




Applying quantitative medicine to regulatory science: case studies in Alzheimer's Disease and Tuberculosis

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Clinical Trial Simulator for AD



What the tool is:

- A clinical trial simulation tool to help optimize clinical trial design for mild and moderate AD, using ADAS-cog as the primary cognitive endpoint

What it is based on:

- A drug-disease-trial model that describes disease progression, drug effects, dropout rates, placebo effect, and relevant sources of variability

What it is NOT intended for:

- Approve medical products without the actual execution of well conducted trials in real patients

Data Standards: the key to success

The diagram illustrates the process of data integration. It starts with 'Disparate Legacy Data' represented by several small tables with columns for Study Number, Visit Number, MMSE, and ADAS-cog. An arrow points to 'CDISC Data Standards', which is shown as a funnel collecting data from multiple sources. Another arrow points to 'Integrated Data', represented by a single larger table. A final arrow points to a line graph showing 'ADAS-cog (change from baseline)' on the y-axis (ranging from -4 to 6) and 'Time (Week)' on the x-axis (ranging from 0 to 52). The graph shows four curves: 'underlying disease progression' (upward), 'symptomatic drug response' (downward), 'disease modifying' (upward), and 'placebo response' (downward). A vertical arrow labeled 'Deterioration' points upwards on the right side of the graph.

Romero K, et al. Striving for an integrated drug development process for neurodegeneration: The Coalition Against Major Diseases. *Neurodegen Dis Manage* 2011;1(5): 379-85.


Comprehensive data integration

The diagram shows the integration of various data sources into an 'Integrated Knowledge Model'. The sources include:

- ADNI (ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE)**: 186 patients, with bullet points: Natural History, Interpatient Variability, Patient Specific Factors, Imaging and CSF Biomarkers.
- Literature Meta-Data**: 73 Trials (1990 to Present), Interstudy variability, Effects of marketed therapeutics (magnitude onset, offset). This leads to a 'Longitudinal Drug Disease Model'.
- Sponsor Proprietary Data**: Preclinical, Related products, Hypothesized effects of novel therapy. This leads to 'Trial Design Options Doses/ N Duration/Sampling Enrichment (BMx, etc.) Dropouts'.
- CAMD Database**: 9 trials, 3179 patients, Interpatient Variability, Patient Specific Factors, Placebo Effect.

 The 'Longitudinal Drug Disease Model' and 'Trial Design Options...' feed into the 'Integrated Knowledge Model'. The 'Integrated Knowledge Model' also feeds into 'Statistics' and 'Range of Possible Outcomes'.

How to request access To CAMD database:
www.codr.c-path.org

Model Endpoints/Covariates

Longitudinal cognitive instrument:

- ADAS-Cog: 11 items, 0-70 points

Basal cognitive instrument:


- MMSE: 8 items, 30-0 points

Demographics:

- Gender and baseline age

Genetics:

- Number of APOE4 alleles


Regulatory conclusions

This model adequately captures relevant information regarding disease progression, drug effects and clinical trial aspects (placebo effect and dropouts)




Clinical Trial Simulations based on this tool allows the objective, prospective and realistic evaluation of the operating characteristics of different trial designs.

FDA fit-for-purpose decision on CAMD CTS tool. 2013
EMA qualification opinion on CAMD CTS tool. 2013

A Clear and Successful Pathway for Regulatory Endorsement of DDTs



C-Path pioneered the pathway for Regulatory endorsement (Fit For Purpose) of Model Based DDTs






Modeling & Simulation for Medical Products Workshop
 September 26, 2013

SHORT REPORT


Modeling and simulation for medical product development and evaluation: highlights from the FDA-C-Path-ISOP 2013 workshop


Klaus Romero · Vikram Saha · Sandra Allerheligen · Meindert Danhof · Jose Pinheiro · Naomi Kraljick · Yanning Wang · Sue-June Wang · John-Michael Sauer · J. F. Marier · Brian Corrigan · James Rogers · H. J. Lambers Heerspink · Tawanda Gumbo · Peter Vis · Paul Watkins · Tina Morrison · William Gillespie · Mark Forrest Gordon · Diane Stephenson · Debra Hanno · Marc Pfeiter · Richard Lalonde · Thomas Colakly



<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm505485.htm>

A Clear and Successful Pathway for Regulatory Endorsement of DDTs





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21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft

Draft agreed by Modelling and Simulation Working Group	April 2016
Draft agreed by Pharmacokinetic Working Party	May 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	29 July 2016
End of consultation (deadline for comments)	31 January 2017

Comments should be provided using this [template](#). The completed comments form should be sent to plkvsecretariat@ema.europa.eu

Keywords
pharmacokinetics, modelling, simulation, qualification, predictive performance

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012¹
Revision 2: January 2014²
Revision 3: November 2014³
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

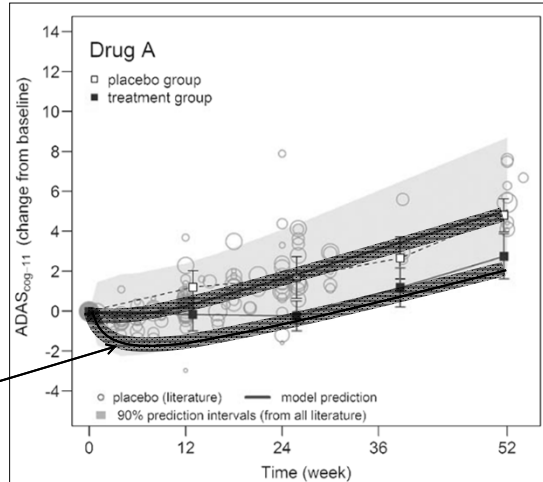
Keywords EMA, CHMP, Novel methodology, Qualification, Scientific Advice, Biomarker.

Case study 1



- 52-week phase II study:
- 141 AD patients
 - MMSE: 15-26
 - AChE-Is allowed if stable treatment for >3MO

Model prediction (drug effect)



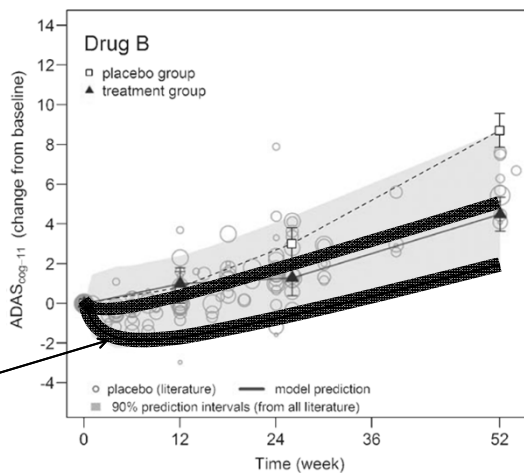
Ito K, et al. Understanding placebo responses in Alzheimer's disease clinical trials from the literature meta-data and CAMD database. J Alzheimer's Dis. 2013;37(1):173-83.

Case study 2




- 52-week phase II study:
- 101 AD patients
 - MMSE: 11-25
 - AChE-Is allowed if stable treatment for >3MO

Model prediction (drug effect)



Ito K, et al. Understanding placebo responses in Alzheimer's disease clinical trials from the literature meta-data and CAMD database. J Alzheimer's Dis. 2013;37(1):173-83.

Key lessons from this Consortium Approach



Data management and standardization

- CDISC standards are a valuable resource

Partnering with regulators


- Establish clarity in position especially around the “context of use”
- First example helped to drive “quantitative regulatory science”

Model support:

- Include early in planning
- User fora with the help of professional organizations (ISoP, AGRE, etc.)

Success breeds success

- Qualification of total kidney volume in polycystic kidney disease
- C-Path currently working on similar platforms for TB, Parkinson’s, Duchenne...



**Physiologically-based pharmacokinetic models:
 Lung model component that incorporates
 pathophysiological changes related to TB infection.**

Critical Path to TB Drugs (CPTD) Initiative.

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High-level PBPK representation of a human

The diagram shows a human silhouette with internal organs highlighted. To the right is a large empty box representing the compartmental model for the entire human body.

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Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13. 13

PBPK description of the lungs

LUNGS

breathmatters.org

Right Main Stem Bronchus
Right Lobes

Trachea
Left Stem Bronchus
Bronchi
Bronchioles
Left Lobes
Pleura
Pleural Fluid
Stomach
Diaphragm
Alveoli

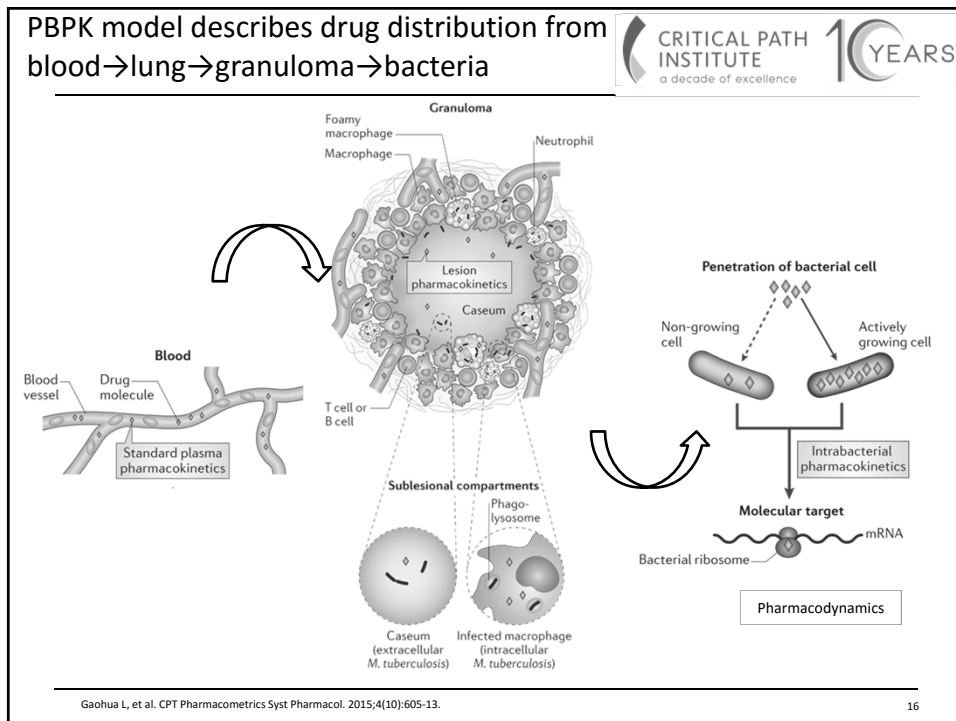
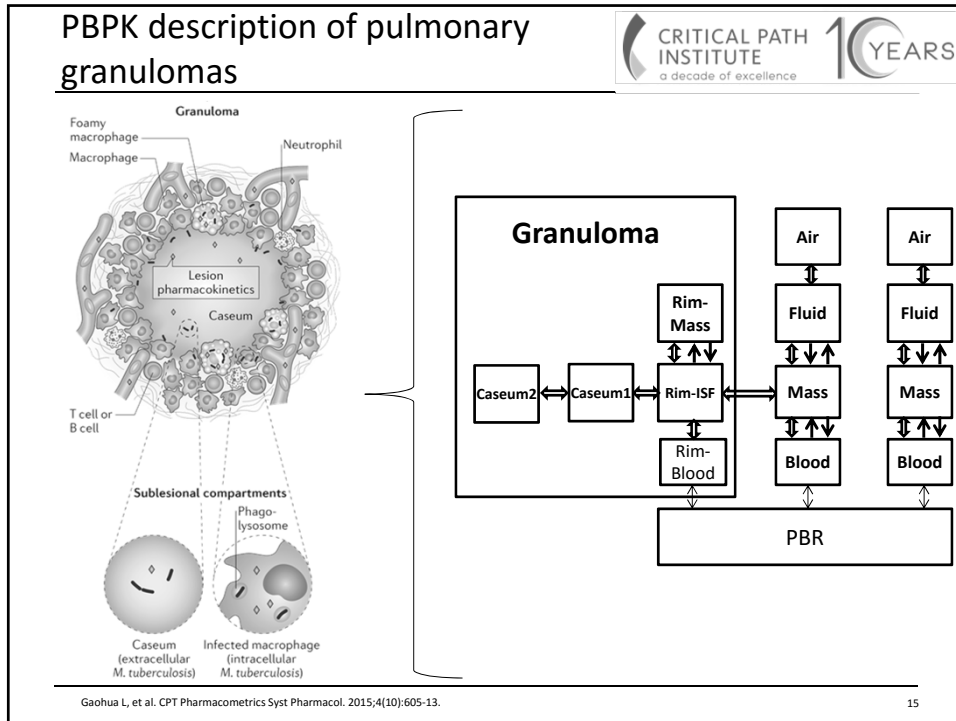
Pulmonary Blood Reservoir

Airways
Alveoli
Epithelial-lining Fluid
Tissue mass
Capillaries

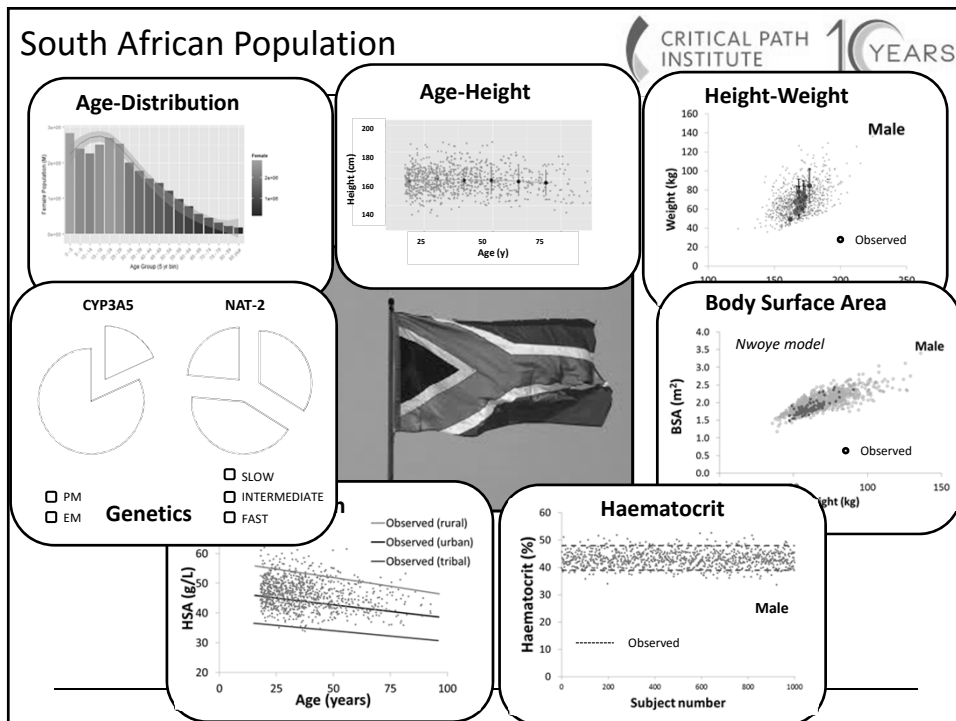
The diagram illustrates the anatomical structure of the lungs and a corresponding compartmental model. The model shows a hierarchy of compartments: Airways, Alveoli, Epithelial-lining Fluid, Tissue mass, and Capillaries, all connected to a central Pulmonary Blood Reservoir. Arrows indicate the flow of air and blood through these compartments.

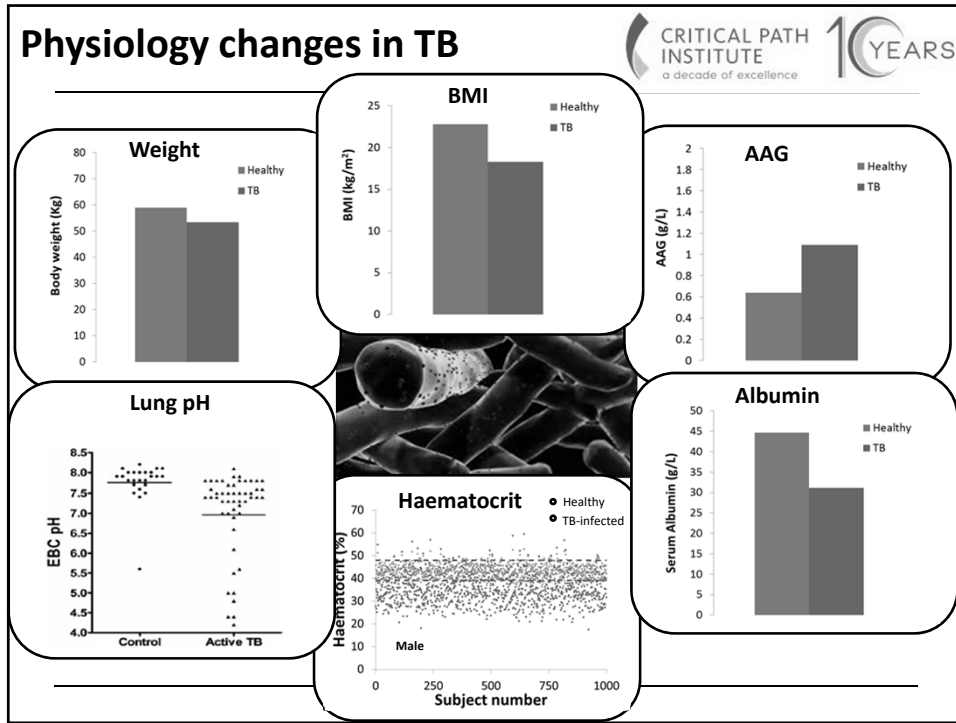
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Gaohua L, et al. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13. 14



Physiologically-based pharmacokinetic models:
Virtual South African population component that also
accounts for TB-related changes

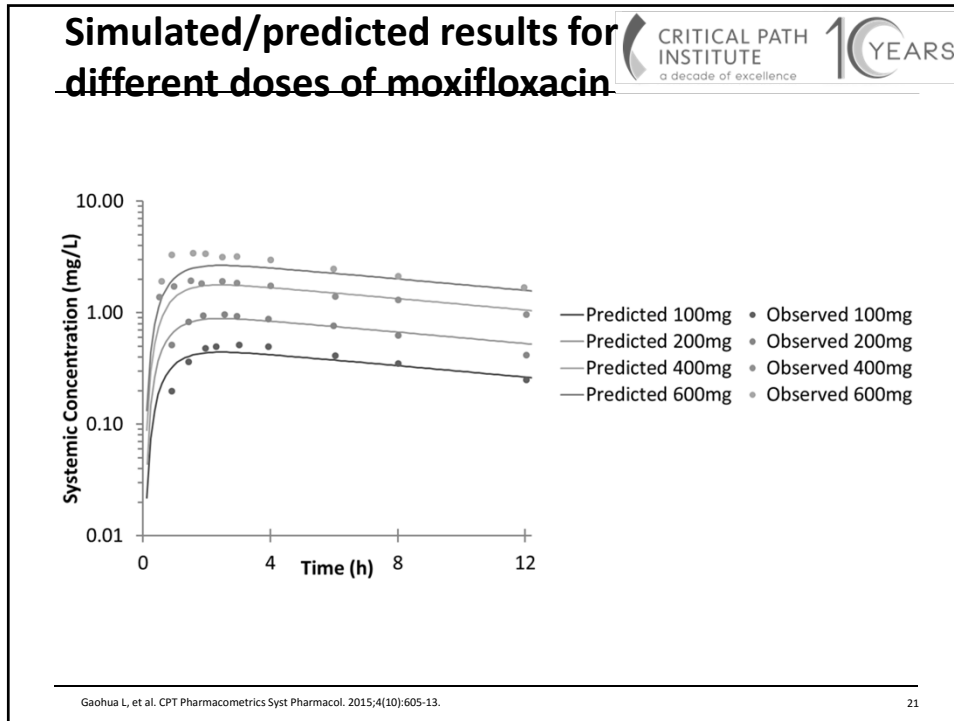




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Simulations based on the model

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Key lessons from this Consortium Approach

$$S = f(t, p)$$



Thank You

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