The Future of Technology and Regulation:
Opportunities for Drug Development, Regulatory Review and Clinical Practice

June 11, 2007

10th Annual FDA – OCRA 2007 Educational Conference
Celebrating 10 Years of Regulatory Affairs Education

Orange County OCRA REGULATORY AFFAIRS Discussion Group

The Future of Technology and Regulation- Opportunities in Drug Development, Regulatory Review & Clinical Practice

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"Our ongoing assessment of the drug and medical product safety system has affirmed that it is essential that our processes and scientific methods keep pace with the rapid evolution of science, technology and the health care system."

Andrew C von Eschenbach
Commissioner,
Food and Drug Administration
January 30, 2007

http://www.fda.gov/bbs/topics/NEWS/2007/NEW01551.html- in response to the IOM report:

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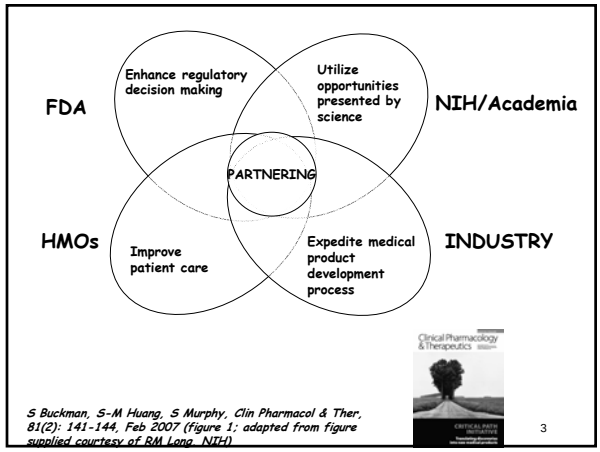

S Buckman, S-M Huang, S Murphy, Clin Pharmacol & Ther, 81(2): 141-144, Feb 2007 (figure 1; adapted from figure supplied courtesy of RM Long, NIH)

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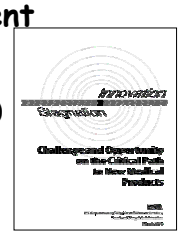
Traditional Inefficiency in Drug Development

- Only 8% IND's for NME's reached the market (worse than the historical success rate, 14%)
- Estimated cost per NME about $.8 – 1.7 billion

→a drug entering Phase 1 trials in 2000 was not more likely to reach the market than one entering Phase 1 trials in 1985



<http://www.fda.gov/oc/initiatives/criticalpath/>
< http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

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Developing better drugs, faster, hinges on "new science"
-- biomedical research into the cause of disease; nanotechnology; bioinformatics to capture and synthesize health data, and biological/micro assembly methods

Janet Woodcock
April, 2006, "Transforming American Healthcare: Pathways to Change"

A treatment with a 10% advantage over a comparator could still be the wrong drug for many people.
And a drug with a severe side effect may be the best treatment for people who are not at risk for that problem.

Janet Woodcock
February, 2007, "Personalized Medicine", Clin Pharmacol Ther 81:164-169, 2007

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Critical Path Opportunities

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into 21st century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations--Pediatrics

March 2006

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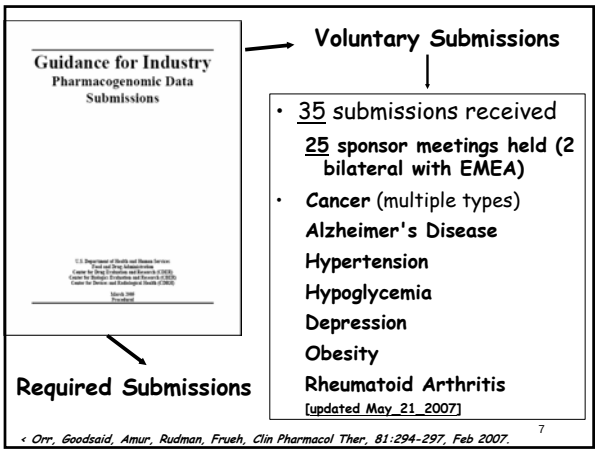

< Orr, Goodsaid, Amur, Rudman, Frueh, Clin Pharmacol Ther, 81:294-297, Feb 2007.

VGDS Recent Discussion Examples

Biomarker selection
Novel clinical trial design
Labeling language
Others

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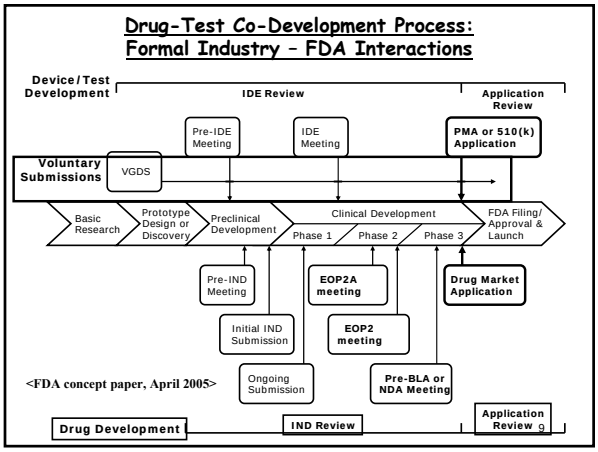

Biomarker Qualification

- **Develop conceptual framework**
  Reach general consensus on amount/type of data needed for various uses- FDA guidance
- **Develop consortia for qualification of specific biomarkers**
  - OBQI (Oncology Biomarker Qualification Initiative)
  - Predictive Safety Test Consortium
  - The Biomarkers Consortium
  - Serious Adverse Events Consortium
- **Exploratory Biomarker Qualification Process Pilot**

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Preclinical Biomarker qualification Process Map

- Pilot process described in more detail by Goodsaid, et al

< Goodsaid F, Frueh F, Pharmacogenomics, 7, 773-782, 2006: Process map proposal for the validation of genomic biomarkers. >

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Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or (CBER) Toni Stifano, 301-827-6190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2006
Clinical Pharmacology

-Metabolism, transport, drug-interaction info key to benefit/risk assessment

- Integrated approach (in vitro and in vivo) may reduce number of unnecessary studies and optimize knowledge

< September 2006 guidance- http://www.fda.gov/cder/guidance/6695dft.pdf>

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What's New?

- In vitro models to determine whether in vivo evaluation is needed
  - CYP inhibition (additional CYPs)
  - CYP induction
  - Transporter- based interactions
- Classification of inhibitors, substrates
- Others

< Huang, Temple, Throckmorton, Lesko, Clin Pharmacol Ther 81:298-304, 2007>

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FDA Internet
- Drug Development and Drug Interactions-

http://www.fda.gov/cder/drug/drugInteractions/default.htm

Launched in May 2006

→More frequent updates- tables, models for decision-making, etc

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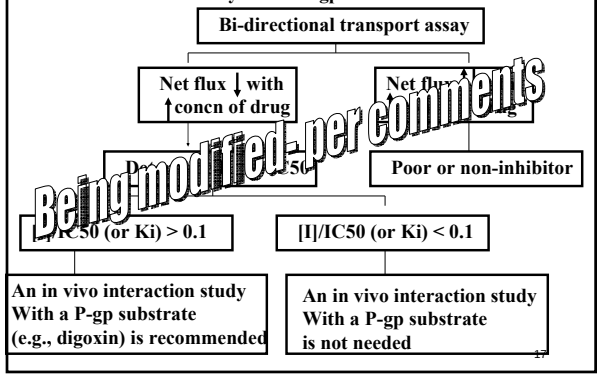
Drug Development and Drug Interactions

- Overview
- Background Information
- Tables of Substrates, Inhibitors and Inducers
  - CYP Enzymes
    - In vitro
    - In vivo
      - Examples of in Vivo Substrate, Inhibitor, and Inducer for Specific CYP Enzymes
      - Classification of Inhibitors
      - Classification of Substrates
  - P-gp Transporters
  - Major Human Transporters
- Possible Models for Decision-Making
  - CYP-Based Drug-Drug Interaction Studies
  - P-gp-Based Drug-Drug Interaction Studies (updated 9/25/2006)
- FDA Drug Interaction Working Group Members
- Regulatory Guidance and Manual for Policies and Procedures (updated 9/25/2006)
- Publications
- Presentations
- Advisory Committee Meetings (updated 9/25/2006)
- Related Links
- Contact Information

Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for P-gp and whether an in vivo drug interaction study with a P-gp substrate is needed



Being modified per comments

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Key Opportunity for Improving Outcomes

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DNA based biomarkers of enzyme activities considered as valid biomarkers

Enzyme	Model drugs	Outcome measures	Study results
CYP2C9	Warfarin	Maintenance dose Time to reach stable dosing	Patients with *2 and *3 maintained with lower doses and took longer time to reach stable dosing
CYP2C19	Proton pump inhibitors	Plasma levels Gastric pH Gastroesophageal reflux disease cure rate	Higher in PM (20mg) Higher dose (40 mg) showed no difference
CYP2D6	Atomoxetine	Pharmacokinetic measure	PM higher AUC (10-fold)
UGT1A1	Irinotecan	Grade ¾ neutropenia	UGT1A1 7/7and 6/7 more frequent than 6/6
TPMT	6-MP	Dose-limiting hematopoietic toxicity	More in TPMT deficiency or heterozygosity

<Huang, S-M, Goodsaid, F, Rahman, A, Frueh, F, and Lesko LJ, application of Pharmacogenomics in Clinical Pharmacology, Toxicology Mechanisms and Methods, 2006;16:89-99>

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Irinotecan
(Camptosar®)

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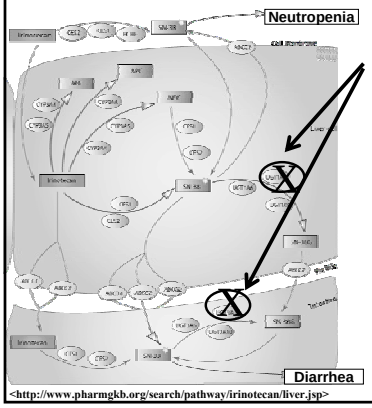
Irinotecan (Camptosar ®)



The UGT1A1*28 allele is common (30%) in Caucasians and is associated with a significant decrease in UGT1A1 activity.

Carriers of UGT1A1*28 when treated with irinotecan can experience AEs

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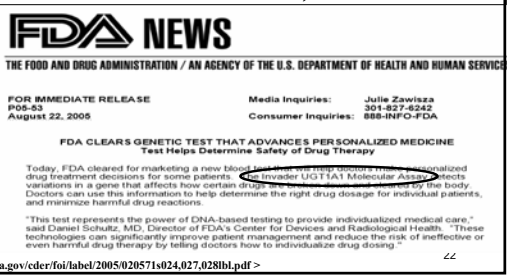
<http://www.pharmgkb.org/search/pathway/irinotecan/liver.jsp>

CAMPTOSAR (irinotecan) [Dosage & Administration]
When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele
(See CLINICAL PHARMACOLOGY and WARNINGS).



FDA NEWS

THE FOOD AND DRUG ADMINISTRATION / AN AGENCY OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
P05-53
August 22, 2005

Media Inquiries: Julie Zawisza 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA CLEARS GENETIC TEST THAT ADVANCES PERSONALIZED MEDICINE
Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

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< http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf >

Warfarin
(Coumadin®)

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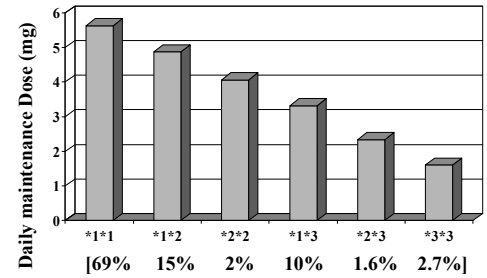
Effect of CYP2C9 genotype on Warfarin Maintenance Dose



N=185, median time= 543 days (14-4032 days)

< Adapted from Higashi MK et al, JAMA 2002; 287:1690>
<Huang, S-M, http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm>

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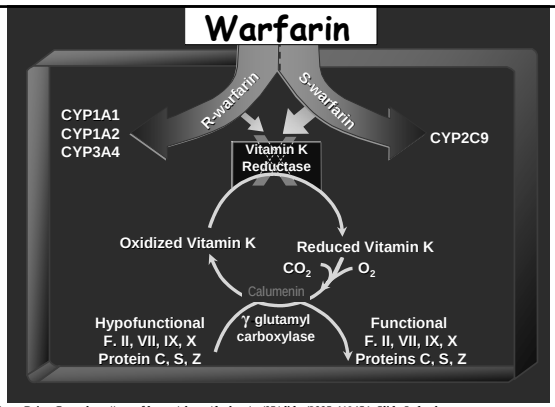
Warfarin



From Brian Gage; http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm
Other relevant slides: http://www.fda.gov/ohrms/dockets/ac/05/slides/5
http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_02_02-Huang.ppt

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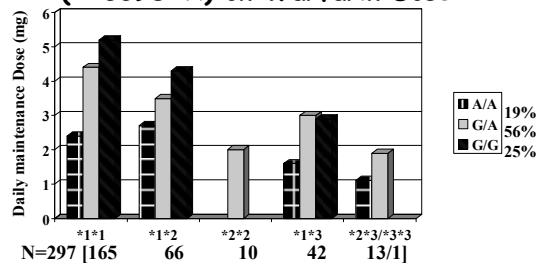
Effect of CYP2C9 (*1, 2, 3) & VKORC1 (-1639G>A) on Warfarin Dose



N=297 [165 66 10 42 13/1]

→ **Within a CYP2C9 genotypes, further differentiation among VKORC1 genotypes**

< Adapted from Sconce et al, Blood, October 2005>
<Huang, S-M, http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm>

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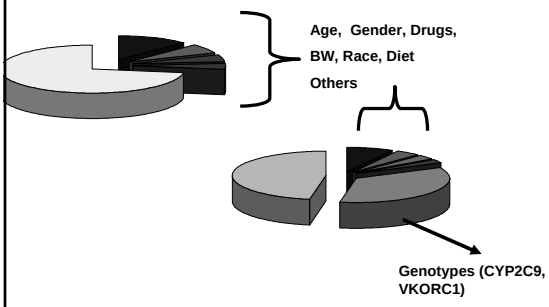
Predicting the Warfarin Stable Dose



<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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Advisory Committee Recommendations:

Does the committee agree that sufficient mechanistic and clinical evidence exists to support the recommendation

- **to use lower doses of warfarin for patients with genetic variations in CYP2C9 that lead to reduced activities?**
  10 YES, 0 NO
- **to use lower doses of warfarin for patients with genetic variations in VKORC1 that lead to reduced VKORC1 activities?**
  10 YES, 0 NO

<Clinical Pharmacology Subcommittee- Advisory Committee Meeting, November 14, 2005
http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4194T1.pdf>

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Critical Path Opportunities

- **Better Evaluation Tools**
- **Streamlining Clinical Trials**
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- **Developing Products to Address Urgent Public Health Needs**
- **Specific At-Risk Populations--Pediatrics**

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PDUFA IV Negotiated Deliverables - Responsibility of Office of Biostatistics

- **Three guidances with substantial scientific and biostatistical content**
  Non-Inferiority study design and analysis
  Adaptive Clinical Trial Designs
  Multiple endpoints in clinical trials
- **Consensus building - possible guidance**
  Missing data in clinical trials

<Nevius E, PhRMA (Clin Pharm/Metab)/FDA (OCP) meeting, May 7, 2007, Bethesda, MD>

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Pharmacometric analysis

Bhattaram, V.A. et al. Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. AAPS J 7, E503–E512 (2005). Access at http://www.aapsj.org/view.asp?art=aapsj070351

Bhattaram, V. et al. Impact of pharmacometric reviews on new drug approvals; survey of 31 new drug applications. Clin. Pharmacol. Therap., Feb 2007

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Model-based analysis

- Trileptal case

	Adjunctive	Monotherapy
Adults	Clinical trials	Clinical trials
Children (4-16 years of age)	Clinical trial	"Model Based Bridging" approach proposed by FDA

FDA's proactive model-based analysis alleviated the need to conduct additional clinical trial for the approval of Trileptal monotherapy in pediatrics

FDA/Sponsor pursued approaches to best utilize knowledge from the positive trials to assess if monotherapy in pediatrics can be approved without new controlled trials

<AAPS Journal 2005>

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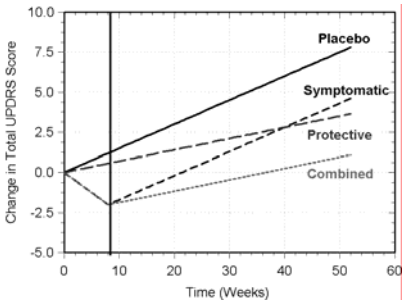
Parkinson's Disease- Model Based Approach



Single point will not differentiate "symptomatic" vs. "protective" effects

Unified Parkinson Disease Rating Scale (UPDRS) -The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. It is made up of the 1) Mentation, Behavior, and Mood, 2) ADL and 3) Motor sections. These are evaluated by interview. 199 represents the worst (total) disability), 0--no disability.

<Bhattaram, Siddiqui, Gobburu, October 2006, Advisory committee meeting, http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s2-index.htm>

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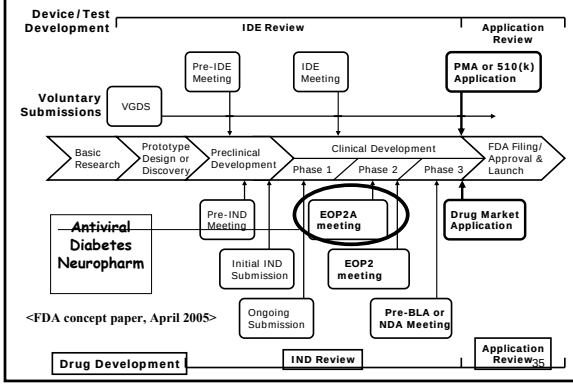
Drug-Test Co-Development Process: Formal Industry – FDA Interactions



<FDA concept paper, April 2005>

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Summary

Identified Critical Path opportunities can enhance drug development, regulatory review and clinical practice [safe and effective use of medical products in individual patients]

Collaborative efforts are required/ongoing
- **knowledge and data- sharing**
- **standard toolkit development**
- **guidance development**
- **others**

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As Yogi Berra once said,
"The future ain't what it used to be"

In the next 5-10 years, ,, a unique opportunity to integrate viable innovation (new scientific, clinical, technological ideas)….. add significant value, drug development, regulatory-decision-making, and clinical practice".

Lawrence J Lesko, PhD
February, 2007, Clin Pharmacol Ther 81:170-177, 2007

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Acknowledgement

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Federico Goodsaid
Myong-Jin Kim
Larry Lesko
Atik Rahman

Office of Translational Sciences

ShaAvhree Buckman
Shirley Murphy
Robert Powell

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