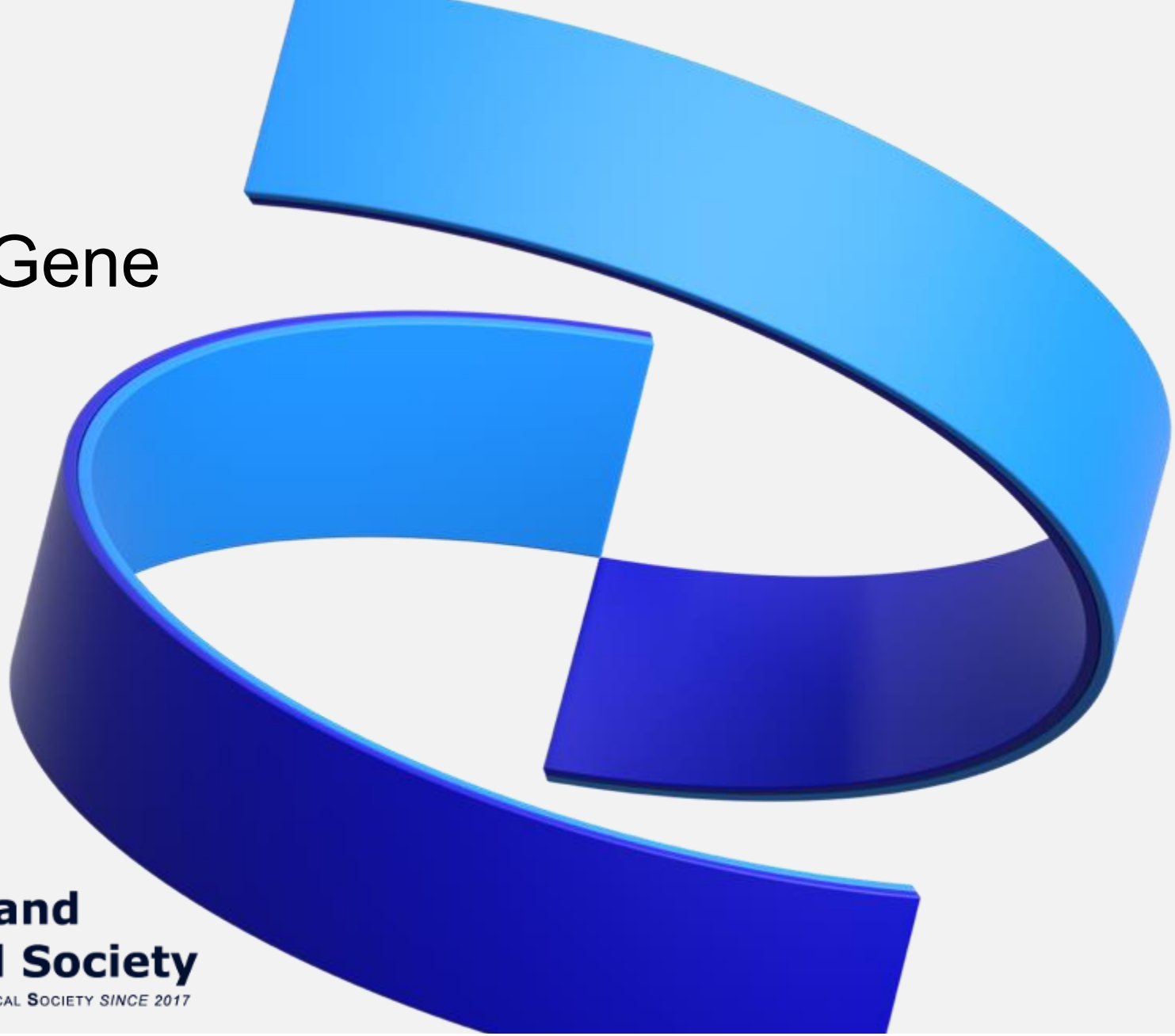
Model Informed Drug Development for Cell & Gene Therapy

Avery McIntosh

Oct 2025



NESS | New England Statistical Society

New England Statistics Symposium *since 1987* & New England Statistical Society *since 2017*

Disclaimer

The perspectives in this talk are those of the presenter only and do not necessarily represent the views of Pfizer

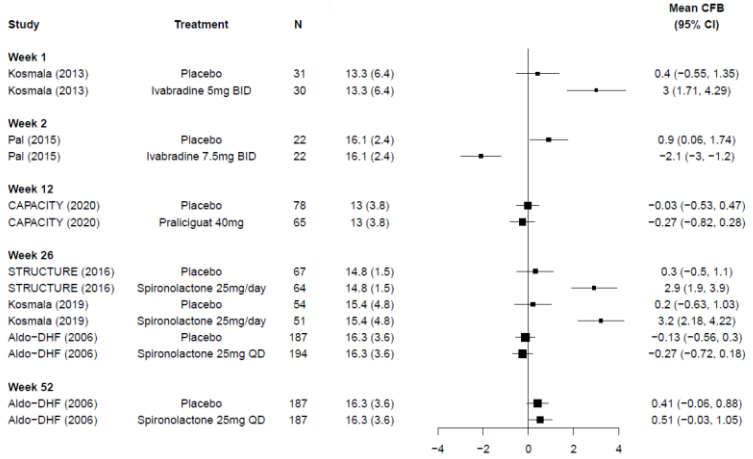
Acknolwedgements: Jeff Palmer, Anindita Banerjee, Donal Gorman, Susie Collins

Agenda

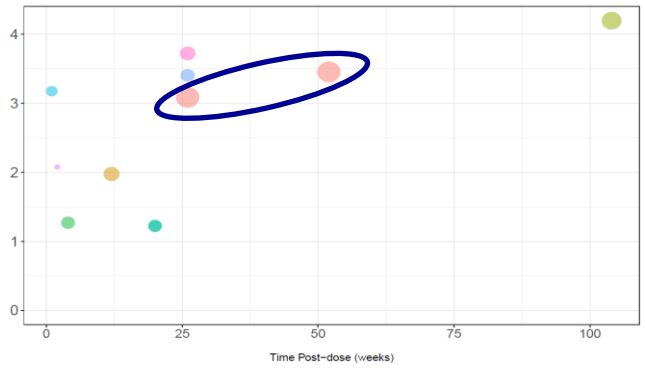
1. What is MIDD?
2. Brief history of MIDD
3. MIDD in Pfizer
4. MIDD in cell and gene therapy

Some examples of MIDD

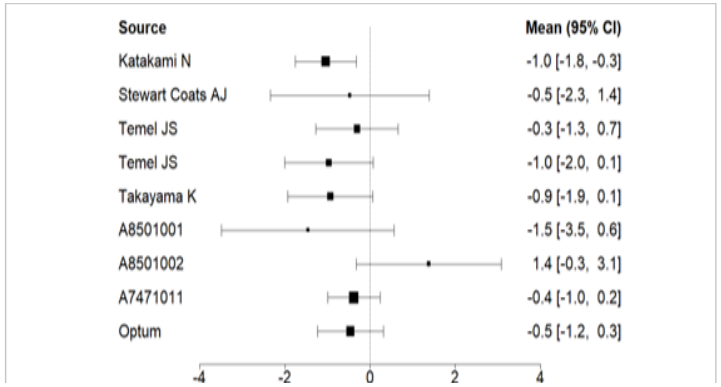
Summarising historical effect sizes



Estimating standard deviation for a future study



Deriving a placebo prior to reduce sample size



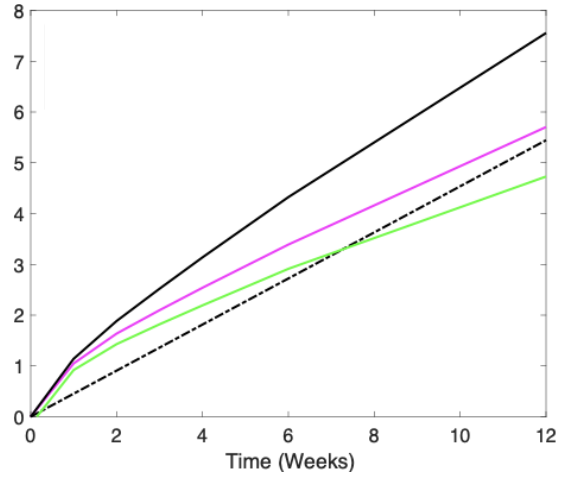
Sample sizing based on Bayesian Emax Model

No. of arms	No. of completers/arm	Probability of Passing Stat. Sig. Criteria				Probability of Passing TV of 2%			
		5 mg	15 mg	40 mg	100 mg	5 mg	15 mg	40 mg	100 mg
5 arms	50	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**69%**	**97%**	**99%**	**100%**
	40	**99.9%**	**99.9%**	**99.9%**	**99.9%**	**68%**	**96%**	**99%**	**100%**
4 arms	50	**99.9%**	**99.9%**	**99.9%**		**68%**	**97%**	**97%**	**99%**
	40	**99.7%**	**99.7%**	**99.7%**		**68%**	**95%**	**99%**	

"MBMA" of competitor effect sizes

Dosing Regimen	Efficacy* (8 weeks)	Efficacy* (12 weeks)	Efficacy* (16 weeks)
3 mg/day	-0.42 [-0.47 to -0.38]	-0.51 [-0.57 to -0.46]	-0.55 [-0.61 to -0.49]
7 mg/day	-0.66 [-0.71 to -0.60]	-0.80 [-0.86 to -0.73]	-0.85 [-0.92 to -0.78]
14 mg/day	-0.83 [-0.89 to -0.77]	-1.00 [-1.08 to -0.93]	-1.08 [-1.15 to -0.99]
0.5 mg/week	-0.77 [-0.83 to -0.72]	**-0.94 [-1.00 to -0.87]**	**-1.00 [-1.07 to -0.93]**
1 mg/week	-0.94 [-1.00 to -0.87]	**-1.13 [-1.20 to -1.05]**	**-1.21 [-1.29 to -1.13]**
2 mg/week	-1.05 [-1.11 to -0.98]	-1.26 [-1.34 to -1.18]	-1.36 [-1.44 to -1.27]
3 mg/day	-0.52 [-0.59 to -0.46]	-0.63 [-0.71 to -0.56]	-0.68 [-0.76 to -0.60]
7 mg/day	-0.81 [-0.90 to -0.73]	-0.98 [-1.08 to -0.88]	-1.05 [-1.16 to -0.94]
14 mg/day	-1.02 [-1.13 to -0.92]	-1.23 [-1.36 to -1.11]	-1.33 [-1.46 to -1.20]
0.5 mg/week	**-0.95 [-1.04 to -0.86]**	-1.15 [-1.26 to -1.04]	-1.24 [-1.35 to -1.12]
1 mg/week	**-1.15 [-1.26 to -1.05]**	-1.39 [-1.52 to -1.27]	-1.49 [-1.63 to -1.36]
2 mg/week	-1.29 [-1.41 to -1.17]	-1.55 [-1.70 to -1.41]	-1.67 [-1.82 to -1.52]

QSP model to predict longer-term responses



Evolution of MIDD Concept

- **M&S** — Modelling & Simulation
- **PMx&SP** — Pharmacometrics; System pharmacology
- **MBDD** — Model-Based Drug Development
- **MIDD** — Model-Informed Drug Development
- **MID3** — Model-Informed Drug *Discovery* and Development

2007 → 2013 → 2019 → 2020

Model-Informed Drug Development

Model-based Drug Development

RL Lalonde[1], KG Kowalski[2], MM Hutmacher[1], W Ewy[2], DJ Nichols[1], PA Milligan[1], BW Corrigan[1], PA Lockwood[1], SA Marshall[1], LJ Benincosa[1], TG Tensfeldt[1], K Parivar[1], M Amantea[1], P Glue[1], H Koide[1] and R Miller[1]

[1]Department of Clinical Pharmacology, Pfizer Global Research and Development, Groton, Ann Arbor, Sandwich, New York, La Jolla, Tokyo; [2]Department of Statistics, Pfizer Global Research and Development, Groton, Ann Arbor, Sandwich, New York, La Jolla, Tokyo. Correspondence: R Lalonde (richard.lalonde@pfizer.com)

Published online 23 May 2007. doi:10.1038/sj.clpt.6100235

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 82 NUMBER 1 | JULY 2007 21

Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

PA Milligan[1], MJ Brown[2], B Marchant[3,10], SW Martin[1], PH van der Graaf[4,1], N Benson[4,11], G Nucci[5], DJ Nichols[5], RA Boyd[6], JW Mandema[7], S Krishnaswami[6], S Zwillich[8], D Gruben[2], RJ Anziano[2], TC Stock[9] and RL Lalonde[6]

[1]Global Clinical Pharmacology, Pfizer, Sandwich, UK; [2]Department of Statistics, Pfizer, Groton, USA; [3]Department of Clinical Development, Pfizer, Sandwich, UK; [4]Department of Pharmacokinetics Dynamics and Metabolism, Pfizer, Sandwich, UK; [5]Global Clinical Pharmacology, Pfizer, Cambridge, Massachusetts, USA; [6]Global Clinical Pharmacology, Pfizer, Groton, Connecticut, USA; [7]Quantitative Solutions, Inc., Menlo Park, California, USA; [8]Department of Clinical Development, Pfizer, Groton, Connecticut, USA; [9]Department of Clinical Development, Pfizer, Collegeville, Philadelphia, USA; current affiliations: [10]Marchant Biopharm Consulting Ltd, Kowloon, Hong Kong; [11]Xenologiq, Denne Hill Business Park, Canterbury, UK. Correspondence: PA Milligan (peter.a.milligan@pfizer.com)

Received 27 December 2012; accepted 4 March 2013; advance online publication 1 May 2013. doi:10.1038/clpt.2013.54

502 VOLUME 93 NUMBER 6 | JUNE 2013 | www.nature.com/cpt

Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

[1]Office of Clinical Pharmacology, Office of Translational Sciences, US Food and Drug Administration, Silver Spring, Maryland, USA.
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FDA Perspective on MIDD

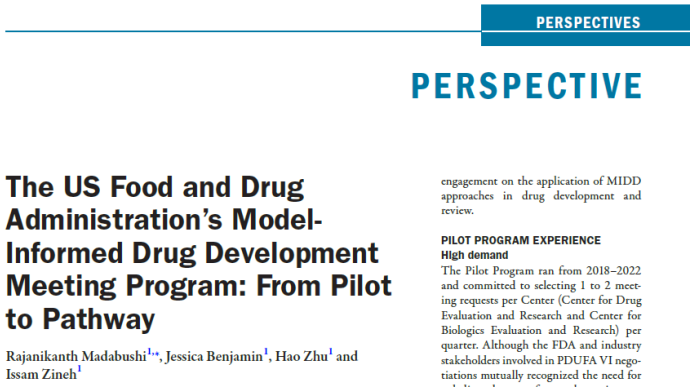
- PDUFA VII (2023) legislation ensures continued FDA commitment to several MIDD initiatives

†
- **MIDD Paired Meeting Program**

Jointly administered by CDER and CBER for IND, NDA, and BLA holders to support the use of innovative modeling tools in a specific development program.

1. **Creating an environment that increases stakeholder acceptance of MIDD approaches**
2. **Developing standards and best practices that lead to consistent application and evaluation**
3. **Increasing capacity and expertise to address growing demands and innovation**

*: Model-Informed Drug Development Paired Meeting Program | FDA



PERSPECTIVES

PERSPECTIVE

The US Food and Drug Administration's Model-Informed Drug Development Meeting Program: From Pilot to Pathway

Rajanikanth Madabushi[1,*], Jessica Benjamin[1], Hao Zhu[1] and Issam Zineh[1]

engagement on the application of MIDD approaches in drug development and review.

PILOT PROGRAM EXPERIENCE

High demand

The Pilot Program ran from 2018–2022 and committed to selecting 1 to 2 meeting requests per Center (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research) per quarter. Although the FDA and industry stakeholders involved in PDUFA VI negotiations mutually recognized the need for

†
- **FFP Program**

The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs.

Disease Area	Submitter	Tool	Trial Component
Alzheimer's disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out
Multiple	Janssen Pharmaceuticals and Novartis Pharmaceuticals	Statistical Method: MCP-Mod	Dose-Finding
Multiple	Ying Yuan, PhD The University of Texas, MD Anderson Cancer Center	Statistical Method: Bayesian Optimal Interval (BOIN) Design	Dose-Finding
Multiple	Pfizer	Statistical Method: Empirically Based Bayesian Emax Models	Dose-Finding

FDA Quantitative Medicine Center of Excellence (QM CoE)

[CDER Quantitative Medicine Center of Excellence (QM CoE) | FDA]

CDER Quantitative Medicine Center of Excellence (QM CoE)

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The Center for Drug Evaluation and Research (CDER) Quantitative Medicine (QM) Center of Excellence (CoE) is established to facilitate and coordinate the continuous evolution and consistent application of QM for drug development and regulatory decision-making across CDER.

For decades, CDER offices have been at the forefront of advancing QM approaches to inform premarket product review and post-market product assessment. Given the tremendous growth in QM, we see many opportunities to maximize synergies across CDER by centrally coordinating efforts through strategic planning and execution. The QM CoE seeks to strengthen collaborations in outreach, education, scientific and regulatory initiatives, as well as policy development and implementation. The QM CoE will be a CDER-wide enterprise that will function as a cooperative, coordinating body that spurs innovation and fosters integration of QM approaches to advance therapeutic medical product development, inform regulatory decision-making, and promote public health.

To learn more about the establishment of the QM CoE, view the CDER statement.

Activities of the CoE

The CoE will introduce new activities and coordinate existing activities in three main areas: Applied Science Policy, Strategic Planning and Coordination, and Multidisciplinary Education and Exchange.

Remit

Influencing Policy

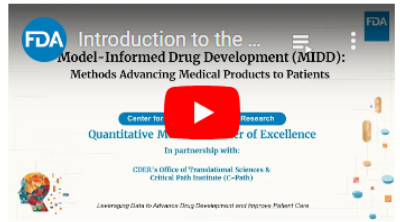
Strategic Planning

Multidisciplinary Training/Education

Discover educational resources available under the QM CoE.

FDA/C-Path Institute Model Informed Drug Development Web-Based Training

- The U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) Quantitative Medicine Center of Excellence (QM CoE), in collaboration with CDER's Office of Translational Sciences and the Critical Path Institute (C-Path), is pleased to provide free, web-based training modules on model-informed drug development (MIDD). Watch the playlist on YouTube.



FDA QM CoE Public Workshop (April 25, 2024)

[Streamlining Drug Development and Improving Public Health through Quantitative Medicine: An Introduction to the CDER Quantitative Medicine Center of Excellence - 04/25/2024 | FDA]

FDA Workshop

Streamlining Drug Development and Improving Public Health through Quantitative Medicine

APRIL 25, 2024

QM at CDER

CDER has been at the forefront of advancing QM to inform pre-market product review, post-market product assessment, policy development, and policy implementation.

- Model-informed drug development (MIDD)
- Complex innovative trial design (CID)
- Fit-for-purpose initiative (FFP)
- Model integrated evidence (MIE)
- Physiology based biopharmaceutics modeling (PBBM)

Opportunity to maximize synergies across CDER by centrally coordinating efforts

‹#›

QM CoE Workshop: Excerpt from Statistics Presentation

THE ROLE OF THE OFFICE OF BIOSTATISTICS

Stella Grosser
DBVIII/OB/OTS
April 25, 2024

MIDD: Leverage the Strengths of 2 Disciplines

FDA

While both disciplines may work on all aspects, they have particular strengths

Clinical Pharmacology:

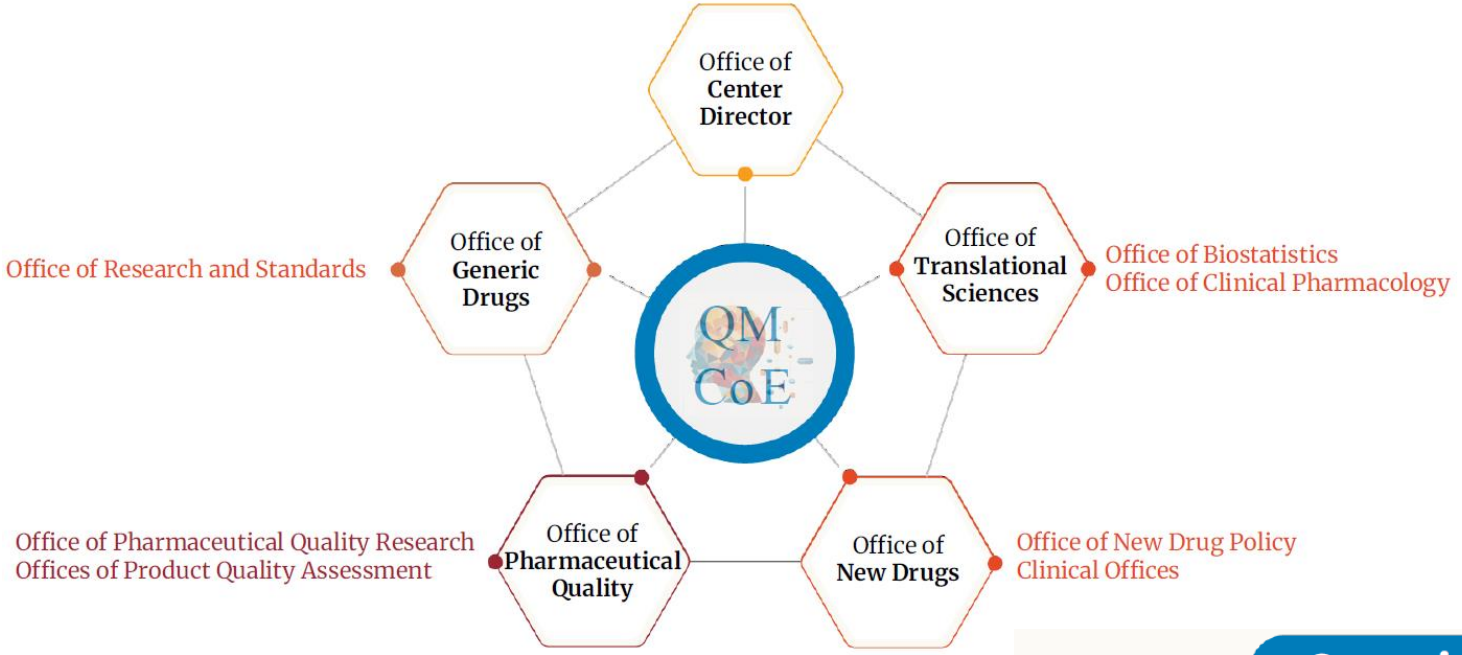
- Understanding of principles of clinical pharmacology (PK & PD), patient characteristics, and diseases.
- Leading to adoption of useful predictions including extrapolation

Statistics:

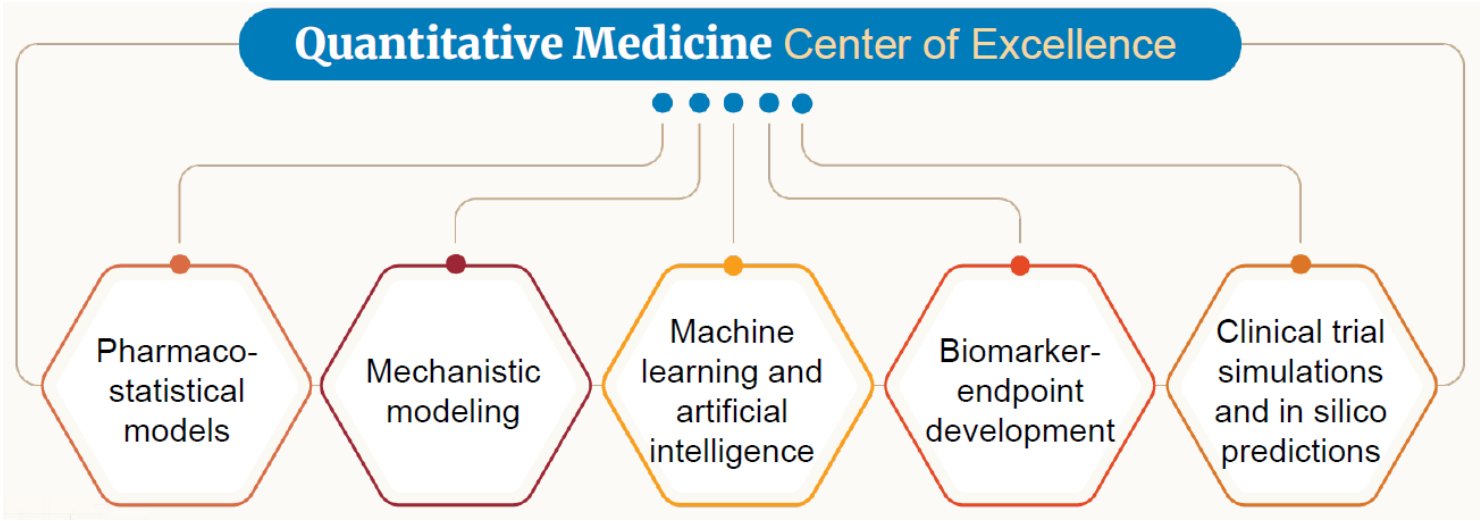
- Separating exploration vs. confirmatory
- Detecting signal vs. noise, sometimes through advanced statistical tools
- Distinguishing association vs. causation, and promoting appropriate interpretation

QM CoE Workshop: Participating Offices and Scope

Participating Offices



Scope



History of MIDD (ECTD*/EQDD*) in Pfizer (from 2003 to 2020)

*ECTD = Enhanced Clinical Trial Design
*EQDD = Enhanced Quantitative Drug Development

Robust implementation history and evolution of MIDD principles across Pfizer portfolio have been made possible only through the right **behaviors** by the right **stakeholders**

Behaviors
- Alignment
- Engagement
- Collaboration

Stakeholders
- Statistics
- Clinical Pharmacology
- Clinical
- Pharmacometrics

History of MIDD in Pfizer (2020 onwards)

MIDD Reboot 2020

1. Substantial evidence of value that MIDD (EQDD) has brought to Pfizer (millions saved each year)

2. Expectation from multiple regulatory authorities for MIDD implementation

3. Efficient implementation of MIDD practices will require wider cross-functional alignment than ever before

4. Initiative aims to:

    - Align internal practices with industry
    - Influence external stakeholder and future directions
    - Further establish MIDD as integral part of development at Pfizer
    - Connect experts throughout the organization to foster knowledge sharing and maximize opportunities
    - Training materials and monthly MIDD forum

- MIDD is an integral part of the clinical develop plan/ integrated evidence plan

- MIDD discussions should occur prior to FIH and quantitative lines in the pre-clinical space

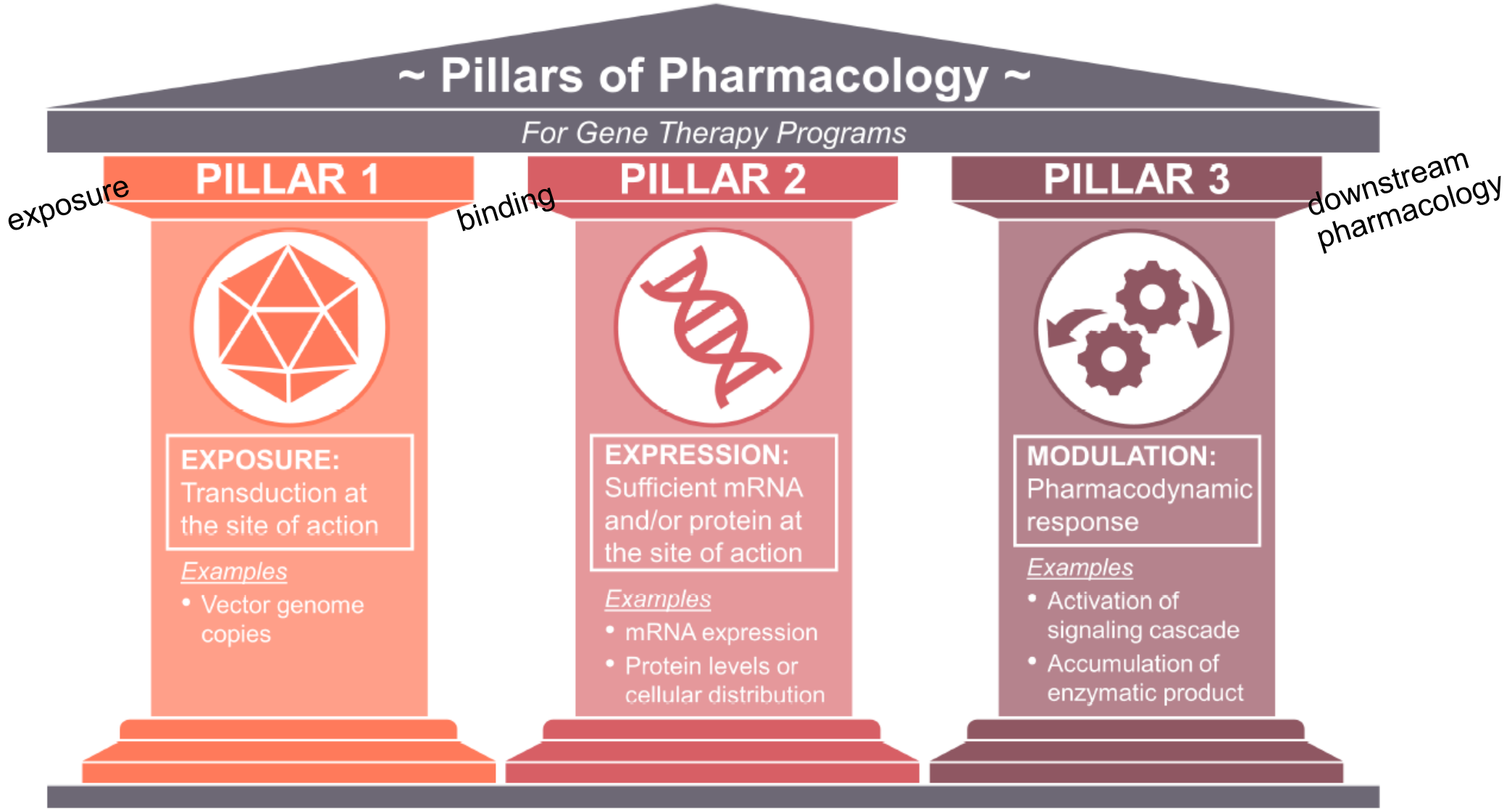
- The MIDD discussions must start between all the quantitative lines no later than when the compound goes into phase 1, while the team is developing the CDP.

Cell/ Gene Therapy Clinical Development Has Unique Challenges

- Kinetics/ clearance are unique to the MoA(s)
- First study in GTx is non placebo controlled in a very small number of patients
- Transition to second study may be pivotal trial leading to BLA submission
- Natural history data are a key factor (if they exist!)
- Extremely competitive space with rapidly emerging data – not always comparable (different vectors, transgenes, regulatory elements)
- Safety remains a key question
- How do we ensure we take the correct decision with a one-time therapy? How much risk is appropriate?

All These Points Should be Addressed with a Quantitative [Model-Informed] Strategy!

Defining Success by Pharmacology Principles in GTx



Mohamed Hassanein, Kelly A Fader, David Beidler. "Biomarkers in Gene Therapy Development for Rare Diseases." ISBN 9781032136554

Opportunities for MIDD in the GTx Space

Trial Design / CDP/ IEP Areas

- Characterization of genetic subpopulations
- Seamless trial design FIH → Pivotal
- Assay/ CMC characterization impacts on immune response
- Meta-analysis to benchmark efficacy of a candidate GTx
- Extrapolation of in vitro/vivo data to multiple systems or cell types
- Quantitative dose finding with models used in oncology (BLRM) retro fit to the GTx space
- Bayesian borrowing to inform AE profiles in LTFU
- Incorporating digital endpoints into PK-PD modeling

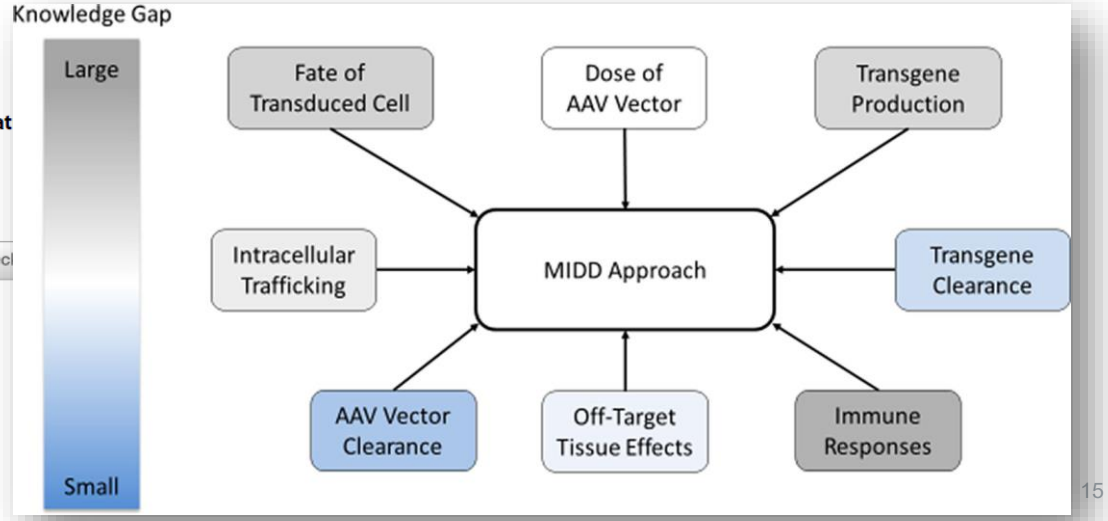
A Pharmacometrics-Informed Trial Simulation Framework for Optimizing Study Designs for Disease-Modifying Treatments in Rare Neurological Disorders

Yevgen Ryeznik[1] | Ralf-Dieter Hilgers[2] | Nicole Heussen[2,3] | Emmanuelle Comets[4,5] | France Mentré[4] | Niels Hendrickx[4] | Mats O. Karlsson[1] | Andrew C. Hooker[1] | Alzahra Hamdan[1] | Xiaomei Chen[1] | Rebecca Schüle[6,7,8] | Matthis Synofzik[6,7] | Oleksandr Sverdlov[9]

Evaluation of Mitochondrial Complex 1 Density with [^{18}F]BCPP-EF in a Murine Model and Individuals with Friedreich Ataxia

Laigao Chen*[1], Gaia Rizzo*[2,3], Christine Bulawa[1], Koene R.A. Van Dijk[1], Erica C. Henning[1], Alain Martelli[1], Jeffrey Palmer[1], Avery McIntosh[1], Marko Pregel[1], Pengling Sun[1], Emmanuel Adewunmi[4], Mark Aldridge[5], Jackson Chan[6], Roger N. Gunn[2,3], Mickael Huiban[2], Allan Listanco[2], Peter T. Loudon[7], Sara Moz[2], Jan Passchier[2], Lauren Sauvage[2], Rachel Stewart[5], Lisa Wells[2], Eugenii A. Rabiner[2], Lawrence R. Charnas[1], and Richard J. Festenstein[4,6]

Belov, Artur, et al. "Opportunities and challenges for applying model-informed drug development approaches to gene therapies." *CPT: Pharmacometrics & Systems Pharmacology* 10.4 (2021): 286-290.



Gene Therapy

ANNALS of Clinical and Translational Neurology
Open Access
ANA AMERICAN NEUROLOGICAL ASSOCIATION

Research Article | Open Access

Digital endpoints for self-administered home-based functional assessment in pediatric Friedreich's ataxia

Arne Mueller, Elaine Paterson, Avery McIntosh, Jens Praestgaard, Mary Bylo, Holger Hoefling

www.nat

Check

ARTICLE OPEN

Dystrophin/mini-dystrophin expression analysis by immunoaffinity liquid chromatography–tandem mass spectrometry after gene therapy for DMD

Jason Walsh[1], Joe Palandra[1], Nicole Duriga[1], David Beidler[2], Avery McIntosh[3], Michael Binks[4] and Hendrik Neubert[1]

Opportunities for MIDD in the GTx Space

Mechanism of Action/ PK-PD Areas

- Kinetics / clearance
- On/off target integration
- Adverse event risk (cytokine release syndrome, thrombotic microangiopathy, etc.)
- Durability

CPT: Pharmacometrics & Systems Pharmacology

Article | Open Access

Tisagenlecleucel Model-Based Cellular Kinetic Analysis of Chimeric Antigen Receptor–T Cells

Andrew M. Stein, Stephan A. Grupp, John E. Levine, Theodore W. Laetsch, Michael A. Pulsipher, Michael W. Boyer, Keith J. August, Bruce L. Levine, Lori Tomassian, Sweta Shah, Mimi Leung, Pai-Hsi Huang, Rakesh Awasthi, Karen Thudium Mueller, Patricia A. Wood, Carl H. June
... See fewer authors

First published: 07 March 2019 | https://doi.org/10.1002/psp4.12388 | Citations: 89

Cardiac safety of fordadistrogene movaparvovec gene therapy in Duchenne muscular dystrophy: Initial observations from a phase 1b trial

Sarah P. Sherlock,[1] Daniel I. Levy,[1] Avery McIntosh,[1] Perry B. Shieh,[2] Edward C. Smith,[3] Tara G. McDonnell,[1] Kelly A. Ryan,[1] Marielle Delnomdedieu,[1] Michael Binks,[1] Ashwin K. Lal,[4] and Russell J. Butterfield[4]

Practical and Statistical Considerations for the Long Term Follow-Up of Gene Therapy Trial Participants

Maximilian Rohde[1,2], Seoan Huh[3], Vanessa D'Souza[4], Steven Arkin[1], Erika Roberts[5] and Avery McIntosh[4,*]

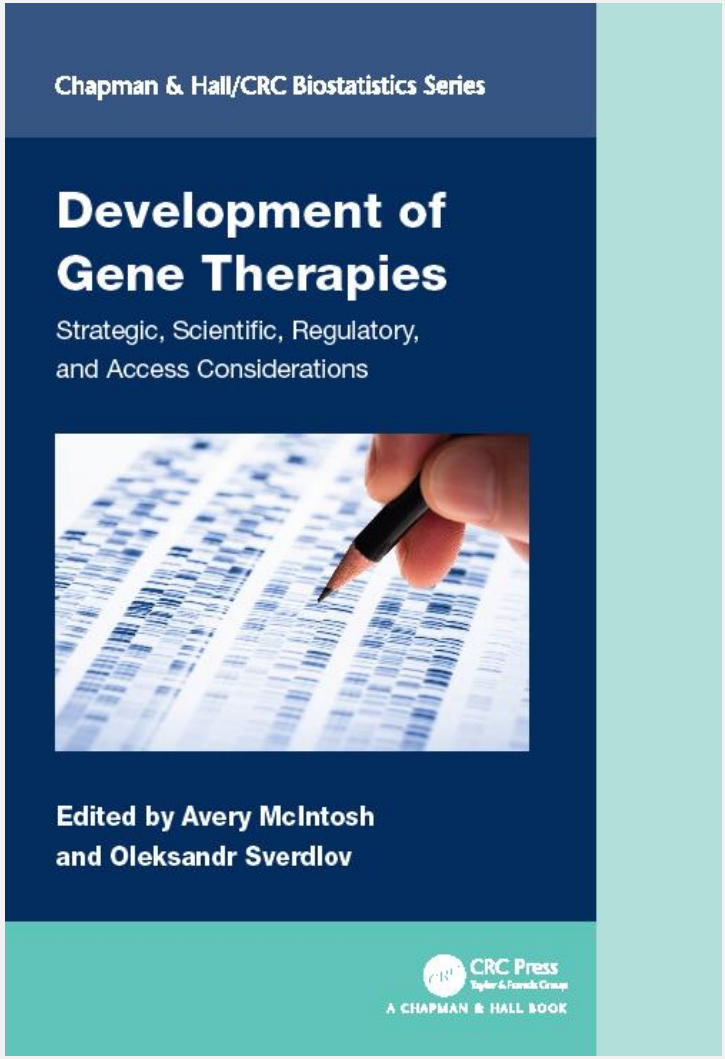
Chapter

Quantitative Systems Pharmacology Modeling of Adeno-Associated Virus Gene Therapies: Mechanistic Identification of Species-Translation Using Preclinical and Clinical Data

By Satyajit Rao, Jatin Narula, Glen Ko, Haobin Luo, Zhiwei Zhang, Cynthia J. Musante, Nessy Tania

Book Development of Gene Therapies

Thank You


Chapman & Hall/CRC Biostatistics Series
Development of Gene Therapies
Strategic, Scientific, Regulatory, and Access Considerations
Edited by Avery McIntosh and Oleksandr Sverdlov
CRC Press
A CHAPMAN & HALL BOOK