

Public-Source Meta-database Offering

Supporting Strategic Decision-Making
in Clinical Drug Development

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Introduction: Why Public Source Data Modeling?

- The development of a new drug is a high risk and costly activity that involves multiple decisions and tradeoffs
- Model-based approaches for combining proprietary data on a specific compound with literature data of its likely competitors offer powerful tools for managing:
 - Risks concerning dose selection
 - Efficient and effective trial design
 - Key "go/no-go" decisions
- FDA has a growing base of experience with literature modeling and model-based drug development, as part of its Critical Path Initiative

Pharsight Meta-database Offering

- Pharsight compiles therapeutic area data and information from public source scientific literature to provide a ready context for model-based meta-analysis that can accelerate quantitative assessment of a compound's performance relative to competing treatments
- Indication-focused databases in multiple therapeutic areas have been compiled with a deliberate focus to enable knowledge build-out and enhanced client deliverables for decision-making
- All data are formatted and entered in a “ready-to-model” meta-database that undergoes multiple quality design and check stages

The Pharsight Meta-database Group

- Dedicated team functioning within Pharsight Strategic Consulting Services (SCS) Group
- Provides a quality-driven means of building deliverable public source bibliographies and clinical databases while ensuring that M&S consultants can focus on M&S methods and results
- The Meta-database group works collaboratively with SCS therapeutic domain experts and modelers
- Responsible for design, assembly, quality control, and maintenance of Pharsight meta-databases
- Operates to proprietary set of internal procedures
- Uses industry-standard tools (e.g., Thomson/ISI® Reference Manager®, Golden Digger® software to capture graphical data from industry journals)
- Twenty-year Registered Clinical Pharmacist heads the group

Public Data Sources

- Public data sources on competitors and analogues from the clinical and scientific literature, collectively called “meta-data”, are diverse and include:
 - Published journal articles
 - Regulatory documents (e.g., FDA Summary Basis for Approval)
 - Package inserts or promotional materials from the drug manufacturer
 - Published abstracts or poster presentations
 - Meeting proceedings
 - Web documents (e.g., press releases about new clinical trial results)
 - Online clinical trial registries

How Pharsight Meta-databases Can Be Leveraged

- Assess literature and engage clinical teams to address key program questions about NCE attributes vs. competitors
- Build dose-response models of the competitive landscape for a new drug before NCE patient-level data are available
- Combine public-source literature models with proprietary sponsor/NCE data to produce an evolving picture of a compound's competitive product profile
- Update models as new proprietary and public information on the NCE becomes available to assess likely clinical benefits and trade-offs
- Make modeling results readily available to the team and communicate predictive results of modeled product profiles using visualization software tools, such as Pharsight's [Drug Model Explorer](#)[®] (DMX[®])

Benefits of Integrated, Comparative Literature Modeling

- Make explicit quantitative assessments between competing treatments when no direct within-study comparisons are available
- Predict clinical outcomes for NCEs even when no new clinical data are collected
 - At unstudied doses
 - Extrapolation of steady-state effect from early short-duration dose ranging trials
- Bridge preclinical-to-clinical or biomarker-to-clinical relationships within a common therapeutic class
- Greater objectivity when predicting and inferring an NCE's critical efficacy/safety/tolerability attributes
 - Compare NCE attributes and uncertainty with competing therapies
 - Compare with draft launch label targets

Currently Available Public-Source Meta-databases: Summary by Therapeutic Area and Disease/Indication

Therapeutic Area	Disease State/Indications
Anti-infectives	Fluoroquinolone Anti-infectives Hepatitis C Virus (HCV)
Anti-inflammatory	Rheumatoid Arthritis (RA)
Cardiovascular	Congestive Heart Failure (CHF) Hypertension Hyperlipidemia/Dyslipidemia Hypercholesterolemia Thrombosis
Central Nervous System	Depression Migraine Headache Schizophrenia Sleep Disorders
Endocrine	Type II Diabetes Obesity
Gastro-intestinal	Gastro-esophageal reflux disease (GERD) Irritable Bowel Disease (IBD)
Genito-urinary	Female Sexual Arousal Disorder (FSAD)
Pain	Osteoarthritis Pain
Respiratory	Asthma Chronic Obstructive Pulmonary Disease (COPD)

Anti-infectives Public Source Meta-database: Fluoroquinolones

- Abstracts Reviewed: 600
- Studies Included: 21
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Moxifloxacin, Levofloxacin, Ciprofloxacin, Ofloxacin, Gemifloxacin, Garenoxacin, Gatifloxacin, Sitafloxacin
- Scope of Therapies
 - Treatment of bacterial infections of various body sites, structures, and severities
- Disease State/Indication
 - Bacterial infections
- Time Period: 1993-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Anti-infectives Public Source Meta-database: Hepatitis C Virus (HCV)

- Abstracts Reviewed: 81
- Studies Included: 17
- Literature Databases
 - PubMed, Medline
- Drugs Included
 - Interferon, Interferon alpha, Interferon beta, Pegylated Interferon alpha
- Scope of Therapies
 - Treatment, induction of remission, and maintenance of remission of Hepatitis C-type viral infection
- Disease State/Indication
 - Viral infection
- Time Period: 1998-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Anti-inflammatory Public Source Meta-database: Rheumatoid Arthritis (RA)

- Abstracts Reviewed: 170
- Studies Included: 28
- Literature Databases
 - PubMed, Medline, Meeting Abstracts, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Adalimumab, Anakinra, Etanercept, Methotrexate
- Scope of Therapies
 - Drugs intended to mitigate the signs and symptoms of rheumatoid arthritis
- Disease State/Indication
 - Rheumatoid arthritis
- Time Period: 1996-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Cardiovascular Public Source Meta-database: Lipids

- Abstracts Reviewed: 34
- Studies Included: 16
- Literature Databases
 - PubMed, Medline, Summary Basis of Approval
- Drugs Included
 - Atorvastatin, Cerivastatin, Ezetimibe, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin
- Scope of Therapies
 - Drugs to treat lipid profile abnormalities
- Disease State/Indication
 - Hyperlipidemia
- Time Period: 2000-2003
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Cardiovascular Public Source Meta-database: Plant Stanols

- Abstracts Reviewed: 29
- Studies Included: 18
- Literature Databases
 - PubMed, Medline, Summary Basis of Approval
- Drugs Included
 - Atorvastatin, Simvastatin, Pravastatin, Lovastatin, Ezetimibe, Plant Stanols
- Scope of Therapies
 - Reduction of low-density lipoprotein (LDL) cholesterol
- Disease State/Indication
 - Hypercholesterolemia
- Time Period: 1994-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Cardiovascular Public Source Meta-database: Bleeding Cascade Disorders and Control (Factor Xa)

- Abstracts Reviewed: 940
- Studies Included: 104
- Literature Databases
 - PubMed, Medline, ISI Web of Science, Cinahl, OVI
- Drugs Included
 - Dalteparin, Enoxaparin, Fondaparinux, Heparin, Melagatran, Razaxaban, Warfarin, Ximelagatran, BAY 59-7939, Naproxen
- Scope of Therapies
 - Drugs intended to prevent abnormal or undesired blood clots
- Disease State/Indication
 - Pulmonary embolism, deep-venous thrombosis, venous thromboembolism, prevention of post-surgical clot
- Time Period: 1980-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Cardiovascular Public Source Meta-database: Combination Aldosterone Antagonist/Diuretic

- Abstracts Reviewed: 43
- Studies Included: 11
- Literature Databases
 - PubMed, Medline
- Drugs Included
 - Torsemide
- Scope of Therapies
 - Treatment of hypertension, congestive heart failure, abnormal fluid pooling or swelling, edema
- Disease State/Indication
 - Hypertension, edema, congestive heart failure
- Time Period: 1985-2004
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

CNS Public Source Meta-database: Antidepressants

- Abstracts Reviewed: 940
- Studies Included: 129
- Literature Databases
 - PubMed, Medline, Summary Basis of Approval, www.clinicalstudyresults.org
- Drugs Included
 - Citalopram, Duloxetine, Fluoxetine, Fluvoxamine, Nefazodone, Paroxetine, Reboxetine, Sertraline, Venlafaxine
- Scope of Therapies
 - Drugs intended to treat clinical and behavioral manifestations of depression
- Disease State/Indication
 - Major depressive disorder (MDD), mild to severe depression
- Time Period: 1980-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

CNS Public Source Meta-database: Antipsychotics

- Abstracts Reviewed: 620
- Studies Included: 90
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Aripiprazole, Chlorpromazine, Clozaril, Haloperidol, Olanzapine, Risperidone, Ziprasidone, Quetiapine, Amisulpride
- Scope of Therapies
 - Drugs intended to treat clinical and behavioral manifestations of schizophrenia
- Disease State/Indication
 - Acute and chronic schizophrenia, schizoaffective disorder, schizophreniform disorder
- Time Period: 1980-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

CNS Public Source Meta-database: Sleep Disorders

- Abstracts Reviewed: 195
- Studies Included: 51
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Diazepam, Flunitrazepam, Flurazepam, Lorazepam, Lormetazepam, Triazolam, Zaleplon, Zolpidem
- Scope of Therapies
 - Drugs intended to promote the onset of sleep, to decrease sleep latency, and to treat insomnia and "Shift Sleep Disorder"
- Disease State/Indication
 - Primary insomnia, transient insomnia, chronic insomnia
- Time Period: 1986-2004
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

CNS Public Source Meta-database: Migraine Headache

- Abstracts Reviewed: 20
- Studies Included: 14
- Literature Databases
 - PubMed, Medline
- Drugs Included
 - Almotriptan, Eletriptan, Frovatriptan, Rizatriptan, Sumatriptan, Topiramate, Zolmitriptan
- Scope of Therapies
 - Treatment and prophylaxis of signs and symptoms of migraine, cluster, central, and vascular headaches
- Disease State/Indication
 - Migraine headache treatment and prophylaxis
- Time Period: 2000-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Endocrine Public Source Meta-database: Diabetes

- Abstracts Reviewed: 750
- Studies Included: 106
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Glyburide, Glipizide, Metformin, Glimepiride, Tolazamide, Chlorpropamide, Exenatide, Liraglutide, Pioglitazone, Rosiglitazone, Troglitazone, Vildagliptin, Sitagliptin
- Scope of Therapies
 - Drugs intended to normalize blood sugar abnormalities in the treatment of Type II Diabetes Mellitus
- Disease State/Indication
 - Type II diabetes mellitus (insulin-dependant and non-insulin-dependant)
- Time Period: 1988-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Endocrine Public Source Meta-database: Obesity

- Abstracts Reviewed: 95
- Studies Included: 64
- Literature Databases
 - PubMed, Medline, Meeting Abstracts
- Drugs Included
 - Fenfluramine, Orlistat, Phentermine, Rimonabant, Sibutramine
- Scope of Therapies
 - Drugs intended to promote weight loss
- Disease State/Indication
 - Obesity, overweight
- Time Period: 1972-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Gastro-intestinal Public Source Meta-database: Gastro-esophageal reflux disease (GERD)

- Abstracts Reviewed: 250
- Studies Included: 70
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA), clinicalstudyresults.org
- Drugs Included
 - Cisapride, Esomeprazole, Lansoprazole, Metoclopramide, Mosapride, Omeprazole, Pantoprazole, Rabeprazole, Tegaserod, Zaccopride
- Scope of Therapies
 - Drugs intended for esophageal healing and for control of symptoms
- Disease State/Indication
 - Gastroesophageal reflux disease (GERD), heartburn, reflux, erosive esophagitis, endoscopy-negative reflux disease, endoscopy-positive reflux disease
- Time Period: 1975-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Gastro-intestinal Public Source Meta-database: Irritable Bowel Disease (IBD)

- Abstracts Reviewed: 1140
- Studies Included: 56
- Literature Databases
 - PubMed, Medline, Cinahl, Biosis, Web of Science, Healthstar, clinicaltrialsresults.org
- Drugs Included
 - Adalimumab, Alicaforfen, Basiliximab, Certolizumab, Daclizumab, Etanercept, Fontolizumab, Infliximab, Interferon, Natalizumab, Onercept, PEG-IFN, Visilixumab, Rosiglitazone
- Scope of Therapies
 - Treatment of signs and symptoms, induction of response and remission, and maintenance of response and remission of Ulcerative Colitis, Crohn's Disease, and Irritable Bowel Syndrome
- Disease State/Indication
 - Ulcerative colitis; Crohn's disease
- Time Period: 1992-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Genito-urinary Public Source Meta-database: Female Sexual Arousal Disorder (FSAD)

- Abstracts Reviewed: 60
- Studies Included: 25
- Literature Databases
 - PubMed, Medline, Cinahl, Biosis, Web of Science, Healthstar, clinicaltrialresults.org
- Drugs Included
 - Alprostadil, Bremelanotide, Sildenafil, Testosterone, Tibolone, Apomorphine, Bupropion, Esterified Estrogens, Methyltestosterone
- Scope of Therapies
 - Treatment of sexual dysfunction, lack of sexual interest, and sexual desire disorders in females
- Disease State/Indication
 - Female sexual arousal disorder; hypoactive sexual desire disorder in females
- Time Period: 2000-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Pain Public Source Meta-database: Osteoarthritis (OA) Pain

- Abstracts Reviewed: 150
- Studies Included: 33
- Literature Databases
 - PubMed, Medline, Cinahl, Biosis, Web of Science, Healthstar, clinicaltrialresults.org
- Drugs Included
 - Oxycodone, oxymorphone, codeine, tramadol, dextropropoxyphene, dihydrocodeine, fentanyl
- Scope of Therapies
 - Analgesics intended to mitigate painful symptoms of osteoarthritis
- Disease State/Indication
 - Osteoarthritis
- Time Period: 1989-2006
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Respiratory Public Source Meta-database: Asthma

- Abstracts Reviewed: 118
- Studies Included: 31
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Beclomethasone dipropionate, Montelukast
- Scope of Therapies
 - Drugs intended to control and treat the symptoms of asthma and to prevent asthma symptoms from occurring
- Disease State/Indication
 - Bronchial asthma, persistent or chronic asthma, mild to severe asthma
- Time Period: 1989-2004
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

Respiratory Public Source Meta-database: Asthma/Chronic Obstructive Pulmonary Disease (COPD)

- Abstracts Reviewed: 570
- Studies Included: 104
- Literature Databases
 - PubMed, Medline, FDA Summary Basis of Approval (SBA)
- Drugs Included
 - Beclomethasone dipropionate, Fluticasone, Montelukast, Albuterol, Theophylline, Cilomilast, Ipratropium, Tiotropium, Salmeterol
- Scope of Therapies
 - Drugs intended to control and treat the symptoms of asthma and to prevent asthma symptoms from occurring and drugs intended to treat the signs and symptoms of Chronic Obstructive Pulmonary Disease (COPD) and to slow the progression of COPD
- Disease State/Indication
 - Bronchial asthma, persistent or chronic asthma, mild to severe asthma, stable asthma, COPD
- Time Period: 1985-2005
- Displays and Summaries
 - Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

APPENDIX

- Literature Models at FDA
- Selected Pharsight Metadata Resources

Literature Models at FDA: A Critical Path Initiative

- Literature estimates for comparative drug effects are included as a deliverable in FDAs voluntary End of Phase IIa meeting*
- FDA is developing an internal library of therapeutically-focused drug-disease models (e.g., in diabetes, Parkinson's) based on public source data and from previous NDAs/SNDAs
- Proprietary source data from sponsors used to develop and validate models would not be shared publicly, but FDA is considering how to begin sharing the models with industry
- FDA recently engaged with leaders from industry and academia to discuss opportunities and challenges for sharing drug-disease models to make better clinical development and regulatory decisions**

*Powell R. [FDA Experience with End of Phase IIa Meeting: An Attempt to Improve Drug Development Decisions](#). Presented at Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Sciences. November 14, 2005.

**Drug Information Association Forum: [Sharing Knowledge to Improve Clinical Drug Development and Regulatory Decisions: Data/models of Diseases, Drugs, Placebo, Baseline, and Dropouts](#); January 24-25, 2007; Washington, DC.

Selected Pharsight Metadata Resources: Methods, Case Studies

- ## Articles

- Ebling W et al. [The Role of Literature Models To Support Strategic Decision-Making in Clinical Drug Development](#). Pharsight *Insights*, Summer 2006.
- Mandema JW, Hermann D, Wang W, Sheiner T, Milad M, Bakker-Arkema R, Hartman D. [Model-Based Development of Gemcabene, a New Lipid-Altering Agent](#). *AAPS Journal*. 2005; 7(3).

- ## Presentations

- Gillespie B. [Model-Based Meta-Analysis for Integration of Data from Multiple Sources](#). Modeling and Simulation online webinar. February 15, 2006. Available at www.pharsight.com.
- Hermann D, Wang W, Falcoz C, Hartman D, Mandema J. [Strategies to Improve Model-Based Decision-Making During Clinical Development](#). [poster]. Presented at: Annual Meeting of the Population Approach Group in Europe (PAGE); June 2005; Pamplona, Spain.