FDA DOCUMENTATION FOR THE GENERIC CLEARANCE ON DATA TO SUPPORT DRUG PRODUCT COMMUNICATIONS (0910-0695)

TITLE OF INFORMATION COLLECTION: Educating Groups Influencing Generic Drug Use (Survey)

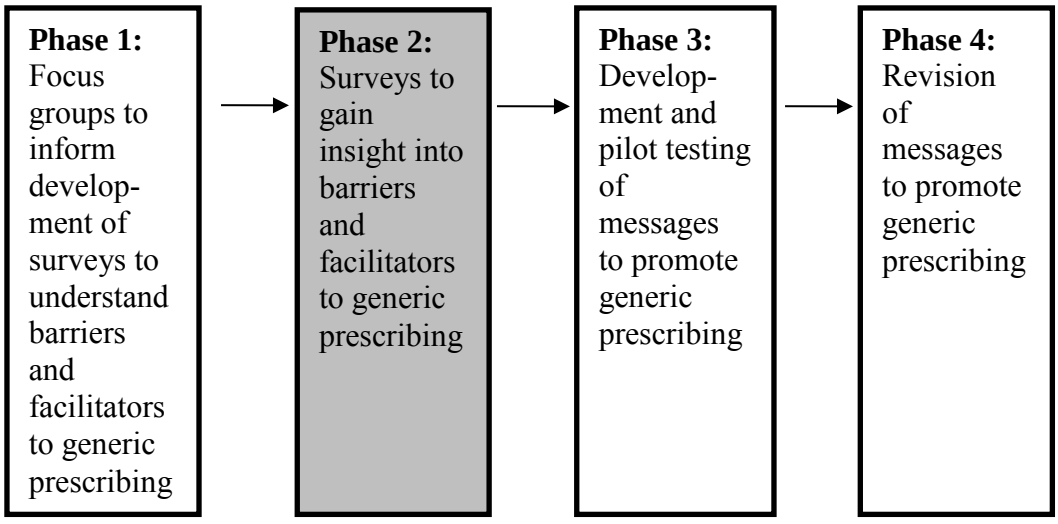
DESCRIPTION OF THIS SPECIFIC COLLECTION

1. Statement of Need:

The Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD) is seeking OMB approval under the generic clearance 0910-0695 to conduct surveys for the project "Educating Groups Influencing Generic Drug Use."

Based on the supporting statement for generic clearance 0910-0695,[1] the purpose of information collection under this generic clearance is "to provide tools to assess the need for communications on specific topics and to assist in the development and modification of communication messages to promote public health and compliance with regulations." The specific collection described in this memo aims to assess the need for communications directed at healthcare providers on the use of generic drugs for certain drug classes. Exhibit 1 illustrates the full set of research phases for this project. Our previous submission addressed only the focus groups in Phase 1, which informed the development of the survey that is the subject of this information collection. Please note that this information collection request concerns only Phase 2.

Exhibit 1. Overview of Research Phases



[1] http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=201509-0910-002

Congress passed the Generic Drug User Fee Amendments (GDUFA, Title III of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144)) in July 2012. Under GDUFA, FDA obtains industry and public input to create regulatory science initiatives regarding research on generic drugs that advance public health.[2] Once marketed, certain generic drugs are often not preferred over brand drugs[3] even though generic drugs generally cost less than brand drugs.[4] Research to characterize the key influencers of generic drug use (particularly for drug classes with low generic drug use), including their knowledge base and perceptions toward generic drugs, is needed to effectively design and deliver communications about generic drugs to the key groups influencing consumer acceptance and use of generic drugs. To address this regulatory science need regarding generic drugs, the FDA entered into a cooperative agreement with the University of Chicago (UChicago) (Grant number 1U01FD005485-01).

As prescribers of brand or generic drugs, healthcare providers can influence consumer use of generic drugs. Many healthcare providers have been slow to adopt generic drugs[5] despite data suggesting clinical equivalence between generic and brand drugs.[6]

In primary care practice, both clinicians and patients express concerns regarding use of certain generic drug classes such as antidepressants, oral contraceptives, and cholesterol lowering drugs.[7] Through a cooperative agreement with

[2] http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm
[3] Scher, S. (2013) The Branded Advantage. *Ophthamol Mgmt*. July: p18
http://www.ophthalmologymanagement.com/printarticle.aspx?articleID=108618

Alloway, RR, Isaacs R, Lake K, Hoyer P, First R, Helderman H, Bunnapradist S, Leichtman A, Bennett MW, Tejani A, Takemoto SK. (2003) Report of the American Society of Transplantation Conference on Immunosuppressive Drugs and the Use of Generic Immunosuppressants. *A J Transpl* 3: 1211.

Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW. (2007) Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. *Neurology* 68: 1249.

American Thyroid Association, The Endocrine Society, and American Association of Clinical Endocrinologists. (2004) Joint Statement on the U.S. Food and Drug Administration's Decision Regarding Bioequivalence of Levothyroxine Sodium. *Thyroid* 14: 486.
[4] Avoidable Costs in U.S. Healthcare: The $200 Billion Opportunity from Using Medicines More Responsibly. Report by the IMS Institute for Healthcare Informatics.
http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS Institute/RUOM-2013/IHII_Responsible_Use_Medicines_2013.pdf
[5] Shrank WH, Liberman JN, Fischer MA, Girdish C, Brennan TA, Choudhry NK. Physician Perceptions about Generic Drugs. Ann Pharmacother. 2011;45(1):31-8.
[6] Kesselheim AS, Misono AS, Lee JL, et al. Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-Analysis. JAMA: the journal of the American Medical Association. 2008;300(21):2514-2526.
[7] Bolton JM, Dahl M, Sareen J, Enns MW, Leslie WD, Collins DM, Alessi-Severini S. A population-based study of the use of selective serotonin reuptake inhibitors before and after introduction of generic equivalents. Can J Psychiatry. 2012;57(4):223-9.

UChicago, the barriers and facilitators to consumer use of these drug classes will be explored by conducting surveys of primary care physicians and nurse practitioner prescribers.

2. Intended use of Information:

Information collected in these surveys will be used to improve understanding of the barriers and facilitators to prescribing generic drugs, with a particular interest in knowledge gaps regarding generic drugs.

Information collected in the Phase 2 surveys will be used to inform development of educational messages regarding generic drugs (Phase 3). By understanding why healthcare providers may sometimes not prescribe generic drugs, effective educational messages may be developed.

3. Description of Respondents:

The survey will be disseminated through the American College of Physicians (ACP) and the American Association of Nurse Practitioners (AANP).

ACP is the largest medical-specialty organization and the second largest physician group in the United States. General internist primary care physicians typically provide comprehensive longitudinal care and coordinate complex treatment for adults. The Internal Medicine Insider Research Panel is a community of approximately 1100 U.S. ACP members and 300 non-members who participate in research surveys distributed by the ACP Research Center.

AANP is a union of the American Academy of Nurse Practitioners and the American College of Nurse Practitioners. It is currently the largest full-service national professional membership organization for nurse practitioners (NPs) of all specialties. AANP maintains the only national NP database of all practicing NPs. NPs are authorized to prescribe medications in all fifty states and Washington, D.C.

The AANP Network for Research (AANPNR) is a practice-based research network open to all members and allows them to participate in research surveys

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Committee on Gynecologic Practice, American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 375: Brand versus generic oral contraceptives. Obstet Gynecol. 2007;110 (2 Pt 1):447-8.

Green JB, Ross JS, Jackevicius CA, Shah ND, Krumholz HM. When choosing statin therapy: the case for generics. JAMA Intern Med. 2013;173(3):229-32.

Drug Benefit News. As Competitors Encroach, Pfizer Seizes A Few More Glory Days With Lipitor Promo. http://www.silverlink.com/assets/pdfs/silverlinknews/dbn020411.pdf

distributed by the AANP. The AANPNR consists of approximately 1400 NPs from a variety of practices.

The ACP and AANP serve as collaborators in this study under the 1U01FD005485-01 collective agreement. The well-established networks and infrastructures of the ACP and AANP guarantee the success of this study by ensuring feasibility and a representative recruitment pool that can be surveyed with minimal logistical burden.

4. Date(s) to be Conducted:

The survey will be launched and conducted electronically in January, 2017.

5. How the Information is Being Collected:

Recruitment

This survey will utilize ACP and AANP's preexisting research panel of participants. Both panels select using stratified random sampling to ensure they are representative of membership within the US across multiple demographics. Participants fill out profiles to confirm their eligibility and ensure the panels is representative of the organization's membership. These profiles include information including member ID numbers, names, gender, member class, primary specialty, primary practice site, and time spent in patient care. These profiles are updated by the organizations regularly. Non-members are recruited to the panel using a similar profile database to be representative of the larger provider population.

Using their respective database of information on panel participants, ACP and AANP will work with UChicago to identify eligibility requirements for survey participation (see attached screening criteria) to ensure participants have adequate experience with patients and the survey subject matter. The eligibility screening process is conducted using a preexisting database and bears no burden on participants.

Eligible participants will receive an invitation email with the survey URL. All survey communication will be from the respective organizations' CEO or Director of the Research Center. Emails will contain the ACP/AANP logo and will be formatted to match standard survey practices of the respective organization.

One week after the initial invitation email, up to 10 email reminders will be sent at intervals of 4-21 days to participants who have not yet completed the survey. The survey will be closed and all contact regarding the survey will end when an approximate response rate of 50% is reached or when all planned contact has been completed.

Emails to participants will follow the standard format and structure used by the ACP and AANP (see attached example). Emails will include basic information about the survey topic, expected length of time to complete the survey, privacy information, and consent process. As with other AANP and ACP panel surveys, participants' submission of the survey is considered implied consent. Participation is voluntary and participants may choose to not participate at any time.

Survey

Given the eligibility criteria for the survey, the target sample size for the ACP survey and AANP survey is 850 participants and 900 participants, respectively with an approximate goal response rate of 50% based on past surveys administered by these organizations. Participants will access the survey via a URL provided in the recruitment emails. The survey will include an introductory section (see attached example) including the statement, "Submission of this survey is considered implied consent."

The survey is divided into two parts- a section of Likert questions focused on generic skepticism and general perceptions and a vignette section where participants answer Likert questions in response to a series of proposed prescribing scenarios.

Individual participants will be randomized to one of four blocks. Each block has one of four different combinations of **[A – WHOM]** and **[C – PATIENT DRUG PREFERENCE]** that are held constant over two vignettes**.** Two sets of identical questions per vignette will vary **[B – MESSAGE]**. **[D – DRUG]** will vary between vignettes. The order of the vignettes and question sets will be randomized across blocks.

Variable Options

[A – WHOM]

- a_0 FDA – "from/by the FDA"
- a_1 professional societies – "from/by your professional society"

[B – MESSAGE]

- b_0 "equally as effective as"
- b_1 "bioequivalent to"

[C – PATIENT DRUG PREFERENCE]

- c_0 neutral – "has never expressed a preference for brand or generic drugs"
- c_1 brand name preference – "expressed concern that the generic drug will not work for her"

[D – DRUG]

- d_0 "antidepressants"
- d_1 "oral contraceptives"

Vignette Structure

One of your patients comes to your clinic for a medication refill. She is currently taking a brand name **[D – DRUGb]**. She has no complaints and is doing well. In previous visits, the patient **[C – PATIENT DRUG PREFERENCEa].**

Recently you received a notification from **[A – WHOMa]**. The message highlighted the importance of prescribing generic **[D – DRUGb]** since they are **[B – MESSAGEa]** brand name **[D – DRUGb].**

Exhibit 2. Survey Design

	VIGNETTE 1		VIGNETTE 2	
BLOCK 1 (A_0C_0)	$a_0b_0\,c_0d_0$	$a_0b_1\,c_0d_0$	$a_0b_0\,c_0d_1$	$a_0b_1\,c_0d_1$
BLOCK 2 (A_0C_1)	$a_0b_0\,c_1d_0$	$a_0b_1\,c_1d_0$	$a_0b_0\,c_1d_1$	$a_0b_1\,c_1d_1$
BLOCK 3 (A_1C_0)	$a_1b_0\,c_0d_0$	$a_1b_1\,c_0d_0$	$a_1b_0\,c_0d_1$	$a_1b_1\,c_0d_1$
BLOCK 4 (A_1C_1)	$a_1b_0\,c_1d_0$	$a_1b_1\,c_1d_0$	$a_1b_0\,c_1d_1$	$a_1b_1\,c_1d_1$

Survey

Draft: **https://qtrial2016q3az1.az1.qualtrics.com/jfe/form/SV_8iVlufkwzVUpaF7**

The ACP and AANP will use its own established survey platforms to survey its members, thus we anticipate some slight differences in survey formatting. The ACP utilizes Questback for survey administration, while the AANP utilizes FluidSurveys or Qualtrics. UChicago has worked extensively with the ACP and AANP to ensure consistency and equipoise not only between the ACP and AANP surveys, but also with other surveys administered by these organizations.

6. Confidentiality of Respondents:

UChicago and FDA will comply with safeguards for ensuring participant information is kept private to the extent permitted by law. All data will be collected with an assurance that the respondents' answers will remain confidential. The study instrument will contain a statement that their responses will be kept confidential.

Personally identifiable information, including membership ID numbers, names, and emails, are used by ACP and AANP in order to contact participants and re-contact non-respondents for this survey. All identifiable data is password-protected and stored on a secured platform according to each organization's respective data security and confidentiality protocols. Only research staff working on this project will have access to identifiable data. Once survey responses are collected by ACP/AANP, a deidentified data set is sent to UChicago for combined analysis.

All results from the study will be reported only in the aggregate. Data will be kept for six years after the close of the study. At the end of this period, written documentation will be destroyed according to proper University of Chicago protocol and channels. Any digital data will be destroyed using commercial software applications designed to remove all data from the storage device.

7. Amount and Justification for any Proposed Incentive:

Compensation to subjects participating in focus groups is proposed in accordance with the ACP and the AANP standard practices regarding surveys. To maintain equipoise with other surveys, physician and nurse practitioner survey respondents are proposed to receive a $10 Amazon gift card.

The incentive is not a reward or salary. Rather, it is a stimulus to ensure adequate participation, high-quality data, and that participants are reasonably representative of the ACP and AANP membership.

8. Questions of a Sensitive Nature:

There will be no questions of a sensitive nature asked of participants.

9. Description of Statistical Methods:

Survey data will be analyzed using descriptive statistics to summarize means, medians and measures of spread (confidence intervals, standard deviations). In addition, whether differences in perceptions about generic substitutions exist by drug classes, or between PCPs and NPs, will be ascertained.

Data will be analyzed in aggregate. We will use basic cross tabs and frequencies to identify trends and patterns in the data. We will test research hypotheses with ANOVAs, linear regression, chi-square tests, and correlations, as appropriate for the type of data (discrete, continuous, binary) and the research question.

We conducted a power analysis to assess whether the expected sample size of 425 will be sufficient to detect the hypothesized differences. Of primary interest is whether there is a main effect of MESSAGE (effective, bioequivalent) or PATIENT DRUG PREFERENCE (neutral, brand). The response choices are on a 5-point Likert scale, but the distribution of responses is expected to be skewed. For this reason, a binary outcome was considered for the power calculations. Specifically, the outcome was whether a participant answered extremely likely or likely. For MESSAGE, the hypothesized difference is 60% (effective) versus 40% (bioequivalent), and the analysis would involve a within-participant comparison. To generate a conservative estimate of power, the smallest possible sample size of 106 (i.e., the number in each of the four blocks) was used with a two-sided alpha = 0.05 and gave 91% power assuming a correlation between

proportions of 0.25, based on McNemar's test. Even if the correlation is weaker (0.1), the power would be 86%. For PATIENT DRUG PREFERENCE, the hypothesized difference is 50% (neutral) versus 30% (brand), and the analysis would involve a between-participant comparison. To generate a conservative estimate of power, the smallest possible sample size of 106 per group (i.e., the number in each of the four blocks) was used with a two-sided alpha = 0.05 and gave 85% power based on a Pearson's chi-squared test. Of note, more powerful models that would leverage the full sample size of 425 would actually be utilized for analysis (e.g., standard logistic regression model with robust standard error estimates or generalized estimating equations (GEE) regression model).

BURDEN HOUR COMPUTATION *(Number of responses (X), estimated response or participation time in minutes (/60) = annual burden hours):*

The survey takes approximately 12 minutes to complete.

Type/Category of Respondent	**No. of Respondents**	**Participation Time** (minutes)	**Burden** (hours)
General internist primary care physicians (ACP)	425	12	85
Nurse practitioners (AANP)	425	12	85
Total	850	12	170

REQUESTED APPROVAL DATE: By November 1, 2016 (or earlier, if possible). Approval later than early November would likely hinder the planned survey deployment and delay Phases 3 and 4.

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