The Serious Adverse Event Consortium, Ltd.

Phase One Summary

August 2007

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Deerfield, Illinois 60015

I. Introduction and Summary of the Serious Adverse Event Consortium [SAEC]

The Serious Adverse Event Consortium [SAEC] is a pharmaceutical industry and FDA led international consortium, focused on identifying and validating DNA-variants useful in predicting the risk of drug induced, rare serious adverse events [SAEs]. The SAEC will be launched in early September with the scientific, technical and financial support of eight initial research funding members [*i.e Abbott, GSK, J & J, Novartis, Pfizer, Roche, Sanofi-Aventis, and Wyeth*]. Additional members will be added as the consortium executes its Phase 1 research program and develops its future plans. The FDA and other regulatory bodies responsible for drug and medical products safety will be involved in all facets of the SAEC as "Associate Members". The SAEC plans to collaborate with leading [academic and industrial] scientists to identify the optimal computational methods to apply whole-genome SNP mapping technology to discover and validate rare SAE genetic markers. As part of its commitment to enable and facilitate research in this important area, the SAEC will release all "allowable" data [i.e. as specified in the informed consents and allowed by IRBs] to all qualified researchers via its web-based "SAE knowledge" site.

The impetus for the SAEC arose from a series of interviews conducted in late 2005 and early 2006, with senior research and development leaders in major pharmaceutical companies and government. The goal of these interviews was to explore how to best leverage the success of previous private-public consortia [e.g. The SNP Consortium] to identify additional areas to apply this effective "collaborative model". Out of ten possible collaborative opportunities, the highest priority was assigned to exploring the genetic and molecular basis of drug induced, rare serious adverse events. "Scale' is critical in the practical realization of such a research focus, as no one company or organization is likely to have the clinical, patient, and genomic research resources to identify, screen and enroll adequate numbers of high quality subjects. Research on rare, drug induced SAEs is ideally suited to the "consortium model".

Concurrent with the above mentioned market research, an FDA's Industrial Advisory Board recommended an "<u>independent</u> industrial biomedical consortium" be formed to bring industry and regulators together to build a better understanding of the biology of drug induced serious events. Such a private sector led scientific collaboration was likely one of the initiatives the FDA had in mind when it developed and published its "The Critical Path: Accelerating the Development of Medical Products". Since July of 2006, Janet Woodcock, MD [Deputy Commissioner and Chief Medical Officer] has co-chaired the "Organizing Committee" of the SAEC with Arthur Holden, Chairman and CEO of the SAE Consortium, Ltd. In addition, the European Medicines Agency is supportive of the SAEC, reflecting their number one 2006-07 organizational priority of improving the safety of medicines used in humans.[1]

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[1] Summary of the 2006 Work Program of the European Medicines Agency, March 2006.

Drug-induced, rare SAEs can be a severe health issue; and pose significant issues for the use of approved drugs and the development of new drugs. SAEs are a significant issue for patients, FDA, industry, and payors; and an important element contributing to healthcare cost inflation. Examples of drug-induced, rare SAEs include hepatotoxicity, QT prolongation, rhabdomyolosis, serious skin rashes [e.g. SJS], edema, acute renal failure, acute hypersensitivity, anemias/ neutropenias, excessive weigh gain, retinopathy, vasculitis etc. The rarity of such drug induced SAEs and the absence of effective government surveillance/research networks, makes it extremely difficult for any one company/research entity to accrue enough SAE cases and controls to conduct effective whole genome studies. Central to the notion of the SAEC is that industry, government and health care providers will join forces and work together to make use of a variety of sample and data resources to research the genetic basis of rare, drug induced SAEs.

Specifically, the SAEC will work to coordinate with existing SAE research networks, while fostering the development of new networks to obtain well phenotyped SAE cases and controls. The SAEC plans to collaborate with leading academic and industrial clinicians/scientists to identify the optimal computational methods to apply whole-genome SNP mapping technology to SAE marker discovery and validation. All "allowable" data [i.e. as specified in the informed consents and approved by the relevant IRBs] from these efforts will be released to qualified researchers via a web-based "SAE knowledge" site. **[*See Appendix A: SAEC Data Release and IP Policy*]**

Although the Consortium's scientific scope is broad in principle, it will initially focus on two "discovery" research projects. It will work to identify DNA variants associated with drug-induced liver-disease [DILI] and Serious Skin Rash [SJS]. These two projects, while critical in their own right, will also allow the SAEC to generate initial results in a relatively short time frame [due to the availability of case-control DNA sample collections]. In addition, these projects will facilitate the development of the consortium's informatics and data analysis/coordinating center at Columbia University, as well as other important operational capabilities. Simultaneously, while the Phase 1 discovery research is being executed, the SAEC will explore the feasibility of research on additional SAEs, develop hypothesis driven follow on studies, and examine the feasibility of international networks to identify and obtain greater numbers of SAE cases and controls.

The SAEC commenced its formation activities in early September of 2006. Over the past year, its efforts have been focused on strategy development, operational feasibility and planning activities, organizational development, research collaboration development, service partner development, feasibility studies and numerous legal and formation activities. To date, twenty one agreements have been negotiated and completed to give birth to the SAEC Ltd. It is expected the consortium will announce its formation and initial research activities the third or fourth week of September, 2007.

II. Organization and Formation Status of the SAEC

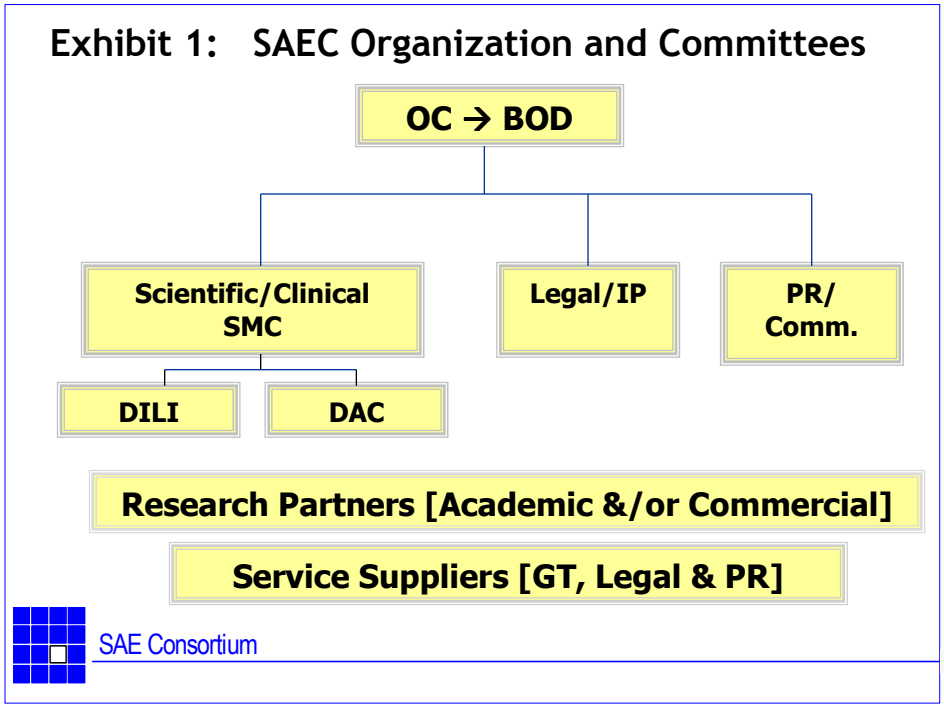
The SAEC is a 501 c3 non-profit membership corporation [under the Internal Revenue Service Code] formed to engender the required organization, processes, and resources to identify and validate DNA-variants useful in predicting the risk of drug induced serious adverse events [SAEs]. As such, it functions with the explicit purpose of enhancing the "public good". Its members are (i) organizations engaged principally in the business of discovering, developing and marketing pharmaceutical products, or (ii) a charitable, governmental, or other non-profit organization with an interest in the field of medical science. To protect its members from the risk of frivolous law suits associated with such intra-industry sponsored research, the SAEC is registered under the National Cooperative Production and Research Act of 1993.

The sole purposes of the SAEC are:

- To carry out research directed toward the discovery of DNA-variants that are clinically useful in understanding and predicting the risk of drug induced serious adverse events and similar scientific research.
- To ensure the widespread availability of the results of such research to the scientific research community and the public at large for no charge through publication or other methods; and
- To educate the scientific research and medical communities about issues related to severe adverse drug reactions and about issues related to the Corporation's research.

The SAEC is governed by a Board of Directors [BOD] which has management control over the property, activities and funds of the Corporation. The BOD consists of one director from each Sponsoring Member and the Chief Executive Officer, ex officio. The Board structure also allows for involvement of other non-profit research and governmental organizations via "Associate Membership". The SAEC BOD functions and makes its decisions using a "majority rules" model. All key research collaborations are formed via a rigorous "RFP Process", with final selection determined by the Scientific Management Committee. All sponsored research collaborations are governed by milestone based agreements, whereby the SAEC preserves its right to restructure or exit any collaboration where "underperformance" is a recurring issue. The SAEC retains independent financial management and has the right to audited financial statements. The SAEC also retains legal counsel from WilmerHale LLP.

The SAEC BOD has appointed three major Committees to advise the SAEC on research and policy matters. The initial Advisory Committees are the Scientific Management Committee [SMC], Legal/Intellectual Property Committee and the Public Relations/Communications Advisory Committee. The Scientific/Clinical Management Committee will have two subcommittees, the DILI Subcommittee and the Data Analysis Subcommittee. Exhibit 1 below summarizes the current organizational structure of the SAEC.



The **SMC** is chaired by Eric Lai [GSK] and Duncan McHale [Pfizer]. Its charter is to provide the membership with sound research strategies, well defined research programs; including plans, milestones & performance monitoring and guidelines. It also provides advice on study design and methodology, phenotyping, clinical collaborators, CRF design, informed consent, genomic research matters, whole genome data analysis, and data release policies. The SMC will facilitate SAEC publications arising from its research activities, prior to public data release. The committee will encourage active participation of scientific and clinical experts from each of the SAE's scientific collaborators [*DILIGEN, EUDRAGENE, Columbia, etc*]. Each funding member will have a minimum of one representative on the SMC. Associate members, such as the FDA, may have multiple members on the committee. In addition, the SMC will invite adhoc [scientific or clinical] experts to consult on its research activities. Drs. Lon Cardon [FHCRC/Oxford] and David Goldstein [Duke] are currently two such SMC advisors. Others will be added as the SAEC moves into its operational phase [September, 2007].

The SMC plans to develop sub-committees to bring additional expertise [from members and external advisors] to the SAEC's research activities. Initially, two such committees will be established; the Data Analysis Committee [**DAC**] and the DILI Committee [**DILI**]. The DAC will provide the SMC with specific expertise on phenotypic and [whole genome] data management, analyses/computational methods and release policies. The DILI Committee will provide the SMC with specific expertise on clinical, biological, and pharmacological aspects of drug induced liver injury. The DAC is fully functional under the leadership of Quingqin Serena Li [J & J], in-conjunction with the SAEC Data Analysis and Coordinating Center [DACC] at Columbia University. The DILI Committee will be finalized after the feasibility of collaboration with NIH/NIDDK/DILIN is determined. Currently, the committee has DILI experts from the member companies, the FDA, and external DILI research networks.

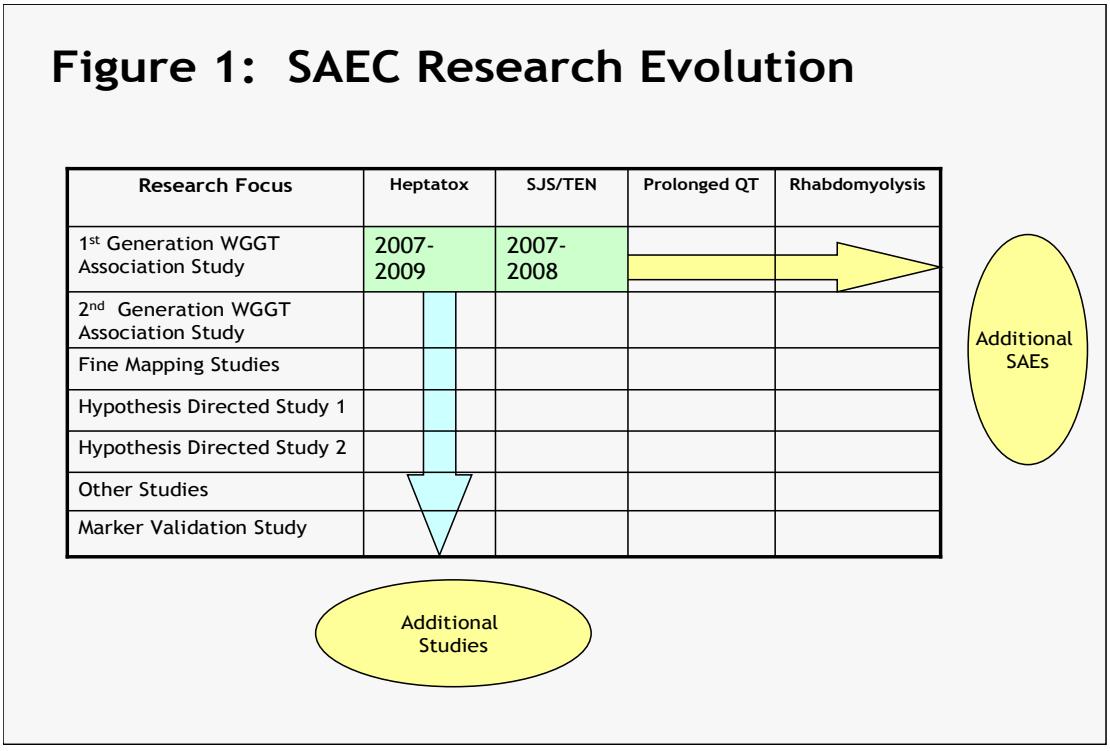
The Legal/IP Committee is chartered to provide independent advice critical to developing the SAEC's contracts and agreements, IP strategy & policies, and ensuring compliance with Anti-Trust law. The Legal/IP Committee is chaired by Owen Hughes of Pfizer.

III. Summary -- Phase 1 Serious Adverse Event Research Plan Summary
September 2007- October 2009

Introduction

Although the Consortium's scientific scope is broad in principle, it will focus initially on two projects. It will first identify DNA variants associated with drug-induced liver-disease ("DILI") and Serious Skin Rash [*Stevens-Johnson Syndrome ("SJS") and Toxic Epidermal Necrolysis ("TEN")*]. These two projects, while important in their own right, will also allow the SAEC to generate initial results in a reasonable time frame [*due to the availability of established case-control DNA sample collections*]. It will afford the Consortium the chance to build its core operational processes and facilitate the timely development of the informatics and data analysis/coordinating center at Columbia University.

Simultaneous with the Phase 1 research focus described above, the SAEC will plan follow on, hypothesis driven studies [post whole genome association studies] for DILI and SJS and explore the feasibility of whole genome research on additional SAEs. As shown in **Figure 1** below, the SAEC will work over time in two research dimensions [i.e. within existing SAEs and expand to additional SAEs].



SJS/TEN Phase 1 Project

The clinical and genotyping data from the SJS and TEN cohorts will be donated to the SAEC, by GSK and Illumina, for analysis and follow up study. [*Illumina contributed the WGGT of all SJS cases and related controls.*] SJS and TEN are related, rare, and severe mucocutaneous blistering disorders associated with over 200 medicines. Current estimates place the incidence rate of SJS at 1-6 cases per million person-years and TEN at 0.4-1.2 cases per million person-years. The SJS/TEN cases were gathered via clinical investigators in both the US and UK during the period 2001-2004. Each case was externally adjudicated by Prof. Robert Stern, MD of Harvard University. Over 200 potential cases were reviewed, netting the SJS/TEN cohort. The cohort consists of 37 SJS cases, 34 TEN cases, and two cases with SJS/TEN overlap. Cases were collected both retrospectively & prospectively. In addition, there are 140 controls matched for age, gender, and ethnicity. The mean age of subjects is 41.2 yrs. 69% are female and 31% are male. Their ethnic mix is as follows: White (79.5%), Black (9.6%), Hispanic (5.5%), and Asian (2.7%).

The inclusion criteria for enrollment in the SJS/TEN case cohort were as follows:

- Males and females aged 18+ at enrollment (hospitalized)
- Widespread exanthema with 1% or more detachment of epidermis; more than one blister, not only accral extension, with or without mucous membrane erosions in the spectrum of SJS-TEN
- Able to complete adequate phenotyping including detailed clinical histories, photographs and biopsies, where available

Subjects were ineligible to participate in the study if they met any of the following exclusion criteria:

- Any condition or disease, which, in the judgement of the investigator, would place the subject at undue risk, interfere with evaluation of the objectives of the study, or interfere with the ability of the subject to complete the study;
- The subject is known to be HIV positive;
- The subject has undergone bone marrow transplantation;
- The subject is immuno-compromised; or
- Subject is judged by the investigator as being mentally unfit to give informed consent.

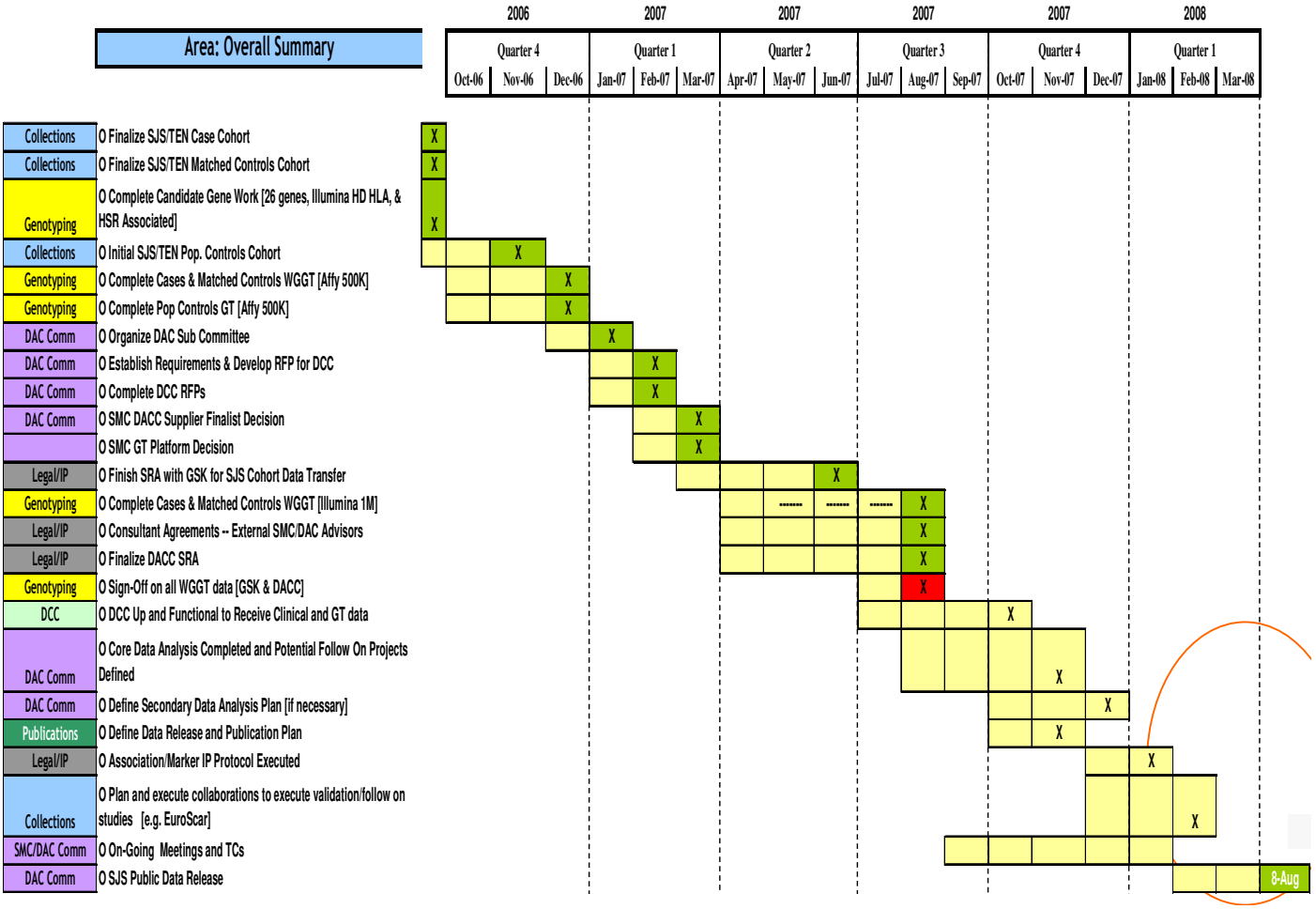
The primary objective of the SJS/TEN phase 1 project is to identify genetic susceptibility factors for the development of severe rash. An important secondary objective is to assess the effectiveness of a population control study design versus case/control design. In support of this objective, GSK will also donate 1,500 population controls to be used in support of both the SJS/TEN and the DILI studies. **Some of these data and the resulting informatics infrastructure will be leverage in the initial DILI study summarized below**.

The genotyping data for the SJS/TEN cases will include 26 SJS/TEN candidate genes, classic HLA-A, B, C, DR, DQ; a high density (7,000) SNP panel manufactured by Illumina, as well as HSR associated markers (19 genes) identified in the Abacavir study. Whole genome association scans using both the Affymetrix 500K Mendel Chip and the Illumina 1M chip will also be completed.

Standard statistical genetic analysis will be completed at the end of the genotyping phase of this project. In addition, the Data Analysis and Coordinating Center will coordinate analyses using novel whole genome analysis techniques suggested both by the members and academic advisors to the project.

Figure 2 below summarizes the SJS/TENS research operating plan and associated milestones, as of August 2007.

Figure 2: SJS Operating Plan



DILI Phase 1 Project

The Drug Induced Liver Injury (DILI) case cohorts will be furnished to the SAEC in collaboration with two initial European DILI research networks (i.e. DILIGEN and EUDRAGENE). As quoted in the DILIGEN proposal to the SAEC, *"The vast majority of DILI is due to idiosyncratic reactions not predictable from drug dosage/concentration. These reactions place a considerable burden on healthcare services worldwide and pharmaceutical industry during drug development. The fact that most of the agents commonly associated with DILI are very useful medicines means that simply limiting their use is not a feasible option. Instead, it is important that we understand the genetic and environmental factors associated with these adverse events, with the aim of developing strategies to identify susceptible individuals prior to prescription allowing the option of substituting alternative therapies. Many different drugs can cause DILI, with the precise pattern of injury varying between drugs. Typically, DILI reactions are classified as "hepatocellular" when the injury is focused on the hepatocyte and "cholestatic" when the damage occurs at the hepatocyte canalicular membrane or further downstream in the biliary tree. The precise mechanisms of either type of reaction remain unclear; however, there is emerging evidence that both drug metabolites and immune factors play a role. Consequently, common variations (polymorphisms) in genes encoding proteins involved in either the production or clearance of drug metabolites, or in immune regulation offer a potential explanation for inter-individual susceptibility to DILI."*

There are approximately 180 DILI cases presently available to the SAEC through its collaboration with DILIGEN and EUDRAGENE. Both groups have entered into sponsored research agreements with the SAEC to continue to yield additional cases through out the first year of the SAEC's research activities. It is expected these efforts will yield an additional 130 DILI cases. **In addition, the Consortium will continue to cultivate collaborative relationships [post formation] with the NIDDK/DILIN (US), Spanish DILI (Spain), and the Japanese Biobank (Japan). Were all of these parties to collaborate with the SAEC, the total available DILI case cohort could approach 1,000 patients.**

In general terms, the DILI inclusion criteria are defined as patients with either (a) clinically apparent jaundice or bilirubin > 40 mol/l (after exclusion of cases due to hemolysis), or (b) an ALT >5x ULN (upper limit of normal) or (c) an ALP >2x ULN plus any raised bilirubin above ULN. These cases were be recruited both prospectively and retrospectively via the two networks. 47% of the DILI cohort is male and 53% female, with a mean age of ~53. The cases are primarily Caucasian (98.0%), with the remainder Black (0.5%), and Asian (1.5%). Over 30 different drugs have been cited as being associated with onset of DILI [including a variety of different drug combinations]. The 1,500 population controls for this study will be matched as closely as possible on ethnicity, age and gender. **Appendix A** presents a high level comparison of the clinical report format [CRFs] from three major DILI case aggregation efforts, i.e. EUDRAGENE, DILIGEN, and DILIN.

The genotyping data for the DILI cases will be generated from the 1+ Million SNP panel manufactured by Illumina. This panel includes 1,072,820 SNPs, with a mean spacing between SNPs of 1.5kb, 565,000 SNPs in genes, 24,000 nsSNPs, 15,486 SNPs in ADME genes, and 10,073 SNPs in MHC regions. The exact genomic spacing is profiled in the table below:

Region	Total Marker Set	SNPs Only	SNPs in Stats Only	Probes Only
Total	**1072820**	**1055618**	**1049008**	**17202**
Mitochondrial	163	163	163	0
Y	2283	1418	1054	865
PAR (X/Y)	686	413	399	273
X	40097	38749	38201	1348
SNPs in CNV Region (DGV-6/2007 and/or deCODE)**	259916	242714	236104	17202

As part of its genotyping approach, the SAEC will accommodate a "candidate gene component" of 50 -100 hepatotoxity related genes, with SNP coverage of at least 80% genomic information across three populations.

Parenthetically, power calculations and sample size considerations are an important factor to consider in any study design to ensure the quality of the proposed scientific experiment and to provide one factor into our expectations of the likely results. In reality, the weight that can be given to the power calculation depends upon the certainty of the assumptions made in the underlying calculation. In many genetic and non-genetic situations these are not known and so we estimate based on what we know and in the case of drug development based on what would be a meaningful result e.g. we power many studies to detect a clinically meaningful benefit from placebo. The study may be over or underpowered to detect the true benefit but a decision is made that it has to be at least a minimally important clinical benefit over placebo. Power calculations in genetic studies have the additional complexity of not knowing the magnitude of the effect of the polymorphism. We also do not know how common it is (not to mention the fact that we are usually measuring a surrogate linked to the causative variant by LD).

The SAEC SMC reached the following consensus relative to powering considerations in SAE WG Association studies:

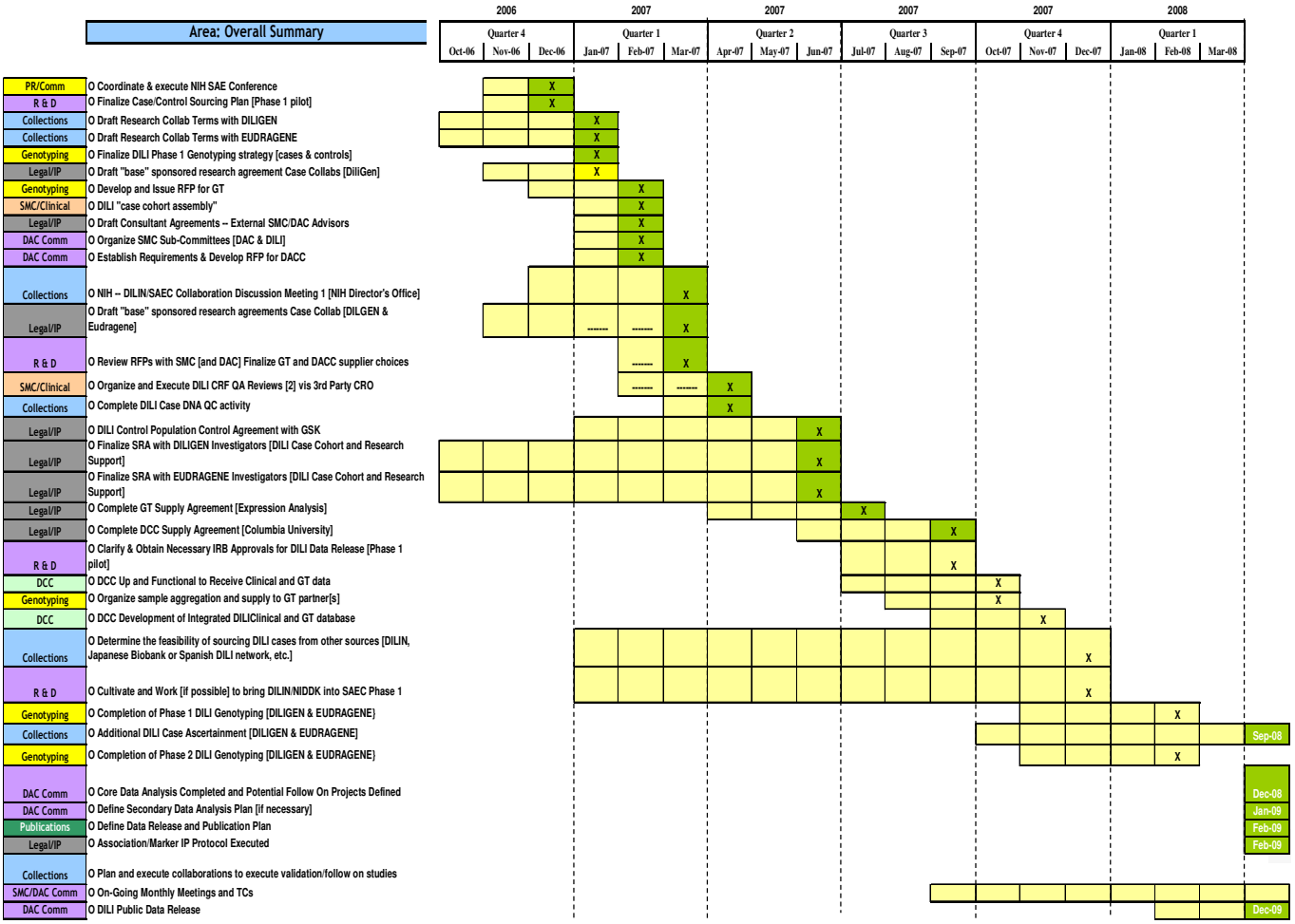
1. There are clear examples in the literature of pharmacogenetic effect sizes in SAEs of significantly greater than 3 and detectable with sample sizes well below those identified by the consortium.
2. Formal power calculations are of limited value here as the range of values for the assumptions is large i.e. true genetic effect could be as low as 2 or 3 or as high as 50 and the frequency of the genetic variant could range from 1-5% all the way up to 50%.
3. To be clinically useful the size of the genetic effect needs to be at least moderate and so we are looking for polymorphisms with effect sizes of greater than 3.
4. The SAEC has sufficient samples to detect a clinically significant pharmacogenetic effect which is common across DILI reactions; but additional are always beneficial,
5. The study proposed by the SAEC should answer the question of are there polymorphisms which have sufficient predictive power to be used as a meaningful clinical test and guide prescribing.

A number of fine PGx studies have generated important results, powered to the level of our first two studies. [*i.e. For Gefitinib (Diarrhea), RR = 5, number of cases required for detection = ~30. For Abacavir, RR = 36, number of cases required for detection = ~15. For Carbemazipine (SJS), RR = 1000, number of cases required for detection = ~ 6-9.*]

Standard statistical genetic analysis will be completed at the end of the genotyping phase of this project. In addition, the Data Analysis and Coordinating Center [DACC] will coordinate all analyses using novel whole genome analysis techniques suggested both by the members and academic advisors to the project. Those data (clinical and genotype) able to be released as dictated by informed consent and reasonable ethical practice, will be released (via a dedicated web portal) to qualified researchers within 12 months after the completion of the genotyping phase. This will allow amble time for the preparation of publications. No individual researcher working within the Consortium will have preferential access to the raw data set. All analysis requests will be brokered through SMC, and will be executed by the DACC staff. The results of these analyses will be presented to and discussed by participating researchers via the SMC's deliberations and meetings.

Figure 3 below summarizes the DILI research operating plan and associated milestones, as of August 07.

Figure 3: DILI Operating Plan



IV. Summary -- SAEC Research Policies

As note above, the SAE Consortium is organized as a private 501 c 3 organization which functions in the "public good"; thus, tax law influences its research/operational policies. In addition, its dues paying members are the world largest pharmaceutical companies which represent a significant percentage of the global [ethical] pharmaceutical industry; thus, considerations under international anti-trust law have an important influence on the SAEC's research policies.

In light of these factors, as well as the requirements of SAEC's clinical collaborators, their institutional requirements, and the current genomic/personal data handling policies by international research organizational such as the Wellcome Trust, the following policies currently guide the Consortium's translational research programs:

- **Public Research Data Release:** To promote the public welfare and enable the broadest beneficial use of the results of the Consortium's research efforts, all research data, except those specifically excluded by patient informed consent or institutional IRB policies, will be made available on a non-discriminatory basis to all qualified researchers, at the same time, at no charge. These data will be made available to the public no later than twelve (12) months following the QC approval of the complete genotyping data set by the DACC at Columbia University. This will provide participating researchers with the requisite time to analyze the data and generate publications. In order to limit the privacy risks and to comply with any other data use limitations (e.g., informed consents), specific Program Data will not be classified as Public Data unless and until it has been so designated by the SMC.
- **Restrictions on Public Data Access:** The DACC will make the Public Data available through a controlled-access database to all researchers worldwide who have agreed (and whose institutions have agreed) to comply with certain restrictions determined by the SMC. Such restrictions will include the following: (i) not to share the Public Data with any person who is not employed by a Public Researcher, (ii) not to attempt to identify individual subjects represented by genotype or phenotype data, (iii) not to use the Public Data for other than legitimate pharmaceutical or biological research purposes, and (iv) such other reasonable restrictions consistent with this Policy as determined by the SMC. Public Researchers shall be required to agree to comply with the foregoing restrictions through a signed agreement or certification and/or a "click-wrap" document that must be accepted prior to accessing online Public Data. Any Public Researcher using Public Data shall acknowledge the Consortium in any resulting oral or written presentation, disclosure or publication relying on such Public Data.
- **Genotyping Data:** SAEC Genotyping Vendors will perform the genotypic analyses (including quality control) required by the Consortium on the Samples received from Clinical Sources. At the Consortium's request, Genotypic Data generated by a Genotyping Vendor

may be submitted to one or more QC Vendors for quality control purposes. Such QC Vendor will receive only sufficient quantities of Sample and Genotypic Data to assess the quality of such Genotypic Data. The SMC will not have direct access to Genotypic Data. Unused portions of the Samples will be returned to the supplying Clinical Source in a timely manner.

- **Data Analysis:** The Data Analysis Committee [DAC], in cooperation with the DACC, will determine suitable strategies for analysis of the Clinical Data and Genotypic Data. The DACC will perform such analyses in accordance with such strategies and will report any Analytic Results to the DAC. The DAC, in consultation with the SMC, will evaluate the Analytic Results and may request additional analyses from the DACC. Data Analysis Committee and SMC members who have access to Analytic Results shall use such Analytic Results solely in connection with the Consortium's Research Program, and not for the individual benefit of any institution or company, whether or not a Member of the Consortium. Each such individual will be bound by confidentiality agreements associated with Consortium membership, and will be prohibited from sharing Analytic Results with any individual who is not a member of the SMC or DAC.
- **No Preferential Data Access for Members:** The DAC or any other member of the Consortium will not have direct access to Clinical Data or Genotypic Data and shall only be permitted to access the Public Data on the same terms and conditions as all researchers.
- **Treatment of Program Data:** Each recipient of Program Data (whether a member of the SMC or Data Analysis Committee, a Genotyping Vendor or the DACC) shall be responsible for complying with all applicable national, state and local laws, rules, regulations, enactments, directives, orders and standards and relevant institutional policies and requirements, and shall be required to maintain the strict confidentiality of any Individual Data. All persons and organizations having access to Program Data (other than Public Data) shall be required to take reasonable security measures to ensure that such Program Data is not compromised, improperly disclosed or misappropriated. Individual Data shall be protected to the greatest extent practicable. Program Data (including Individual Data) other than Public Data shall be used solely in support of the Consortium's Research Program.
- **Publication Preparation:** Following the receipt of the final Analytic Results, members of the Data Analysis Committee and SMC may prepare scientific papers based on such Analytic Results for publication in peer-reviewed scientific journals. Each such paper must be provided to the SMC prior to its first submission to a journal. The SMC shall have a period of 45 days in which to provide any comments and to determine whether all appropriate authors have been credited in such paper, and the author shall comply with the SMC's recommendation as to any additional authors. All such papers shall acknowledge the support of the Consortium.
- **Intellectual Property:** It is the goal of the Consortium to maximize the public benefit of research supported by the Consortium and, accordingly, to make freely available DNA markers for susceptibility to drug-induced severe adverse events and related data and analyses to all parties. The Consortium intends to release all Public Data as early as possible so as to place it in the public domain and reduce the likelihood that use of the Public Data will be

encumbered by patents. In some cases, the Consortium may determine that the most effective way to ensure that Public Data is placed in the public domain, with the earliest available priority date, is to file a provisional patent application covering all novel discoveries made prior to the filing. Such filings shall include one or more claims directed toward the Program Data (including genetic markers and genotype/haplotype-phenotype associations). Subsequent to this provisional application, the Consortium may file additional utility applications to further validate or expand on its initial utility. At the end of the Research Program Activities, with respect to a given indication, patent counsel may file a final utility application, with the intention that such application either be abandoned following publication or converted to a statutory invention registration in the U.S. Researchers who develop intellectual property funded by the Consortium will be required to assist the Consortium in any such filings or other procedures deemed necessary by the Consortium to ensure the contribution of such intellectual property to the public.

- **Inventions Based on Public Data:** Each person accessing or using SAEC's Public Data, and his/her institution/organization, must agree not to file or support any patent application claiming any DNA marker(s), genotype/haplotype-phenotype association or other attribute disclosed as part of, or derived from, the Public Data or that would prevent or block access to, or use of, any element of the Public Data, or conclusions drawn directly from the Public Data.
- **No Limitation of Downstream Protection:** Subject to the previous point, the Consortium acknowledges that intellectual property protection may be appropriate for inventions and discoveries made by Members and/or Public Researchers, where such inventions and/or discoveries have been enabled by the Public Data and/or the Research Program Activities, but are not directly derived from the public data. Such "downstream" inventions may include novel assays, drug targets, therapeutics and diagnostics developed using DNA markers discovered through analysis of the Public Data, but whose utility is not solely derived from the associations or other information contained in, or generated directly from, the Public Data. The SAEC acknowledges such developments does not provide the Consortium with any ownership or control of such downstream intellectual property and, accordingly, Members are not prohibited hereunder from filing or supporting any patent application claiming such "downstream" inventions. P

Please refer to **Appendix B** [***The SAEC's "Data Release and IP Policy***] for more details on these policies.

In addition, there are a number of "values" which influence the SAEC's approach to collaborative research and the expectations it holds for its research collaborators and partners. These are summarized below:

- **Business Objectivity and Prudence**: SAEC projects will be selected solely on the basis of the ability to achieve results in a given timeframe, with acceptable risks, and a clear

understanding of the investment required and the return expected. The consortium will function in a "business prudent manner" in all of its research dealings. It will select the best available collaborators as partners without bias. Projects will only be undertaken with strong, experienced collaborators.

- **Strong, Focused Management**: The affairs of the SAEC will be directed and lead by dedicated management, with strong professional management experience across the life sciences research continuum. This will included leadership experience specifically in the definition, development and execution of international research consortia.
- **Strong Project Management** – All SAEC projects will have an agreed upon project strategy, including firm milestones deliverables, and actions to deal with "under-performance".
- **Innovation**: The Consortium will look to create and deploy innovative research and organizational methods, which leverage the skills of parties that heretofore have not exploited their ability to work together to generate research outcomes desirable to the public.
- **Pro-Competitive Activities:** All SAEC projects will be "pre-competitive" [i.e. not serving directly the competitive interest of SAEC members], which result in data of a broad scientific utility that are "pro-competitive [i.e. increase the ability of all parties to develop more and better products and/or services].
- **Strong Member and External Expert Involvement:** The effectiveness and efficiency of the SAEC's program depend entirely on the volunteerism of its members and top academic to serve on the consortium's various administrative and scientific committees. The SAEC will strive to get the best talent involved in its scientific affairs.
- **Regulatory Involvement**: The research agenda of the SAEC will be developed in-conjunction with the FDA and other international drug regulatory bodies. As such, the SAEC will mindful of these organizations' priorities and strive to include the relevant clinical and scientific talent from these agencies. Where appropriate, the SAEC will apply GLP, GCP, etc. practices to maximize the utility [in drug regulatory submissions] of the research data generated from its SAE research projects.
- **Global Orientation**: The SAEC research orientation is global. It will strive to build diverse research coalitions across geographies, without bias to any one market.

Drafted by:

Arthur L. Holden
Chairman and CEO
SAE Consortium, Ltd.

Appendix A

Comparative DILI Clinical Report Format Data Elements Analysis

[DILIGEN, EUDRAGENE and DILIN]

Clinical Data Element	DILIN	DILIGEN	EUDRAGENE
DILI Symptom Profile [Self/Interviewer]	X	X	X
Smoking History	X	X	X
History of Alcohol Consumption	X	X	X
Co-Morbid Medical Conditions & Surgeries	X	X	X
Hospitalization/Outpatient History	X	X	X
Causal Rx/concomitant Rx data	X	X	X
Major Health Outcome Data [transplant, death, steroids, etc.]	X	X	X
Research Materials Obtained [Blood, Urine]	X	X	X
Consent Status	X	X	X
Standard Lab Data	X	X	X
Hepatitis Status	X	X	X
HIV Status	X	X	X
Routine Demographic Data	X	X	X
Family History/Ethnicity Data	X	X	X
Periodic Follow Up Medical Evaluations	X	X	
Medical Appt History	X	X	
Liver Test/Flow Evaluations	X	X	
Abdominal Imaging Study Data	X	X	
HBeAg Flow Data	X	X	
Anti HBeAg Flow Data	X	X	
Explicit exclusion data		X	X
View of Health Survey [Patient]	X		
Quality of Life Survey [Peds]	X		
ER History [DILI related]	X		
Concomitant CAM Products Used	X		
Language proficiency			X

Source: *DILI CRFs by Arthur Holden*

APPENDIX B

SAEC DATA RELEASE AND INTELLECTUAL PROPERTY POLICY

1. SAEC Background and Mission. The SAE Consortium (the "Consortium") is a non-profit corporation formed to carry out scientific research in the public interest. The mission of the Consortium is to identify DNA variants that are clinically useful in understanding and predicting the risk of drug-induced serious adverse events and to make the results of its work publicly available, in a responsible manner, so as to maximize the public benefit. Upon publication of Public Data (as defined in Section 3), such data will be made available on a non-discriminatory basis to all qualified researchers as set forth in this Policy. No charges will be assessed for access to or use of Public Data. Further, any rights that may be retained by the Consortium will not be exploited for commercial purposes.

2. Application of Policy. This Policy applies to all signatories to the Consortium's Formation and Funding Agreement ("Members") and all researchers and other organizations whose work is sponsored, contracted or funded by the Consortium. The agreement to comply with this Policy is a prerequisite and condition to membership in the Consortium or participation in any Consortium activity, including contracted research and development undertaken on behalf of the Consortium, and for use of any Public Data. Specific provisions of this Policy may be implemented and described in greater detail in agreements between the Consortium and the applicable parties. The application of this Policy will be overseen and monitored by the Scientific Management Committee of the Consortium.

3. Definitions. The following terms shall have the meanings set forth below for purposes of this Policy:

"Analytical Results" means all data and associations generated by the analysis of Genotypic Data and/or Clinical Data by or on behalf of the Consortium for the Consortium's Research Program. Analytical Results include genotype, haplotype and allele frequencies, genotype/haplotype-phenotype associations, identification of markers, copy number variation and other genetic variations associated with drug related serious adverse events.

"Ancillary Invention" means any invention created by third parties while performing work funded by the Consortium and covering methods, tools or discoveries ancillary to the work directly funded by the Consortium. Ancillary Inventions do not include DNA markers, genotype/haplotype-phenotype associations, or the conclusions derived therefrom, but may, unless otherwise specified in any agreement between the Consortium and such researchers, include reagents, genotyping and other equipment, analytical or statistical methodologies or tools, sample collection, storage, preservation and cataloging methodologies and technologies and software and database designs and technologies.

"Clinical Data" means the clinical data that is provided or made available for the Consortium's Research Program, whether or not associated with a particular Sample, and including, without limitation, sample quantity, biochemical characteristics and collection data, as well as subject identification, family history, phenotype, pathology, demographic data, drug exposure or control status, consent status and other subject data, and may include Individual Data.

"Clinical Source" means any supplier of Samples and/or Clinical Data for the Consortium's Research Program. A Member that supplies Samples or Clinical Data shall be considered a Clinical Source solely with respect to those Samples and Clinical Data that it supplies.

"Consortium's Research Program" means research conducted by or on the behalf of the Consortium to identify DNA variants that are clinically useful in understanding and predicting the risk of drug-induced serious adverse events.

"DACC" means the third party (non-Member) Data Analysis and Coordination Center designated by the Consortium, together with any additional third party consultants and/or contractors engaged by the Consortium to perform software, data or statistical analysis activities in conjunction with such Data Analysis and Coordination Center.

"Data Analysis Committee" means the Data Analysis subcommittee of the SMC which, for the avoidance of doubt, may include representatives of Members, Clinical Sources, the DACC and additional third party consultants and/or contractors engaged by the Consortium.

"Genotypic Data" means genotypic sequence data generated from any Sample by or on behalf of the Consortium or which is otherwise provided or made available for the Consortium's Research Program.

"Genotyping Vendors" means those third party (non-Member) providers of genotyping services that are selected by the Consortium to provide such services in support of the Consortium's Research Program.

"Individual Data" means individually-identifiable subject data (including, without limitation, name, address, date of birth, social security number and the like) and any connection between individual subjects and phenotype data.

"Member" has the meaning set forth in paragraph 2 above.

"Policy" means this Data Release and Intellectual Property Policy as it may be amended from time to time by a two-thirds majority of the Board of Directors of the Consortium.

"Program Data" means all data generated from Research Program Activities funded or supported by the Consortium, including but not limited to Clinical Data, Genotypic Data and Analytical Results. For purposes of this Policy, all Clinical Data associated with Samples used in the Consortium's Research Program shall constitute Program Data, even if such Clinical Data was collected prior to or without funding from the Consortium.

"Public Data" means Program Data that has been designated by the SMC for controlled public release in accordance with the terms of this Policy. Public Data shall not include any Individual Data.

"Public Researcher" means a bona fide scientific researcher with a legitimate research purpose for accessing and using the Public Data who has entered into a data access agreement with the Consortium in a form approved by the Consortium. For the avoidance of doubt, the for-profit or non-profit status of a researcher or the researcher's employer shall not be a factor in determining Public Researcher status.

"Research Program Activities" means discrete activities, and/or phases of research that are carried out under the Consortium's Research Program.

"QC Vendor" means a third party provider of genotyping quality control services selected by the Consortium to assess the quality of Genotypic Data generated by a Genotyping Vendor. A Genotyping Vendor may act as a QC Vendor with respect to Genotypic Data generated by a different Genotyping Vendor.

"Sample" means any biological material provided or made available for the Consortium's Research Program, including, without limitation, DNA, tissue samples and cell lines.

"SMC" shall mean the Scientific Management Committee of the Consortium as it is constituted from time to time.

"Sponsored Invention" means any invention created by third parties while performing work funded by the Consortium (such as rights in DNA markers and genotype/haplotype-phenotype associations, as well as the conclusions derived therefrom) and pertaining to the Consortium's Research Program and mission of the Consortium, but excluding Ancillary Inventions.

4. Data Generation, Access, Usage and Release. The following outlines the anticipated pathways for collecting, generating and analyzing data within and on behalf of the Consortium, as well as commitments of the Consortium, Members and others with respect to such data.

a. *Samples and Clinical Data*. The Consortium intends to fund the collection and aggregation of Samples and related Clinical Data from one or more Clinical Sources. Samples will be provided by the Clinical Source only to the Genotyping Vendors designated by the Consortium for use in accordance with paragraph 4.b below. Clinical Data will be provided by the Clinical Source only to the DACC for use in accordance with paragraph 4.c below.

b. *Genotyping Data.* The Genotyping Vendors will perform the genotypic analyses (including quality control) required by the Consortium on the Samples received from Clinical Sources. At the Consortium's request, Genotypic Data generated by a Genotyping Vendor may be submitted to one or more QC Vendors for quality control purposes. Such QC Vendor will receive only sufficient quantities of Sample and Genotypic Data to assess the quality of such Genotypic Data. The QC Vendor will report its results to the CEO and the co-chairs of the SMC, who may require additional genotyping work from the Genotyping Vendor based on such results, as well as additional quality control from the QC Vendor. The SMC will not have direct access to Genotypic Data. A particular Genotypic Data set will not be "approved" for usage unless and until the SMC issues a written or electronic approval thereof. Following approval of a Genotypic Data set, the Genotyping Vendor will provide the Genotypic Data set only to the DACC for use in accordance with paragraph 4.c below. Unused portions of the Samples will be returned to the supplying Clinical Source in a timely manner.

In some cases, Genotypic Data may be offered by a third party for the benefit of the Consortium's research. Such Genotypic Data will be subject to the same quality control procedures described above and released to the DACC only upon SMC approval as described above.

c. *Data Analysis*. The Data Analysis Committee, in cooperation with the DACC, will determine suitable strategies for analysis of the Clinical Data and Genotypic Data. The DACC will perform such analyses in accordance with such strategies and will report any Analytic Results to the Data Analysis Committee. The Data Analysis Committee will not have direct access to Clinical Data or Genotypic Data. The Data Analysis Committee, in consultation with the SMC, will evaluate the Analytic Results and may request additional analyses from the DACC. Data Analysis Committee and SMC members who have access to Analytic Results shall use such Analytic Results solely in connection with the Consortium's Research Program, and not for the individual benefit of any institution or company, whether or not a Member of the Consortium. Each such individual will be bound by confidentiality agreements associated with Consortium membership, and will be prohibited from sharing Analytic Results with any individual who is not a member of the SMC or Data Analysis Committee.

d. *Publication Preparation*. Following the receipt of the final Analytic Results, members of the Data Analysis Committee and SMC may prepare scientific papers based on such Analytic Results for publication in peer-reviewed scientific journals. Each such paper must be provided to the SMC prior to its first submission to a journal. The SMC shall have a period of 45 days in which to provide any comments and to determine whether all appropriate authors have been credited in such paper, and the author shall comply with the SMC's recommendation as to any additional authors. All such papers shall acknowledge the support of the Consortium.

e. *Treatment of Program Data.* Each recipient of Program Data (whether a member of the SMC or Data Analysis Committee, a Genotyping Vendor or the DACC) shall be responsible for complying with all applicable national, state and local laws, rules, regulations, enactments, directives, orders and standards and relevant institutional policies and requirements, and shall be required to maintain the strict confidentiality of any Individual Data. All persons and organizations having access to Program Data (other than Public Data) shall be required to take reasonable security measures to ensure that such Program Data is not compromised, improperly disclosed or misappropriated. Individual Data shall be protected to the greatest extent practicable. Program Data (including Individual Data) other than Public Data shall be used solely in support of the Consortium's Research Program.

f. *Public Data Release.* In order to promote the public welfare and to enable the broadest beneficial use of the results of the Consortium's Research Program, Public Data will be made available to the public at no charge in the manner described in this Policy. In order to limit the risks to privacy of the data subjects and to comply with any other limitations on the use of such data (e.g., limitations contained in consents obtained from data subjects), specific Program Data will not be classified as Public Data unless and until it has been so designated by the SMC. Public Data will be made available in the manner described in this Policy no later than twelve (12) months following approval of the corresponding Genotypic Data set in accordance with paragraph 4.c above.

g. *Restrictions on Public Data Access.* The DACC will make the Public Data available through a controlled-access database to all Public Researchers worldwide who have agreed (and whose institutions have agreed) to comply with certain restrictions determined by the SMC. Such restrictions will include the following: (i) not to share the Public Data with any person who is not employed by a Public Researcher, (ii) not to attempt to identify individual subjects represented by genotype or phenotype data, (iii) not to use the Public Data for other than legitimate pharmaceutical or biological research purposes, and (iv) such other reasonable restrictions consistent with this Policy as determined by the SMC. Public Researchers shall be required to agree to comply with the foregoing restrictions through a signed agreement or certification and/or a "click-wrap" document that must be accepted prior to accessing online

Public Data. Any Public Researcher using Public Data shall acknowledge the Consortium in any resulting oral or written presentation, disclosure or publication relying on such Public Data.

h. *No Preference for Members*. For the avoidance of doubt, except for the limited access granted to Member employees who serve on the SMC and Data Analysis Committee under paragraph 4.c above, Members shall have no preferential or early access to the Program Data, and shall only be permitted to access the Public Data on the same terms and conditions as all Public Researchers.

5. Intellectual Property. It is the goal of the Consortium to maximize the public benefit of research supported by the Consortium and, accordingly, to make freely available DNA markers for susceptibility to drug-induced severe adverse events and related data and analyses. Accordingly, the Consortium has adopted this Policy in order to establish rules and procedures regarding the treatment of intellectual property arising from the Research Program Activities conducted and/or funded by the Consortium.

a. *Existing Patents*. The Consortium may seek to identify patents that are essential to the conduct of the Consortium's Research Program or that pose a risk of blocking the effective use of the results of the Consortium's Research Program. The Consortium may request that the holders of such patents (whether or not Members of the Consortium) either contribute them to the public domain or, failing this, grant the Consortium a non-exclusive, royalty-free license to practice such patents without a right to sub-license. Any such request shall be made in a neutral manner without any explicit or implicit promise of positive or negative consequences from the grant or refusal to grant a license. In certain cases, when a royalty-free license is not available, the Consortium may seek (with the approval of its Board of Directors) a royalty-bearing license on the most favorable terms possible in order to enable the Consortium to carry out the Consortium's Research Program in the most effective manner possible. Any such royalties or other consideration to such a licensor shall be paid by the Consortium from its funds, and not by any Member. The Consortium will not knowingly infringe, nor instruct others to infringe the valid and enforceable claims of any issued patents. Notwithstanding the foregoing, the Consortium will not warrant to any Member or other third party that its activities do not infringe third party patents or other intellectual property rights.

b. *Consortium-Funded Inventions*. The Consortium shall own all intellectual property rights arising from Sponsored Inventions, provided that if the assignment of rights in such Sponsored Inventions is prohibited by applicable law, the inventors shall grant to the Consortium an exclusive, perpetual, irrevocable, royalty-free license with respect thereto. In no case shall any researcher performing work funded by the Consortium file or support any patent application covering any Sponsored Invention without the prior written consent of the Consortium. Ancillary Inventions shall be licensed to the Consortium on a non-exclusive, perpetual, irrevocable, royalty-free basis. The inventor may retain the right to conduct academic

or other non-commercial research using the results of work performed on behalf of the Consortium.

c. *Contribution of Intellectual Property to the Public Domain; Preventative Patent Filings.* The Consortium intends to release all Public Data as early as possible so as to place it in the public domain and reduce the likelihood that use of the Public Data will be encumbered by patents. In some cases, the Consortium may determine that the most effective way to ensure that Public Data is placed in the public domain with the earliest available priority date is to file a provisional patent application covering all novel discoveries made prior to the filing, and shall include one or more claims directed toward the Program Data (including genetic markers and genotype/haplotype-phenotype associations). Subsequent to this provisional application, the Consortium may file additional utility applications to further validate or expand on its initial utility. At the end of the Research Program Activities with respect to a given indication, patent counsel may file a final utility application, with the intention that such application either be abandoned following publication or converted to a statutory invention registration in the U.S. Researchers who develop intellectual property funded by the Consortium will be required to assist the Consortium in any such filings or other procedures deemed necessary by the Consortium to ensure the contribution of such intellectual property to the public.

d. *Inventions Based on Public Data*. Each person accessing or using Public Data, and his/her institution/organization, must agree not to file or support any patent application claiming any DNA marker(s), genotype/haplotype-phenotype association or other attribute disclosed as part of, or derived from, the Public Data or that would prevent or block access to, or use of, any element of the Public Data, or conclusions drawn directly from the Public Data.

e. *No Limitation of Downstream Protection*. Subject to the foregoing, the Consortium acknowledges that intellectual property protection may be appropriate for inventions and discoveries made by Members and/or Public Researchers, where such inventions and/or discoveries have been enabled by the Public Data and/or the Research Program Activities, but are not directly derived therefrom. Such "downstream" inventions may include novel assays, drug targets, therapeutics and diagnostics developed using DNA markers discovered through analysis of the Public Data, but whose utility is not solely derived from the associations or other information contained in, or generated directly from, the Public Data. The Consortium acknowledges that this Policy does not provide the Consortium with any ownership or control of such downstream intellectual property and, accordingly, Members are not prohibited hereunder from filing or supporting any patent application claiming such "downstream" inventions.

APPENDIX C

Current SEAC Scientific Committees Membership

As of 9/07

SAEC Sub-Committee

as of 8/28/07

Scientific Management Committee

- **Co-Chairs:**
  - Eric Lai [**GSK**] and Duncan McHale [**Pfizer**]
- **Members**
  - Brian Spear [**Abbott**]
  - Nadine Cohen & Adrian Thomas [**J&J**]
  - Joanne Meyer [**Novartis**]
  - Klaus Lindpaintner & Karen Wilcock [**Roche**]
  - David Chen [**Sanofi-Aventis**]
  - Ted Burczynski [**Wyeth**]
  - Wendy Sanhai **[FDA]**
- **Pending Members**
  - Martin Armstrong [**A-Z**]

At large scientific advisors:
- Lon Cardon [Fred Hutch]
- David Goldstein [Duke]

SAE Consortium, Ltd.

SAEC SMC Sub-Committee

as of 8/28/07

Data Analysis & Coordination

- Quingqin Serena Li [**J&J**] **, Chair**
- Matt Nelson [**GSK**]
- Stephen Dobson [**Pfizer**]
- Sally John [**Pfizer**]
- Steve Lewitzky [**Novartis**]
- Klaus Lindpaintner [**Roche**]
- David Chen **[Sanofi-Aventis]**
- Maha C. Karnoub [**Wyeth**]
- XXXX **[Abbott]**
- Robert O'Neill [**FDA**]
- Steve Wilson [**FDA**]

At large advisors:
- Andrea Califano [Columbia]
- Lon Cardon [Fred Hutch]
- David Goldstein [Duke]

Collaborators Representatives:
- Heather Cordell [NewCastle]
- Paul Mckeigue [Dublin]
- Paul Watkins [DILIN]

SAE Consortium, Ltd.

SMC Sub-Committee

as of 8/28/07

DILI

- Chairman [TBD]
- Holly Read **[Abbott]**
- Beena Koshy **[GSK]**
- Monica Franc **[J&J]**
- Karen Wilcock **[Roche]**
- Jonathan Solsky **[Roche]**
- Geoff Johnston **[Pfizer]**
- XXX **[Novartis]**
- XXX [Sanofi-Aventis]
- XXX **[Wyeth]**

Collaborator Representatives:

- Chris Day, MD [Manchester]
- Ann Daly, PhD [Manchester]
- Mariam M ,MD [LSPHTM]

At Large Representatives:

- John Senior [FDA]
- Paul Watkins, MD [UNC]

Pending Members:

- Marianne Keisu [A-Z]

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