Pharmacogenomics Session:

Overview, Progress to Date and Discussion

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Overview of Session

- Review SACGHS activities to date and goals for session
- Briefing from Dr. Woodcock on Critical Path Initiative and FDA's vision for personalized medicine
- Approximately 4 hours of discussion of draft recommendations

SACGHS PGx Activities to Date

- March 2004: PGx identified as high-priority issue warranting in-depth study
- June 2005: First informational session
- October 2005: Second informational session, report outline approved
- March 2006: Review of Federal efforts in PGx, discussion of draft recommendations

SACGHS PGx Efforts to Date

- Report outline (October 2005)
- Compilation of Federal activities in pharmacogenomics (March 2006)
- Draft recommendations (March 2006)

PGx Task Force Activities Since March 2006

- **Literature review**
  - The Lewin Group, through a contract with ASPE, prepared PGx literature review
  - PGx Task Force submitted comments on PGx literature review
  - PGx Task Force held conference call to discuss comments on literature review
  - The Lewin Group revised literature review based on comments from PGx Task Force and SACGHS staff

PGx Task Force Activities Since March 2006

- **Draft recommendations**
  - SACGHS staff and PGx Task Force further developed draft recommendations based on discussion at SACGHS March meeting
  - PGx Task Force held conference call to discuss draft recommendations
  - SACGHS staff continuing to revise draft recommendations based on PGx Task Force discussion and review of literature review
  - SACGHS staff developed 13 new recommendations for SACGHS consideration
    - ➢Basis of today's discussion

PGx Discussion Documents

- Literature review
  - Tab 4 of briefing book
- Draft recommendations
  - Table folder handout
    - New strawman recommendations lettered (A, B, C,…)
    - Draft recommendations discussed at March meeting numbered (1, 2, 3,…)

Planned Next Steps on PGx

- Work with SACGHS PGx Task Force, ASPE, The Lewin Group, and SACGHS staff to:
  - Develop draft report using the literature review and draft recommendations as the basis for the content
  - Refine the previously developed draft recommendations so that they are more comprehensive and specific
  - Reflect today's discussion in new set of draft recommendations
- Organize day-long in-person PGx Task Force meeting to work on precise recommendation language (early September)
- Review draft report and recommendations at November SACGHS meeting
- Public comment period
- Finalize report

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Goals of Today's Discussion

Goals

1. Review the remaining issues/gaps and the new strawman recommendations proposed to address them
2. As needed, develop other approaches in addition to or instead of the strawman recommendations
3. Consider whether the strawman recommendations need more specificity

Goals of Today's Discussion

Goals (cont)

4. Discuss the earlier set of draft recommendations and whether any of the "old" and "new" draft recommendations should be merged or grouped together
5. Develop draft recommendations for any topics for which no draft recommendations currently exist
6. Discuss whether there any topics not covered in the literature review that should be added to the draft report

Issue:
Co-developed PGx Products

- One of the potential goals of PGx technologies is to tailor drug treatment based on companion diagnostic test results
- Co-developing products will present significant challenges both to the private sector and regulatory authorities
  - For example, many co-developed products are likely to be made by different companies, complicating the development process
- Additionally, drugs currently on the market may benefit from companion tests

Co-developed PGx Products
Strawman Recommendation A

- Option #1: FDA should continue to foster collaborative opportunities between the public and private sectors that encourage and facilitate the co-development of PGx products. Specifically, the FDA Critical Path Initiative/Office should develop a supplement to the Critical Path Opportunities List that discusses the opportunities specific to PGx. The list would serve as a mechanism to organize companies and researchers around specific projects that have a significant public health impact.

- Option #2: FDA should continue to provide industry with guidance about best practices associated with co-development of medical and PGx products.

Issue:
Need for Drug Dosing Guidance

- Drug labels lack sufficient information to guide dosing decisions based on PGx test results
- Dosing recommendations for PGx products are not yet available
- Medical providers are not adequately trained to make dosing decisions based on PGx test results
- Dosing decisions based on uninformed interpretation of PGx tests may cause harms

Drug Dosing Guidance
Strawman Recommendation B

- Option #1: To assist health providers in determining optimal therapeutic dosage, FDA should provide adequate information as part of the label for both the drug and its companion diagnostic test. The diagnostic product labeling should clearly describe the test's analytical and clinical validity and, if appropriate, include a general warning about the need to monitor patients to ensure that the drug is producing the desired response.

- Option #2: Given that inaccurate test results from diagnostic tests used to optimize drug dosing could lead to incorrect dosing and the possibility of adverse drug reactions or lack of patient response, FDA should establish a threshold of specificity and sensitivity for each of these tests that accounts for the unique relationship between drugs and their companion diagnostic tests.

Adverse Event Monitoring and PGx Testing

Draft Recommendation 1

- HHS could have a role in establishing thresholds for the frequency and severity of adverse reactions that would trigger requirement of pharmacogenetic testing. In particular, FDA should provide guidance on the factors that will result in labeling changes, including but not limited to severity of disease, level of efficacy, and risk for adverse events.

Issue:
Oversight of "Home Brew" PGx Tests

- FDA currently does not directly regulate genetic tests developed in clinical laboratories
- Lack of FDA regulation may lead to PGx products that are not as safe and effective as FDA-reviewed PGx products
- The public may not know that home brew PGx tests were not reviewed by FDA

FDA Regulation of "Home Brew" PGx Tests

Strawman Recommendation C

- Option #1: The Secretary should encourage FDA, CMS and CDC to develop other mechanisms to enhance the oversight of home brew genetic tests.

- Option #2: The Secretary should clarify whether FDA has statutory authority to regulate home brew genetic tests and, if it does not, should encourage Congress to pass legislation closing this gap.

Issue:
Inconsistencies in Human Subjects Protection Regulations

- There are currently two sets of regulations for the protection of participants in clinical trials:
  - HHS “Common Rule” regulation (Title 45 CFR Part 46)
  - FDA-specific regulation (Title 21 CFR Part 50)

- The two sets of regulations sometimes conflict with each other

- FDA recently issued a guidance on the two sets of regulations clarifying their interpretation for leftover human specimens. The specific FDA guidance is entitled “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable-…”

Inconsistencies in Human Subjects Protection Regulations

Strawman Recommendation D

Although some progress has been made, and further work is underway within HHS, to enhance the consistency of human research protections, the Secretary should make the effort to increase compatibility between FDA and HHS regulations a high priority in order to minimize difficulties in study design and IRB approval that could otherwise complicate the development of PGx products, this could be especially important for studies involving broad collaborations among government, academia and industry. Enhancing the consistency of the regulations need not and should not affect the protections provided to human subjects. Indeed, by facilitating compliance with the regulations, greater consistency may enhance the safety of clinical research.

Inconsistencies in Human Subjects Protection Regulations

Strawman Recommendation D

- Option #1: The Secretary should make the harmonization of HHS and FDA regulations on the protection of human research subjects a high priority and encourage FDA and OHRP to work together to enhance the consistency of their human subjects research policies, regulations and guidances.

- Option #1: The Secretary should work with Congress to promote the passage of legislation creating a unified regulatory framework for the protection of human research subjects.

Disclosure of Research Results

Draft Recommendation 2

- Broader thinking on the need to return information back to research participants is needed; particularly when that information may be used in clinical decisions unrelated to ongoing studies. HHS should provide guidance to researchers on how they may provide the option of disclosure of information to research participants and remain compliant with CLIA. CDC, HRSA, and the NIH Office of Rare Diseases (ORD), working with non-governmental groups, have done substantial work in this area for rare diseases, which could provide a model for furthering this effort.

Issue:
Rescue of Failed Drugs

- Less then 15% of candidate drugs that enter phase I clinical trials ever reach market
- Some of these potential drugs may work in more targeted genetically-based subpopulations

Rescue of Failed Drugs
Strawman Recommendation E

HHS should promote public access to data on pharmaceutical products that have failed to demonstrate effectiveness in studies involving a general population cohort but might be successful in specially tailored clinical trials using PGx technology and targeting specific subpopulations. With the cooperation of the pharmaceutical industry, HHS should establish a publicly accessible database cataloging these data. The database's intent will be to rescue failed pharmaceutical products by encouraging diagnostic device manufacturers to collaborate on research, leading to the development of companion medical products. Submission of data should be voluntary, and provisions should be made to limit the extent of disclosure of confidential and/or proprietary information.

Issue:
New Indications for Existing Drugs Based on PGx Tests

- Many existing drugs would benefit from PGx tests designed to guide dosage decisions and/or prevent adverse reactions
- Few financial incentives currently exist for companies to that would identify subpopulations that would benefit from dosage adjustments or are at high risk for adverse drug reactions
- The regulatory process for approving new indications for existing drugs is likely to be costly and time consuming

New Indications for Existing Drugs Based on PGx Tests

Strawman Recommendation F

To be developed

Intended Use Population and PGx Products

Draft Recommendation 3

- FDA should identify biologically-based population stratifications that may include but must go beyond self-identified racial and ethnic categories. The FDA should also develop guidance to encourage the inclusion of diverse populations in pre-market and post market trials. Additionally, when appropriate, FDA should require integration of genetic analyses into clinical trial designs including Phase IV post-market safety evaluations.

Issue:
Phase IV Clinical Trials for PGx Products

- Identifying genetically-based subpopulations as a condition for enrollment in drug trials may reduce the need for large numbers of participants
- However, smaller clinical trials may reduce the ability to detect rare adverse drug reactions

- The current system to detect adverse drug reactions depends on voluntary reporting of information
- Health providers, considering their busy schedules, have few incentives to report adverse drug events

- Currently, FDA cannot require pharmaceutical companies to fund new studies for approved drugs

Phase IV Clinical Trials for PGx Products

Strawman Recommendation G

- Option #1: FDA should mandate phase IV clinical trials for pharmaceutical products developed in conjunction with diagnostic tests. Furthermore, HHS should ensure that FDA has appropriate resources to monitor compliance of required studies

- Option #2: The structure of the current FDA Adverse Event Reporting System (AERS) is difficult to search and use. FDA should modify the AERS system to enhance its usability and utility. For example, FDA should continue with ongoing efforts to develop a standardized set of terminology (e.g., “myocardial infarction” instead of “heart attack”). The new standardized terminology should facilitate data searches and analyses and identification of potentially problematic adverse event patterns. Additionally, to ensure that data submitted to the new AERS are accurate and represent actual adverse drug events, only health providers should be permitted to submit reports. FDA may consider developing a separate adverse events reporting system to allow the general public to submit problems arising from use of medical products.

Issue:
Direct-to-Consumer Marketing of PGx Tests

- Information about PGx and genetics is complex
- Most consumers are not likely to be able to correctly interpret PGx test results without additional training and/or information
- There is current debate about the benefits and risks of direct consumer access to tests and whether it should be limited
- Some PGx test results may necessitate counseling

Direct-to-Consumer Marketing of PGx Tests

Strawman Recommendation H

- Option #1: Due to the complexities of interpreting gene-based test results, FDA should require the labels of PGx tests offered directly to consumers to include information sufficient to enable consumers on their own to make informed decisions about use of the product, accurately interpret the results, and make informed health decisions based on the test results. FDA should take steps to prohibit direct-to-consumer marketing of any PGx tests that could not be appropriately and safely used by a consumer without the involvement of a health provider.

- Option #2: FDA should require as a condition for premarket approval that companies offering PGx tests directly to consumers without the involvement of a health provider should make available telephone-mediated genetic counseling.

Direct-to-Consumer Marketing of PGx Tests

Strawman Recommendation H

- Option #3: HHS should support measures for CLIA waived tests that are approved for sale over the counter to be allowed to be directly marketed to the consumer, as these tests must already meet the requirements for having detailed directions for use and interpretation of the results. All other tests (low, moderate, high complexity) should involve a consultation with a health professional.

- Option #4: Due to the complexities of interpreting gene-based test results, the Secretary should encourage Congress to pass legislation prohibiting the marketing of PGx tests offered directly to consumers without the involvement of a health provider.

Issue:
Monitoring of Direct-to-Consumer PGx Tests

- Some consumers may lack the knowledge base to correctly interpret results of PGx tests
- As with other medical products, consumers are likely to rely on packaging materials for information
- FDA and the Federal Trade Commission (FTC) monitor direct-to-consumer advertisements
- Advances in PGx technologies may result in an increase in PGx tests offered directly to consumers

Monitoring of Direct-to-Consumer PGx Tests

Strawman Recommendation I

- Option #1: Studies should be conducted to examine the effect that future PGx products will have on FDA and the Federal Trade Commission's ability to monitor direct-to-consumer marketing of PGx tests. Specifically, the ability of the two organizations to act on misleading claims should be assessed.
- Option #2: The Secretary should encourage Congress to provide FDA and the Federal Trade Commission with sufficient resources to monitor direct-to-consumer marketing of PGx tests and act on any misleading claims.

Issue:
Prioritization of PGx Research Needs

- Finite resources available to devote to PGx research
- Public health might benefit more by allocating resources to tackle certain research needs before others

Prioritization of PGx Research Needs

Strawman Recommendation J

HHS should convene a group of experts (comprised of academia, industry and other private sector organizations) to develop criteria for prioritizing all PGx research needs according to feasibility, public health need and impact on public health. The group should also assess both current and potential PGx projects and rank them according to their relative priority. The group's ranking should be used by the HHS agencies for decision-making regarding support and resources.

Issue:
System-wide View of Drug Metabolism

- In general, most drug responses are the products of nucleotide variation in the sequence of multiple genes, not single SNPs
  - For example, nucleotide polymorphisms in Vitamin K Oxidoreductase C1 affect about only 30% of Warfarin metabolism
- Future studies of drug metabolism across multiple biochemical pathways are likely to provide the basis for the development of the most effective PGx products and therapies

System-wide View of Drug Metabolism

Strawman Recommendation K

Drug metabolism is a complex process that typically involves multiple biochemical pathways. Understanding genome-wide pathway interactions will be key to the success of PGx. PGx research efforts at NIH should focus on improving our knowledge of the protein-protein interactions occurring between biochemical pathways. The knowledge gained should be applied to future PGx products yet to be developed.

Issue:
Neglected Diseases

- Many diseases that affect large numbers of people do not receive adequate research funding comparable with their public health impact.
  - E.g., Malaria, African Sleeping Sickness, and Tuberculosis
- In addition to the U.S., many neglected diseases disproportionately affect people in developing nations, which are often not equipped to handle significant public health problems
- Neglected diseases, such as African Sleeping Sickness, often have treatment options that can result in serious adverse effects. These health problems might be averted if new drugs are developed using PGx technologies
- There is little incentive for the private sector to invest in PGx products when the financial returns are predicted to be small or meager

Neglected Diseases

Strawman Recommendation L

NIH, in collaboration with FDA, should support research that encourages the development of PGx products for diseases not actively being addressed by research and development in the private sector. Additionally, the Secretary should urge Congress to provide the private sector with additional economic incentives, such as extension of patent protection and tax incentives, to encourage research and development of PGx products for these neglected diseases.

Orphan Status for Companion PGx Tests

Draft Recommendation 4

- To facilitate development of therapeutics and diagnostics for subpopulations with specific genetic variation affecting etiology and progression of a condition and/or response to treatments, the Secretary should encourage Congress to amend the Orphan Drug Act so that FDA's designation of orphan drug status triggers orphan status for the companion diagnostic.

Measurement of Health Outcomes
Draft Recommendation 5

- The role of PGx in medicine will ultimately hinge on its potential to improve actual patient outcomes and/or the cost of care. The simple demonstration of genetic influence on drug levels or secondary endpoints, while relatively easy to measure is insufficient; health outcomes must be assessed if PGxs is to fulfill its promise. Thus,
  - HHS agencies should work together to encourage rigorous prospective randomized studies to test whether promising PGx findings actually translate into improved (or equivalent but less expensive) patient care.
  - FDA should encourage routine submission of information on the effect of genetic variation on the efficacy and safety prior to approval of therapeutics, and consideration of the effect of genetic variation on safety and effectiveness of therapeutics in post-marketing surveillance activities.

Measurement of Health Outcomes
Draft Recommendation 5 (Cont.)

- HHS should identify federally managed databases such and NHANES, HCUP, and Medicare claims that could contribute data on outcomes from PGx use in the clinical setting and link such databases to post marketing surveillance and outcomes research infrastructure.

- Data collection and analysis efforts should be done in close coordination with on-going health information technology efforts aimed at creating portable and inter-operable electronic health records.

Linkage and Compatibility of Clinical Databases

Draft Recommendation 6

- HHS should engage non-federal health organizations and stakeholders (health maintenance organizations, hospital networks, payer organizations) to link databases that collect relevant clinical and public health data such as diagnostic test results, pharmacy data, clinical outcomes data, and administrative data on PGx to post-marketing surveillance and outcomes research infrastructure, while taking care to maintain patient confidentiality. As much as possible, incentives should be developed for private health care organizations so that they can become actively involved in PGx research to facilitate the gathering of evidence on clinical outcomes.

Linkage and Compatibility of Clinical Databases

Draft Recommendation 6 (cont)

- HHS should explore the potential for novel and existing mechanisms and partnerships (e.g., CMS's coverage with evidence development (CED) initiative, AHRQ and FDA's Centers for Education and Research in Therapeutics (CERTs) program, AHRQ's DEcIDE program) to further develop the evidence base on long-term clinical outcomes of the use of PGx.
- HHS (agency?) should establish standards for hospitals to report on laboratory testing in a way that informs PGx and health services research and facilitates data collection and communication of results to physicians.
- A national clinical outcomes reporting system that can be used to improve patient safety, in the form of rapid reporting and evaluation of adverse events, evaluate the effectiveness of using gene-based tests with therapeutics, and facilitate communication between reporting physicians. A National Registry for severe adverse reactions could be one major element of this reporting system.

Increased Evidence Base on the Economic Value of PGx

Draft Recommendation 7

Numerous stakeholders, both public and private, need to act to improve the quality of public health. HHS should devote additional attention to improving data collection and to strengthening the evidence base for measuring and understanding the economic value of PGx testing, and its reimbursement. HHS should explore existing and novel ways that HHS may contribute to developing the evidence base to measure and understand the economic value of PGxs. CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP), AHRQ's Research Initiative in Clinical Economics (RICE), NHGRI's ELSI program, and NIGMS's EELSI program may contribute to these efforts.

Issue:
Government Officials' Knowledge of PGx

- Limited awareness and understanding of the health, economic and social impacts of PGx could affect its adoption and use not only by the public but also by government officials
- Regulators and payers face a range of challenges integrating PGx technology into clinical practice
- Government officials will need to be able to make informed decisions about PGx technologies

Government Officials' Knowledge of PGx

Strawman Recommendation M

HHS should take steps to ensure that staff with relevant policy and programmatic responsibilities are sufficiently knowledgeable about PGx issues to meet the coming challenges expected from the integration of PGx technology into routine clinical practice. PGx knowledge among HHS staff can be enhanced by through training programs, educational modules such as formal coursework, seminars, workshops, case studies and practice models, and attendance at PGx conferences. Efforts should also be made to recruit individuals with expertise in genetics and PGx for research, medical product review and clinical outcomes analysis.

Public Awareness of PGx

Draft Recommendation 8

As new technology emerges, the public's awareness of the benefits, risks, and limitations of PGx will need to be assessed. HHS should continue to fund studies to better understand the public's willingness to adopt PGx technologies.

Issue:
PGx Liability Issues

- Significant liability issues are likely to arise from the use of PGx technologies in clinical practice
- Health providers are likely to initially shun new PGx technologies due to fear of malpractice law suits
- Confusion exists as to when PGx becomes “standard of care,” which might pressure health providers to prematurely adopt PGx technologies into clinical practice.

PGx Liability Issues

Strawman Recommendation N

HHS should convene a group of experts to explore liability issues associated with PGx products and to devise strategies and recommendations to address the societal and legal challenges associated with the clinical use of PGx technologies

PGx Best Practices

Draft Recommendation 9

There is a need to determine best practices for PGx testing to ameliorate liability concerns. As the evidence base for PGxs increases, HHS should develop strategies to disseminate the information to health providers and offer guidance on when a practice becomes “standard of care.”

Distribution of PGx Information

Draft Recommendation 10

As evidence on the clinical validity and utility of PGx testing accrues and guidelines are developed, professional organizations are best positioned to distribute the information. HHS should develop a process that allows information to flow from agencies to professional organizations to physicians to patients.

Interpretation of Test Results

Draft Recommendation 11

HHS should explore mechanisms to provide clinicians with the guidance and tools needed to respond appropriately to pharmacogenetic test results.

Medicare Coverage of PGx Tests

Draft Recommendation 12

- Medicare coverage of PGx tests may vary depending on whether it is run as part of a diagnostic work-up for a preexisting medical condition or is considered a preventive service. It is unclear whether PGx tests would be considered diagnostic or screening tests.

- CMS should develop guidance that clarifies their policies in regard to coverage of PGx tests. Also, the Secretary should urge Congress to add a benefit category for preventive services. Furthermore, the Secretary should direct CMS to clarify that in certain cases, as scientific evidence warrants, a "personal history" of disease can include a family history of disease. [See SACGHS Report on Coverage and Reimbursement of Genetic Tests and Services]

Inclusion of PGx Data in Electronic Health Records

Draft Recommendation 13

- HHS should identify mechanisms to make PGx information more user-friendly and more likely to be used, especially in the context of its current health information technology initiative. For example, clinicians need reminders that can be used in every day practice such as a mechanism to flag prescriptions for which PGx testing would aid in dosing or identifying those at risk for adverse events.
- HHS should fund studies examining ways electronic health records can be used in the development of PGx products.
- PGx information in the form of genetic data codes should be included as part of the standards for electronic health records.