Foresight Scanning: Future Directions of Clinical and Pharmaceutical Research.

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ABSTRACT

The Canadian Society for Pharmaceutical Sciences Satellite Symposium on Foresight Scanning, May 26 and 27, 2008, Nordegg, Alberta, Canada, focussed on the future directions of clinical and pharmaceutical research. The symposium brought together a group of clinicians, regulatory scientists, researchers and students to examine where clinical, pharmaceutical, and regulatory science might be in 10 to 15 years. Industry, regulatory, analytical, and clinical perspectives were presented and discussed, as well as the impact of exogenous (indirect) and endogenous (direct) change drivers. Unconditional funding was provided by Bayer HealthCare; they had no input on the direction of the meeting or selection of speakers. It was envisioned that the more important endogenous drivers may not be new information or changes in technology, policy, regulation, or health care delivery, but amplification of long-term underlying trends by emergence of new technologies, convergence of existing technologies or new communication and collaboration vehicles such as Web 2.0.

INTRODUCTION

Regulatory foresight is a systematic exploration of the future of science and technology (S&T) to allow for early detection of significant technological changes and to make appropriate regulatory adjustments. At present, the federal environment is favourable for this initiative. For example, the 2007 Speech from the Throne stated that the Government will support Canadian researchers and innovators in developing new ideas and bringing them to the marketplace through Canada's Science and Technology (S&T) Strategy. In 2007, the document "*Mobilizing Science and Technology to Canada's Advantage*" was published, setting out a comprehensive, multi-year science and technology agenda. In particular, the S&T Strategy refers to new biotechnology products and nanotechnology which will need to be supported by strong science and effective regulation in order to protect human health and the environment as well as to support Canadian competitiveness. Health Canada's Health Products and Food Branch (HPFB) has introduced a blueprint for renewal which supports the creation of both a regulatory foresight program and a progressive licensing model encompassing all stages in the life cycle of a drug product.

Why proceed with regulatory foresight? In recent years, science and technology have evolved and converged rapidly, resulting in new and complex products, treatments and diagnostics. Regulators need to be able to forecast trends in order to adapt quickly. Since the Canadian market is small, the need for appropriate and timely tools is necessary to preserve and increase Canadian competitiveness. Another important element to the government regulations is the need to address social, ethical, economic and legal issues raised by new science and technology.

Benefits and Barriers to Regulatory Foresight for the Regulator

The benefits of proceeding with foresight include developing strategic capacity and regulatory preparedness, thereby avoiding surprises and allowing for better decision making. It strengthens the knowledge base so existing staff can be trained or new staff can be hired in anticipation of submissions using new science and technology. Moreover, it provides time to address social, ethical, economic and legal issues raised. Enhanced regulatory foresight capacity will also reduce the possibility of overwhelming the regulatory system and consequently delaying commercialization of beneficial innovation.

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At the same time, there are some potential barriers to progress on this initiative. Because foresight is not an exact science, what is anticipated today may not materialize in the future. Furthermore, results are not immediate and are difficult to assess. It is also possible that changing priorities could affect time and resources dedicated to the initiative.

Work is progressing at Health Canada on the implementation of the S&T Strategy, and it has been noted that awareness and interest in foresight are growing. Despite limited funds, several Branches are working on implementing processes and tools to address foresight.

The panel was reminded that in order to move forward, it is occasionally useful to look at the drivers of the past.

Notable quotes:

-Trying to predict the future is like trying to drive down a country road at night with no lights while looking out the back window (Peter F Drucker).

-The future, according to some scientists, will be exactly like the past, only far more expensive (John Sladek).

-Prediction is very difficult, especially about the future (Niels Bohr).

-The future ain't what it used to be (Yogi Berra).

Greatest drug regulatory change in the past two decades was due to the then unprecedented pressure from persons with AIDS (Table 1). HIV infection is lifelong and if untreated is usually fatal within a decade. There are currently about 55,000 persons living in Canada with HIV and ongoing spread within broad range of communities is well documented and difficult to arrest.

In less than 20 years, the field has evolved from not having any therapeutic options to the current situation where there are 25 licensed drugs for therapy of HIV in 6 distinct different classes. Within each class there are now even generations of agents offering improved activity, toxicity and convenience profiles. These drugs, usually taken in a combination of 3 agents, provide potent regimens that suppress HIV replication, allowing for recovery of the immune system and improved health and longevity.

Do we need more drugs? The answer lies in the propensity of HIV to rapidly become resistant if the antiretroviral agents are not taken properly. Providing lifelong HIV management is a complex clinical challenge requiring experience as well as both clinical skills and scientific knowledge.

The field has continued to evolve rapidly with treatment paradigms changing as data from new studies become available. For example, drug holidays were considered a useful clinical tool until the SMART Study showed that untreated HIV is far worse for an individual than the side effects of the treatment. It also showed that HIV infection has many previously unrecognised deleterious effects on the body beyond the immune system.

Advances in HIV treatment mean that longevity in HIV-infected patients has increased by about 20 years compared to the pre-treatment era. However, there is ongoing legitimate concern regarding drug toxicities and the need for further simplifying treatment and clinical trail management. The future has many hurdles as the target has moved; current tests and paradigms do not always work. Host genetics will affect disease susceptibility and response to therapies together with social cultural factors that can affect adherence and perception of health will affect outcomes. HIV has been a driving force in public health policy. Community and opinion leaders are experienced and enjoyed changing the playing field, and may do so again.

PHARMACEUTICAL DRIVERS

The pharmaceutical industry (Pharma) is in flux. Current trends affecting Pharma include internal trends such as consolidation from multiple players to a few large players, a move to market-based R&D, shifting of focus from general to speciality drugs, decreasing innovation and shortening of product lifecycles. In addition, there are a number of external trends, summarized in Table 2, that are shaping the nature of drug development including globalization, an aging population, changes in the regulatory environment, government cost-containment efforts, increasing patient sophistication and rapid advances in information technology. These internal and external trends are accompanied by a significant increase in the cost of drug development ($0.8-1.5 billion to develop a new drug).

Many of these trends are interconnected with one trend driving the other. Thus, market-based research is at least partly responsible for a decrease in innovation which, in turn, has led to consolidation as companies without full R&D pipelines acquiring companies that do have a better pipeline. Similarly, the

high cost of drug development is also driving the trend towards consolidation as bigger companies can better afford the high cost of drug development and are also better able to withstand the aftermath of a candidate failing during the development process. The consolidation though, may also lead to a decrease in innovation as the total number of companies actively involved in R&D efforts is reduced.

Another important trend is the move from developing "block buster" drugs to a focus on speciality areas such as oncology. This trend is driven by the high cost of drug-development and the shortening of product lifecycles such that the first entry in the field is rapidly followed by multiple other drugs for the same indication. A new drug now costs more to develop but has to recoup its research and development costs over a shorter period of time. One way to recoup this investment is to focus development on indications where the drug can earn a high return for the investment. This has led to more drugs being developed for chronic indications with high net present value (NPV), where the present value of future cash inflows minus the cost including cost of investment is calculated using an appropriate discounting method, such osteoporosis, neurology and oncology while fewer drugs are being developed for short term, low NPV categories such as antimicrobials.

Thus, paradoxically, R&D spending has increased but the number of new drugs being developed has actually dropped. Innovation is now more likely to occur in the biotechnology arena and it is not surprising that many of the new drugs being developed are biologics. The decline in internal innovation at big pharmaceutical companies is also driving the trend towards building the pipelines by an increased focus on inlicensing new drug candidates.

Another important trend, as would be expected in the setting of shorter product lifecycles is the increased genericization of the pharmaceutical market (Table 2) with a concomitant greater generic focus. For example, generics are projected to contribute 50% of the current and future growth of the Pharma in Canada.

As mentioned above, the use of NPV as a selection criteria for drug development has also resulted in reduced research and development for drugs that treat acute diseases and a focus on drugs for chronic diseases because drugs for the treatment of chronic diseases generally have higher NPVs. Thus, drugs are now less likely to be developed for general medical indications such antibiotics for the short-treatment of respiratory infections as these have relatively lower NPVs compared to specialty drugs for therapeutic areas such as oncology that are associated with high NPVs. This will lead to the development of fewer blockbuster products but more "niche" products. The trend towards development of drugs for chronic conditions rather than acute conditions may well be exacerbated by the demographics changes that are underway in developed countries with a larger proportion of the population consisting of elderly individuals. The future elderly will be better educated and more knowledgeable about their diseases and will have higher expectations of their healthcare providers and healthcare services.

Historically, drug development has focused on molecules that are easy to formulate and generally have higher aqueous solubility. Many of the newer drug development candidates are hydrophobic and more difficult to formulate. Developing such drugs takes longer and is both more expensive as development of an acceptable formulation can take much longer.

Drug development has also been impacted by increasing concern about drug safety from both the public and the regulatory agencies. This has a significant impact on drug development as the development of many promising candidates is terminated during the early development period because of potential safety signals. For example, widely used drugs such as erythromycin, a drug known to prolong the QT interval to a significant extent is unlikely to be developed or approved in the current safety climate.

The overall outcome of these internal and external trends is that the pharmaceutical companies will increasingly be developing drugs for chronic indications and conducting longer term safety studies as well as more post-marketing observational studies to document product safety. Thus, more epidemiologists and biostatisticians with knowledge of chronic conditions will be required for the appropriate evaluation of these future drugs submissions and for the post-marketing safety surveillance.

Another important trend is the availability of increasing computing power and dramatic growth of information technology and web 2.0 based applications. Appropriate use of these resources has the potential to improve the efficiency of the drug development process by allowing computer aided drug design and innovative

trial designs that lead to significantly shorter development times.

The future will be marked by the convergence of many of the current emerging trends such as the aging population, technological improvements and advances in fields such as genomics and proteomics that have been made possible in part by the advances in computing technology.

The present will be markedly influenced by an ageing population (Table 2). This population will have higher expectations that the emerging trends (Table 3) will give them a better, healthier lifestyle. The emerging trends for the near future (Table 3) will mostly be the continuation of trends that are apparent now including the continuing consolidation of big Pharma, an ongoing drug development focus on chronic diseases, and innovation by way of inlicensing and acquisition. There will also be a move towards drug development in large developing countries such as India and China. The re-imbursement environment will remain difficult and the regulatory environment will continue to evolve with initiatives such as progressive licensing being implemented.

The long term future trends (Table 4) will also be marked by the convergence of many of the current trends. Convergence of advances in Pharma, biotechnology, diagnostics and computing will lead to the development of novel pharmaceuticals and will also increase the efficacy and safety of pharmaceuticals. The dramatic increases in raw computing power will also enable increasing use of innovative trial designs thus shortening the overall development time for new pharmaceuticals. There will be a return of innovation as new technologies allow the development of promising candidates that were considered poor development candidates because of characteristics such as low solubility.

Substitutability of Generic Drug Products: Current and Future Issues in Bioequivalence

The primary bioequivalence (BE) issue with generic substitution is: can two products be declared BE according to current standards show clinically important differences in either safety or efficacy? Is it safe to switch from one generic to another generic, or from a brand to a generic, or ultimately to prescribe generic instead of brand (interchangeability)?

As the number of marketed generic drug products continues to rise, there are increasing concerns about the substitutability of generic products (Table 5). Switching from one generic to another generic product, switching to generic from brand product, or prescribing generic instead of a brand product can lead to clinically important differences in either safety or efficacy, even though the products have been declared bioequivalent according to current regulatory standards for pharmacokinetic endpoints.

Products that are pharmaceutical equivalents have the same active ingredient, strength, dosage form, and route of administration but they are not necessarily bioequivalent. They may be bioequivalent yet have different drug release mechanisms. Pharmaceutical alternatives have the same therapeutic moiety, but may differ in chemical form of that active compound (i.e., counter-ion, ester, complex), dosage form, or strength (e.g., 10 mg tablet and capsule) and may be bioequivalent. Current pharmacokinetic BE standards set by Health Canada require the geometric test-to-reference (T/R) ratio for maximum drug concentration (C_{max}) or corresponding 90% confidence interval (CI) of the T/R ratio for C_{max} and area under-the-concentration-time curve (AUC) to be entirely within pre-defined equivalence limits (80 to 125%: 90% CI of AUC T/R ratio for non-critical dose drugs, 90% CI of C_{max} T/R ratio for critical dose drugs, C_{max} T/R ratio for non-critical dose drugs; 90 to 112%: 90% CI of AUC T/R ratio for critical dose drugs).

Pharmacokinetic (PK) BE based on comparative bioavailability (C_{max}, AUC) is the best measure for comparability of product performance. This, however, allows for (assumes) a variation of 20% between product performance as measured by drug concentrations that may not be clinically relevant in some patients and for some products. When such pharmacokinetic measures are not possible or relevant, more than one end point may be required for some products. This may include pharmacodynamic (PD) BE studies, for example, using comparative forced expiry volume in one second and exhaled nitrous oxide measurements for oral inhalers; and clinical BE studies, for example, using total nasal symptom scores or the Physician's Global Assessment Score as a measure of cure rates or clinical response. The US FDA recommends a placebo group in clinical-endpoint studies, which can be questionable when the placebo effect is very low. Currently few equivalence determinations have been successful with such approaches and the standards tend to decided case-by-case.

Concerns are being raised for BE studies conducted outside of North America where there may be strong cultural influences on dietary factors and less heterogeneity in population genetics that the findings may potentially be different from those obtained in a more diverse North America study. PK differences have been observed with diet and in different ethnic populations, but there are few studies to demonstrate their effect on BE and PD.

The prescribing of two widely used drugs, carbamazepine and bupropion, highlights examples of when patients complained of undesirable effects (worsening of side effects or loss of efficacy) when they were switched from the brand product to one of the generic products. Are the undesirable effects related to shape differences in the concentration-time profiles?

For carbamazepine, exposure-response analysis revealed that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. Partial AUC was a much better measure of the early neurological adverse effects observable during the drug absorption phase.

For bupropion, between January 1 and June 30, 2007, FDA received 85 post-marketing reports in which patients who switched from the brand product (Wellbutrin XL 300 mg, manufactured by Canada's Biovail Corp. and marketed by GlaxoSmithKline PLC) to a generic bupropion formulation (Budeprion XL 300, manufactured by Impax Laboratories Inc. and distributed by Teva Pharmaceutical Industries Ltd.) either experienced loss of antidepressant effect or had a new onset or worsening of side effects. Although the two products were deemed bioequivalent and interchangeable based solely on the acceptability of bupropion C_{max} and AUC parameters, there was a clear difference in the shape of the concentration-time profiles under fasting and fed conditions, with the time required to reach C_{max} about 3 hours faster for the generic product.

For these types of drugs in which acute toxicity is related to drug absorption rates, partial AUC can be a more sensitive indicator than C_{max}, and the use of partial AUC for evaluation of bioequivalence of a narrow therapeutic index or critical dose drugs should be considered to serve as an index of early drug exposure. Shape differences in pharmacokinetic concentration-time profiles of two bioequivalent products may explain clinically important differences in either safety or efficacy. For narrow therapeutic range products an almost exact shape may be required but there are questions on confidence intervals and what is the best matrix shape to be used. Although the FDA recommends the use of partial AUC as a relevant metric, no regulatory limits have been established. Narrowing the bioequivalence limits from 80-125% to 90-112% will not address shape differences in concentration-time profiles and potential clinically important differences in safety and efficacy that result from these shape differences. As well, the relevance of shape differences in concentration-time profiles when there are multiple C_{max} peaks in the profiles may need to be considered to support the BE of modified-release products that contain both an immediate-release and extended-release components.

NANOTECHNOLOGY

Public support revolving around safety and health issues for nanotechnology are key drivers. High costs of these products will pressure the need for regulatory approval. There is no official international definition of nanotechnology, but the general understanding is that it deals with substances from 1 nm to 100 nm (DNA strand 2 nm, buckyball 0.7 nm). Nanomedicine refers to highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues. To date most applications of nanotechnology in the drug field have been extensions of the micronization first applied to griseofulvin in the 1950s. That resulted in a doubling of exposure (relative bioavailability). In general, the regulatory requirements for this type of an established drug usually require adjustment of the dose-response information, some PK and bioavailability studies with at least one clinical trial to confirm efficacy, e.g., cyclosporine, Neoral, and fenofibrate. In general, this improves the bioavailability of sparingly soluble drugs from 20 to 50% and reduces within subject variability.

There are more than 600 consumer nano products globally, many are electronic, but new drugs and medical device (imaging) products are on the horizon. Market value of nanoproducts is estimated to be worth about $3 trillion by 2015. Current concern is that nano size of particles will change toxicology profiles and not enough resources are being spent on safety aspects. Little is known about engineered nanoparticles (NP, carbon nanotubes, and dendrimers). Many government and learned society reports note concerns, including Canadian and Health Canada. US

has a national nanotoxicology program with emphasis on occupational health. NP brain penetration is worrisome: depends on size, shape and solubility impact on biopersistance. Sun screens and cosmetics (anti-wrinkle) are among the first health products. Consumer Reports noted that of 19 sun screens tested (July 2007), 8 were found to contain NP of ZnO or TiO_2, but only one product was so labelled. Concern also remains about exposure with these products with wounded skin where there could be unintentional systemic exposure. Other transdermal skin products, such as estrogen and fentanyl are emerging using NP liposome technology.

Older NP includes carbon black, diesel fumes, metals and oxides (Ag, Fe, TiO_2, SiO_2 and $_{ZnO2}$) and there is considerable knowledge of results from exposure from those. There is much debate about NP sun screens, especially if skin abrasions or cuts are present? Little knowledge of exposure from newer engineered NP "nanotubes" carbon or metal, fullerenes, dendrimers and whether the carbon nanotubes would behave as asbestos. The basic safety concern is whether nanoscale elements behave differently than they do in their bulk form. Also, NPs are so small; they could easily cross the blood-brain barrier. If carbon, titanium oxide, asbestos and silver NP are used to coat everything from our clothing to our highways, there is a stringent need to ensure that they are non-toxic. Respiratory and some cardiovascular diseases have been common pathologies from occupational NP exposures. From occupational health studies, asbestos and silica NP have been well documented to cause cancer (lung, mesothelioma). Fibre lengths of >10-15 µm and diameter of < 3 µm are factors influencing toxicity. Size matters: In rat, 14 nm but not 95 nm carbon black caused alteration in brain inflammatory parameters after inhalation and similar findings have been reported for inflammatory responses from TiO_2. The major concern is that nanotubes and engineered NPs may share those characteristics and there is little information on their potential release during the lifecycle of the different applications. US, European and Canadian health officials and learned societies have agreed that there is a need for proper risk assessment of NPs.

More NPs from the simple to complex may be dangerous in occupational and environmental exposures and much research is needed to provide regulators with tools to assess risk. For drugs, the old models for exposure suffice for enhanced absorption as nanocrystals. For targeted delivery there are many more questions than answers. As new systems become more complex, with differences in bio-distribution and fate and increasing complexity of clinical use, a new regulatory environment may emerge. With imaging and targeting drug and medical device regulations may be bridged. How are NPs presented and transported within and between cells remains unknown. Studies of appropriate cell and molecular biology systems will be needed. *In vitro* models will be helpful, but require validation to relate to the clinical situation. *In vivo* animal models require proof of concept and validation. Organ exposure and "leakage" from delivery vehicles will be concerns of site specific delivery. Disease models will need to be developed. Canadian researchers must keep up with this expanding area of interdisciplinary effort.

Most NP drug products now marketed are to improve absorption of sparingly soluble lipophilic drugs. FDA approved products with Elan's nanocrystals are Rapamune®, sirolimus, Emend®, TriCor® fenofibrate, Megace®, and megesterol acetate. Original products were given with fatty meals to enhance absorption-not ideal conditions for the treated patients. New products increase absorption by 20-50% in the fasted state with less variability. Current drug review regulations could deal with safety of these products. However, there are more than 150 nano drugs on the horizon. The next group of drugs in oncology are for targeting tumours, decreasing general exposure Doxil® (doxorubicin) delivered in lipid nanoparticles with polyethylene glycol (PEG) coating and Abraxane™, paclitaxil, and albumin-bound form of paclitaxil. Others noted were campothecin, cisplatin as well as other doxorubicin products. A variety of nanodelivery vehicles including polymers of endogenous substance (lactates, aspartates), micelles and liposomes are being used. Risk benefit is easier with cancer treatments, so concerns about lack of tests are attenuated. Other uses of nanovehicles ahead are in gene therapy (replacing viral vectors), vaccines and in aminoglycoside delivery. This includes pulmonary delivery by airways. Such research frontiers including merging of devices and drugs (such as imaging agents) will require bridging of regulatory review. Challenges in this area are the reliability of cell and animal models for assessing risk and benefit of targeted delivery, "leakage' from delivery vehicles, disease models. Two main nanotechnology issues facing regulator and therefore industry are: i) identification of the data

requirements to evaluate long term safety; and ii) formulation quality, to establish consistency of batches as dissolution testing is not useful for these products. These will require proof of concept and validation. Canada alone cannot resolve regulatory issues and it is suggested that some type of International Conference on Harmonisation (ICH) process be encouraged. This allows regulatory management to participate in steering committees, leaving technical issues for qualified expertise to work on appropriate guidance's. One weakness of the ICH process is that only industry and regulatory scientists are involved. There is a need for outside academics and clinicians to participate. The panel suggests that there be an advisory committee on nanotechnology at the department level, with drug-device technical committees in TPD to ensure that the regulators have experts "on tap" to contribute to international discussions. HIV has been leader in activism and both community and opinion leaders are experienced and enjoy changing the playing field.

CONVERGENCE OF CONVENTIONAL AND ALTERNATIVE MEDICINE

Convergence has also lead to the joining of conventional and alternative medicine. Concurrent use of multiple products in Phase IV or off label use is much more widespread use than in phase III trials. Partly as a consequence of passive surveillance of adverse events (AE), "new" AE lawsuits combined with bad public relations has led to many unhappy consumers, health care providers, and regulators. Passive surveillance grossly underestimates AE and is marked by poor quantity and quality of reports, making assessment of causality extremely challenging. This is leading some to ask for novel therapeutic products or consideration of other approaches. The reasons are varied and ranges from huge time, money, human resources to get from molecule through to phase I, II, III trials), a changing regulatory environment to high product costs where some formularies cannot afford them. Others note that Phase III trials do not predict clinical effectiveness.

NHPs are the basis of 25 to 33% of modern day pharmaceuticals and are widely used in Canada and around the world, and continue to offer considerable potential for discovery as they may offer reduced costs since most can start with clinical evaluation (NHPs are available as over-the-counter products), reserving the need for basic science investigation for products that demonstrate efficacy or harm. With thousands of products, and hundreds of therapies available, each used for multiple reasons, randomized clinical trials (RCT) for every condition-intervention pair is simply not feasible, leading to the question of "Is there another way?". One alternative for evaluation of effectiveness is N-of-1 testing (Table 6) as they are less expensive to conduct through clinical service than RCTs, and offer results that are relevant to individual patients (rather than population based answers yielded by RCTs). N-of-1 trials with strict inclusion criteria having 3 to 5 pairs over a 6 month trial can offer opportunity to evaluate pharmaceutical or NHP therapies in a single individual, promoting evidence-based therapeutics for co-morbid conditions or concurrent therapies. The results are evaluated using an evaluation tool such as MYMPO2 to determine if the desired clinical efficacy was achieved. There is a need to partner with basic scientists to identify potential mechanism of action. Safety is paramount and absence of harm cannot be taken to mean confirmed safety. Physicians tend to look at the differential - was the desired affect achieved and are generally less likely to consider product-based adverse reactions? Population-based harms reporting are important. Meta-analysis of a series of N-of-1 trials may offer a population-based estimate that is more "real world" than phase III trials. Discussion also examined the placebo effect and whether it is effective medicine. Are we looking at safety in the correct way - does belief affect outcome and are those in clinical trials representative of others in the patient population?

Enhanced evaluation of safety of therapeutic products is required. In a pilot, we are assessing for NHP-drug interactions and other NHP related adverse events through active surveillance in community pharmacies with pharmacists trained to recognize product-related harms. The pharmacist is not asked to assess causality, only to identify patients who have experienced potential harm. Although pharmacists report more than any other health care provider, under-reporting remains a problem in the current passive surveillance system. Early findings show it is feasible to introduce active surveillance into a community pharmacy setting, allowing for rapid screening of patients who identify any unexpected/undesirable effects in preceding 3 months. This approach can (and should) be taken for pharmaceuticals, enhancing both the quantity and quality of reports (enhanced pharmacovigilance).

The last 10 years have shown remarkable progress in identifying specific mechanisms that are involved in NHP and food interactions with drugs. The human genome project led to the identification of the large families of genes and enzymes involved in drug metabolism or clearance, including a large number of cytochrome P450s (CYPs) and Phase 2 metabolism enzymes, ABC transporters (such as P-glycoprotein), and regulatory genes such as PXR and CAR. Furanocoumarins from grapefruit were identified as mechanism-based inhibitors (MBIs) of CYP 3A4; however these are not the only botanical MBIs and 3A4 is not the only isoforms that can be so affected. Other herbal and food products were found to inhibit 3A4 and many other CYPs, including CYP19 which is not generally considered a drug metabolizing isozyme. Other studies demonstrated the potentially fatal drug lowering effects (anti-retrovirals and anti-rejection drugs) of hyperforin from St John's wort through upregulation of CYPs via regulatory genes. Research on the NHP and food occurrence of these modulators of drug metabolism has been somewhat anecdotal. It is clear, however, from the study of plant herbivore co-evolutionary interactions, that these plant modulators are produced naturally by plants as a means of reactivating plant anti-herbivore defence compounds that can be metabolized by adapted herbivores, including humans. There is no systematic evaluation of why these inhibitors appear in plants. Information is anecdotal rather than systematic as there is no database listing which families of plants or natural products have these activities. Although the work on CYP inhibitors is advancing, there is little systematic information on p-glycoprotein inhibiting plants and natural products, CAR and PXR activators, Phase 2 enzyme inhibitors, and activators (Table 7).

Pervelleine A from *Erythroxylon pervillei* from Madagascar, which inhibits the P-glycoprotein efflux pump, is slated for rapid development. It is not a cytotoxic anti-cancer drug and has been shown to restore sensitivity to vinblastine in MDR cancers. From the top down side, we clearly need better reporting of adverse drug reactions, more pharmacokinetic studies in humans and animals models. Outcomes of this research would allow us to better predict potential interactions, even when new drugs are introduced. The pharmacoenhancement side may have important benefits in restoring efficacy to drug resistance to antibiotics or as drug sparing agents for very expensive drugs.

Future research needs to create predictive models of drug interactions to better predict potential herb-drug interactions, develop pharmacoenhancers, combating resistance to current drugs, and restore sensitivity to old drugs. Information systems on plant families, genera and species as well as specific biosynthetic classes of natural products with modulatory activity, using plant evolution as a guide to these models are required. Traditional and conventional medicine will converge further with the development of binary drugs.

ANALYTICAL

Increasing sophistication in analytical instrumentation and the development of more potent products is driving three major currents trends in analytical development: need to go faster, need for greater sensitivity, and why blanks are not blank. Typically constituent analysis must take less than 10 minutes of run time per sample otherwise it is not possible to analyze enough samples in a batch (assumes 18 samples per phase, 2-4 phases and at least 20 ancillary samples, QCs, calibrators and controls). Auto-samplers are not the limiting feature, chromatography is the bottleneck. In the past 5-10 years analysts and regulatory bodies were content with sensitivity of ng/mL of matrix but as new therapeutic products are more potent, doses are lower and bioavailability in plasma is lower. The new level of sensitivity is in the picogram per mL range.

Modern detection methods (i.e. mass spectrometry) have no problem in achieving this level of sensitivity. However, increased sensitivity is not without a cost. Part of the cost is interference. As the complexity of the problem goes up the need for more sensitivity and greater specificity also increases, so analysts often run into problems, especially in complex mixtures of multiple analytes.

Characterization for purposes of quality control or comparisons done for establishing bioequivalence is not trivial. Dot product analysis offers a convenient method of comparing data that has more than a single ordinate. In the case of chromatographic or mass spectral data both the x (time or m/z value) and y (absorbance or % ionization) coordinates are important to construct the single value dot product we can obtain a single value which can then be analyzed statistically.

Dot product analysis has most recently been used to compare the multitude of ions generated during the analysis of large molecular weight analytes such as peptides, proteins and polymers. Newer biogeneric

therapeutic entities arising from biotechnology also present complex analytical problems. Heterogeneity in the branded product may be essential for pharmacological efficacy. Again the bioanalytical solution is not straight forward and will likely require specific sample handling (SEC, specific endo- and exo-peptidases followed by sophisticated monitoring schemes. Bioanalysis continues to get more difficult as the newer techniques rely on sensitivity and specificity. Post acquisition analysis can help clarify interference but it must be viewed cautiously. Instrumentation is easier to use but does require fundamental understanding of how data are being treated.

BIOSTASTICAL ISSUES

Bioinformatics is rapidly expanding, putting pressure on industry and regulatory statisticians for new tools and innovative means to evaluate data (Table 8). This will require new means for addressing the statistical problems that includes estimating uncertainty and abundance, building models for replication and cross-laboratory calibration, data mining to match signals with status (e.g. disease) and compartmentalized models that will describe the pathway flow.

As we understand more about disease and treatment there seems to be a trend towards "personalized medicine". This immediately implies smaller sample sizes in clinical trials such as we see with paediatric or rare disease studies or at least more reliance on subgroup analyses which cannot be powered for the usual $p \leq 0.05$. How can we deviate from this "gold standard" of 0.05 and still ensure results are meaningful. This problem must be solved in order to use the scant resources of both the industry and the regulator wisely.

An interesting development in biostatistics has been the recent interest in adaptive designs in which we use the accumulating data to direct modifications to certain aspects of the study without undermining the validity and integrity of the trial. These designs are in marked contrast to the usual fixed design approach where you assign subjects to doses and do not deviate until the study is completed. Although adaptation is a design feature it is not a remedy for poor planning and the changes to the protocol must be *pre-planned* and not *ad hoc.*

Along with adaptive designs comes the acceptance of a "new" philosophy of statistical inference with the use of Bayesian statistics as apposed to the usual frequentist approach. Combining *a priori* information with the new information as it becomes available to modify inference distributions will be challenging not only for the regulator, but also for industry who must decide to invest in these types of designs.

As products enter into lifecycle management under a new regulatory framework for health products, as we have learned from AIDS community, feedback from research community on new technologies will make the regulatory framework more responsive to tomorrow's needs. This interaction is particularly crucial as more post-approval and observational studies will be required to fully address efficacy and safety issues.

SUMMARY

Speakers and panel members at this foresight, horizon or environmental scanning symposium focused on the future for clinical and pharmaceutical research in the next 10-15 years. It is evident that there are many challenges facing both government regulators and industry as advances in manufacturing and information technologies are moving forward. In summary, the key points from the presentations and ensuing discussions can be summarized in three areas:

<u>1. Pharmacokinetic and pharmacodynamic concerns</u>

- Bioequivalence (BE) issues affecting interchangeability, switchability, nanotechnology, different release mechanisms, or relating to regional/geographic studies (i.e. is a BE study in a Chinese, Indian, or US Hispanic population applicable to the diverse Canadian population).
- Partial AUCs or other shape analysis for modified release formulations.
- Pharmacogenomics (and other "omics")
- Analytical issues as new products are more potent requiring greater sensitivity (pg/mL plasma range) and change in dosing mechanisms (may not be possible to determine plasma levels), interference, data analysis, selectivity.
- Adaptive design, small trial analysis, Bayesian statistics, multi-variant (principal component) analysis
- Proof of concept decision making;

2. Safety and efficacy

- Has the safety bar been raised too high to where excessive bureaucracy and development costs stifle innovation, or results in removal of product from market (e.g. QT prolongation: once found in a product, industry will be quick to abandon the drug)?
- Lack of interest on antibiotics with increasing resistance.
- Resistance/interactions, over use of products, changing and emerging sub-types, adherence and changing perspective of health, population-based harms reporting.
- Paediatric, geriatric and use during pregnancy and lactation, or off label use; and

3. Resources and prioritization

- N-of-1 studies (problems of randomized controlled clinical trials)
- Logistics (e.g. common drug review) - need to harmonize
- Need for more biostatisticians and epidemiologists; inter-disciplinary review efforts (more highly skilled reviewers with PhDs rather than MScs)
- Convergence - challenge to existing regulations when two or more scientific areas come together (drug-device-diagnostic in a single product; NHP-drug combinations or pharmacoenhancement, alternative to conventional medicine)
- Importance of regulatory - science research interface: what is new and does the regulator know how to assess information?
- Need for international co-operation on device and medicine guidelines, similar but enhanced ICH (management steering and technical with scientists and clinicians on guidance's).

The main drivers that may impact the future are: the pipeline of new therapeutic products is dry and generics will be the major products with longer market timelines, and both industry and government are moving from science-based to market-based decision making.

In parallel, there will be a convergence of technologies and therapeutic products. New, more complex, products are likely that will challenge regulators, industry, and health care professionals in their safe and effective use. Combination products will include products that are drugs and devices, but also ones which are drugs-devices and diagnostics. Products will include conventional drugs but others will be formulated with natural health products. At the same time, risk tolerance for product development and safety will continue to change. Risk ratios are now much lower but presumed absence of harm does not confirm safety requiring a safer development approach that does not lead to a loss of a new drug or possibly even a class of compounds may leave others at risk if there are no suitable replacement products. A critical question raised during the discussion was "Are we looking at safety in the correct way"? Broader means for safety evaluation along with new clinical protocols are required to assess old and new convergence products. In addition, the evaluation framework needs to consider social and cultural factors that affect adherence and perception of health together with the realization that there are ethno-cultural and population differences.

There is an urgent need for more highly trained individuals with expertise in therapeutic product issues, pharmacokinetics and pharmacogenetics at a time when universities are producing fewer biostatisticians and pharmacologists. Everyone has fewer resources and it will be difficult to meet the growing expectations of a demanding population who want earlier access to safe and effective products with little government interference. The future may very well be determined by blog-based medicine and demand for new technological products that precludes any prediction of the future: emerging trends will spike and then disappear. This creates the quandary where faith in internet promotions and technology may reign over reason.

The presenters at this symposium were: Rachel Dansereau, Departmental Biotechnology Office, Health Canada, Ottawa, Ontario, Canada; Dr. Keith Gallicano, Biopharmaceutics, Watson Pharmaceuticals Inc., Corona, California, USA; Dr. Sunita Vohra, CARE Program, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; Dr. John Gill, Foothills Hospital, Calgary, Alberta, Canada; Dr. Shurjeel Choudri, Bayer Healthcare, Medical and Scientific Affairs, Toronto, Ontario, Canada; Dr. Iain McGilveray, McGilveray Pharmacon Inc., Ottawa, Ontario, Canada; Eric Ormsby, Office of Science, Health Canada, Ottawa, Ontario, Canada; Dr. J. Thor Arnason, University of Ottawa, Ottawa, Ontario, Canada; and Dr. Gordon McKay, University of Saskatchewan, Canada. Discussants were Rui Lui, Carolina Ogrodowczyk, and Teresa Tam from the University of Ottawa.

Table 1. Past, present and future issues affecting the HIV/AIDS community affecting pharmaceutical development.

Time Frame	Issue
Past	- 1985 HIV identified as cause of AIDS - 1987 Azidothymidine (AZT) licensed in USA on the basis of 17 fewer deaths in AZT arm over 24 week study - Fast track approval given in US to AIDS drugs due to clinical urgency - 1989 Ganciclovir was licensed despite absence of controlled data because drug was in widespread compassionate and successful use making clinical trial unethical - 1990 Decline in CD4 count accepted as surrogate marker of disease progression - Suppression of HIV viral load accepted as a marker of drug efficacy
Present	- Less pharmaceutical company interest in HIV drug development (congested marketplace) - When to start therapy? Never stop when therapy started (SMART Study)! - Access to patients increasingly problematic for research as trial patients are increasingly being cared for by primary care physicians with an interest in HIV - Provincial funding based on Common Drug Review (CDR) - Overwhelming and increasing logistical issues for all research trials due to current approval mechanisms and structure of ethics, contracts and review processes

Future	- Changing target new viral subtypes
	- Host genetics - HLA B 5701, CCR5 deletion, effect of genetics on drug metabolism
	- Recognition of importance of social cultural factors, e.g., adherence, perception of health
	- HIV Cohort collaborations: Abacavir experience
	- As all current drugs work if prescribed and taken properly, new agents will try for market based on toxicity, tolerability and resistance profiles. Superiority trials may be impossible in short-term studies
	- Strategy trials have a future, e.g., when to start?
	- Bureaucratic strangling
	  - innovation ethics contracts
	  - marketplace (common drug review)

Table 2. Current internal and external pharmaceutical drivers affecting the industry.

Current trends external to the industry	- Globalization ("flat earth")
	- Aging population
	- Changes in regulatory environment
	  - Increasingly stringent safety requirements
	  - Regulatory agency co-operation, collaboration
	  - Risk assessment shifting toward risk management
	- Cost-containment
	  - Challenging reimbursement environment
	- Patient sophistication
	  - Increased safety consciousness
	  - Litigation
	- Dramatic increase in connectivity, computational power
	  - Internet, Web 2.0

Reasons for decreasing output of new products	- Low productivity
	- Changes in approach to and by management
	  - Conformism
	  - Managers, not leaders
	  - Pressure from shareholders
	  - Merger and blockbuster mania
	  - Shift from R&D to marketing

Expectations of an ageing population	- Increased demand for lifestyle medications, e.g., obesity, baldness, erectile dysfunction, etc.
	- Increased incidences in chronic diseases
	  - diabetes, osteoarthritis, respiratory, heart, kidney
	- The "capacity to treat" increasing, especially for the frail elderly
	  - magnifies potential demand of an aging population
	- Future aged will be better educated and have higher income levels
	  - will have higher expectations of health and health care services and be much more demanding than their current counterparts.

Table 3. Emerging trends affecting pharmaceutical companies and product development.

Trends	

Emerging	- Point of care diagnostics
	  - portable or handheld devices, based on microarray and Lab-on-Chip technologies
	  - capable of carrying out multiple tests
	- Evolution of imaging technology
	  - novel imaging agents that can precisely identify diseased cells
	  - therapeutic interventions based on imaging
	- Nanotechnology
	- Continuing improvements in computing power and connectivity
	  - E-health initiatives
	  - advances in information technology
	- Advances in genetics, genomics, pharmacogenetics, gene therapy

Future and expectations	- 5-10 year horizon, continuation of existing industry trends including:
	  - Further industry consolidation
	  - Ongoing focus on chronic diseases
	  - Innovation by acquisition
	  - Increased marketing of generic products
	  - Increased investments in India and China
	  - Impact of external factors
	  - Increasing patient sophistication
	  - Evolving regulatory environment
	  - Progressive licensing
	  - Continuing challenges for reimbursement
	
	- 15 year horizon
	  - Convergence of multiple trends will lead to a dramatically different playing field

Table 4. Outcomes of convergence of nanotechnology, biotechnology, sensors, computing, materials, telecommunications, robotics, and intelligence that will lead to enhanced diagnostic accuracy, efficacy and safety of pharmaceuticals.

Outcome	
Drug discovery	- Return of innovation as new technology allows development of compounds that were previously considered poor development candidates - Identification of NMEs with predictable efficacy and safety profiles with early identification of potential adverse effects - Use of aggregated genetic information to design/develop new therapies for population subsets
Drug development and marketing	- Testing to determine likelihood of individual response to a particular therapy - Widespread use of adaptive trial designs - Shorter development times - Reduced development costs - Emergence of "true" personalized medicine will allow dynamic dose adjustment based on continuous diagnostic testing, telemetry - First therapeutic stem cell products - Regenerative medicine - Training of more skilled PhD. researchers and evaluators

Table 5. Generic pharmaceutical issues.

- Bioequivalence and therapeutic equivalence: can two BE products show clinically important differences in either safety or efficacy?
- Switchability of generics: is it safe to switch (interchangeability)?
- PK metrics and safety and efficacy concerns
- Borderline bioequivalence
- Different shapes of concentration-time profiles
- Different T_{max} values
- Multiple C_{max} peaks

Table 6. Benefits and criteria of N-of-1 testing in clinical trial design.

- Randomized multiple crossover trial in a single patient
- Balances patient needs with methodological rigour
- Inclusion criteria
    - Condition must be chronic and stable
    - Treatment must have quick onset and offset (cannot cure condition)
    - Patient/Caregiver eager to take part
- Limit therapies to those with demonstrated effectiveness in given individual
- Compatible with pharmacogenomics movement and goal of individualized therapy
- Decrease AE by decreasing number of products
- Decrease costs by decreasing number of products
- Happy consumers, health care providers, 3rd party payers, and so forth

Table 7. Experimental studies required to support natural health products studies.

- *In vitro*: critical lack of information on induction of CYPs which may be most clinically relevant
- *In vivo*: critical lack of animal trials and very few human studies-more needed on priority basis
- Pgp, Phase 2 inhibitors; need for full rational survey
- CYP inhibitors: rational screening of products, species families and classes of natural products - To date, over 300 plant products screened > 40 pure natural products, but this information is not systematic
- Examination of evolution of CYP inhibitors in plant families

Table 8. Biostatistical issues that will need to be considered for the review of future therapeutic product submissions.

- Adaptive design
- Small trial analysis
- Bayesian statistics
- Partial AUC or other shape analysis for modified release formulations
- multivariate (principal component) analysis
- Bioequivalent issues for nanotechnology products
- Prevention claims for diabetes products