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Critical path

The innovative use of a large-scale industry biomedical consortium to research the genetic basis of drug induced serious adverse events

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The International Serious Adverse Event Consortium (SAEC) is a pharmaceutical industry and FDA led international (501 c3 non-profit) consortium, focused on identifying and validating DNA-variants useful in predicting the risk of drug induced, rare 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 researching the molecular basis of drug response.

Drug-induced, rare SAEs present significant health issues for patients; and pose challenges for the safe use of approved drugs and the development of new drugs. 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, among others. The rarity of such drug induced SAEs and the absence of effective government surveillance/research networks, makes it extremely difficult for any one company or research entity to accrue enough SAE cases and controls to conduct effective whole genome studies. Central to the notion of the SAEC is industry, government and health care providers can join forces to make use of a variety of sample and data resources in researching the genetic basis of these events.

The purpose of the SAEC is threefold:

•To carry out research directed toward the discovery of DNA-variants 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 and web-based methods; and

•To educate the scientific research and medical communities about issues related to severe adverse drug

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reactions and about issues related to the Consortium's research.

The SAEC was launched in late September of 2007 with the scientific, technical and financial support of eight founding industrial research-funding members (i.e. Abbott, GSK, J & J, Novartis, Pfizer, Roche, Sanofi-Aventis and Wyeth). Additional members are being added as the consortium executes its phase one research program and develops its future plans.

The Consortium's will focus initially on two research projects. It will attempt to identify DNA variants associated with drug-induced liver-disease and serious skin rashes [e.g. 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 (owing to the availability of established case-control DNA sample collections) and build its core operations. Simultaneous with the Phase I research activities, 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. Our long term goal is to discover and validate genetic markers predictive of the major drug induced, rare SAEs and make these available at no cost at the same time, unencumbered by any intellectual property constraints, to all researchers and developers of clinical diagnostics.

The context – drug induced serious adverse events (SAEs)

The challenges associated with researching and clinical management of drug related, rare adverse events are significant. Although, by definition, these events are rare, they can present serious health issues to patients taking needed medications; and pose significant challenges for the companies that manufacture and market these valuable therapies. Lazarou *et al.* [1], reviewed several hospital-based studies in the United States and found over 100,000 deaths per year attributable to SAEs. These authors ranked SAEs as the fourth leading cause of death in the United Sates, ahead of diabetes. This is a remarkable course of events. ADRs and SAEs caused over 2 million hospitalizations in 1994 alone. One can only imagine how this number has grown over the past 13 years, given increased utilization of medicines in the United States and around the world during this period. In addition, such events are currently not predictable using regulatory approved diagnosis assays. SAEs happen in an idiosyncratic manner. The physician is forced into a trail and error process, hoping the drug therapy prescribed will not result in a SAE. Plainly stated, we are a long way from a world were the physician can preassess his/her patient for their individual risk of encountering a specific SAE, before writing a drug prescription.

SAEs are also a significant issue for employers and payors; and an important contributing element to healthcare cost inflation. Estimates (*in the United States*) of the annual cost of ADR/SAE-related mortality and morbidity vary from a $30 billion to $170 billion. In reality, we have neither the electronic tracking nor accounting systems to fully understand the magnitude of this phenomenon. Ernst and Grizzle used expert panels to estimate probabilities of emergency room visits and hospital admissions associated with ADRs/SAEs. They found 19% of emergency room visits and 28% of hospital admissions were owing to ADRs/SAEs. From these rates, they forecasted the 'US healthcare system cost' of ADRs/SAEs ranged from $90 to 180 billion per year [2]. One can reasonably conclude, despite the deficiencies of such studies, that the economic cost associated with ADRs/SAEs is both significant and growing rapidly. It is not unreasonable to conclude 5–8% of the gross (US) national healthcare product is expended treating patients with ADRs/SAEs.

The World Health Organization defines adverse drug reactions (ADRs) as, 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease [3].' In light of this definition, a SAE can be defined as a response to a drug which is severely debilitating or life threatening and requires the cessation of the drug. SAEs tend to be caused by multiple drugs and not linked to an individual drug. Finally, SAE's clinical complications typically present as in a highly differentiated manner (*versus normal response*) and are readily diagnosis by the well-trained clinical expert.

In light of the above definitions, examples of drug-induced, rare SAEs include hepatotoxicity, QT prolongation, rhabdomyolosis, serious skin rashes, severe diarrhea, hyperbilirubinema, edema, acute renal failure, acute hypersensitivity, anemias/neutropenias, excessive weigh gain, retinopathy, and vasculitis. Such SAEs have resulted in 24 major drugs having been withdrawn from the US market since 1990. These withdrawals averaged approximately 4 years after their introduction. It is noteworthy, that 26% of the new drugs introduced in the period, 1980–2006, now have some form of 'black box warning' [4].

Shifting gears, as seen, in Fig. 1 below, a 2006 Congressional Budget Office (CBO) study highlighted the tremendous growth of spending by ethical pharmaceutical companies to develop new medical entities (i.e. drugs), only to result in a

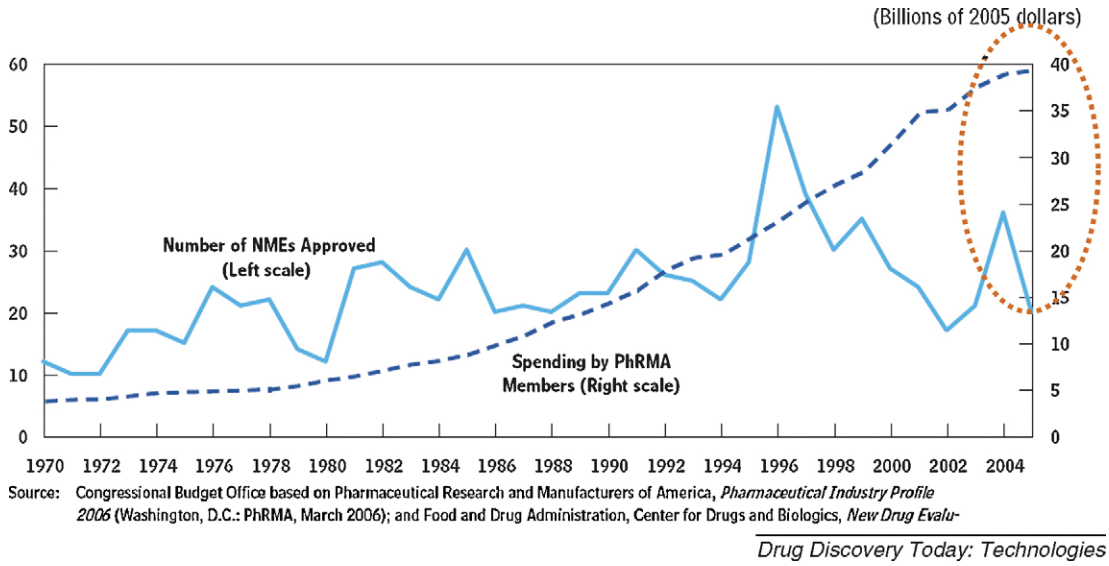

Figure 1. NME Approvals and R & D spend, 1970–2004.

flat to declining rate of newly approved drugs. In 1996, the pharmaceutical industry expended a whopping $40 billion in R & D, which resulted in only 14 new medical entities. Clearly, there are temporal factors at play, but the key point is per dollar spent both productivity and innovation of pharmaceutical new product development are on the decline. Figure 2 below, highlights the decline in pharmaceutical new product innovation. In the same CBO study, the percentage of line extensions of existing drugs versus truly new chemical entities was documented to be on the decline when one compares the decade of the 1980s versus the current decade. Notably, this is in sharp decline to other research intensive industries such as information systems, aeronautics, and electronics where such increases in R & D investment uniformly results in increases productivity and innovation.

This decline of pharmaceutical new product productivity has been the subject of extensive speculation. The central question being, 'What are the ''drivers'' contributing to this decline in pharmaceutical new drug productivity?' I would posit six relevant potential contributing factors. These include:

1. Organizational distractions (i.e. mergers) – The pharmaceutical industry has undergone significant consolidation during the 1985–2005 time frame. The often touted benefit of 'increased scale to take on a broader range of new product development programs' has

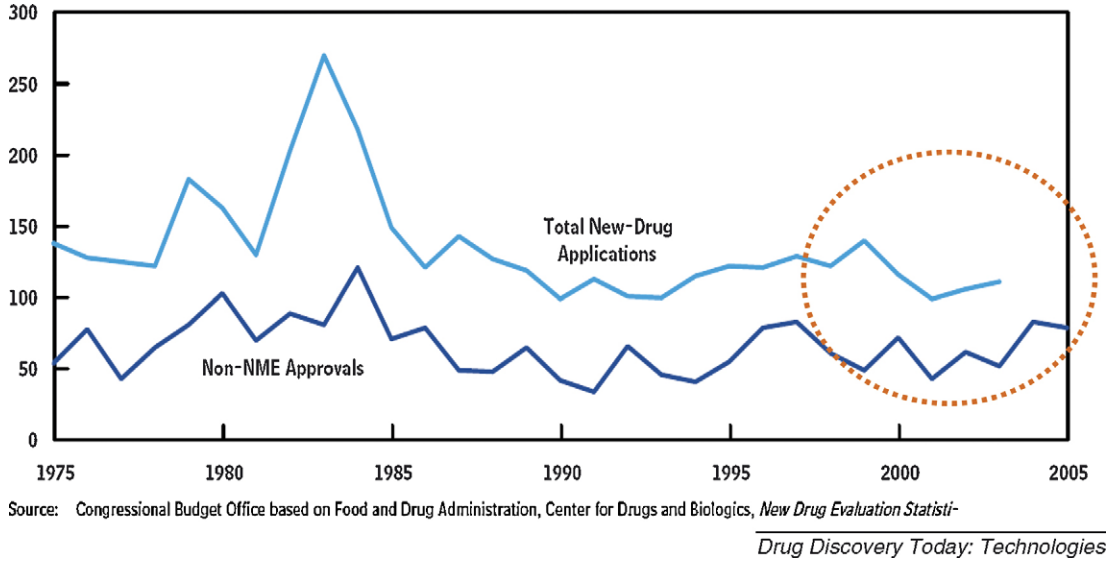

Figure 2. Declining innovation . . . more line extensions vs. NMEs, 1975–2005.

been over shadowed by an endless string of reorganization activities, resulting in a significant negative impact on organizational decision making and R & D productivity.

2. 'New drug' failures are happening too late in the development process' – As documented by Wood *et al.* [5] during the period 1994–1998, the success rates of new drugs in phase 1–3 clinical development studies are falling. In the most expensive phase of new drug development (phase 3), the success rate declined from over 90% in 1994 to less than 50% in 1998.
3. Regulatory pathways are slowing and increasing demanding – the FDA, EMEA, etc have increased their standards for drug safety resulting in larger, longer, and more expensive studies.
4. Integration of new, innovative 'pharmacogenetic methods' into the drug development process has been slower and more challenging than expected earlier in the decade. Many major pharmaceutical companies still lack the processes and core capabilities to practically apply both efficacy and safety pharmacogenetics. The variability is across the industry is striking.
5. Limited understanding of the biology of adverse drug reactions (liver, cardiac, metabolic, among others) – Few companies have the scale (cases and controls) to effectively research the biology of SAEs to enable proactive identification of subjects likely to experience the SAE. Without this ability, drug development programs are increasingly being canceled when an SAE rears its ugly head during a trial.
6. Inadequate surveillance systems to understand and manage long-term safe drug use – 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 translational research studies.

Central to the notion of the SAEC is the essential need for industry, government and health care providers to join forces and work together to make use of a variety of sample and data resources to effectively research the genetic basis many of the rare, drug induced SAEs. Through such a collaborative endeavor, factors 4–6 above can be progressed.

The International SAE Consortium – Introduction

The popularity of the 'consortium approach' to collaborative biomedical research has grown steady on the back of the SNP Consortium (TSC). The numbers of research consortia are proliferating at a rapid pace. The TSC, which ran from 1999 to 2002, was a novel collaboration between 13 major pharmaceutical companies, the world's largest medical research charity (the Wellcome Trust), and five leading academic research centers. It focused on creating the first high-density single nucleotide polymorphism (SNP) map of the human genome. The Consortium had as its original objective to identify and map 300,000 common SNPs evenly spaced across the genome. By the time it had completed its work, it identified 2.7 million SNPs or almost ten times its original target. It was also completed early and significantly below budget. This pioneering map has become be a powerful research tool enhancing our understanding of disease and facilitating the discovery and development of new effective medications. Importantly, the industrial biomedical research consortium model was successfully born!

The basic structure of the 'industrial biomedical research consortium' used for both the TSC and SAEC is highlighted in Fig. 3 below. This model has the following key characteristics:

- It is centered on a concrete research objective; which drives well-defined project[s] with clear objectives and end points. These projects are universality established to be in the 'public good' (i.e. for the benefit of all researchers).
- The funding and a significant amount of the intellectual capacity of the consortium come from industrial members. The 'funding requirements' are uniform and open to all interested parties.
- It strives to collaborate with the very best quality external advisors and investigators, minimizing the resources devoted to overhead and full time staff.
- It may collaborate with governmental bodies to the extent it is beneficial to fulfilling core objectives and/or executing agreed upon projects.
- It is supported by dedicated, highly experienced professional management. This enables a strong 'quality' and 'time to result' orientation.
- Finally, all appropriate project data are made 'public' in a timely manner.

The International SAEC is a joint pharmaceutical industry and FDA developed industrial biomedical research consortium, focused on identifying and validating DNA-variants useful in predicting the risk of drug induced, rare serious adverse events (SAEs). The SAEC was launched in late September 2007 with the scientific, technical and financial support of eight initial founding 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 are involved in all facets of the SAEC as 'Associate Members'. As noted above, the SAEC is collaborating with leading (academic and industrial) scientists to apply state-of-the-art whole-genome SNP mapping technology to discover and validate rare SAE related genetic markers. As part of its commitment to enable and facilitate research in this

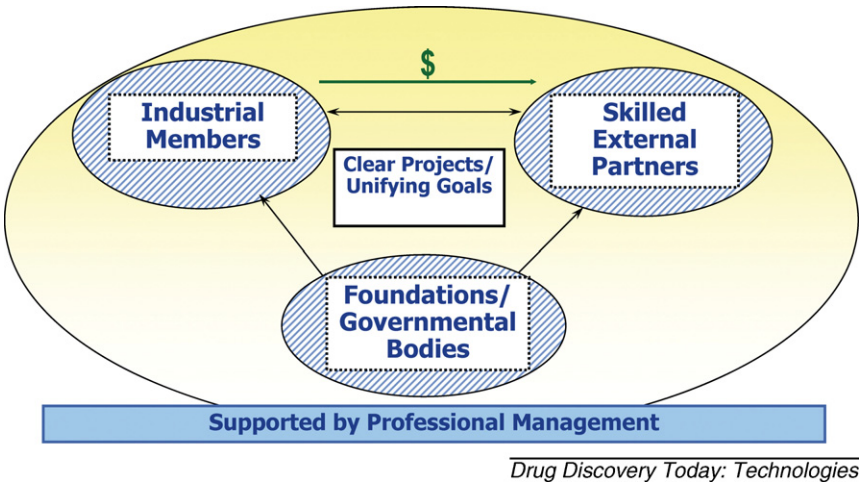

Figure 3. Industrial Biomedical Consortium 'Generic Model'.

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 own web-based 'SAE knowledge' site and other appropriate government (public) databases (e.g. PharmGKB or dbGAP).

The initial impetus for the SAEC arose from a series of interviews conducted in late 2005 and early 2006, with senior R & D leaders in major pharmaceutical companies. These interviews explored how to best leverage the success of previous industrial biomedical research consortium to identify additional areas to apply this effective approach. Out of 10 possible collaborative opportunities, the highest priority was assigned to exploring the genetic and molecular basis of drug induced, rare serious adverse events. The difficulty of any one organization achieving the necessary 'scale' and the financial resources required to successfully accomplish this research was the critical driver. In short, 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'. It is, as I like to say a 'team sport'.

Concurrent with the above mentioned market research, an FDA's Industrial Advisory Board in April 2006 recommended the formation an 'independent industrial consortium' 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'. From July of 2006 to the SAEC's launch in September of 2007, Janet Woodcock, MD (Deputy Commissioner and Chief Medical Officer) co-chaired the 'Organizing Committee' of the SAEC with Arthur Holden. In addition, the European Medicines Agency has been supportive of the SAEC, reflecting their number one 2006–2007 organizational priority of improving the safety of medicines used in humans [6].

Although the Consortium's scientific scope is broad in principle, it will focus in its first research phase, on two SAE 'genetic discovery' projects. It will work to identify DNA variants associated with drug-induced liver-disease (DILI) and Serious Skin Rashes (e.g Stevens–Johnson syndrome and toxic epidermal necrolysis]. These two projects, while critical in their own right, will allow the SAEC to generate initial results in a relatively short time frame (owing to the availability of adequate 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 innovative networks to identify and obtain greater numbers of SAE cases and controls.

The SAEC commenced its official formation activities in early September of 2006. Over the past year, efforts have 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, 21 agreements have been completed to give birth to the SAEC.

The organization and processes of the SAEC

The SAEC is a 501 c3 non-profit membership corporation (under the Internal Revenue Service Code) formed to enable 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'. By legal charter, its members can fall into one of two classes: (i) Organizations engaged principally in the business of discovering, researching, developing and marketing pharmaceutical products, or (ii) Charitable, governmental, or other non-profit organizations with an interest in the field of safety pharmacogenetics. The former are dues paying, voting members. The latter members are not obligated to pay dues, but provide other 'strategic assets' supportive of the SAEC programs. For example, the FDA is an associate member and provides invaluable inputs into both the direction and operations of the SAEC.

Anti-trust considerations are always present when a significant percentage of the world's major pharmaceutical companies come together around any endeavor. To protect its members from the risk of frivolous law suits associated with such intra-industry sponsored research, the SAEC is successfully registered with the United States Justice Department under the National Cooperative Production and Research Act. The U.S. Congress passed this legislation in 1996 to provide clear legal guidelines for large companies to collaborate on major industry wide research and development projects. Specifically, this act was designed to encourage companies to undertake joint research which is typically long-term, risky, and often too expensive for one company to finance. Very importantly, this legislation clarified the application of the anti-trust laws and required that the 'rule of reason' standard apply in determinations of violations of these laws. As a result, several hundred alliances, consortia, and joint ventures have been filed with the U.S. Justice Department since this law was enacted in 1996.

The SAEC is governed by a Board of Directors (BOD) which has management oversight of the property, activities and funds of the Corporation. The BOD consists of one director from each Sponsoring Member and the SAEC's Chief Executive Officer, ex officio. The Board structure also allows for 'non-voting' involvement of associate members. The SAEC BOD functions and makes its decisions using a 'majority rules' model. In addition, all SAEC research collaborations are formed via a rigorous 'RFP Process', with final selection determined by the Scientific Management Committee. The BOD approves all sponsored research and service agreements. All sponsored SAE 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. There are no 'research grants' in the NIH manner of speaking. The SAEC retains independent financial management and has the right to audited financial statements associated with all of its funding activities.

As highlighted in Fig. 4 below, the current organizational structure of the SAEC is relatively simple. The SAEC BOD has appointed three major Committees to advise it on research and policy matters. The committees are the Scientific Management Committee (SMC), Legal/Intellectual Property Committee and the Public Relations/Communications Advisory Committee.

The SMC is co-chaired by Eric Lai (GSK) and Duncan McHale (Pfizer). Its charter is to provide the members with sound research strategies and 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 facilitates, in close conjunction with its academic collaborators, publications arising from SAEC research activities, before 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, among others*). 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 University), Mark Daly (Broad Institute) and David Goldstein (Duke University) are currently three such

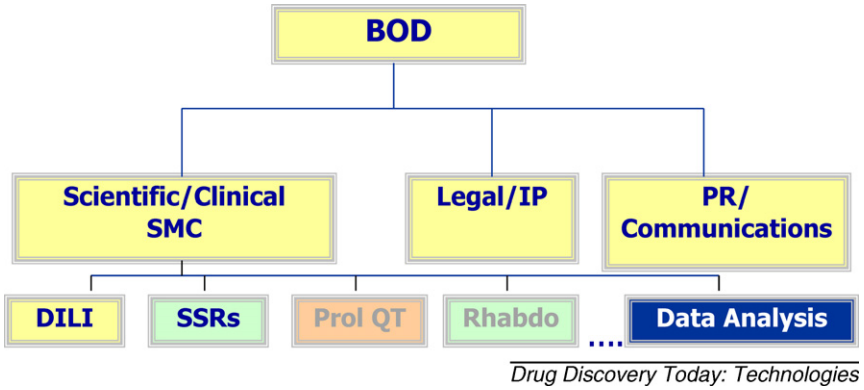

Figure 4. SAEC Organization and Committees.

world-class SMC advisors. Others will be added as the SAEC expands its research activities.

The SMC has several sub-committees to integrate additional expertise (from members and external collaborators) into the SAEC's research activities. Initially, three such committees have been established; the Data Analysis Committee (DAC), The Serious Skin Rash Committee (SSR) and the Drug Induced Liver Injury 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 DAC is fully functional under the leadership of Quingqin Serena Li (J & J) and Matt Nelson (GSK), in-conjunction with the SAEC Data Analysis and Coordinating Center (DACC) at Columbia University. The DILI Committee will provide the SMC with specific expertise on clinical, biological, and pharmacological aspects of drug induced liver injury. Currently, the committee has DILI experts from the member companies, the FDA, and external DILI research networks. The SSR Committee will provide the SMC with specific expertise on clinical, biological, and pharmacological aspects of serious skin rashes. Both of these 'clinical committees' will expand their membership as new collaborators are brought on and the research agenda on a specific SAE progresses. New clinical committees will be established as the SAEC research agenda expands into new SAEs. In essence, these sub-committees function as 'mini consortia' under the supportive umbrella of the SAEC SMC and BOD.

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.

SAEC scientific policies

As note above, the SAE Consortium is organized as a private 501 c 3 organization functioning in the 'public good'; thus, the law influences how it must execute its research/operational policies. In light of these legal 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 SAEC'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 12 months following the QC approval of the complete genotyping data set by the Data Analysis Coordinating Center at Columbia University. This provides 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 Data Analysis Coordinating Center 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 before 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 Data Analysis Coordinating Center, will determine suitable strategies for analysis of the Clinical Data and Genotypic Data. The Data Analysis Coordinating Center 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 Data Analysis Coordinating Center. 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 Data Analysis Coordinating Center) 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 before 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 before 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.

In addition, there are several 'values' which influence the SAEC's approach to collaborative research and expects adherence from its research collaborators. 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, collaborator and external expert involvement: The effectiveness and efficiency of the SAEC's program depend entirely on the volunteerism of its members and leading academics 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, among others 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.

SAEC scientific plan – September 2007 to December 2009

The SAEC 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 (*owing 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 Fig. 5 below, the SAEC will work over time in two research dimensions (i.e. within existing SAEs and expand to additional SAEs).

SJS/TEN phase I 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. SJS and TEN are related, rare, and severe mucocutaneous blistering disorders associated with over 200

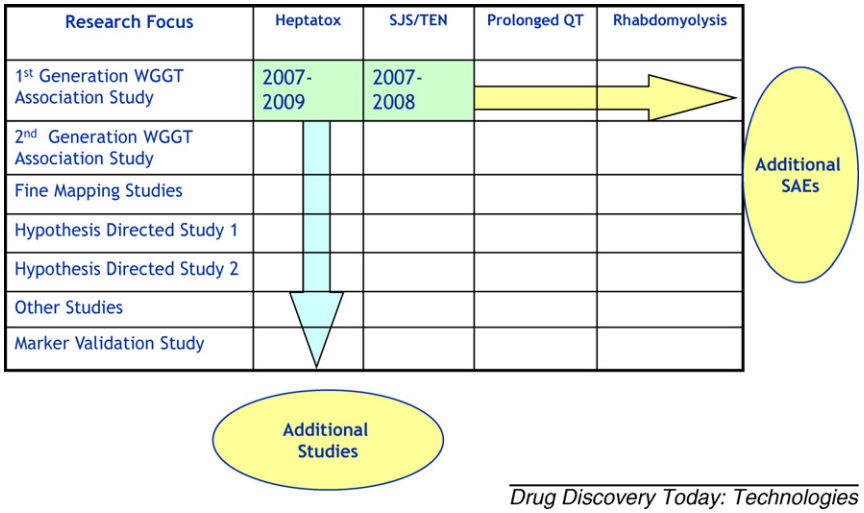

Figure 5. SAEC research pathways.

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 and prospectively. In addition, there are 140 controls matched for age, gender and ethnicity. The mean age of subjects is 41.2 years. Sixty-nine percent 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 judgment 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 1500 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 (7000) 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.

It is presently forecasted the SJS/TENS project will release initial data to the research community in late 2008 or early 2009.

DILI phase I 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 owing 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 before 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 [7].'

There are approximately 197 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 explore collaborative relationships (post formation) with the NIDDK/DILIN (US), Spanish DILI (Spain), and the Japanese Biobank (Japan).

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 owing to hemolysis),

or (b) an ALT >5× ULN (upper limit of normal) or (c) an ALP >2× 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 1500 population controls for this study will be matched as closely as possible on ethnicity, age and gender.

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 [8]:

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 such a project. 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, for example 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 was 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 we are usually measuring a surrogate linked to the causative variant by linkage disequilibrium. The SAEC SMC reached the following consensus relative to powering considerations in SAE whole genome association studies:

- 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.
- 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%.
- 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.
- The SAEC has sufficient samples to detect a clinically significant pharmacogenetic effect which is common across DILI reactions; but additional are always beneficial,
- 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.

Several fine pharmacogenetic 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 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.

It is presently forecasted the DILI project will release initial data to the research community in late 2009 or early 2010.

SAEC – future directions

Concurrent with the phase one research program, the SAEC will focus on several important activities in support of current and potential future SAE research initiatives. These can be summarized as follows:

1. Continued recruitment and sign up of additional funding members. Such members are essential to fund expansion of both of the SSR and DILI cohorts (*for refinement of scientific findings*), international SAE network expansion, follow on validation studies for DILI and SJS, an international initiative to develop standardized (clinical) definitions of the major drug induced serious adverse events, a publicly available 5000 subject representative population matched controls set especially designed for pharmacogenetic studies, and discovery association studies of additional drug induced SAEs.
2. Development of novel SAE research networks. This work will focus on the development of electronic medical record enrollment of SAE cases and matched controls in collaboration with large integrated health care delivery networks such as the VA, the Marshfield Clinic, or the Japanese Biobank. The SAEC will also work on the feasibility of developing a public, intra-industry (pharmaco) SAEC web-based registry, which could enroll SAE cases and matched controls from international pharmaceutical clinical and surveillance trials (*Phase 1 through Phase IV*).
3. Development of additional academic partnerships to support SAE research. For interested and qualified investigators, the SAEC can offer research funding (via sponsored research agreements) for network development and translational studies, the capabilities to quickly and effectively assemble international collaborative SAE networks, free access to a state-of-the-art genetic characterization and analysis pipeline, assess to leading industrial and academic collaborators, and a unique ability to execute a full range of SAE research options; from discovery to validation to translational SAEC 'outcomes studies'. This translates into an ability of willing investigators to better compete in the research arena via faster time to SAE research results, with larger cohorts, less hassle and more resources.

In summary, the International SAEC represents a needed and important development of the field of Genomics, Safety Pharmacogenetics and SAE Research. Giacomini *et al.* [9] in their 2007 Nature editorial summarized several the necessary attributes of an ideal collaborative SAE research entity, all of which and more are possessed by the SAEC. These include:

- Global orientation → ethnic diversity.
- Standardized phenotyping across ADRs.
- Strong research design skills.
- Excellent network development skills and the resources to produce adequately sized cohorts and optimal controls for genomic studies.
- DNA banking and genotyping capabilities.
- Strong data analysis capabilities, and.
- A public 'knowledge base' to support all researchers.

In addition, the SAEC will make all of its data and validated SAE predictive markers widely available to the public, free of any intellectual property constraints. It will also focus significant energy to integrate, on a global basis, industry, academia and regulators to accelerate Safety Pharmacogenetics. It is through enlightened collaborative efforts, such as the SAEC, that the progress towards 'personalized medicine' will be achieved.

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