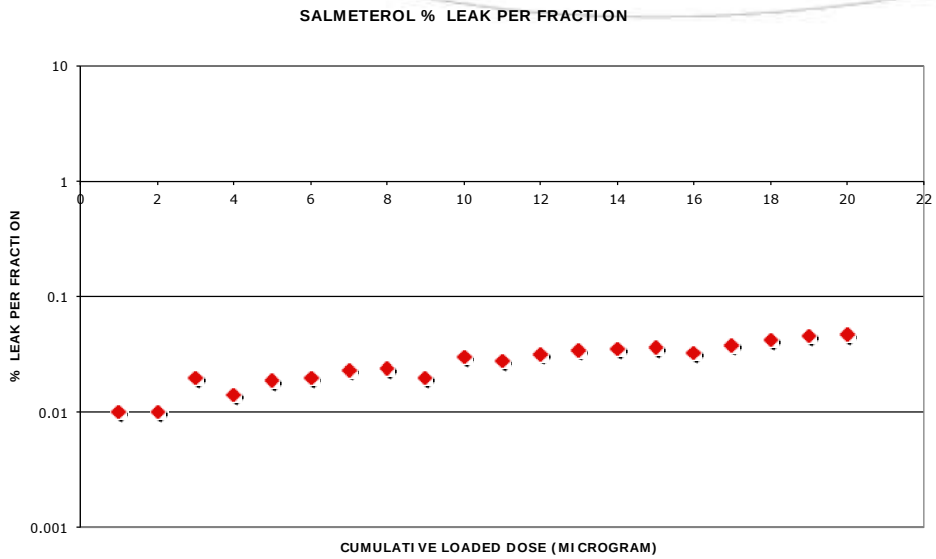

INHALER ADMINISTRATION AND WAYS OF ABSORPTION
BLOOD STREAM
LUNG
DRUG no metab
DRUG + METAB
INHALER
GI TRACT
LIVER
CHARCOAL ADMINISTRATION
METABOLISM

IN VITRO VALIDATION OF THE CHARCOAL ADSORPTION OF DRUGS

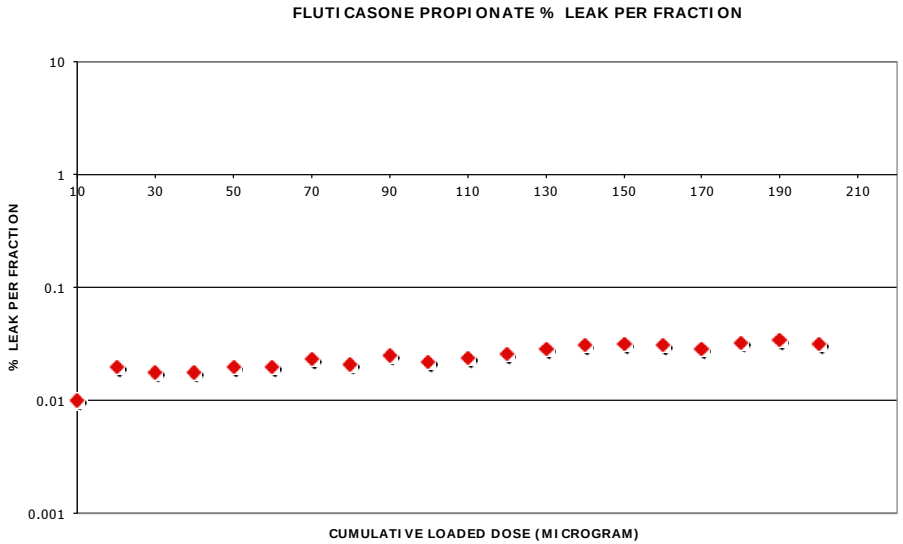


- ***RATIONALE***
- WIDE VARIABILITY OF CHEMICO-PHYSICAL CHARACTERISTICS OF CHARCOAL
- ***EXPERIMENTAL***
- MODEL DRUGS : SALMETEROL (1 MG/L) – FLUTICASONE PROPIONATE (10 MG/L)
- SOLUTIONS IN WATER (20 ML IN TOTAL) OF THE ANTIASTHAMTIC DRUGS WERE FILTERED THROUGH A SMALL COLUMN FILLED WITH 100 mg of ACTIVATED
- THE DRUG CONTENTS WERE EVALUATED IN THE COLLECTED FRACTIONS (N=20) AND PLOTTED IN FUNCTION OF THE LOADED DOSE

EXPERIMENTAL RESULTS



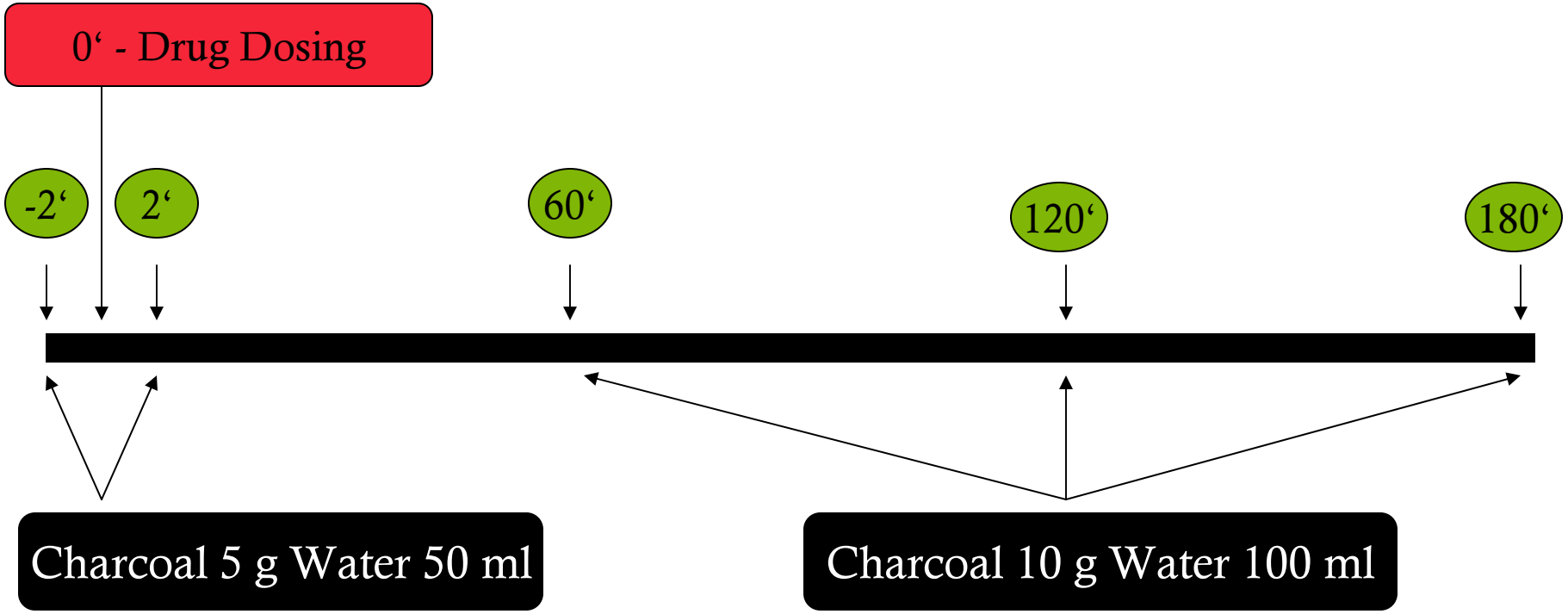
AN OPTIMAL CHARCOAL ADSORPTION WAS OBSERVED WITH BOTH DRUGS



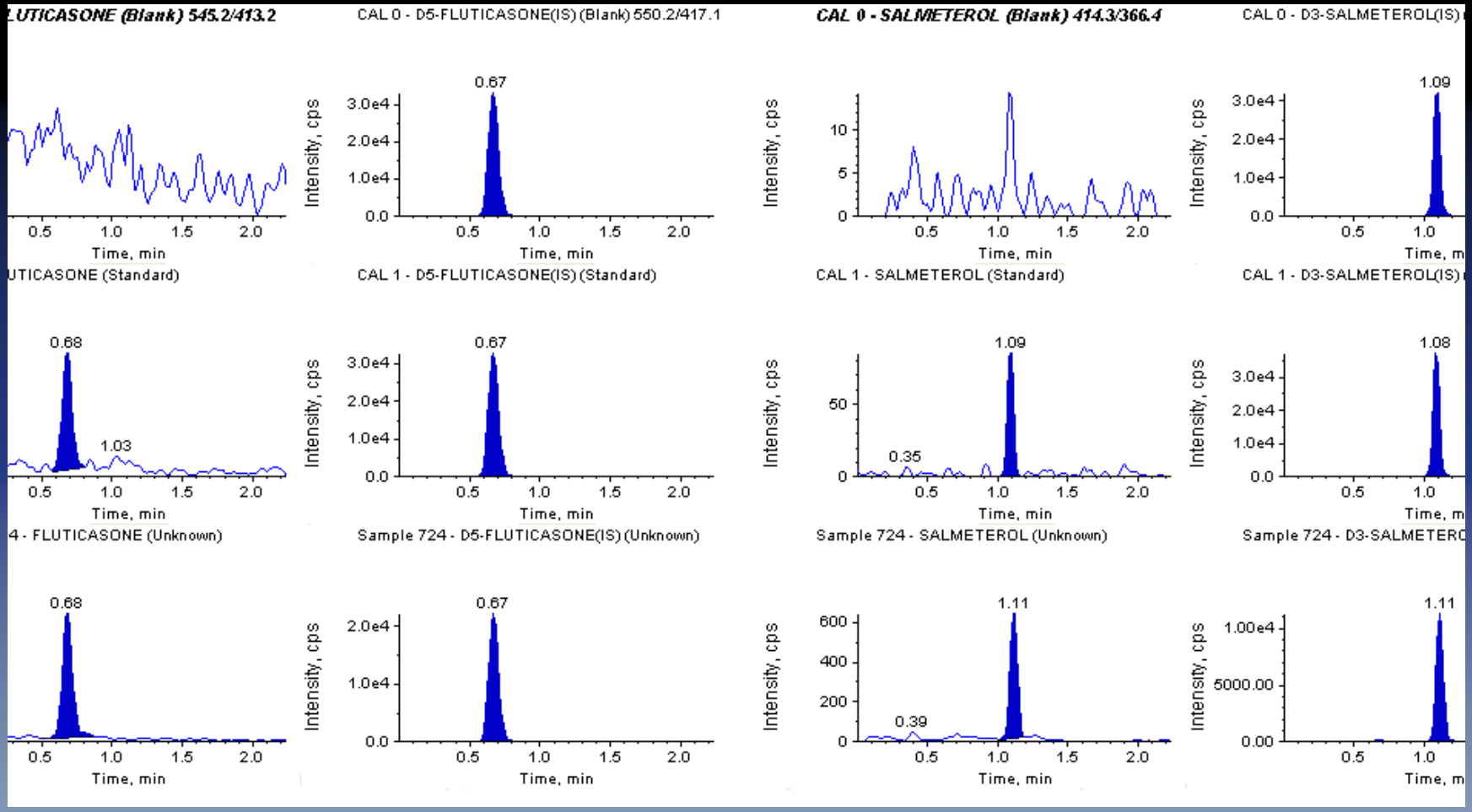
IN VIVO PK STUDY (VOLUNTEERS) TO COMPARE ROLENIUM (TEST) TO SERETIDE (REFERENCE) ; FLUTICASONE PROP. 500 MCG / SALMETEROL 50 MCG

- **STUDY DESIGN :** 2 WAY, CROSS-OVER, BLOCK RANDOMIZED
- **SAMPLE SIZE** : 60 VOLUNTEERS MALES AND FEMALES
- **ADMINISTRATION SCHEME IN RANDOM ORDER :**
- 1) ROLENIUM INHALATION (1 PUFF) WITH CHARCOAL COADMINISTRATION
- 2) SERETIDE INHALATION (1 PUFF) WITH CHARCOAL COADMINISTRATION3)
- **BLOOD SAMPLING :** BEFORE DOSING THEN OTHER 23 SAMPLING FROM 10‘ AFTER DOSING UP TO 72 HOURS
- **ANALYTICAL METHODS :** HPLC-MS/MS

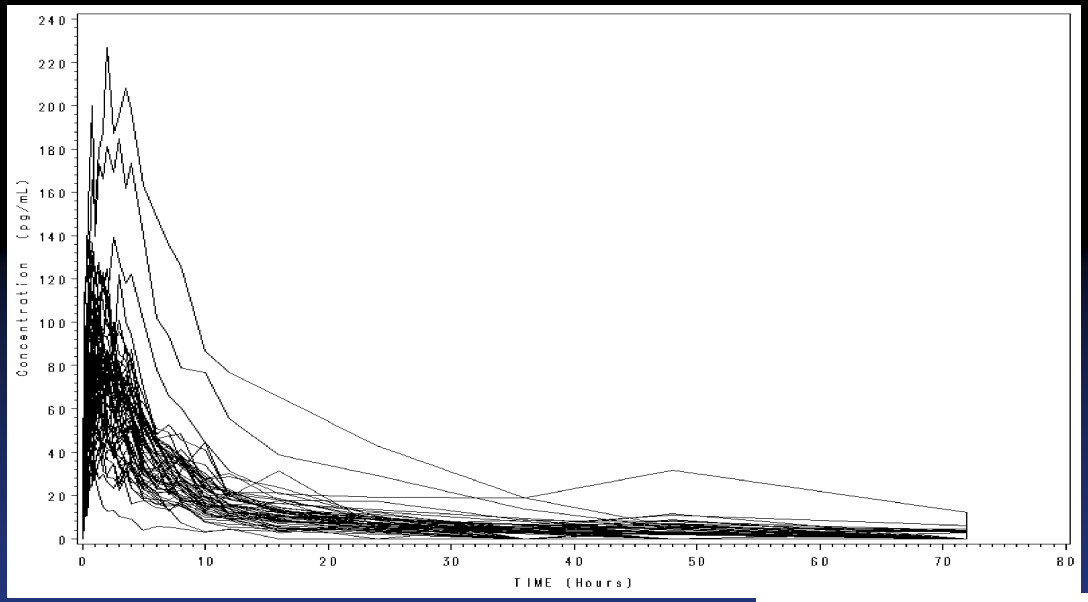
SCHEME OF CHARCOAL ADMINISTRATION

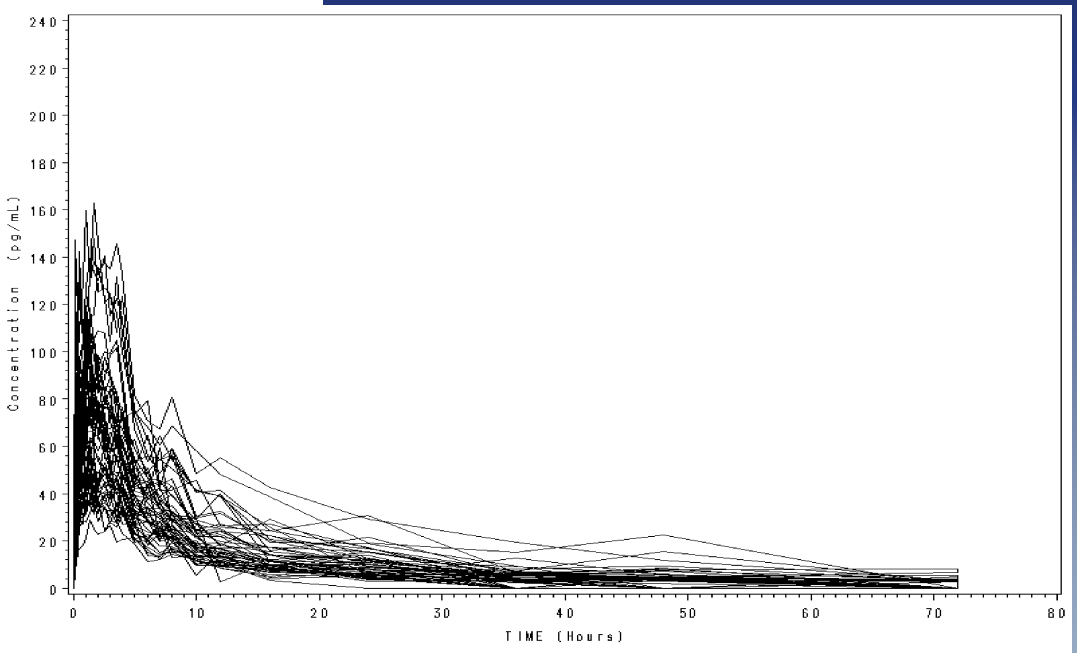


AN EXAMPLE OF FLUTICASONE PROPIONATE, SALMETEROL DETECTION BY HPLC-MS/MS

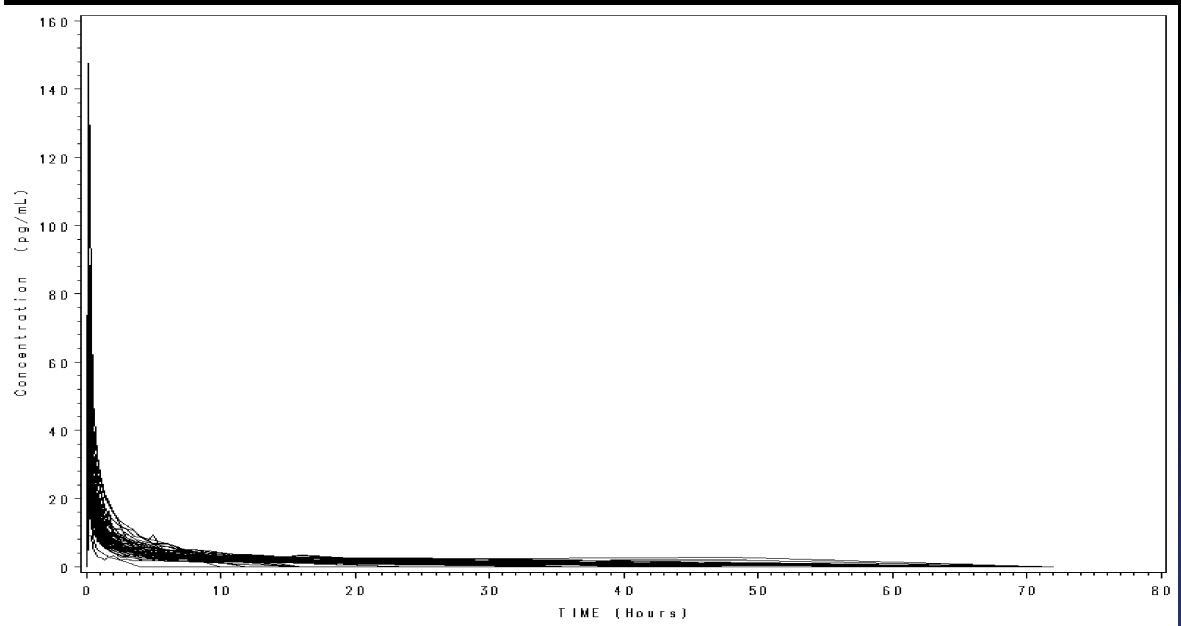


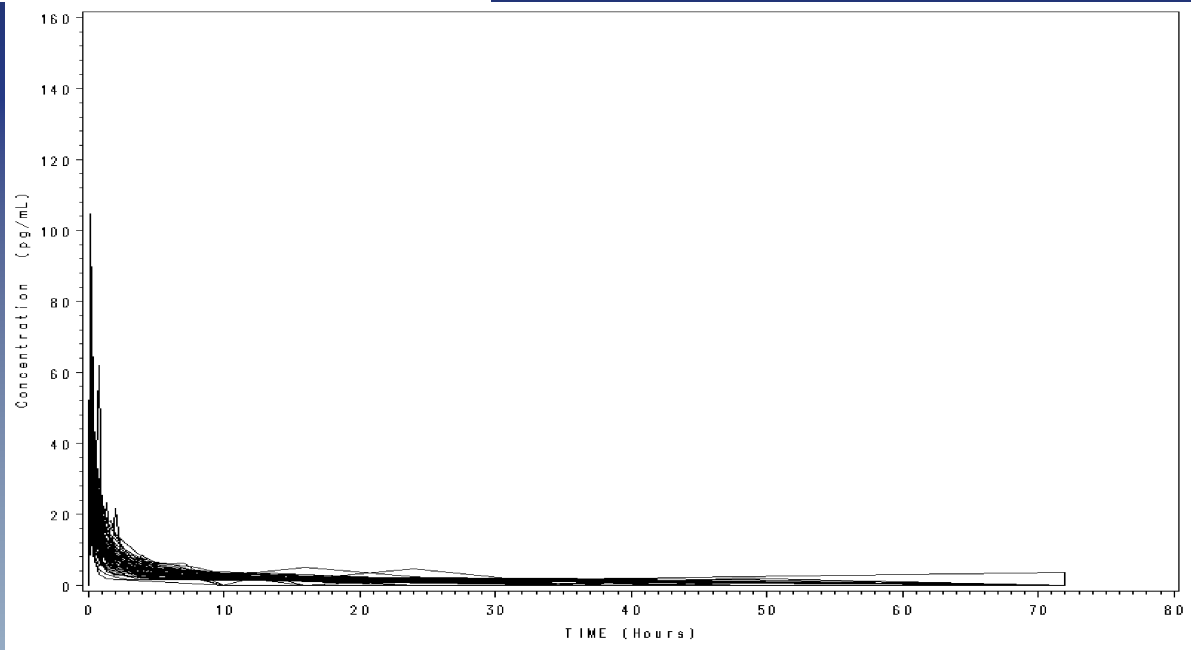
FLUTICASONE PROPIONATE INDIVIDUAL PK CURVES



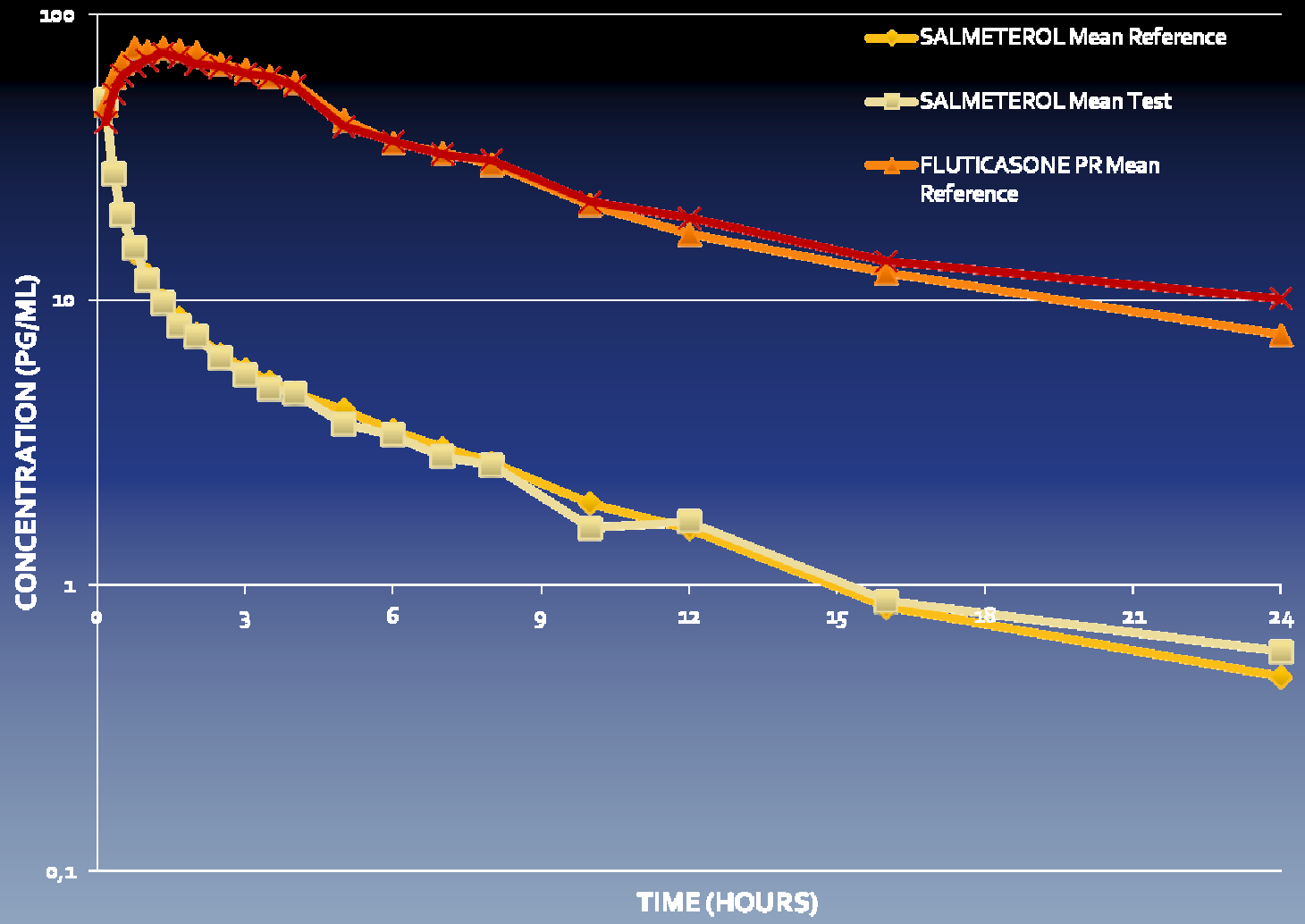


SALMETEROL INDIVIDUAL PK CURVES

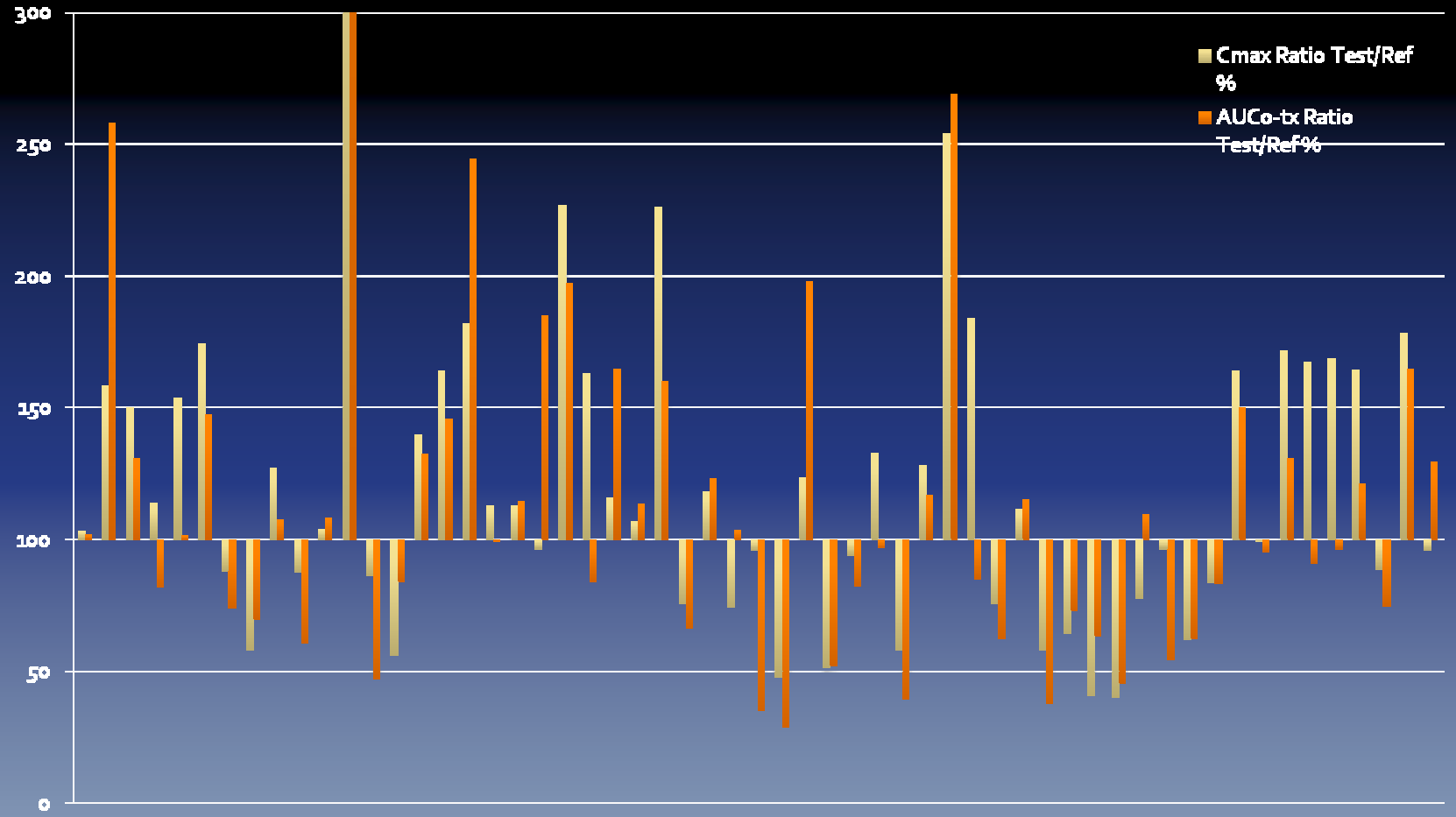




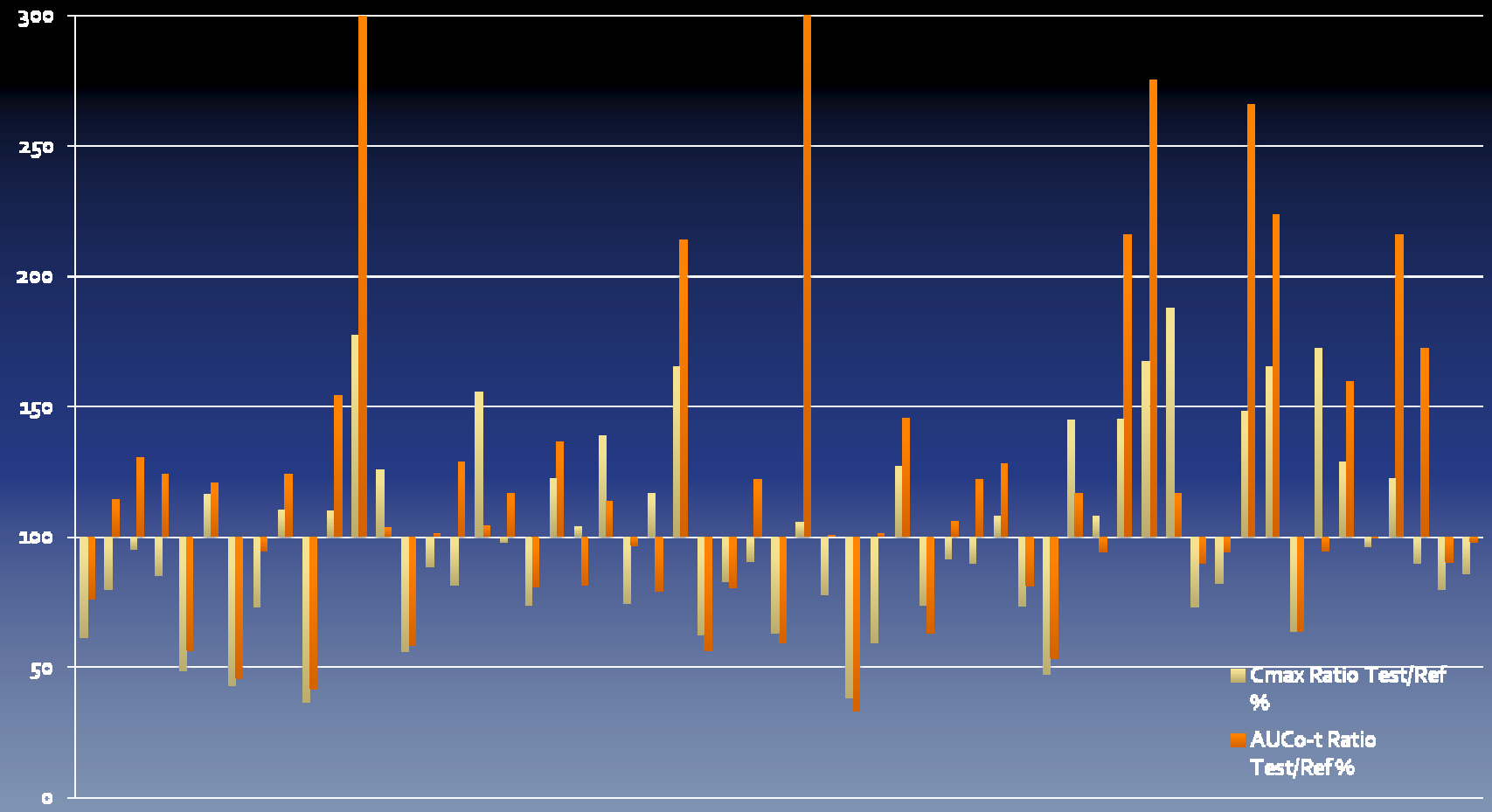
MEAN CURVES FLUTICASONE PROPIONATE SALMETEROL BY TREATMENT



INDIVIDUAL RATIOS FOR CMAX AND AUCo-T OF SALMETEROL



INDIVIDUAL RATIOS FOR CMAX AND AUCo-T OF FLUTICASONE PROPIONATE



BIOEQUIVALENCE COMPARISON RESULTS

FLUTICASONE PROPIONATE RESULTS

Test name	Parameter	Test value	Lower 90% CL	Upper 90% CL	Bioequiv
Classic 90% CI	AUC0-t	107.339	96.242	119.716	YES
Classic 90% CI	AUCinf	109.499	98.613	121.586	YES
Classic 90% CI	Cmax	92.844	85.134	101.252	YES

SALMETEROLRESULTS

Test name	Parameter	Test value	Lower 90% CL	Upper 90% CL	Bioequiv
Classic 90% CI	AUC0-t	100.915	88.441	115.149	YES
Classic 90% CI	AUCinf	100.765	88.835	114.298	YES
Classic 90% CI	Cmax	110.506	99.739	122.434	YES

CONCLUSIONS OF THE PK BIOEQUIVALENCE COMPARISON ROLENIUM VS. SERETIDE

- THE TEST WAS SUCCESSFULLY PERFORMED (ADEQUATE PK CURVES) IN ALL SUBJECTS ENROLLED
- THE MEAN CURVES OF BOTH DRUGS WERE VERY CLOSE WITH THE 2 ADMINISTERED TREATMENTS
- INDIVIDUAL RATIOS OF MAIN PK PARAMETERS (CMAX, AUC0-t) WERE HOMOGENEOUSLY DISTRIBUTED WITHOUT THE 100% RATIO
- THE STATISTIC CALCULATIONS PROVED THAT THE **2 MAIN PK PARAMETERS ARE WITHIN THE BIOEQUIVALENCE ACCEPTANCE LIMITS**
- THE ABOVE RESULTS, OF THIS VERY STRINGENT PK TEST, PERMIT TO CONCLUDE **THAT ROLENIUM AND SERETIDE ARE BIOEQUIVALENT; SO FAR COMPARABLE PHARMACOLOGICAL RESULTS ARE EXPECTED**

MANY THANKS TO THE ORGANIZER OF THIS CONFERENCE AND TO THE AUDIENCE