

# Public-Source Meta-database Offerings

Supporting Strategic Decision-Making  
in Clinical Drug Development

June 2009

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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 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

Pharsight has compiled indication-focused databases in multiple therapeutic areas with a deliberate focus on providing a framework upon which to build decision enabling models

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 according to proprietary internal procedures

Uses industry-standard tools (e.g., Thomson/ISI<sup>®</sup> Reference Manager<sup>®</sup>, Golden Didger<sup>®</sup> software to capture graphical data from industry journals)

# 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

# Utilization of Pharsight Meta-databases

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](#)<sup>®</sup> (DMX<sup>®</sup>)

# 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 (including Excessive Daytime Sleepiness) Alzheimer's Disease
Endocrine	Type II Diabetes Obesity
Gastro-intestinal	Gastro-esophageal reflux disease (GERD) Irritable Bowel Disease (IBD) Chronic Idiopathic Constipation
Genito-urinary	Urinary incontinence Female Sexual Arousal Disorder (FSAD)
Pain	Osteoarthritis Pain
Respiratory	Asthma Chronic Obstructive Pulmonary Disease (COPD)

# Anti-infectives Public Source Meta-database: Fluoroquinolones

Time Period: 1993-2006

Clinical Studies Included: 9

References Included: 21

## Literature Sources

- 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

## 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)

Time Period: 1998-2005

Clinical Studies Included: 6

References Included: 17

## Literature Sources

- 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

## 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)

Time Period: 1996-2Q2008

Clinical Studies Included: 11

References Included: 70

## Literature Sources

- PubMed, Medline, Meeting Abstracts, FDA Summary Basis of Approval (SBA)

## Drugs Included

- Adalimumab, Anakinra, Etanercept, Methotrexate, Abatacept, Infliximab, Rituximab

## Scope of Therapies

- Drugs intended to mitigate the signs and symptoms of rheumatoid arthritis

## Disease State/Indication

- Rheumatoid arthritis

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Cardiovascular Public Source Meta-database: Lipids

Time Period: 2000-1H2007

Clinical Studies Included: 43

References Included: 74

## Literature Sources

- PubMed, Medline, Summary Basis of Approval

## Drugs Included

- Atorvastatin, Ezetimibe, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, Omega-3 fatty acids, Fenofibrates, Ezetimibe/Simvastatin (fixed combination)

## Scope of Therapies

- Drugs to treat lipid profile abnormalities

## Disease State/Indication

- Hyperlipidemia

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Cardiovascular Public Source Meta-database: Plant Stanols

Time Period: 1994-2005

Clinical Studies Included: 6

References Included: 18

## Literature Sources

- 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

## 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)

Time Period: 1980-1Q2008

Clinical Studies Included: 27

References Included: 132

## Literature Sources

- PubMed, Medline, ISI Web of Science, Cinahl, OVI

## Drugs Included

- Apixaban, Dabigatran, Dalteparin, Enoxaparin, Fondaparinux, Heparin, Melagatran, Razaxaban, Rivaroxaban, Tinzaparin, 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

## 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

Time Period: 1985-2004

Clinical Studies Included: 1

References Included: 11

## Literature Sources

- 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Antidepressants

Time Period: 1980-2006

Clinical Studies Included: 18

Studies Included: 129

## Literature Sources

- PubMed, Medline, Summary Basis of Approval, [www.clinicalstudyresults.org](http://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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Antipsychotics

Time Period: 1980-2005

Clinical Studies Included: 11

References Included: 90

## Literature Sources

- 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Sleep Disorders

Time Period: 1986-2004

Clinical Studies Included: 3

References Included: 51

## Literature Sources

- 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, “Shift Sleep Disorder”

## Disease State/Indication

- Primary insomnia, transient insomnia, chronic insomnia

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Excessive Daytime Sleepiness

Time Period: 1998-2008

Clinical Studies Included: 5

References Included: 23

## Literature Sources

- PubMed, Medline, FDA Summary Basis of Approval (SBA)

## Drugs Included

- Armodafinil, Modafinil

## Scope of Therapies

- Drugs intended to treat narcolepsy, shift worker disorder, excessive daytime sleepiness

## Disease State/Indication

- Improvement of excess daytime sleepiness

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Migraine Headache

Time Period: 2000-2006

Clinical Studies Included: 3

References Included: 14

## Literature Sources

- 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# CNS Public Source Meta-database: Alzheimer's Disease

Time period: 1987-2007

Clinical Studies Included: 2

References Included: 38

Literature sources:

- PubMed, Medline, Summary Basis of Approval, clinicaltrials.gov

Drugs Included:

- Donepezil, Vitamin E

Scope of therapy:

- Treatment of signs and symptoms of Alzheimer's disease

Disease State/Indication:

- Alzheimer's disease

Displays and Summaries:

- Study characteristics, data listings including all extracted data elements  
treatment characteristics, database conventions

# Endocrine Public Source Meta-database: Diabetes

Time Period: 1988-2Q2008

Clinical Studies Included: 44

References Included: 126

## Literature Sources

- PubMed, Medline, European Medicines Agency (EMA), FDA Summary Basis of Approval (SBA)

## Drugs Included

- Alogliptin, Glyburide, Glipizide, Metformin, Glimepiride, Tolazamide, Chlorpropamide, Exenatide, Liraglutide, Pioglitazone, Rosiglitazone, Saxagliptin, Sitagliptin, Troglitazone, Vildagliptin

## 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)

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Endocrine Public Source Meta-database: Obesity

Time Period: 1972-2007

Clinical Studies Included: 11

References Included: 74

## Literature Sources

- PubMed, Medline, Meeting Abstracts

## Drugs Included

- Fenfluramine, Orlistat, Phentermine, Rimonabant, Sibutramine, Topiramate

## Scope of Therapies

- Drugs intended to promote weight loss

## Disease State/Indication

- Obesity, overweight

## 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)

Time Period: 1975-2005

Clinical Studies Included: 8

References Included: 70

## Literature Sources

- PubMed, Medline, FDA Summary Basis of Approval (SBA), [clinicalstudyresults.org](http://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

## 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)

Time Period: 1992-2006

Clinical Studies Included: 13

References Included: 56

## Literature Sources

- PubMed, Medline, Cinahl, Biosis, Web of Science, Healthstar, clinicaltrialresults.org

## Drugs Included

- Adalimumab, Alicaforsen, 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Gastro-intestinal Public Source Meta-database: Chronic Idiopathic Constipation

Time Period: 1998-2007

Clinical Studies Included: 14

References Included: 58

## Literature Sources

- PubMed, Medline, Summary Basis of Approval, clinicaltrials.gov

## Drugs Included

- Tegaserod, Lubiprostone, Lactulose, PEG-3350

## Scope of Therapies

- Treatment of signs and symptoms of chronic constipation

## Disease State/Indication

- Chronic Idiopathic Constipation

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Urology Public Source Meta-database: Urinary incontinence

Time Period: 1998-2007

Clinical Studies Included: 3

References Included: 32

## Literature Sources

- PubMed, Medline, Summary Basis of Approval, clinicaltrials.gov

## Drugs Included

- Tolterodine

## Scope of Therapies

- Treatment of signs and symptoms of urinary incontinence

## Disease State/Indication

- Treatment of urinary incontinence

## 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)

Time Period: 2000-2006

Clinical Studies Included: 3

References Included: 25

## Literature Sources

- 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

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

Time Period: 1989-2006

Clinical Studies Included: 6

References Included: 33

## Literature Sources

- PubMed, Medline, Cinahl, Biosis, Web of Science, Healthstar, [clinicaltrialresults.org](http://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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

# Respiratory Public Source Meta-database: Asthma

Time Period: 1989-2004

Clinical Studies Included: 5

References Included: 31

## Literature Sources

- 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

## Displays and Summaries

- Study characteristics, data listings including all extracted data elements, treatment characteristics, database conventions

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

Time Period:1985-2006

Clinical Studies Included: 19

References Included: 50

## Literature Sources

- PubMed, Medline, FDA Summary Basis of Approval (SBA)

## Drugs Included

- Albuterol, Cilomilast, Fluticasone, Ipratropium, Roflumilast, Salbumatol, Salmuterol, Tiotropium and Placebo

## Combination drugs

- Fluticasone + Salmeterol and Budesonide + Formoterol

## Scope of Therapies

- Drugs intended to treat the signs and symptoms of Chronic Obstructive Pulmonary Disease (COPD) and slow the progression of COPD

## Disease State/Indication

- Chronic obstructive pulmonary disease

## 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. **An initial Oncology model developed at FDA has been published and used by Pharsight for modeling drug candidates**

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

- Ezzet F. The Role of Literature-Based Disease Progression Models to Support Knowledge Management and Decision-Making in Clinical Drug Development. [oral presentation]. AAPS National Biotechnology Conference; June 22-25, 2008; Toronto, Canada.
- Poland B. Using *in Vitro* and Literature Data to Predict Effects of New Anti-Retrovirals. [oral presentation]. ASCPT Annual Meeting; April 2-5, 2008; Orlando, Florida.
- Prins K. Modeling and Simulation Using Metadata: Away from Inventing the Wheel Again. Presented at: ROeS Seminar (Austrian-Swiss Region of the International Biometric Society); September 9-13, 2007; Bern, Switzerland.
- Fredrickson J., Barbee T., Using Biomarker and Literature Data in Type II Diabetes [Pharsight webinar], May 30, 2007