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REGULATORY ISSUES ASSOCIATED WITH THE DEVELOPMENT AND LICENSING OF SARS VACCINES AND IMMMUNOTHERAPY PRODUCTS

Report from a Workshop, Health Canada, 18-19 August 2003, Ottawa, Ontario, Canada

Introduction

As part of its on-going measures to support the fight against Severe Acute Respiratory Syndrome (SARS), Health Canada hosted an international workshop on August 18 - 19th, 2003, which addressed specific scientific and regulatory issues associated with the development and licensing of vaccines and immunotherapy products against the disease. The workshop brought together regulatory scientists from the WHO, USA, Europe and Canada, representatives of the Canadian SARS Research Consortium, manufacturers of vaccines and immmunotherapy products, experts in veterinary coronavirus infections and vaccines, and SARS experts from Canada, Hong Kong and the Netherlands.

The aim of the workshop was to facilitate the necessary regulatory process by identifying critical issues early on in product development and establishing a scientific basis for making regulatory decisions concerning the clinical testing and licensing of SARS vaccines and immunotherapy products.

According to a report from the WHO, the last human chain of transmission of SARS had been broken by July 5, 2003, less than 4 months from the time when the infection had been recognized as a global threat. However, it was considered that SARS remained a global public health threat and, not surprisingly, efforts to accelerate the development of effective diagnostic, therapeutic and prophylactic measures against the disease had been initiated in several countries. Dr Bhagirath Singh from the Canadian Institute of Health Research reported on the establishment of the Canadian SARS Research Consortium (CSRC). The mandate of the Consortium is to coordinate and support SARS research across Canada by funding research projects and establishing national and international linkages that would facilitate and accelerate the development of appropriate diagnostics, therapeutics, vaccines and other prophylactic measures against the disease. The Consortium management group includes individuals from academia, industry, interest groups and government.

A number of gaps in knowledge, as well as critical areas needing further investigation, were highlighted at the Workshop and these can be addressed as product development continues in Canada and other countries, so as to ensure that vital regulatory issues are adequately dealt with in a timely way and not delay development, clinical testing and licensing. Possibilities for collaborative work between laboratories were also identified.

SARS - the Disease

Dr. Susan Poutanen from the University of Toronto gave an overview of the SARS outbreak. She indicated that the case fatality rate of the disease in Canada was around 17% and that this figure varied by country. Dr. Poutanen presented data on the clinical features and short-term outcomes of 144 patients in the greater Toronto area. Those with fatal outcomes were associated with increased age, co-morbidity, high LDH, low lymphocyte count and high neutrophil count. Although diagnostic tests had been developed, issues such as sensitivity, timing of sample collection and type of specimen remained to be established. These are currently being evaluated by the Ontario Laboratory Working Group for the Rapid Diagnosis of Emerging Infections headed by Dr S. Richardson. Transmission of the causative viral agent is mediated by contact with contaminated droplets/aerosol and possibly by the fecal-oral route. The clinical progression of the disease correlated with the viral load in the nasopharyngeal aspirate and stools, as assessed by the reverse transcriptase polymerase chain reaction (RT-PCR) assay for the SARS-CoV virus, which is considered to be responsible for the infection. Only 5% of patients had positive SARS-CoV by RT-PCR in the blood. Post-mortem studies showed death was not only associated with an overwhelming immune response, but also with viral replication. The SARS-CoV virus was found to be present in large numbers in the lungs and gastrointestinal tract of patients who died as late as 51 days post symptom onset. An important observation was that these patients had negative sputum and blood samples in the presence of high viral load in the lower lungs. A number of questions needed to be addressed and these included: the extent and type of tissue damage, the protective role of humoral and cellular immunity and the receptor and tissue tropism of the SARS-CoV.

Dr. Jagdish Butany from the Toronto General Hospital presented the initial results from 15 autopsies of SARS patients. Due to the uncertainty of the disease at the time, only selected tissues were chosen for analysis by electron and light microscopy, and by microbiology. These preliminary results showed lungs with congestion, oedema and consolidation, the presence of diffuse alveolar damage, intra-alveolar/interstitial mononuclear cells, focal haemorrhages and thrombi, but no viral cytopathic effects. There was heavy fibrin deposition in the lungs which explains why breathing was nearly impossible for these patients. There were also fatty changes and cholestasis in the liver but again no viral inclusions were seen. Viremia was low and inconsistent, but viral load in the lungs correlated with pathology. Interestingly, no sign of pathology was observed in the gastrointestinal tract, even though high viral loads were found in this location.

The Causative Agent of SARS

Much evidence had accumulated to show that the coronavirus SARS-CoV is the primary cause of SARS in humans. Dr. Yan Li from Health Canada, National Microbiology Laboratory

(NML), Winnipeg, presented the Laboratory's experiences during the Canadian SARS outbreak. The investigation of the outbreak had began in March 2003 when the SARS-CoV was isolated from four patients using Vero cells, and in April 2003 scientists from the NML and the British Columbia Genomics Centre jointly published the sequences of the virus in *Science.* Human metapneumonia virus was identified in five patients using RT-PCR and sequencing.

Phylogenetic analysis suggested that the SARS-CoV is distantly related to group 2 coronaviruses. The nucleoprotein (N) appeared to be a major viral protein recognized by convalescent SARS patient sera, and showed strong binding in Western blot assays. The N protein had been used to develop an ELISA test based on recombinant N protein, which was comparable with whole virus lysate-based ELISA in terms of sensitivity. Of the 34 patients tested by ELISA, 94% were positive for both IgA and IgG, while 61% of patients were positive for IgM. It was unclear why the N protein, which is not exposed on the viral surface, was a major immunogen. Immune responses to the S protein were also detected, but at much lower levels.

Dr. Antonio Giulivi (Health Canada) gave the presentation of Dr. Mike Coulthart (NML) who was unable to be present. Analysis of the full genome sequence of SARS-CoV from different isolates was being used to establish the molecular evolution of SARS-CoV. Although normally most mutations do not translate into changes in protein sequence, a surprising number of potential structural changes had been noted between SARS-CoV isolates, suggesting that the virus had undergone microevolutionary changes during its recent association with the human host. This may have significance for development and updating of vaccines. Two clades had been identified and this information may be useful in tracing outbreaks. In addition, such studies will help establish the rates and patterns of molecular evolution of the virus. The information also had important implications in the design of effective vaccines against SARS.

The Immune Response in SARS

Dr. Susan Richardson, Toronto Hospital for Sick Children presented preliminary data on diagnostic serological assays, including ELISA, indirect immuno-fluorescence assay, neutralization assay, and immunoblot for the S (spike protein) and N (nucleocaspid protein) of SARS-CoV. In a retrospective review of diagnostic serology on 364 patients from the two Toronto SARS outbreaks, approximately 500 serum specimens were taken at various stages of infection (median 3 per person, range 2-14). Results indicated that 100% of sera from 24 patients tested to date were positive for IgG antibodies and 52% for IgM antibodies.

Studies in China had also demonstrated that virtually 100 % of SARS patients developed IgG and IgM antibodies to the nucleocapsid antigen by the third week post-infection. An indirect

immuno-fluorescence assay appeared to be highly sensitive and specific. Although most diagnostic serologic assays are still being optimized and evaluated, the results from these preliminary studies had led to the establishment of some important laboratory criteria to support the diagnosis of SARS infection.

Dr. David Kelvin from the Toronto General Research Institute presented preliminary data on cytokine profiles in serum and FACS analysis of peripheral blood mononuclear cells (PBMCs) isolated from SARS patients. In addition, PBMCs from these patients were being used for gene expression profiling of 19,000 genes using a cDNA ImmuneArray. Ongoing studies included: single-nucleotide polymorphism (SNP) analysis and MHC analysis. Studies using PBMCs from more than 50 convalecent SARS patients may help elucidate potential T-cell epitopes in the N and S proteins of the SARS-CoV.

The working immunological model of SARS indicates an early interferon response, early elevated levels of the chemokine IP-10 and infiltration of activated Th1 cells expressing CXCR3 into infected tissues (lung). Where the disease resolved, the levels of IP-10 rose initially but then fell again. In contrast, severely ill patients maintained a high level of IP-10, possibly leading to a destructive T cell/monocyte infiltration.

Lessons from other Coronaviruses and other Viral Pathogens

Dr. Lorne Babiuk from the Vaccine and Infectious Diseases Organization, Saskatoon, gave an overview of coronaviruses, highlighting the fact that SARS-CoV appeared to belong to an antigenic group which differed from all other coronaviruses. Coronaviruses are species and tissue specific and their replication method allows for high frequency of recombination. The environmental persistence of many coronaviruses is mediated by the presence of asymptomatic carriers, alternate hosts and susceptible individuals. Whether SARS-CoV is capable of persisting in asymptomatic carriers remained to be established. In livestock animals, young animals are the most susceptible to coronavirus infections and many of the successful vaccination strategies involved immunization of the mother to stimulate the induction of virus-specific antibodies in colostrum. In this way, passive immunity was used to control coronavirus infections in cattle and pigs. These observations indicated that antibodies alone can protect against disease in young animals but Dr. Babiuk cautioned on the extrapolation of these models to the infection cause by the SARS-CoV in humans.

Dr. Peter Rottier from the University of Utrecht, the Netherlands, reviewed current information on veterinary coronavirus vaccines. Both live and inactivated vaccines had been developed and were now commercially available. However, their efficacy was quite variable. For example, a live attenuated vaccine against the infectious bronchitis virus, a coronavirus that infects poultry, is highly effective (>90%), whereas vaccines against canine and porcine coronavirus provided only partial protection. It emerged that an important consideration concerning the development

of a human SARS vaccine was the potential for some coronavirus vaccines to enhance disease. Different vaccine against Feline Infectious Peritonitis Virus (FIPV) had been shown to exacerbate the infection caused by the FIPV. This appeared to be mediated by antibodies directed to the S (spike) protein of the FIPV which enhance the infection of macrophages. Therefore, new experimental approaches to vaccination against FIPV were being investigated and these were based on strategies that induced strong cellular immunity (e.g. live attenuated vaccines).

Dr. Philip Minor, from the National Institute of Biological Standards and Control in the UK, continued the debate concerning possible vaccine associated exacerbation of disease by discussing the experience with the use of killed paramyxoviurs vaccines in humans (parainfluenza, measles and respiratory syncitial virus). The early killed measles vaccine induced protection for two to three years, but subsequently vaccine recipients became highly susceptible to developing atypical measles upon infection with measles virus. Some patients presenting with atypical measles had been immunized with the killed vaccine more than 12 years before onset of the atypical disease which was characterized by pneumonia, high fever, atypical rash and high fatality rate. Death was attributed to secondary infections and malnutrition. It was found that in a rhesus monkey model, atypical measles was associated with an exaggerated Th2 response, much more than the response observed during a normal measles infection. Killed measles vaccines were quickly withdrawn from use and replaced by live attenuated vaccines. A similar situation has been found with candidate respiratory syncitial virus (RSV) vaccines. Vaccination of children with a killed candidate RSV vaccine was shown to be associated with enhancement of disease caused by RSV, and little progress had been made to date in developing a vaccine for this infection.

Together, these data from the veterinary field and from past experience with killed paramyxovirus vaccines raised a note of caution about the safety of inactivated vaccines against the SARS-CoV and their possible potential for enhancing disease in some recipients.

Animal Models

Dr. Albert Osterhaus (Erasmus University, Rotterdam) discussed the results of the etiological studies of SARS using a Cynomolgus monkey model. Four monkeys were inoculated with the SARS-CoV. Two monkeys were euthanised, on days 5 and 8 respectively, and subjected to gross and histopathological examination. Pathological changes in the lungs were clearly observed and virus was detected by immunohistochemistry and electron microscopy. During the first week of infection, SARS-CoV was isolated from nose swabs, throat swabs and faeces. The virus was detected in post-mortem tissues. Furthermore, specific immune responses similar to those observed in humans against the viruses (SARS-CoV) were detected. These findings fulfilled Koch's postulates indicating that SARS-CoV is the etiological agent of SARS. To assess the potential role of human metapneumovirus (hMPV) in the development of SARS, SARS-CoV

infected monkeys were subsequently inoculated with hMPV. Although hMPV replicated in these animals there was no exacerbation of the SARS-CoV infection. In summary, the monkey appeared to be a good model for SARS-CoV infection and could be useful for future studies including vaccine development and immunotherapy.

Dr. Antonio Guilivi presented very preliminary data from the laboratory of Dr. Anton Andonov, (NML). The objective of the study presented was to assess whether pigs, chickens and mice were susceptible to infection with SARS-CoV. Infection of pigs and chickens did not induce clinical disease or gross pathology. Although there was some evidence of limited viral replication and induction of neutralizing antibodies, there was no virus shedding. These results suggested that both pigs and chickens can not be used as models for SARS-CoV infection. Preliminary experiments in mice indicated that the virus was present in liver, kidney, lung and spleen 3 days after administration by the oral route. However, the potential of using mice for a model of SARS-CoV infection remained to be established. The possibility of using the ferret as a model was raised in discussion. It was pointed out that the ferret had been used very successfully in studies of influenza virus infection.

Immunotherapy

Given the fact that a vaccine is very unlikely to be available for the winter of 2003 - 2004, passive transfer of antibodies is likely to be considered for therapy and prophylaxis should SARS recur. The use of convalescent plasma is thought to be the first step, possibly followed by the use of purified antibody preparations and such approaches are being actively developed in Hong Kong and in Canada. Dr. Che Kit Lin from the Hong Kong Red Cross presented data on the treatment of SARS with convalescent plasma. Over 200 SARS infected patients have been treated with convalescent plasma in hospitals in Hong Kong. In one study, patients who had failed to respond to ribavarin and steroids were subsequently treated with either steroid or one infusion of convalescent plasma from a single donor. 73% of the 19 patients treated with the plasma were discharged by day 22, compared to 19% of 21 patients treated with steroids. Further, 23.8% of the patients treated with steroids died compared to 0% of those treated with convalescent plasma. Younger patients responded faster and early administration of convalescent plasma resulted in a better response.

Generally, antibody titre in infected individuals, including neutralizing antibody, increased over a period time but eventually dropped. It would therefore be important to monitor antibody levels in recovering patients to ensure adequate levels at the time of plasma collection. Recovering patients should also be monitored to ensure they are negative for the SARS-CoV by RC-PCR at the time of plasma collection. The possibility of enhancing safety by solvent detergent treatment of plasma was raised, as was the possibility of using monoclonal antibodies to circumvent safety issues related to residual contamination of the product by SARS-CoV.

Clinical issues discussed included conditions for use of convalescent plasma (e.g. urgent medical need), intravenous versus intra-muscular formulations for hyper-immune globulin, prophylactic versus therapeutic use, and donor management.

Dr. Wendy Johnson presented Cangene's experience with the general issues related to the manufacture of hyperimmune globulins for various indications, some of which are in clinical trials or have already been approved for marketing. The major steps involved in the manufacturing of hyperimmune immunoglobulin included:

- donor screening;
- donor stimulation with appropriate antigens and monitoring of antibody levels;
- plasma collection by plasmapheresis;
- nucleic acid amplification testing of plasma pools for HIV-1, HBV, HCV, HAV and parvovirus B19;
- purification of hyper-immune globulin by chromatographic methods
- viral inactivation and/or removal by solvent detergent treatment and nanofiltration.

Existing technology at Cangene could be used for contract manufacturing of SARS hyper-immune globulin at the 500 L or 1000 L scale: other manufacturing scales could be validated. SARS derived from humans could be manufactured from either convalescent individuals or vaccine - stimulated donors. The preferred approach of Cangene would be to co-develop a SARS hyper-immune globulin with SARS vaccines by using plasma from immunized clinical trial patients. Hyper-immune globulin could also be produced in appropriate animals, such as the horse, but the products would need to be despeciated and concerns regarding prions in certain animals, like sheep, had to be considered. Safety concerns relating to the transfer of SARS-CoV antibodies with possible disease enhancing properties would also need to be considered if antigens such as inactivated SARS-CoV had been used to stimulate hyper-immune globulin production. Appropriate animal models (e.g. monkey) were therefore urgently needed for pre-clinical studies.

SARS Vaccine Devlopment

Dr. Rachel Roper from the SARS Accelerated Vaccine Initiative (SAVI) introduced the SAVI programme. She indicated that SAVI was funded initially by the Government of British Columbia but was now an international consortium working to fast-track the development of a SARS vaccine. The SAVI funded scientists were working on several vaccine strategies: 1) inactivated SARS virus vaccine; 2) recombinant proteins; 3) live recombinant – adenovirus for spike and nucleoprotein. The SARS-CoV coronavirus had already been adapted to grow in Vero cells. To support vaccine development efforts, SAVI also funded projects in other areas such as SARS genome and proteins, and bioinformatics (www.sarsresearch.ca). SAVI has a website

(www.savi-info.ca) which provides a variety of databases/information ranging from basic science to clinical investigations. The goals of SAVI are to support research, facilitate collaboration and co-operation, and establish a paradigm for rapid vaccine response in emerging infectious diseases.

Dr. Judith Atkins from Aventis Pasteur presented the challenges faced by industry in developing and licensing a SARS vaccine. She outlined the steps involved in the development of a vaccine and the important issues which must be addressed as the product advanced through the development process. For SARS vaccines in particular, animal models would be expected to play a pivotal role as indicators of efficacy and safety of candidate preparations. A good understanding of the mechanisms of pathogenesis will also be required in order that the animal data could be extrapolated to humans. Phase IV studies will be very important once a vaccine is developed and marketed. A major regulatory challenge will be the need for a facility at biocontainment level 3 for producing live SARS-CoV prior to inactivation. Such manufacturing facilities were thought to be rare, but one is available in Canada.

Regulatory Issues

Detailed information on SARS, such as its pathogenesis, immunopathology, the nature of protective immune responses, or possible enhancement of disease by vaccines or immuotherapy products is not yet available or is incomplete. The identification of critical regulatory issues was therefore vital to ensure that work could be undertaken to address these issues as early on during product development as possible, so as not to delay clinical testing and licensing. The Consultation considered that regulatory research focussed on the standardization of methods and the development of animal models should play an important role in expediting the licensing of both vaccines and immunotherapies for SARS. A validated animal model to assess safety of a candidate SARS vaccine would be needed in light of the potential immunopotentiation induced by coronavirus vaccination, as shown with inactivated Feline Infectious Peritonitis vaccine. Another major regulatory challenge was the difficulty of undertaking clinical trials of candidate SARS vaccines if SARS did not reappear or if it remained very focal in nature.

European Perspective

Dr. Roland Dobbelaer from the Science Institute of Public Health, Brussels, presented the vaccine regulatory framework of the European Union (EU). European regulatory authorities would play a role at different levels during the development of a SARS vaccine, in its licensing and also in post marketing surveillance. The EU Commission had invested EUR 9 million into research for SARS prevention and acknowledged the importance of addressing this and similar Public Health threats. EU regulatory activities for vaccines are carried out through interactions between National Authorities within the EU and the European Agency for the Evaluation of Medicines (EMEA). More information can be found under: http://pharmacos.eudra.org, http://www.emea.eu.int, and http://www.pheur.org. Committee for Proprietary Medicinal

Products (CPMP) guidance on preclinical and clinical evaluation of new vaccines, as well as that of the European Pharmacopoeia and, where appropriate, CPMP/ICH guidelines for quality assessment would apply to the development of SARS vaccine. However, more specific guidelines for SARS vaccines may be available in the future from the CPMP Vaccine Expert Group. The CPMP Vaccine Expert Group is a multidisciplinary group with expertise in the assessment of quality, safety and efficacy of vaccines and can be supplemented with *ad hoc* experts, when necessary. The role of this Group is to address product specific regulatory issues, develop guidance documents and communicate with external parties. The Official Medicines Control Laboratories (OMCL) are responsible for the batch (lot) release of vaccine in the EU. It is the responsibility of the OMCL to develop the technical competence to test vaccines for release.

The regulatory framework for the development, licensing and the surveillance of safety and efficacy of a potential SARS vaccine is available in the EU. In addition, this regulatory framework has the flexibility to function in emergency situations when needed, such as a pandemic of a human disease. Legal provisions are in place that allow European Union regulations for marketing authorization to be modified temporarily to enable very rapid review and release of much needed products. Under such circumstances, post marketing surveillance of a SARS vaccine for safety and efficacy would be very important. Within Europe, the European Network for Surveillance of Communicable Diseases, the European Centre for Disease Prevention, National authorities, EMEA and OMCL (lot release) would all play a role. To enable these measures to work well, continuous dialogue between vaccine producers and authorities was essential.

Perspective of USA

Dr. William Egan from the Food and Drug Administration (FDA), USA, presented the FDA regulatory approach to licensing a SARS vaccine. The FDA is committed to fostering the efficient and rapid development of a SARS vaccine and to providing ample opportunity for sponsors and regulatory authority to meet during the different stages of development (pre-IND, end of Phase 2 and at the pre- license application stage). Dr. Egan highlighted the safety considerations of different types of vaccines and the regulatory issues regarding vaccine production in general. Of particular importance to the SARS vaccine are the challenge and protection studies in an appropriate animal model. These are important because they should provide a rationale for use in humans and may also provide insights as to whether a candidate vaccine elicited an immune response which could lead to exacerbation of subsequent disease caused by the wild-type virus. The FDA Animal Efficacy Rule applies to new drug and biological products when evidence is needed to demonstrate effectiveness in cases where human efficacy studies are not ethical or practical. This rule is used for products that are intended to treat or prevent life-threatening or serious conditions and it will not apply to products where surrogate markers or clinical endpoints, other than survival or irreversible morbidity, already exist. This rule does not address overall safety of the product. The information obtained by the animal model should be transferable to the human situation (similar challenge, susceptibility and protective antibody levels). During the IND stage, chemistry and manufacturing aspects of the

product are developed including: manufacturing process, assays, lot-release criteria, stability studies and validation of process and assays. The Office of Vaccines Research and Review provides Sponsors with guidance on manufacturing concerns (e.g. recommendations on cell substrates etc.), animal studies (non-clinical safety and efficacy evaluation), development of assays and clinical trial design. Dr. Egan invited Sponsors to consult FDA and to use the documents and resources available. More information can be found under www.fda.gov/cber/.

Canadian Viewpoint

Dr. Harold Rode (Health Canada) discussed the Canadian Regulations and Policies that apply to the licensing of new biologics. These require that sponsors present scientific evidence to prove the acceptable safety and efficacy of a new product. It is, however, recognized that before sufficient scientific evidence is available, development may be based on empirical grounds. Different regulations and policies apply to the various stages of product development. Although there are no regulations and policies applicable to the research at the early developmental stage, it is advisable that good documentation be established in the event that this information may be included as part of a submission. Furthermore, early stage development includes the establishing of manufacturing processes, animal models and pre-clinical testing to support the production of a product of acceptable quality for human use. To conduct clinical trials in Canada, a Clinical Trial Application is required for which regulations and guidelines are in place. In Canada a marketing authorization (New Drug Submission) application for a biologic, such as a vaccine, involves submission of clinical and quality information on the product itself, an Establishment Licence Application and also product specific on- site evaluation of the production facility , the production process and quality control procedures. Pre-licensing laboratory evaluation of lots by Health Canada scientists also occurs. Under normal conditions, manufacturing and clinical development must be completed prior to submission. Submissions for greatly needed products containing all the required information can be given Priority Review status. However, under special and/or emergency situations, where incomplete data are available but where the benefits would far outweigh the risks, requirements can be temporarily adjusted or postponed to accommodate such special needs through an expedited review process. Good Practices (GMP, GCP, GLP) must be followed throughout product development. Health Canada encourages manufacturers to discuss problems and specific issues during pre-submission meetings to facilitate the regulatory process. Health Canada also recognizes the importance of international harmonization, coordination and collaboration.

Peter Neumann (Health Canada) discussed regulatory issues regarding the licensing of immune therapy products in Canada, including an assessment of product safety, efficacy and quality.

From a Canadian perspective, key safety measures regarding the plasma used for manufacturing include:

- plasma sourced from countries of appropriate TSE status;

- donor screening to exclude individuals at high risk for certain infectious diseases;
- donor testing for HIV, HBV and HCV using test kits approved by Health Canada
- quarantine of plasma units for 60 days before pooling to enable withdrawal due to post-collection information which indicates a donor is at high risk of transmitting infectious diseases;
- nucleic acid amplification testing of plasma pools for HIV and HCV, etc.

Manufacturing considerations include:

- the acceptability of USP and EP for methods and product specifications where available;
- pool size (i.e., lower limit set to reduce pool to pool variation and upper limit to reduce infectious disease risks);
- viral inactivation/removal (e.g., heat treatment, pH, solvent detergent treatment, nanofiltration) based on viral validation studies using relevant/model viruses;
- product characterization with respect to potency (i.e., neutralization assays or surrogate tests, and correlation of IgG subclass distribution with efficacy in clinical studies);
- use of appropriate standards for product characterization
- use of approved or approvable albumin as excipient.

Dr. Peter Ganz (Health Canada) led the discussion which highlighted some of the key factors that needed to be considered in the development and licensing of immunotherapy products in Canada. Issues relating to the plasma source include antibody titre, and the absence of coronavirus is convalescent plasma. Decisions needed to be made regarding the appropriate tests for SARS, taking into consideration the strains detected and limitations of the various tests. It was also important to assess the effects of viral inactivation processes on antibody potency, and to determine product efficacy and dosage in appropriate animal models. Other issues included consideration of the differences between convalescent plasma and purified hyper-immune globulin as well as consideration of the appropriate recipient groups (eg, prophylaxis in health care workers versus treatment).

Dr. Denise Denicourt (Health Canada) presented specific regulatory issues regarding licensing of viral vaccines. Emphasis was given to the importance of the selection, characterization and establishment of seed banks for virus strains and cell substrates used in vaccine production. In order to facilitate the rapid development, clinical evaluation and possibly licensing of vaccines, it was strongly advised that, where possible, well tried and already established procedures and biotechnologies should be used for production. New and untried biotechnologies, such as the use

of a novel cell lines for producing virus, might be expected to raise considerable regulatory issues and possibly delay vaccine licensing. Assay standardization and issues regarding production of vaccine in biocontainment level 3 were also discussed. WHO had recently developed guidelines for the production of an inactivated polio vaccine under biosafety level 3 conditions, a situation that will come into effect once global eradication of wild polio virus has been confirmed, and these guidelines may be helpful to potential developers of SARS vaccines.

Dr. Agnes Klein (Health Canada) discussed clinical trails and highlighted issues regarding clinical endpoints. Canadian regulations for clinical trials involving human subjects are found in Division 5 of the Food and Drug Regulations. These requirements are stringent and there is continuous safety review during clinical study which could be suspended or cancelled for safety reasons. Guidelines on Good Clinical Practices should be followed, including ethical requirements defined in the regulations. There is also an inspection/audit program in place and the submission of a Clinical Trial Application is required irrespective of the sponsor.

Once a successful pivotal clinical study has been carried out and a vaccine licensed and correlates of protection identified and agreed, then the licensing of subsequent entry vaccines of the same kind is generally based on surrogate markers, such as antibody titre. Considerable information regarding disease pathogenesis, protective immunity induced by the original vaccine, and safety profile would already be known. However, due to the lack of scientific information on SARS, detailed regulatory answers regarding the applicability of specific end points to the SARS vaccines are not yet possible.

Concluding Remarks and Recommendations

A number of regulatory issues relating to vaccines and immunotherapy products were discussed in considerable detail during the general discussion led by Dr G Schild (UK) .

- In order to facilitate the rapid development, clinical evaluation and possible licensing of new diagnostic, therapeutic or prophylactic products for SARS it was strongly advised that, where possible, well tried and already established procedures and biotechnologies should be used for production.

- Production of the SARS-CoV virus for the manufacture of, for example, inactivated vaccine will need to be carried out under biocontainment level 3 and this may pose a significant hurdle.

- The standardization of biological assays, especially commonly used assays, such as those for measuring immune responses to candidate vaccines in different trials, will be essential in order to compare data from different clinical studies and different locations. The meeting recommended this be given a high priority.

- The availability of validated animal models for SARS was considered to be of paramount importance in the development of vaccines and immunotherapy products against SARS. They will be essential in investigating the mechanisms of pathogenicity, immune responses and disease, as well as the evaluation both of the potential efficacy and safety of candidate products. Before human clinical trials of inactivated SARS-CoV vaccines are undertaken, research into animal models will be needed in order to provide insight into whether a vaccine-elicited response leads to exacerbation of subsequent disease upon challenge with the SARS-CoV virus. No model had yet been developed for assessing immunopotentiation effects of anti-SARS products and this was an urgent issue. Work was in progress in several laboratories on small animal models for SARS, but no details were yet available.

- A significant regulatory challenge is the difficulty of undertaking clinical trials to evaluate protective efficacy of the vaccine if SARS does not reappear or if it remains very focal in nature. It may be possible to develop validated surrogate markers of protection and use them as clinical end points in trials.

- In the event of an emergency, various regulatory processes are already in place in Canada, Europe and the USA to expedite the use of medicinal products where the usual requirements to demonstrate effectiveness in humans is impractical or indeed not possible. The importance of regular dialogue between vaccine developers/manufacturers and the regulatory agencies as vaccine development progresses was emphasized.