Seventh Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction

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Review of the operation of the Convention as provided for in its Article XII

New scientific and technological developments relevant to the Convention

Background information document submitted by the Implementation Support Unit

Addendum

Annex

Submissions from States Parties

China

1. Modern biological sciences and technologies are developing very fast and playing a daily more important role in helping mankind combat disease and improve health. At the same time, the use of new kinds of biotechnology for hostile purposes, posing a latent threat to human society, is also growing. The "dual use" nature of biotechnology enables it, on the one hand, to pose many challenges to full and strict compliance with the Biological Weapons Convention (hereinafter referred to as "the Convention"); on the other hand it also spurs States parties to the Convention constantly to boost compliance in response to changing circumstances. How to prevent the use of biotechnology for hostile purposes while prompting its peaceful exploitation is, within the framework of the Convention, an issue confronting international society at large.

2. Current Chinese thinking on the development of new science and technology pertinent to the Convention may be reported to the Seventh Review Conference is as follows:

A. Major developments in biotechnology pertinent to the Convention since the Sixth Review Conference

3. Since the Sixth Review Conference there have been almost daily developments in biotechnology — rapid advances in synthetic biology, genomics, systems biology, drug-targeting technology and microbial forensics, for instance — throwing up fresh challenges and opportunities for compliance with the Convention.

1. Synthetic biology enabling the creation of man-made pathogens

4. The many technological strands of synthetic biology constitute a new science which is making rapid advances, from the chemical synthesis of the genome to the ability to create man-made living organisms. American scientists transplanted the genome from *mycoplasma mycoides* to replace that of *m. capricolum* in 2007; in 2008 they successfully synthesized, assembled and cloned the 582-kilobase *m. genitalium*; in 2009, using yeast as a host, they cloned the genome of *m. mycoides* and successfully introduced it into the genome of *m. capricolum*; and in 2010 they took the chemically synthesized genome of man-made *m. mycoides* and introduced it into *m. capricolum*, obtaining a self-replicating man-made bacterium. Advances in synthetic biology are turning the synthesis and transformation of life into reality and mean that the basic regulation of biological research, the preparation of new drugs and the promotion of new sources of energy are groundbreaking endeavours, but they also have the potential to be used for evil ends. Theoretically speaking, synthetic biotechnology poses a huge latent threat to mankind, as it could be used in the future to create pathogens of even greater toxicity and infectiousness than those currently known, and which are resistant to traditional vaccines and drugs as well as hard to isolate and identify with present day technology.

2. Genomics laying the foundations for pathogen transformation

5. Modern genomic technology is developing rapidly. The speed with which genes can be sequenced is rising continuously, while the costs are constantly falling and industrial applications are already appearing. With the analytical tools offered by the "cloud optimization" of bioinformatics that has recently begun, it is possible to use the Web to conduct large scale bioinformatic analysis and boost genetic data analysis capacity immensely. To date, the genomes of about 7,000 viruses, bacteria, fungi and protozoa have been fully sequenced. The sequencing of pathogen DNA has opened the way to the development of new diagnostic methods, drugs and vaccines. But the same data can also be used to synthesize new pathogens and modify pathogen antigenicity, infection specificity, toxicity and resistance to drugs, causing traditional means of dealing with infectious disease to fail and rendering the prevention and control of such disease even harder.

3. Systems biology further revealing population-specific genetic markers

6. Since the completion of the Human Genome Project, systems biology, a busy field of the life sciences, has been developing rapidly. In particular, the international 1000 Genomes Project will provide a map of variations in human DNA at unprecedentedly high resolution, helping to reveal population-specific genetic variations across the genome. New genome sequencing and assembly technology has shown for the first time that about 5 Mb of population-specific DNA sequences are conserved in the human genome; genome-wide association studies have found variations in the genes for susceptibility to infectious diseases among different populations; epigenomic studies further indicate the existence of population-specific genetic markers of susceptibility to disease. Thorough study of systems biology in the body can systematically analyse differences in genes and susceptibility to disease in the population and lay the theoretical foundations for an across the board

improvement in levels of human health, but it can also create the potential for biological weapons based on genetic differences between races. Once hostile elements grasp that different ethnic groups harbour intrinsically different genetic susceptibilities to particular pathogens, they can put that knowledge into practice and create genetic weapons targeted at a racial group with a particular susceptibility.

4. Targeted drug-delivery technology making it easier to spread pathogens

7. Thanks to incessant advances in pharmaceutical technology, targeted drug-delivery techniques such as aerosols and viral vectors have also made substantial progress. Drugs can be administered through aerosol inhalation, which can be of benefit in reducing recipient non-compliance. Viral vectors offer genetic therapy for many diseases by bringing about fundamental changes to disease-causing genes within the body to attain the therapeutic goal. But these two targeted drug-delivery technologies can also be used to spread biological agents. Aerosol technology can be used effectively to spread pathogenic microbes, infecting humans through the respiratory tract. And viral vectors can very easily carry special genes into the body, thereby causing damage. Further, there is potential for the effects of aerosol delivery, specifically targeted viral vectors, transfection and gene expression to combine, greatly increasing the overall effect. Both technologies can be used by certain States and terrorist groups for malicious purposes, efficiently spreading pathogens and disease-causing genes.

5. Microbial forensics facilitating the detection and tracing of pathogens

8. Microbial forensics is an important new area of research on biological defences. DNA information can be used to identify specific disease-bearing microbes, narrow the range of suspect pathogens more efficiently and trace pathogens. For some years now scientists have been perfecting a microbe classification system, and have refined microbial taxonomy by testing samples of microbial DNA, yielding a wealth of information. Developments in microbial forensic can help to detect specific pathogens and open up a means of tracing them; this can be of huge value in scientific research and efforts to counter bioterrorism.

B. Impact of biotechnology development on the Convention

1. Increased threat of biological weapons

9. The rapid development of biological sciences and technologies may significantly increase the destructiveness of biological weapons. One way it may do so is by increasing the virulence of pathogenic micro-organisms. Microbial genomic research can enhance the virulence or pathogenicity of a pathogen by modifying its antigenic properties. Another way is by rendering traditional medicines and vaccines ineffective. Supergenes conferring resistance to antibiotics can be synthesized by DNA recombination technology, making pathogens highly drug-resistant. Pathogens with detoxifying genes can also be produced, as can pathogens that can evade recognition and attack by the immune system, rendering vaccines and medicines useless. A third way is by making the target population more susceptible to pathogenic microbes. RNA interference can inactivate specific genes in the body, inhibit expression of important bodily proteins, disrupt physiological function and heighten the effects of a bioweapon attack. And a fourth way is by making biological attacks more stealthy. Foreign genes or viruses can be introduced into the target population asymptomatically by means of gene-therapy vectors, enabling a biological weapon attack to be mounted covertly.

2. Increased difficulties in monitoring biological compliance with the Convention

10. Developments in biotechnology have created many new problems and challenges for biological arms control and treaty monitoring, making it harder to monitor compliance with the Convention in the biological sphere. One way this occurs is through the synthesis of new agents of biological warfare. Theoretically speaking, synthetic biology can create microbes possessing any special attributes people may wish – new varieties of virus and bacteria more virulent, more infectious and more drug resistant than any known to mankind today. Gene sequencing is getting steadily faster and the costs are coming down; industrial applications of sequencing technology are already appearing and can be used to synthesize new pathogens. Another way is through making it easier to create biological weapons. Modern genetic technology can be used to bring about genetic modifications in traditional agents of biological warfare, making their production more efficient and increasing their stability. A third way is through the gestation of a new generation of biological weapons. Research into genetic differences and susceptibility to pathogens among different populations and species can lead to the creation of racial bioweapons based on genetic differences between races.

3. More critical situation as regards bioterrorism

11. Developments in biotechnology have come within the reach of some groups and even individuals, and some non-State actors have become more capable of malevolently causing disease, putting international security under great threat. Terrorist groups are improving their mastery of sophisticated biotechnology. With the spread of synthetic biology, some small scale research groups and even some individuals are now able to make the deadly Ebola and smallpox viruses and even some viruses against which all drugs are ineffective, thus making it much harder to counter bioterrorism. Furthermore, it has become much easier to obtain sensitive information. Using publicly available DNA sequences, terrorists can quickly synthesize pathogenic microbes that had previously been eradicated or give existing ones new pathogenic properties. And the means of perpetrating a bioterrorist attack have multiplied. Aerosol and viral vector technology can both be used to spread biological agents and it is highly likely that some terrorist groups will use them to mount a biological attack.

4. More prominent risk of biotechnology misuse

12. With advances in bioinformatics, genomics, synthetic biology and related fields, the threshold for performing biotechnology is steadily dropping and many ordinary biology laboratories are becoming able to do research that could previously be done only in sophisticated State research institutions, right up to obtaining genetic sequences over the Internet and synthesizing man-made pathogens in the laboratory. The science and technology of synthetic biology are spreading rapidly and synthetic DNA technology has already become a basic tool of biological research; the related reagents and equipment are becoming ever easier to obtain. Accidental mistakes in biotech laboratories can place mankind in great danger. Synthetic biology in some civilian biotechnology research and applications may unintentionally give rise to new, highly hazardous man-made pathogens with unforeseeable consequences.

C. Proposals

1. Promote multilateral processes in biological fields

13. Take comprehensive, multilateral action drawing on the collective efforts of all members of the international community to advance the multilateral process of making the

Convention more effective; ensure that, after full consultation and discussion, recommendations on international biological arms control issues are put into effect.

2. Implement biosafety regulation

14. States Parties should, in keeping with the purposes and principles of the Convention, apportion responsibility and assign tasks for biosafety regulation, constantly tighten biosafety management — especially of virulent pathogens — in their laboratories, refine the related systems, standardize import and export regulations governing dual-use biological products and technology, and eliminate biosafety risks.

3. Institute biosafety training

15. States parties should take practical steps to carry out broad ranging biosafety and ethical training to all personnel in academia, industry and government who are involved in the life sciences, thoroughly popularize biosafety awareness pertinent to the Convention, and promote uniform standards of conduct and self-regulation among personnel employed in biological fields.

4. Increase international exchanges and cooperation

16. Cooperation among States parties in responding to public health incidents should be increased; bilateral and multilateral consultations and negotiations in the field of biosafety to counter biological terrorism should be boosted; and international exchanges and cooperation over biological matters relating to forensic microbiology should be increased, along with exchanges of personnel so as to improve States parties' abilities to respond to biosafety incidents.

Czech Republic

17. Universities and research institutes in the Czech Republic are highly active in many research projects funded by national or international agencies. This activity represents a significant contribution to the basic and applied research and to the development of knowledge in many fields. The research is driven by general intrinsic effort to enhance quality of life in peaceful and harmless way. In the context of the BWC this effort is translated into the projects aiming at enhancing capabilities to prevent and cure diseases and to protect people from pathogenic influence of any kind. This effort, however, uncovers also possibility of the risk of misuse of new discoveries, and consequently the probable and potential misuse generates the dual use threat. The authorities of the Czech Republic continue to consider and to monitor advances in new and evolving technologies that may be relevant to biological weapons proliferation, including synthetic biology, micro-reactors, nanotechnology, and the automatization of biological equipments, with implications of these recent advances in biological science and technology.

18. Significant scientific and technological advances, relevant to the BWC, have come into existence since 6th Review Conference in 2006. Rapid development has arisen mainly in the area of nanotechnology, including nanobiotechnology. Moreover, many other areas have marked noteworthy progress.

19. The nanotechnology has recorded revolutionary development in many fields. In connection with the BWC the Czech Republic registered boom of the nanofiber as well as nanoparticle research, especially in relation to environment (water filtration, cleaning waste water and gases, removing pollutants from underground and surface water, filtration and disposal of toxic gases) and healthcare (nanofibers and carriers of active elements,

controlled dosage and localization of medicine, antimicrobial substances with nanoparticles, easier and more reliable diagnostics, new contrast substances).

20. New optical microscope, the two-photon microscope was developed under leadership of Czech scientists. This microscope allows three-dimensional localization of fluorescent molecules which are often used in biology for visualisation of otherwise colourless biological molecules. The two-photon microscope allows not only visualize where in cell the fluorescent molecules are, but also how they are oriented. The new microscope allows discovering new pharmaceutical drugs, by providing a new way to see whether a chemical (a potential drug) affects particular process in cell. Apart from applied science uses, furthermore the microscope contributes to advancement of basic science, by improving understanding of how cells and organisms work.

21. A substantial progress has been made in methodology of detection, identification or monitoring of biological agents and toxins. This applies to all bacteria, viruses and toxins and many techniques such as mass spectrometry. Improvement of instrumentation and procedures led to the wide spread of MALD-TOF mass spectrometry technique for rapid identification of bacteria including highly pathogenic species. It is part of the military as well as civilian biodefense system. The technique has found the way into clinical laboratories where it is replacing classical microbiological techniques. Other mass spectrometric techniques (LC-MS/MS) have pushed the detection limits of many agents and toxins and have established itself as standard analytical method.

22. Czech scientists participated in seeking of new techniques for specific recognition of biomolecules. These techniques include biosensoric systems exploiting surface plasmon resonance. The sensors offer benefits of label-free real-time analytical technology that can provide quick reliable results. The surface plasmon resonance has been applied onto the monitoring of microcystin in drinking water as well as whole bacterial pathogens in variety of matrices.

23. In last decades the climate change influenced the distribution of natural occurrence of biological agents and their vectors in Europe. In the Czech Republic for example it influenced presence of West Nile virus in southern part of the Czech Republic, or occurrence of tick and tick-borne diseases on the Czech territory. Especially occurrence of tick-borne diseases is very disturbing for public and animal health. Recent discovery of ferritin 2 may help with the control of tick-borne diseases. Ferritin 2, gut-specific protein secreted into the tick hemolymph, acts as an iron transporter after tick feeding. Ferritin 2 helps maintain iron homeostasis in tick organism and has no functional orthologs in vertebrates. Thus, ferritin 2 is promising candidate antigen for vaccination against tick infestation. Czech scientists in collaboration with scientific centres worldwide focus their effort on development of vaccine for cattle protection based on ferritin 2.

24. It is necessary to synchronize the monitoring of the geographical and endemic occurrence with neighbouring countries. The same apply to the exchange of the typing data of biological agents and toxins. The detailed phenotypic and molecular characteristic is indispensable for accurate identification. The Czech scientists in cooperation with their European colleagues have launched a project of creation a database of typing data for the purpose of accurate identification and microbial forensic analysis. This demonstrates that the demands of research and development of all mentioned projects is not possible without a close international collaboration.

Germany

25. Germany provides the following information about S&T developments. The following text is restricted to certain fields of new developments in life sciences and does

deliberately not intend to cover all new scientific and technological developments since the last Review Conference in 2006.

A. In detail

1. Bioinformatics

26. The development in the field of bioinformatics and computational tools for making best use of available information was driven by the rapid development of gene sequencing techniques, building of specific databanks and development of analytical tools in the five year period between 2006 and now. Comparison of information provided in the Database Issue of the journal Nucleic Acid Research of January 2011 with information contained in the respective issue of January 2006 demonstrates the impressive increase of information and retrieval as well as analytical tools.

27. The 2011 Nucleic Acids Research online Database Collection lists 1330 carefully selected molecular biology databases. This is an increase of more than 50 percent compared with 2006. An even more impressive picture of increase in S&T knowledge is provided by data about GenBank published by different authors in the Database Issues 2006 and 2011.

28. GenBank is a comprehensive databank publicly available on the homepage of the US National Center for Biotechnology Information (NCBI) that currently contains nucleotide sequences from more than 380,000 organisms named at the genus level or lower. The reference figure for 2006 is 205,000 organisms. The figures for available complete genomes of bacteria and archaea and for eukaryotes increased by the factor five from 2006 to 2011. Data for GeneBank are submitted by individual laboratories and from large-scale sequencing projects, including whole genome shotgun (WGS) and environmental sampling projects. GeneBank exchanges data with the European Nucleotide Archive (ENA) and the DNA Data Bank of Japan (DDBJ) to ensure worldwide coverage.

29. NCBI and the European Bioinformatics Institute (EBI), which operates ENA, do not only provide databases on their homepages, but also publicly available analytical and computational tools which allow data mining for a wide variety of highly specific purposes. After 9/11 this caused discussions whether such publicly available data and tools provide a source for bioterrorist attacks. Such risks cannot be denied generally, but each approach to genome and/or proteome alterations requires testing and characterization activities. Such activities need expertise, are costly, and time-consuming. For this reason the probability of misuse of open access to databases and computational tools currently is rather with state actors than with non-state actors.

2. Synthetic biology

30. Synthetic biology is a field for which several definitions exist. Common to all definitions is the understanding that synthetic biology combines a variety of science and technology approaches for the design and construction of biological functions and systems, including those lacking natural templates. The synthesis of poliovirus by assembling nucleotides, including synthesized oligonucleotides, and the reconstruction of the 1918 influenza virus are the most common examples when addressing synthetic biology progress in the years up to 2006. Synthesis of DNA to date is an industrial business. The market is split between companies that produce so-called oligonucleotides, i.e. short DNA fragments typically up to 100 base pairs, and a limited number of suppliers synthesizing gene- as well as genome-length cassettes of double stranded DNA up to the length of some 10,000 base pairs.

31. The longest synthesized DNA strand to date consists of more than 1 million base pairs assembled from more than 1,000 overlapping DNA cassettes in three steps and

belongs of the first bacterial cell controlled by a chemically synthesized genome. This work was done by the J. Craig Venter Institute to create a so-called synthetic cell. The creation of the first living cell controlled by a synthesized genome demonstrated that it is possible to re-boot one bacteria species into another. In addition, it was a step forward on the way creating a minimal genome bacterium. Bacteria with a minimal genome, possessing only the relevant genes necessary for sustaining life, could function as biological chassis for adding natural or synthesized gene sequences that encode for the metabolic production of desired substances. The transfer of a synthetic genome into a genome-less cell proved to be more difficult than synthesizing the genome itself.

32. Production of desired substances by engineering the metabolic pathways does not necessarily require synthetic cells, but can be done in well-known bacteria. The production of a precursor of the anti-malaria drug artemisinin in *E. coli* is an example. One of the driving factors behind synthetic biology is making the production of desired substances easier, faster and cheaper or creating new resources for substances that by other ways cannot or cannot sufficiently be produced like drugs or biofuels. Expectations linked with synthetic biology also evoked military interest in design and development of biological host organism concepts and synthetic regulatory elements.

3. Drug delivery systems

33. The pharmaceutical industry has developed over years new methods and procedures to improve the application of drugs via the inhalation, oral and trans-dermal entry routes. The developments are driven by the requirement to protect drugs against digestion or denaturing before they reach their respective receptors, or by linking active compounds with vectors that guide them to the foreseen receptor, and last but not least by drug application forms that increase consumer compliance. The methods and procedures in all these fields can be utilized to stabilize biological active substances or use biological materials as shuttle systems for delivery of drugs or toxic substances.

34. In some areas aerosol technologies are increasingly applied to improve consumer compliance by replacing medical treatment with pills or injections. Applications are not limited to asthma and pulmonary diseases. Models also exist for treatment of diseases like diabetes, other treatments with peptides or vaccine applications. While in the past aerosol vaccination was more focused on animal applications, immunization of humans by aerosols is getting more interest. One of the biggest projects currently under way is the WHO Measles Aerosol Project. Aerosol applications build usually on the use of surfactants that lower the surface tension and assist transmucosal permeation. The use of viral vectors as carriers is also demonstrated. Particle sizes generated by medical inhaler devices usually cover the same range of size necessary for causing viral and bacteriological infectious diseases via the inhalation route.

35. Active compounds that may be digested or denatured before they reach their receptors can be protected by microencapsulation. They can be coated so that they survive passage through the stomach and can bind to intestinal mucosa for entering the blood stream. Drug coating is a standard procedure in pharmaceutical industry.

36. Nanoparticles as carriers are tested to overcome problems in gene and drug delivery for cancer therapy but also for treatment of other diseases. Drugs or genes are either encapsulated in or attached to the surface of nanoscale particles which enable transport through small capillaries and up-take by cells. Systems investigated include quantum dots, silica nanoparticles, dendrimers, micelles, liposomes and others.

37. All the technologies addressed in this contribution may be relevant in the context of the Article I BWC reference to means of delivery.

B. Response to risks in synthetic biology

38. Irrespective of existing legislative restrictions or guideline recommendations regarding export control and genetic engineering activities, commercial producers of DNA sequences have started discussions on best practices of responsible care for synthesized products and customer control. The discussion was less driven by new risks linked to synthesized products than by easier access to DNA sequences by a wide spectrum of actors, including actors that could use synthetic biology based approaches to develop biological weapons.

39. The International Association Synthetic Biology (IASB) in Germany started in 2007 one of the first initiatives drafting a code of conduct. The Association represents companies and organizations with a stake in Synthetic Biology, for instance as providers of double-stranded recombinant DNA synthesis or bioinformatics products. Before formal adoption of the IASB Code of Conduct for Best Practices in Gene Synthesis in 2009, the code was developed in a public process, in which academic and other constituents participated. With regard to their activities the companies signing the Code commit themselves to risk assessment and risk management. This includes screening DNA sequences submitted as inquiries or orders for DNA synthesis by customers against GenBank for reasonable sequence similarity to pathogens, screening the legitimacy of the customer when an ordered synthetic gene is identified as a risk-associated sequence, keeping records and statistics of suspicious inquiries and positive screening hits at least for 8 years, cooperation with authorities, and provision of evidence of inquiries and orders that strongly suggest illegal activities. A Technical Expert Group on Biosecurity (TEGB) formed by IASB will regularly review the implementation of the measures under the Code and will propose and initiate improvements. Currently, the IASB Code is signed by six German and two Chinese bio-companies.

40. In 2009, four US and one German gene synthesis companies that form the International Gene Synthesis Consortium (IGSC) agreed on a similar Harmonized Screening Protocol. The principles and procedures contained in the Protocol are similar to those of the IASB Code. The reason why IASB and IGSC could not agree on a consolidated approach is not quite transparent and may be an obstacle for other gene synthesis companies to join the Code or the Protocol. IASB and IGSC members count less than half of the worldwide approximately 25 commercial gene synthesis companies, but are estimated to manage currently over 80% of the gene synthesis orders.

41. In 2010, the US Department of Health and Human Services (HHS) released the final version of its Screening Framework Guidance for Synthetic Double-Stranded DNA Providers. The provisions of the Guidance are in line with the IASB Code and the IGSC Protocol and are intended to provide guidance to DNA producers on a voluntary basis. An exchange of views of US and German government experts on the necessity of taking government action beyond the IASB and IGSC self-governance approach preceded the development of the HHS Guidance. Taking into account the restrictive German genetic engineering legislation based on Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, which requires an authorization for genetic engineering activities and does not allow DIYBio or garage biotech approaches, Germany did not see any need for additional government action.

42. The screening procedures addressed in the aforementioned documents apply to double stranded DNA sequences larger than 200 base pairs only. The procedures are regularly not applied to short DNA constructs, so-called oligonucleotides. Due to their short length it is difficult to decide true from false hits when screening against genebank data.

Screening of orders and inquiries against sequence-based virulence factor information databases may provide a focused approach to screening also shorter DNA sequences.

Netherlands

43. The Netherlands has various institutions that monitor developments in the area of science and technology relevant to the Biological and Toxin Weapons Convention, such as Dutch National Institute for Public Health and the Environment (RIVM), Dutch Organisation for Applied Scientific Research (TNO), Netherlands Forensic Institute (NFI), Royal *Netherlands* Water Network (KNW), National Coordinator for Counterterrorism and Security (NCTV).

44. Without trying to be exhaustive, one of the institutions that write about new scientific and technological developments holding possible relevance to the Convention is the Rathenau Instituut. The Instituut promotes the formation of political and public opinion on science and technology. In recent years the Instituut has published papers on a.o. nanotechnology and synthetic biology. The papers of the Rathenau Instituut are available to the public in English.[1] The Instituut also organised a workshop in October 2010, focussing on the implementation of biosecurity in the science system of the Netherlands and the biosecurity implications of synthetic biology as a new emerging field in the life sciences.[2]

Poland

A. Genetic engineering of viruses

45. Recent approaches in the field of the reverse-genetic-engineering of RNA viruses enable the creation of artificial molecules of a given RNA virus with programmed recombination. Because of the programmed diversity, these artificial molecules may imitate a virus quasispecies with expected pathogenic properties. This includes the possibility of creating interspecific hybrids, which naturally occur in the Entero- and Togaviridae as well as mixtures of attenuated (or even inactive) viruses that acquire pathogenic properties during replication cycles.

B. High-throughput '-omics' approach to vaccines

46. Recent advancements in the '-omics' technologies (genomics, transcriptomics, proteomics) associated with the high-throughput protein expression and purification methods provide an innovative approach to vaccine and antiviral drugs development.

47. Genome sequences of microbial pathogens along with multiple isolates of the same species have noticeably changed the timeframe for identification of novel vaccine candidates. Moreover, improvement of existing tools for in silico analysis has led to the identification of novel virulence genes, metabolic pathways and cell surface proteins that represent potential new targets for vaccine strategies. The synergy between increasing knowledge in bioinformatics and computational biology fields give the comprehensive catalogue of vaccine applicants.

[1] http://www.rathenau.nl/en.html

[2] http://www.rathenau.nl/en/publications/biosecurity-at-the-science-policy-nexus-developing-a-vision-for-the-future-1.html

48. Recently, efforts have been also made in design of molecularly defined vaccines against anthrax. New strategies for the improvement of anthrax vaccines are based on recombinant PA protein, sub-unit, DNA, mutants and conjugated vaccines. Innovative approaches allow minimizingthe booster dose, reduce adverse reactions after vaccination (local pain and edema), as well as enhance both, cellular and humoral immunological response.

C. Antiviral peptides discovery

49. Proteomics techniques associated with biodiversity prospecting are an innovative tool for combating viral infection. Some kind of peptides exhibit direct virucidal activity, whereas others interrupt adhesion of virus particles to the host cell surface or interfere with intracellular replication of virus.

50. High-Affinity Binding Reagents (aptamers) that modulate or inhibit the expression of specific peptide targets also demonstrate an antiviral activity. Naturally occurring proteins, acquired from plants, animals, microbes during bioprospecting search, have led to potential candidates for new antiviral compounds, as well.

Portugal

51. The Portuguese Army plans to acquire means of detection and identification of biological agents. A Centre of Excellence in this matter will be established and will focus primarily in simulants and software for simulation purposes

52. Portugal firmly believes that, to cope with the threats posed by the manipulation of pathogenic and nano and biotechnology by States and terrorist groups, Governments should strengthen their capabilities in the field of scientific research in order to promote human and environmental security throughout the World.

53. In that sense, Portugal has improved its capabilities, by renewing the equipment and infra-structures of the National Health Institute Laboratory, in order to increase the effectiveness in the control of biological threats.

54. The National Health Institute is also, since 2002, a member of the experts board of the Health Security Committee Working Group – Laboratory Co-operation of the DGSANCO. Throughout 2006, Portuguese experts have participated in several international meetings in the field of biological weapons, such as the EU Wetlab on Anthrax, organized by the Health Protection Agency (Porton Down, UK) and the EQAE (Robert Koch Institut, Wernigerode, Germany).

South Africa

55. The Seventh Review Conference of the State Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons (BWC) will take into account new scientific and technological developments relevant to the Convention. Since the 6th Review Conference in 2006 there has been increased scientific knowledge and technological development that could be considered to have the potential for "dual-use" and thus could be used for illegitimate intentions or application.[3] Such developments have the potential to impact the design,

[3] Scientific working group on life science research and global health security. Report of the first

modification, production, delivery and/or targeting and hence overall potential risks and harm of would-be biological weapons.

56. Assessing these new scientific and technological developments relevant to the Convention is a large task due not only to the continuous advances in science and technology but the broad number of fields and scientific areas that need to be considered. These include: Bioinformatics; Systems Biology; Synthetic Biology; Advanced Bioreactors; Transgenic plants, insects and animals; Aerosols and aerobiology; Nanotechnology; Neuroscience; Biosensors; Vaccines; Diagnostics; and Epidemiology. There is a vast body of literature covering these subjects and none of them is in practice a defined discipline but incorporates a range of methods and techniques from different disciplines and this makes identifying the critical developments that are relevant to the Biological Weapons Convention particularly difficult. This is coupled with the increase in emerging diseases (e.g. SARS coronaviruses, Avian Influenza), the re-emergence of old diseases (tuberculosis in certain countries), the increased geographical spread of disease (e.g. plague) and increasing drug resistance (e.g. tuberculosis, HIV) means that an understanding of these issues is required. Whilst much of the focus in terms of scientific publications relevant to bioterrorism is focused on the identification, selection and classification of infectious agents, more attention is needed to investigate the potential of technological advances on these agents possible modification, production, delivery and/or targeting, as well as the design of new agents, for nefarious use.

57. Whilst most research covering these areas and the resulting developed technologies could inherently be regarded as potentially dual-use it is perhaps more useful to address those aspects where nefarious use would be the most severe. In order to make such an assessment the focus here is given to technologies that could impact on the criteria published by the Australian Government in 2008 posing risks to biological weapons development and use.[4] These criteria include those technologies that:

(a) Would render existing or future vaccines ineffective;

(b) Would confer resistance to therapeutically useful antibacterial or antibiotics agents;

(c) Would enhance virulence of a pathogen or render a non-pathogen virulent;

(d) Would increase transmissibility of a pathogen;

(e) Would alter the host range of a pathogen;

(f) Would enable evasion of diagnostic/detection modalities;

(g) Would enable weaponisation of a biological agent or toxin.

58 In this document rather than covering all the broad areas we intend to focus on some key recent developments that are considered to be important in understanding potential new threats from this context and then briefly describe the relevance of each to the BWC. The relevance of each field with respect to criteria that pose risks to biological weapons development and use is shown in Annex I. This could be a useful method to assist in future science and technology reviews for the BWC where new technologies could be evaluate against these criteria more thoroughly. The intent of this summary is not to be exhaustive

meeting. Geneva, World Health Organization, 2007 (WHO/CDS/EPR/2007.4)

[4] Miller S and Selgelid MJ. *Ethical and philosophical consideration of the dual-use dilemma in the biological sciences. Dordrecht NE, Springer 2008*. Report prepared by the Centre for Applied Philosophy and Public Ethics at the Australian National University for the Australian Department of Prime Minister and Cabinet, National Security Science and Technology Unit, November 2006.

but to highlight the key issues and demonstrate the complexity of such analysis and thereby encourage more analysis in this area.

59. Four key developments of the last decade that arguably best describe how well intentioned research and resulting technologies could provide tools or opportunities for production of biological weapons are:[5]

(a) Australian scientists finding that introduction of a mouse IL-4 gene into the mousepox virus resulted in a more virulent mousepox that had both enhanced virulence in mice and that was able to infect vaccinated mice.[6] A similar technique could be used enable production of vaccine resistant smallpox or other hazardous viruses. In fact, this had been done earlier by a group in the UK in 1998 that made a recombinant vaccinia virus with an IL-4 gene that had enhanced virulence.[7,8]

(b) American scientists managing to synthesize infectious polio virus using publically available genome sequence information and DNA segments ordered from commercial suppliers over the internet, which when ligated together and added to a key protein produced a polio virus that infected mice. Similar techniques could be used to produce smallpox or Ebola viruses without the need to locate or steal a viable viral stock.[9]

(c) Researchers in the USA use public sequence information to produce a smallpox viral protein which attacks the human immune system.[10] This approach illustrates methodologies that could be used to increase virulence of closely related viruses like vaccinia.

(d) Synthetic genomic approaches were used to produce the influenza virus responsible for global pandemic in 1918-19 again suggesting such an approach could be used for nefarious purposes.[11]

60. Bioinformatics allows for the integration of biological, computing and information sciences. Since the costs of DNA sequencing has reduced significantly from US$700.00 per megabase in 2006 to US$0.10 per megabase in 2011[12] this has resulted in massive increase in the published (and thus publically available) sequences of organism genomes including the human genome and that of pathogens.[13] This combined with computing tools and numerous free software options for analysis and management of genomic data makes analysis, transfer and storage of pathogenic genome sequence data much easier and also

[5] Selgelid, MJ. Governance of dual-use research: an ethical dilemma. 2009 Bull. World Health Organ. 87:72-723.

[6] Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. J Virol. 2001;75:1205–10.

[7] Bembridge GP, Lopez JA, Cook R, Melero JA, Taylor G (1998) Recombinant vaccinia virus coexpressing the F protein of respiratory syncytial virus (RSV) and interleukin-4 (IL-4) does not inhibit the development of RSV-specific memory cytotoxic T lymphocytes, whereas priming is diminished in the presence of high levels of IL-2 or gamma interferon.

[8] Selgelid MY and Weir L. The mousepox experience . 2009. EMBO reports 11:

[9] Cello J, Paul AV, Wimmer E. Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template. *Science* 2002;297:1016-8.

[10] Rosengard AM, Liu Y, Nie YZ, Jimenez R. Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement. *Proc Natl Acad Sci USA* 2002;99:8808-13.

[11] Tumpey TM et al. Characterization of the reconstructed 1918 Spanish influenza virus, *Scienc*e 2005, 310: 77-80.

[12] Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program Available at: www.genome.gov/sequencingcosts. Accessed [29 August 2011]

[13] Human genome at ten: the sequence explosion. *Nature*, 464: 670-671. 2010

widely accessible. The complete sequencing of the human genome and subsequent tools to identify both genes and the importance of non-coding regions is also likely to lead to both improved understanding to develop both improved therapies but with the potential to also design biological warfare agents.

61. One of the areas where relevant scientific developments have advanced significantly since the 2006 Review conference has been in the area of synthetic biology which covers the design and construction of new biological parts, devices and systems, as well as the re-design of existing, natural biological systems for useful purposes.[14] Synthetic biology can either improve existing biological function or even perform new functions. The misuse of synthetic biology could enable the synthesis and re-creation of known pathogens overcoming the existing legal and practical barriers needed to obtain such pathogens as already described. The ability to synthesize longer DNA sequences, the fact that pathogen sequences are publically available, and the proliferation of gene synthesis technologies and companies means that the ability and ease with which to recreate pathogens will likely increase over time, and could thus result in viable assembly and re-creation of pathogens (e.g. like variola which causes smallpox). In many cases synthesis of the genome either on its own or when cloned into a suitable plasmid and then simply injected or transformed into a suitable host results in replication and corresponding production of the pathogen. The size of synthetic genome synthesis was previously limiting but in 2008 it was shown that synthetic genomes of >500,000bp are now feasible meaning that synthesizes genomes many time larger than Ebola and twice that of small pox is now possible, without needing to clone different fragments.[15] And the cost of synthetic genome synthesis has also dropped significantly although not at anywhere near the same rates as DNA sequencing whilst the accuracy of genome synthesis has improved.

62. Whilst recreation of the genome is different from recreation of an infectious organism, the de novo synthesis of new organisms has most recently been demonstrated in May 2010 by researchers who synthesized a bacterial genome and then produced a bacterium that was able to replicate by inserting the genome into a bacterial cell.[16] So the potential to design new bacteria or viruses or even to create drug or vaccine resistant variants could become a more real possibility and such organisms could even eventually be "engineered to attach genetically specific sub-populations".[17] The risk of nefarious use of synthetic genomes could thus be regarded as one of the most important concerns. Producing novel pathogens using the de novo approach is likely to be more difficult and will require better visualization, integration and understanding of biological data. This is being advanced using systems biology approaches to build useful in silico models that can then be used to better understand diseases. This can provide for the design and development of new drugs or/and could allow for the potential to design biological agents that could also be used for nefarious purposes.

63. Systems biology really seeks to better understand the intricate networks and interplay of molecular processes in living systems. A big component of this is the contribution made by structural genomics which is increasing the public domain information on pathogen and host structural interactions which can help to understand

[14] Royal Society. *Synthetic biology Scientific Discussion Meeting Summary.* RS policy document 16/08, 2008.

[15] Gibson DG et al. (2008) Complete chemical synthesis, assembly, and cloning of a *Mycoplasma* genitalium genome. Science 319: 1215–1220.

[16] Gibson DG et al. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science*, 2010, 329:52-56.

[17] de Oliveira MFF, Krassnig C (2007) *Synthetic Biology: A NEST Pathfinder Initiative*. Brussels, Belgium: European Commission.

virulence attenuation, host recognition and neutralising activities of different viruses and bacteria by their hosts. Recent advances in systems biology models and computing infrastructure suggest that it is likely it will contribute significantly towards Biodefence research since as the amount of knowledge grows improved rational design of vaccines (against biological agents) is likely in the same way that rational drug design has led to discovery of a number of drugs. It is anticipated that a systems biology approach would also allow for accelerated vaccine clinical trials by allowing for immunogenicity and safety assessments in silico and thereby accelerate vaccine development in response to biological threats.

64. Advanced commercially available bioreactors (previously called fermenters) pose a risk for bioweapons as they allow efficient production of viruses, bacteria or toxins. New and improved sensors with computerized algorithms provide for the optimal control of the growth environment and nutrients to maximize production greatly improving yields. Many organisms are very sensitive to shear forces and novel devices for mixing have improved contained cultivation of these cells. For growth of viruses, a cell substrate is necessary and many advanced bioreactors can make the large scale cultivation of some of these fastidious virus types possible. The current advantage of these low-shear and complex control bioreactors has been in improved synthesis of multicellular structures or tissues. The main current use is in the growth of shear-sensitive eukaryotic cells. Advanced bioreactors could make large quantities of certain viruses available that were previously difficult to obtain and many are now available as small, disposable units making them easy to move around and potentially conceal.

65. Advances in diagnostics and epidemiology are closely linked mainly with the ability to rapidly detect existing or new pathogens and monitor and predict their virulence, spread and potential for drug or vaccine resistance. The improvements of laboratory infrastructures around the world coupled with point of care test technologies in particular robust lateral flow, real time PCR or other nucleic acid based amplification technologies allows for rapid pathogen detection and could also be rapidly developed to detect a new pathogenic threat. These have been mainly used for diagnosis and surveillance of infectious disease like HIV, malaria and well as drug resistance. Many commercial companies now offer commercial assays for detection of pathogens greatly improving the accessibility and quality of such tests to effectively detect and monitor potential bioterrorism outbreaks.

66. One key issue with the potential for use of biological weapons is the ability to both stabilize and disseminate or disperse the biological agent being used. New technologies in development particularly in the pharmaceutical industry spread these agents effectively to ensure widespread dispersal. Aerosol science is an interdisciplinary field focused on the presence and movement of biological particles in the earth's atmosphere including "the impact of such particles of human populations, agriculture and animals including insect control".[18] An example of how aerosol technology is being used and optimized is in the widespread spraying of Bacillus thuringiensis on crops to prevent pest damage. Aerosol formulations of different drugs are also being used to treat asthma and are being investigated to treat diabetes with inhaled insulin, and even investigated for gene delivery. Compared to oral delivery methods they can provide rapid and homogenous distribution of the required drug. Despite the potential of biological agents to be distributed using aerosol systems their actual biological stability and hence infectivity or activity after atmospheric release is poor, to expand on the Bacillus thuringiensis example described above where the formulation used did not have to be inhalable but had to be "sticky" and have hydrophobic

[18] Globalization, Biosecurity, and the Future of the Life Sciences. Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, National Research Council. 2006.

properties to adhere to the plant and not remain airborne as would be required for weapons. Technologies that improve microencapsulation and stabilization could increase the effectiveness of this route and hence the risk.

67. Nanotechnology developments are also important to be considered as it is a rapidly growing field dealing with small particles that have the potential to penetrate into tissues more easily than larger molecules. A good example of their relevance is the development of a synthetic organic polymer nanoparticle (NP) which can both target and clear peptides in the bloodstream of living mice.[19] Whilst this was developed as a kind of "plastic antibody" to neutralize macromolecules in vivo it is also possible they could be designed to have harmful effects or neutralize or inactivate important blood or cell surface components. Other molecules like RNA or DNA aptamers which are gaining prominence in diagnostic applications have the potential to be used in this way. A large expanding field is drug delivery and this is often focused on the delivery of large biomolecules to regions like the brain and nanoparticles have significant potential in this area. In addition the ability of nanoparticles to aid drugs crossing the blood-brain barrier also means they could be investigate as components of biological agent's delivery systems.[20] There is interplay between nanotechnology and aerobiology. Freeze drying, spray drying, milling and the use of supercritical fluids to dry proteins yield heterogeneous mixes of particles ranging in size between nanometers and micrometers. Recently Kelly and DeSimone presented a nanotechnology-based method to create homogenous protein structures of nanometer size. The method is based on nano-etching and printing and appears to show promise in the drug delivery field; yet the scale of synthesis appears to be relatively low. Therefore unless the technology improves to mass produce homogenous and inhalable particles the risk is relatively low. [21]

68. Neuroscience is the scientific study of the nervous system and currently it is an interdisciplinary science that incorporates other fields such as chemistry, computer science, engineering, mathematics, medicine, philosophy, physics, and psychology. It has also has broadened to include different approaches studying the molecular, cellular, developmental, structural, functional, evolutionary, computational, and medical aspects of the nervous system. This includes molecular and cellular studies of individual nerve cells and imaging of sensory and motor tasks in the brain and recent theoretical advances in neuroscience has been aided by the study of neural networks. This is a rapidly developing field; the utility of neuropeptides, bioregulators and other agents of biological origin (BWC) as so-called non-lethal weapons has been a popular point of discussion.

69. Biosensors are analytical devices used to detect analytes that combine a biological component with a physicochemical detector component. A common commercial biosensor is the blood glucose biosensor, which uses the enzyme glucose oxidase as the biological component to metabolise blood glucose. The oxidation of glucose indirectly charges the electrode generating current as a measure of the concentration of glucose. Recently, arrays of many different detector molecules have been applied in so called electronic nose devices, where the pattern of response from the detectors is used to fingerprint a substance. An interesting example is the portable Wasp Hound odour detector which has a video camera (movement sensor) enclosed with parasitic wasps conditioned to swarm in response to the

[19] Hoshino Y et al. Recognition, neutralization, and clearance of target peptides in the bloodstream of living mice by molecular imprinted polymer nanoparticles: a plastic antibody. 2010. J.Am.Chem.Soc. 132: 6644-5.

[20] Suri SS et al. Nanotechnology-based drug delivery systems. 2007. J Occup Med Toxicol 2:16-21.

[21] Kelly, J., DeSimone, J., Shape-specific, monodisperse nano-molding of protein particles, *JACS*, 2008, 130: 5438-5439.

presence of a specific chemical.[22] Current commercial electronic noses (physico-chemical sensors), however, do not use biological elements. Combinations of biological enzymes and electronic detectors are well developed and combinations of specific monoclonal antibodies with electronic sensors have been developed and have significant scope for use in detection of specific pathogens. It is possible that many of these current systems will be superseded by electronic sensors in the near future and could be developed to specifically detect a variety of biological compounds and/or organisms that are not easy to detect using physico-chemical sensors enhancing biological weapon detection.

70. Vaccine development is critical in being able to provide a biomedical response to biological threats and often vaccine development relies on understanding of disease pathogenesis of a particular infection. The rapid identification of pandemic swine-origin influenza virus A H1N1in less than 2 months and subsequent rapid development of a monovalent vaccine produced in eggs demonstrated the speed with which a vaccine can be produced to a new threat. Subsequently adenovirus based vaccines were also developed showing how vaccine technologies have advanced to the point where they can show both speed of manufacture and efficacy in a single dose.[23] Recently in the case of Ebola virus promising vaccine candidates have been shown to protect non-human primates against lethal infection.[24] These vaccines include replication deficient adenovirus vectors, replication competent VSV, HPIV-3 vectors and virus like particle preparations. Advances in the effective post exposure immunization strategies suggest that it will be possible to develop a single dose Ebola virus vaccine that will provide full post-exposure protection in humans. However, understanding of the basic science of disease has not always resulted in advances in vaccine development. Other diseases like HIV have proved especially difficult to vaccinate against despite significant investments in this area[25] suggesting that vaccination against all infectious diseases or new threats which despite being theoretically possible may not in fact be achievable in the time frames that would be required to respond to biological weapons threat.

Sweden

71. In 2006, Sweden submitted to the Sixth Review Conference a summarising review of the background to and advances in a number of relevant scientific and technological fields (BWC/CONF.VI/INF.4). Developments have continued in such and other scientific areas, with new and refined applications intended for peaceful purposes. The dual-use character of life-science may, however, allow many achievements to be misused and constitute breaches to the objectives and provisions of the Convention. Scientific and technological developments may, on the other hand, also support the objectives of the Convention. This paper focuses on one broad area, where technological developments and scientific achievements come together and build new possibilities for the Convention.

72. One of the greatest technological leaps that have occurred since the Sixth Review Conference is within the area of high-throughput whole-genome sequencing[26] - the rapid

[22] Rains GC et al Behavioural monitoring of trained insects for chemical detection. Biotechnol Prog. 222:2-8.

[23] Steitz J, Barlow PG, Hossain J, Kim E, Okada K, et al. 2010A Candidate H1N1 Pandemic Influenza Vaccine Elicits Protective Immunity in Mice.PLoS ONE 5(5)

[24] Richardson JS et al Recent advances in *Ebolavirus* vaccine development. 2010. Human Vaccines 6:439-449.

[25] Koff W. Accelerating HIV vaccine development. 2010. Nature 464: 121-122.

[26] Sequencing refers to the determining of the sequential order of nucleotides. Whole-genome refers to the sequencing of the entire set of genetic elements in the organism. High-throughput refers to the

unravelling of the sequential order of nucleotides throughout the entire set of genetic elements in an organism. In the potential event, or suspicion of, an illegitimate use of a biological agent, fine scale genetic characterisation of the agent based on whole-genome sequencing, together with concepts drawn from the developing field of microbial forensics, could provide information of importance for several phases during the investigation of the event, such as for:

(a) Identification of the infectious agent responsible for an unusual outbreak of disease;[27]

(b) Characterisation of an outbreak as natural or deliberate in origin; and

(c) Identification of the perpetrator responsible for the release.

73. This contribution attempts, by giving a more comprehensive background, to brief delegates on how these new developments can help strengthen the Convention, and also where additional efforts could further increase the usability to the Convention. In short, it is concluded that:

(a) Analysis and interpretation of results from investigations of whole-genome identity matching between single isolates within microbial species is complex.

(b) New technological developments enable construction of reference strain collection databases that build on whole-genome sequences.

(c) The increased availability of genetic data and enhanced scientific understanding of interpretation of microbial genetic information create new possibilities to investigate alleged uses of biological agents.

(d) The analysis and interpretation of genetic data requires capacity and knowledge that go beyond what can be expected from most routine laboratories.

(e) Not all relevant pathogenic organisms can, due to their relative rareness, be expected to receive extensive attention from public health reference strain collection database constructors.

(f) With collective efforts the recent developments open new possibilities to the Convention to detect and confirm violations, identify a perpetrator responsible and, by this, to deter the use of biological weapons.

74. Until recently, the process of whole-genome sequencing has been a painstaking, costly and time-consuming task. Recent advancements, often referred to as Next Generation Sequencing (NGS) techniques, have during the past few years revolutionized the field of biology. The time and cost[28] required for sequencing of a genome have been greatly reduced, making whole-genome sequencing increasingly more common. The number of laboratories and commercial companies that perform whole-genome sequencing is constantly increasing.

75. It should be acknowledged, though, that raw data from the actual sequencing need comprehensive processing before it can be used for further analysis. The majority of

speed at which the sequencing process is performed.

[27] Not further discussed in this paper.

[28] Examples of actual costs are not relevant to give, as they vary considerably depending on factors like the desired quality of the sequence, if the organism has been sequenced before, level of coverage (how many times a given nucleotide is investigated during the sequencing process), nucleotide composition of agent sequenced etc.

currently used methods produce millions of short[29] overlapping sequence fragments, pieces that need to be assembled into longer fragments to reflect the original sequence. The relative shortness of raw data fragments is a major limitation with these current techniques. The techniques are, however, constantly being improved. It is anticipated that, in the near future, it will be possible to produce considerably longer[30] raw data fragments. This development will considerably facilitate fragment assemblies and, in addition, further increase the quality of attained sequences. Storing of sequencing raw data, assembly of fragments into whole genomes, and genetic comparisons require comparatively high computational capacity, which has in some settings hampered the usability of the new techniques. On-going development of new software and algorithms and adaptations of current sequencing techniques to better suit sequencing of smaller genomes (viruses and bacteria) will, however, reduce requirements of computational capacity.

76. Microbiologists have for decades exploited a variety of methods to compare between different organisms, in order to understand their relatedness.[31] Epidemiological and research laboratories collect microbial isolates into reference strain collections, to which new isolates can be compared. Genetic comparisons have so far typically built on genetic markers that reflect parts of the microbial genome. Such systems, however, may at times falsely suggest, or fail to correctly reveal, relatedness between organisms.

77. It has been acknowledged that comparisons based on whole-genome sequences would provide a more correct understanding of microbial relatedness. The current and anticipated developments within the area of high-throughput whole-genome sequencing will enable the construction of reference strain collection databases that build on whole-genome sequences, rather than on traditional marker systems, which will allow a more correct determination of genetic relatedness within microbial species. In addition, whole genome sequencing is the only method that is informative at all levels of microbial strain identity resolution (i.e. resolves the full spectrum from family to isolate), and thus allows different investigative questions to be addressed at different stages of an investigation.

78. The past decade has also seen major advances in a new scientific discipline, microbial forensics,[32] where the core objective is attribution – the investigative process of identifying and linking a perpetrator to a biological weapons event. This highly interdisciplinary field includes, in addition to more traditional forensic investigative methods, detailed characterisation of samples containing a biological agent or components thereof. Sample characterisation includes investigations of genetic, chemical and physical properties. Results from the genetic characterisation of the agent and investigations of its relatedness to other strains thus constitute some, among several, pieces of evidence.

79. The process of investigating illegitimate use of biological agents, with a forensic quality that will allow results to be used in a judicial process and with the serious consequences of mistaken attribution taken into account, requires both scientific understanding and operational capability. The latter includes methods and strategies, as well as forensic awareness and chain of custody procedures, throughout the entire analytical

[29] Current methods typically produce fragments that are between 50 and 500 nucleotides long.

[30] With future techniques it is anticipated that it will be possible to produce raw data fragments that are several thousands nucleotides in length

[31] Such investigations can be done on a lager evolutionary scale to understand the position of a given organism in the evolutionary tree (family, genus, species, subspecies), or on a finer scale to determine if single isolates of a microbial species originate from one common source. In the context of this paper the latter is of greater importance.

[32] Also known as forensic microbiology.

chain,[33] from sampling to interpretation of analysis results. Such understandings and capabilities are gradually being further developed.

80. The theoretical foundations in microbial forensics have mainly been adopted from the human genetic forensic field, where matching of crime scene DNA to that of a suspect (attribution) has become routine analyses. As the mechanisms for reproduction and genetic variation, and thus population structures, differ between humans and microorganisms there are, however, fundamental differences between microbial and human forensics in how results from genetic comparisons (similarities and differences) can be interpreted.

81. In humans, where in each generation the offspring inherits copies of genes from both its ancestors (parents), there is a high degree of genetic variation in certain parts of the genome. The chance of a coincidental match (identical sequences) when using human DNA fingerprinting[34] is considered to be less than one in eighteen thousand million. Bacteria and viruses, however, reproduce asexually through cell division. All new cells would thus be identical to the ancestor, were it not for a variety of mechanisms[35] that generate genetic variation. These mechanisms may allow offspring to differ from the ancestor, but may also allow unrelated organisms to share some identical genetic sequences. Therefore, when investigating if single isolates of a microbial species are identical (match), a complete or near complete match between two microbial genomes does not theoretically need to reflect identity and thus that they originate from a common source. On the other hand, minor genetic differences between two strains do not necessarily exclude that they originate from the same source.

82. To enable evaluations of to what extent genetic similarities and differences reflect true genetic relatedness, and thus to enable scientifically sound statements on whether an agent used as a biological weapon came from a particular source that e.g. can be linked to a suspect (attribution), a deep understanding of the population structure of the investigated agent is essential. Such understanding can only be achieved through comprehensive characterisation of a large number of strains (on species or subspecies level) of the agent in question. The strains included in such a characterisation need to reflect the best available representation of the known genetic diversity of the agent. This in turn requires that the strains are chosen to well represent geographical and temporal occurrences of the organism as well as different environmental and host origins. In the event of a suspected deliberate release, also strains from laboratory repositories need to be included in the analysis.

83. Differences in the population structures between and within microbial species need to be accommodated for, both in the statistical analysis used to determine relatedness and when making quantitative statements about the strength of support for the results. The analysis and interpretation of sequencing results is, if results are to be used as evidence in juridical processes, complex and require capacity and knowledge that go beyond those that can be expected from most routine laboratories.

84. The existence of databases containing whole-genome sequences from well-represented reference strain collections could also help discern anomalies within the genome of an agent that could be indicative of intentional release, such as the occurrence of an unexpected genetic variant or signs of genetic manipulations in the agent under

[33] The analytical chain here refers to the entire chain of activities, from sampling through sample transportation, sample preparation and analysis to interpretation of results.

[34] The figure refers to the situation when 12 locations are investigated, as specified in Council Resolution, 2009/C 296/01.

[35] There are two major categories of mechanisms that cause genetic variations in bacteria and viruses. The first (mutations) occur within the genome of an individual organism, the other (horizontal gene transfer) allows an individual to pick up genetic material from other organisms.

investigation. The existence of comprehensive and well-represented whole-genome databases could thus assist in characterisation of an outbreak as deliberate in origin.

85. Comprehensive reference strain collections currently exist for a wide range of public health relevant pathogenic organisms, and whole-genome sequences (rather than marker systems) are increasingly being exploited in reference databases. The availability of collections for some, from a Biological Weapons and Toxins Convention perspective relevant but comparatively rare pathogens, is however limited.

86. Technological advancements in the area of whole-genome sequencing and the associated enhanced scientific understanding of microbial population structures constitute an opportunity for the strengthening of BWC and other non-proliferation efforts. The enhanced applicability of these advancements in a BWC context would require further efforts, such as creation of comprehensive whole-genome reference strain databases of relevant biological agents, as well as further refinements in the understanding of population structures and interpretation of results from genetic comparisons of such agents. Complementary abilities, for example in sampling as well as in sample preservation and preparation also need attention. The comprehensive nature of these and other required efforts place them beyond what can be achieved by individual laboratories, institutions and organisations.

87. With collective efforts, however, based on active decisions and coordinated actions, the developments in these areas open new possibilities to detect and confirm violations to the Convention, to identify the perpetrator responsible and, through increased awareness of the existence of such capabilities, to help deter the use of biological weapons.

United Kingdom of Great Britain and Northern Ireland

A. Overview

88. The United Kingdom provides the following information on new scientific and technological developments relevant to the Biological and Toxin Weapons Convention (BTWC). Many of the technologies included in this paper have been described in detail in submissions by the United Kingdom and other States Parties to previous Review Conferences, and in various reviews and other publications. Reports of specific studies and events to examine relevant trends in science and technology in preparation for considerations at the Seventh Review Conference also summarise recent advances[36]. The increasing range of relevant scientific and technological fields and the pace of advances in many of these make it totally impractical to provide a comprehensive review in this paper. Thus our approach here is to cover some of the relevant enabling technologies and give examples of recent advances in those fields, then to consider some potential applications of such advances and their possible implications for the BTWC as a whole, and also for specific Articles where particular developments have noteworthy implications. In general, a number of developments introduce new possibilities for misuse, but many also offer potential benefits for prophylactic protective or other peaceful purposes. Developments which increase the likelihood of detection or provide improved protective or therapeutic

[36] For example: US National Academies, Trends in Science and Technology Relevant to the Biological and Toxin Weapons Convention: Summary of an International Workshop; Harvard Sussex Programme series of papers considering developments in science and technology of relevance to the Convention. http://hsp.sussex.ac.uk/sandtreviews/news/article/4e92f97377a7e

measures may help reduce the impact of misuse, thus making the acquisition and use of BW less attractive.

89. It is worth noting that there are many cross-linkages between advances in various technological areas that should not be overlooked if considering specific themes in a future review process in the context of the BTWC. Many technologies now take a multidisciplinary approach, necessitating the involvement of experts from several fields; therefore consideration of the advances in such technologies and their potential implications would also require multidisciplinary involvement. The convergence of chemistry and biology in the development of some of the technologies described below, such as synthetic biology, nanotechnologies and neuroscience, is a core issue in this context. There is a recognised need to consider implications of progress in such areas for both the BTWC and the Chemical Weapons Convention (CWC). For example, synthetic biology was addressed in the UK paper on technological developments in the chemical industry prepared for the Second Review Conference of the CWC in 2008[37]. Synthetic biology is a key example that highlights the growing convergence of chemistry and biology and presents challenges to both Conventions; as such it also has implications for Article IX of the BTWC, which affirms the recognised objective of effective prohibition of chemical weapons.

90. The rapid pace of relevant advances in a wide range of complex fields underlines the UK view, expressed in previous Review Conference papers on advances in science and technology, that there is a need to consider a process of more frequent assessment of such advances relevant to the BTWC. The brief overviews of scientific and technological topics included in this paper highlight themes that could be addressed in full detail by a future regular and systematic process established by the States Parties for reviewing and responding to relevant scientific and technological advances. We have made a specific proposal on how this might be done in our Working Paper '*Illustrative model intersessional work programme: a proposal for task group structure and agenda items'*.

B. Science and technology review

1. Genomics, proteomics and other '-omics'

91. Recent major advances in genomics, such as next generation sequencing technology, have provided large numbers of genome sequences, from microbes through to plants, animals and humans. Sequencing can now be used for applications that were previously too costly, large or complex, such as comparative genomics analysis and metagenomics, and is the starting point for other '-omics'-based applications, such as transcriptomics, immunomics and proteomics[38]. However, the rapid development of advanced sequencing systems has been largely technology driven, rather than application driven, hence there is now advanced technology in search of applied uses. Future developments in sequencing technologies, such as the use of nanopores integrated with semi-conductor technology should allow hand-held devices for field use.

[37] United Kingdom of Great Britain and Northern Ireland: Technological and Structural Developments in the Chemical Industry and their Implications for the Chemical Weapons Convention, RC-2 NAT.25, 18 April 2008 page 5.

[38] Further descriptions of the –omics mentioned here were given in the UK paper on science and technology developments submitted to the Sixth Review Conference of the BTWC. Briefly, proteomics is the study of the proteins expressed by an organism or system; metagenomics is the genetic analysis of microbial communities in the environment; transcriptomics is the study of RNA trancripts produced under a given set of environmental conditions; immunomics is the study of the immunodominant proteins of an organism.

92. The new ability for rapid sequencing of pathogens has profound implications for epidemiology, disease surveillance, detection and diagnosis, and for bioforensics. It also has the potential to provide a fuller understanding of virulence factors and mechanisms, which may help identify new therapeutic targets and antigens for vaccine developments[39]. The power of whole-genome sequencing was illustrated by its application during the recent *E. coli* outbreak in Europe[40]. It allowed very rapid characterisation of the pathogen, and provided an opportunity to test and benchmark a range of competing sequencing technologies. This was an encouraging precedent for use of whole genome sequencing in combination with epidemiological and geographic data in future outbreaks.

93. Transcriptomics and proteomics are useful tools in understanding at a molecular level the regulation of key metabolic pathways that enable microorganisms to adapt, survive and cause disease. The global gene expression profiles of bacterial pathogens have been studied using high-throughput transcriptomic techniques such as microarrays and RNA sequencing. Gene expression data can also be obtained from experimentally-infected hosts to identify mechanisms of virulence and unique host-response signatures for pathogens, which may provide diagnostic markers for disease identification. Microarrays allow the quantification of tens of thousands of RNA transcripts in a single reaction. This technology can be used to study disease at the genome level, potentially identifying disease-specific host immunological responses, developing novel host clinical biomarkers and investigating drug efficacy. It is also being used to identify mechanisms by which bacterial pathogens cause and establish disease and to investigate host-pathogen interactions. Such research is key to the development of new vaccines, therapeutics and diagnostics for viral and bacterial infections.

94. In the last five years, high-density tiled microarrays have been developed to characterise genomes at a higher resolution. They contain probes for apparently non-coding genome regions, allowing novel transcripts and small intergenic RNAs to be identified. An understanding of how these intergenic regions are expressed in response to antimicrobial chemotherapy can elucidate previously unidentified antibiotic resistance mechanisms.

95. 'ChIP-on-chip' is a new technique that combines chromatin immune-precipitation with microarray technology and is used following on from global gene expression analysis to investigate interactions between regulatory proteins and DNA. It can be used to identify, for example, transcription factor binding sites throughout the genome and regulons (collections of genes under the regulation of the same regulatory protein), enabling the development of interventions focussing on the control points for virulence factor cascades. Recently, transcriptomic studies have also been applied to species or strain comparisons. These studies highlight species-specific transcriptional responses, which is a useful way of identifying virulence factors for species-specific interventions.

96. Protein microarrays now also play a central role in the proteomics approach, particularly for the diagnosis of infectious disease. For example, protein microarrays for serum profiling ('immunomics') provide insight into the pathogen proteins expressed during infection, which may provide diagnostic targets. Arrays can now be fabricated automatically in a week or so for a typical bacterial genome.

97. Proteomics approaches can provide key information on the response to infection or vaccination, and on the differences between them. They have been widely used to study the immune response to infectious disease, derived vaccines and in screening for diagnostic

[39] See for example: Relman, D.A. (2011). Microbial Genomics and Infectious Diseases. The New England Journal of Medicine 365:347-357. http://www.nejm.org/doi/full/10.1056/NEJMra1003071

[40] http://www.nature.com/nbt/journal/v29/n9/full/nbt.1978.html; also discussed elsewhere in this UK paper.

targets. Key proteins involved in disease processes are being revealed, which may be exploited for treatment or prevention.

98. A huge and increasing amount of information derived from genomics, proteomics etc. is now in the public domain and available without control. While this contributes significantly to our understanding and ability to solve biological questions, it also raises the potential for misuse in a BW programme. The more that is learnt about a microorganism, the greater the possibility to genetically engineer a BW agent with designed properties. Similarly, as the understanding of human, animal and plant genomes increases, the greater the opportunity to identify and exploit vulnerabilities in their genetic make-up. However, such misuse is clearly prohibited by Article I of the Convention, which covers all biological agents 'whatever their origin or method of production … that have no justification for prophylactic, protective, or other peaceful purposes'. Article III covers the issue of transfer of technology or information intended to assist in activities prohibited by Article I. Due consideration must be given to the implications of developments in these fields in the context of Article IV obligations to implement nationally the prohibitions of Article I.

99. The wide reaching potential to produce beneficial applications for infectious disease control also applies to the development of biodefence measures, and to the operation of the BTWC. For example, applications in the field of forensic epidemiology where isolates from outbreaks or incidents can be pinpointed to a specific origin by use of comparative genomics would be of great utility in investigation of complaints relating to violation of the Convention. The potential benefits described in epidemiology, diagnostics, therapeutics and vaccine development would also be of use in the provision of assistance under Article VII of the Convention, and be relevant for cooperation and capacity building in the prevention of disease as specified under Article X.

2. Systems biology, bioinformatics and computational tools

100. Systems biology involves the mathematical modelling of biological systems at a variety of levels from the molecular to cells, tissues, organisms and ecosystems progressively, allowing predictions to be made. Mathematical models are developed and tested alongside practical experimentation in an iterative cycle. Progress in the field was reviewed prior to the Sixth Review Conference in a number of sources[41]. The usefulness of systems biology tools for analysing complex regulatory networks of biological systems and for interpreting the vast quantities of data emerging from fields such as genomics and proteomics is recognised. Systems biology is an essential enabling technology for synthetic biology; for example, the full elucidation of the essential genome of *Caulobacter crescentus*, a model organism for the integrated circuitry that runs a bacterial cell cycle, has recently been published[42].

101. Systems biology approaches are being used in the UK to study a range of biological systems such as host/pathogen interactions, ageing and nutrition, immunology, RNA metabolism, circadian rhythms, and microbial signalling networks[43]. Expected benefits

[41] For example: 'Globalization, Biosecurity, and the Future of the Life Sciences' (2006), Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, Institute of Medicine and National Research Council of the National Academies. The National Academies Press, Washington, D.C.; and 'Background Information Document on New Scientific And Technological Developments Relevant to the Convention' BWC/CONF.VI/INF.4 28 September 2006.

[42] Christen B., Abeliuk E., Collier J.M., Kalogeraki V.S., Passarelli B., Coller J.A., Fero M.J., McAdams H.H. & Shapiro L. (2011) The essential genome of a bacterium. Molecular Systems Biology 7:528-534. http://www.nature.com/msb/journal/v7/n1/full/msb201158.html

[43] See http://www.bbsrc.ac.uk/web/FILES/Publications/systems_biology.pdf

from such research include: faster routes to new drug candidates and development of personalised medicines; improved diagnostics for human, animal and plant diseases; and an increased ability to 'design' products such as bio-compatible materials for surgery, biofuels, healthier foods and renewable feedstocks. There are thus many potential benefits relevant to the BTWC, for example, detection and diagnostic techniques and medical countermeasures of utility in the provision of support and assistance in response to disease outbreaks, whether natural, accidental or deliberate.

102. The sheer complexity and quantity of biological data involved demands vast computational resources, which are only now gradually becoming widely available. Bioinformatics uses an interdisciplinary approach combining mathematical, statistical and computational methods to handle and enhance the understanding of accumulating data. It is supported by rapid advances in and greater global availability of computing power and capacity for data storage. 'Grid' and 'cloud' computing solutions, which use distributed computing networks, allow individuals to rent access to high performance computing services for data processing and storage through the internet as required. This has the advantage of speeding up analysis and obviating the need to invest in new infrastructure and software, but has an increased risk of data loss or compromise since it requires data transfer to a third party. However, further advances in computational power are still required to achieve simulation of complex biological systems with more predictive accuracy. Systems biology requires an interdisciplinary process, involving life scientists, information technologists, mathematicians, physicists and engineers, and depends on networks of collaboration. The level of international collaboration in this discipline is also increasing, which is of relevance to cooperation in the further development and application of scientific discoveries as specified in Article X of the BTWC. Free availability of data, standards and protocols, and open exchange of materials and technologies, are important for the support of such multinational collaborative research and development networks.

103. As with other dual-use technologies, systems biology approaches have the potential to be misused, for example to design new BW agents or to identify ways to manipulate biological systems deliberately to cause harm. The prohibitions of Article I of the Convention would cover any biological agents or toxins developed by such approaches. However, continued consideration of the implications of developments is required in this field where there is still limited knowledge, understanding and ability to predict outcomes. Appropriate national implementation measures to prohibit and prevent any misuse of the technology may be required as further developments in systems biology emerge.

3. Synthetic biology

104. Although there is no widely agreed definition of synthetic biology, it is broadly understood as the design and construction of novel biological components, organisms and systems as well as the redesign of existing natural biological systems. It is a multidisciplinary field requiring synergy amongst a range of disciplines, including biology, chemistry, physics, engineering and information technology, and has the potential to lead to applications in areas such as medicine, energy, environment, food and materials, as well as a better understanding of biology. Synthetic biology approaches can be either 'top-down', where functional biological components are synthesised and inserted into entire genomes, or 'bottom-up', where functional components or whole genomes are synthesised from scratch. Synthetic biology is currently being used to construct DNA-encoded gene 'circuits' that can be programmed to control cell behaviour and phenotype, with applications as diverse as infectious disease and cancer therapies, and oil production by algae.

105. Progress in synthetic biology was reviewed comprehensively in background papers to the Sixth Review Conference of the BTWC, including the UK's contribution. Further advances were described briefly in a UK Working Paper to the 2008 Meeting of Experts,

which also outlined UK approaches to the responsible development of this emerging technology[44]. In addition, several side-events during the Intersessional Process have specifically addressed advances in synthetic biology and consideration of safety and security aspects[45].

106. In 2006, although successful reconstruction, *de novo* synthesis and *in vitro* assembly of infectious viral particles had been reported, chemical synthesis of a bacterial genome was still regarded as a possible future development requiring further technological advances and a high level of technical expertise and financial investment. Nonetheless, in less than five years, the J. Craig Venter Institute had reported the creation of a bacterial cell controlled only by a chemically-synthesised genome[46]. Thus the possibility of rationally-designed and artificially-created complex microbial life has become tantalisingly close to fruition, as DNA synthesis and genome assembly technologies have become ever faster and cheaper and advanced computational resources have become much more widely available. Although advances in genome sequencing technologies have greatly outpaced the ability to modify genomes, a recent approach called multiplex automated genome engineering (MAGE) allows modification of genomes on a large and parallel scale producing combinatorial genomic diversity. MAGE thus has the potential to expedite the design and evolution of organisms with new and improved properties[47].

107. Synthetic biology has stimulated much discussion on its technical potential and challenges, including those related to social, ethical and regulatory issues, and many reports and features on the topic have been published[48]. One of the contributions already made by synthetic biology is the synthesis of artemisinic acid, a precursor of the anti-malarial drug artemisinin, in *E. coli* and yeast. This project took considerable effort and funding, but has now entered the development and production phase in partnership with a global pharmaceutical company. However, there are still many challenges to address in developing the tools and techniques to the level required to achieve the promise of potential applications in a range of diverse fields.

108. As the technology becomes more advanced and accessible, risk assessment for such inherently unpredictable systems becomes increasingly challenging. As well as the vast array of potentially beneficial applications, advances in synthetic biology could be exploited for harmful purposes, including by creation of new BW agents, regeneration of otherwise inaccessible agents or by changing the characteristics of existing agents to increase their suitability for BW use. However, such activities are prohibited by Article I of the BTWC, as reaffirmed in the Sixth Review Conference Final Declaration: all naturally occurring or artificially created or altered microbial or other biological agents and toxins, as well as their components, regardless of their origin or method of production are covered.

109. Although it is difficult to quantify the risks, a key issue is the early consideration of a range of policy, social and ethical issues in the development of strategies for control,

[44] BWC/MSP/2008/MX/WP.11

[45] e.g. see: http://www.unog.ch/unog/website/disarmament.nsf/(httpPages)/98DD55F8A0EF259DC12574B200461162?OpenDocument

[46] Gibson et al. (2010). Creation of a Bacterial Cell Controlled by a Chemically Synthesised Genome. Science 329: 52-56.

[47] Wang et al. (2009). Programming cells by multiplex genome engineering and accelerated evolution. Nature 460: 894-898. http://www.nature.com/nature/journal/v460/n7257/pdf/nature08187.pdf

[48] e.g. See the Royal Society synthetic biology web page: http://royalsociety.org/policy/projects/synthetic-biology/, and http://www.sciencemag.org/site/special/syntheticbio

oversight and governance of this emerging technology and its applications[49]. In recent years a significant amount of literature has been produced on governance of this field: a 2011 paper on this topic included a list of 39 reports produced since 2004 by scientific, governmental and non-governmental organisations[50]. Several options for governance have been discussed, including: legal and regulatory frameworks; industry and academia self-regulatory mechanisms, such as codes of conduct and screening frameworks; and education and awareness-raising initiatives. Such measures are relevant to implementation of Article IV of the Convention, in reducing the risk of the exploitation of synthetic biology in violation of Articles I and III. The discussions of the need for improved governance also illustrate why there is a need for a more regular review of scientific and technological issues in a BTWC context.

110. Discussions on governance in this field have tended to focus mostly on commercial gene synthesis. However as research involving standardised biological parts, devices and systems matures, new governance measures beyond those already in place for the biotechnology industry may be required. Wherever possible, these should seek to support innovation and commercial development while protecting the public from potential harm, either from deliberate misuse or from unforeseen damage to health and the environment.

111. Beneficial advances in synthetic biology in fields such as vaccines and therapeutics, diagnostics and bioremediation also have implications for the operation of the Convention, particularly in providing support and assistance to States Parties affected by a violation of the Convention. Synthetic biology also has potential in the development of protective measures in biodefence programmes: as well as advances in medical countermeasures, novel sensor technologies and diagnostics, development of novel materials may provide solutions in decontamination, trauma care and protective clothing.

112. International communication and collaboration by scientists, including those from emerging economies will be a key part in the successful development of synthetic biology[51]. There is evidence of successful international collaboration in the international co-authorship of publications[52]. Participants from a growing number of countries participate in the International Synthetic Biology conferences, and in the annual International Genetically Engineered Machine (iGEM) competition. One element of iGEM is that competitors are required to submit the biological parts they make to the Registry of Standard Biological Parts, so that they are then available openly to other laboratories to build synthetic biology devices and systems[53]. Such activities are consistent with the provisions of Article X of the Convention, in supporting cooperation in the application of advances in science and technology; further international engagement should be encouraged both in technology advancement and application, and in the development of appropriate governance strategies.

4. Nanotechnologies

113. Nanotechnology is the creation and modification of objects in the 1 to 100 nanometre scale, e.g., macromolecules to viruses. It is an enabling technology that encompasses a broad spectrum of nanoscale science and engineering and has opened up

[49] BWC/MSP/2008/MX/WP.11

[50] http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/publications/2011/4294977685.pdf

[51] http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/publications/2010/4294974787.pdf

[52] http://hsp.sussex.ac.uk/sandtreviews/_uploads/4dda180146c53/synthetic%20biology%20and%20the%20bwc.pdf

[53] http://igem.org/IGEM/Learn_About

new avenues of research in a number of fields, including medicine, cosmetics, agriculture and food. A number of nanoparticles are now produced at industrial scales for use in a variety of consumer products. Recent developments in nanobiotechnology have enabled the creation of substances and systems with tailored biological properties[54]. Indeed, viruses, as natural nanomaterials, are attractive for nanotechnological modification and application due to their known and regular shape and size, ability to be used to package small molecule cargoes, and susceptibility to controlled modification and design, both chemically and through manipulation of their genomes. Virus-derived nanoparticles are particularly suited to specific tissue and cell-type targeting for therapeutic payload delivery.

114. In addition to improved drug discovery, formulation and delivery (including using nanoparticles to cross the blood-brain barrier), biomedical applications of nanotechnology include: novel medical treatments; personalised medicines; imaging and diagnostics; physiological monitoring; novel detection surface technologies; organ replacement and wound repair. The first transplanted synthetic organ, a human trachea, was produced using a nanocomposite polymer scaffold seeded with the patient's own bone marrow cells[55]. The development of such an 'integrated nanosystem' represents a third stage in nanotechnology development since 2000, building on the first and second stages, represented respectively by 'passive nanostructures' (nanoparticles, nanotubes and nanolayers) and 'active nanostructures' (e.g., multi-component, nanoencapsulated drug delivery particles). In the near future, 'heterogeneous molecular nanosystems', such as nanoscale genetic therapies, are predicted. The anticipated integration of nanotechnology and nanobiotechnology with information and communications technology and artificial intelligence will also help enable progress in this complex and data-rich field.

115. Nanotechnology will also significantly impact agriculture and food production, with potential applications in research and development worldwide, and promising benefits such as: molecular treatments, smart sensors and delivery systems to combat viruses and other crop pathogens; rapid disease detection; and enhanced nutrient absorption by plants. Nanotechnology also has the potential to increase the efficiency of pesticides and herbicides, allowing lower doses to be used, although such products are yet to be commercially available. When realised, such applications are likely to be adopted on a large scale by the agricultural sector worldwide. Therefore there is scope for collaboration between States Parties, consistent with Article X of the Convention, not only in relation to research and development in this area, but also in developing and implementing adequate, proactive risk management strategies, because applications such as nano-pesticides may pose novel risks to farmers, consumers and the environment.

116. Many nanotechnologies have potential BW defence applications in medical countermeasures, detection, decontamination and protection, which could also have relevance to the operation of the BTWC, e.g., in provision of assistance under Article VII. For example, nanofibre technology has potential military and civilian security applications in improved CBRN protective clothing, respirators and filters, etc. The synthesis of non-biological nanoparticles, which have been demonstrated to mimic some of the functions of natural antibodies, may have potential for therapeutic and diagnostic applications. Such 'plastic antibodies' with designed affinity for a peptide toxin have been shown in initial studies to function effectively in the bloodstream of living animals[56]. Similar approaches

[54] 'nanobiotechnology' is a term used to refer to the application of nanotechnology to the life sciences.

[55] http://www.ucl.ac.uk/news/news-articles/1107/11070701

[56] Hoshino, Y., Koide, H., Urakami, T., Kanazawa, H., Kodama, T., Oku, N., Shea, K. J. (2010) Recognition, Neutralization, and Clearance of Target Peptides in the Bloodstream of Living Mice by Molecularly Imprinted Polymer Nanoparticles: A Plastic Antibody. Journal of the American Chemical Society 132, 6644– 6645. http://pubs.acs.org/doi/pdfplus/10.1021/ja102148f

may in the future offer a cheaper and more stable alternative to antibody therapies, custom tailored to specific disease targets[57].

117. However, there is also the potential for creation of dangerous nanoparticles and nanosystems, leading to environmental damage or with potential applications in an offensive BW programme. Although the misuse of biological agents, toxins or means of their delivery resulting from advances in nanotechnologies would clearly be prohibited by Article I, there is a need to consider the scope of the BTWC as it applies to wider developments in the field. Moreover, the properties of novel nanomaterials, including toxicity, are inherently unpredictable, and the risks they pose are often poorly understood. Conventional physicochemical rules do not fully apply at the nano-scale, and the toxicology of nanomaterials may differ fundamentally from their bulk equivalents. Nanoparticles, unlike larger particulates, may penetrate cellular barriers such as those in the gastrointestinal tract, the brain and the placenta. Thus some experts have suggested that responsible nanotechnology should focus on the use of low-toxicity, non-persistent or biodegradable materials from the earliest stages of research and development. One of the presentations at the OPCW's September 2011 Conference on International Cooperation and Chemical Safety & Security noted that the new concepts of size dependent toxicity, nanotoxicology and nanopathology deserve special attention in the coming years[58]. Such developments underline the need to consider jointly the impact of changes in chemical and biological sciences on both the CWC and BTWC.

118. The UK outlined its approach to the responsible development of nanotechnologies in a Working Paper to the 2008 BTWC Meeting of Experts[59]. Recent initiatives to gauge the risks posed by nanobiotechnology, and suggest response options, include work by the UN Interregional Crime and Justice Research Institute (UNICRI), in cooperation with the EU[60]. This study highlighted the continuing importance of arms control agreements and regulations, but also emphasised the need for reinforcement of a systematic and responsible safety and security culture in biotechnology, involving checks, case-by-case risk assessment and awareness-raising. The report recognised the reaffirmations in Review Conference Final Declarations that the BTWC prohibitions apply also to artificially created biological agents and toxins, whatever their origin or method of production and would thus apply to such products of nanotechnology. However, it also acknowledged the need to consider whether the scope of Article I fully covered all future possibilities offered by nanotechnology due to the degree of artificiality in some products.

5. Neuroscience

119. Developments in neuroscience, the study of the brain and nervous system, have the potential to provide significant benefits, including improved treatment of neurodegenerative disease and mental illness and increased insights into normal human behaviour and mental wellbeing. Such developments are likely to raise social and ethical issues. The Royal Society is considering the implications of developments in neuroscience for society, public policy and governance in its 'Brain Waves' project, which aims to explore what neuroscience can offer, its limitations and the potential benefits and risks posed by

[57] http://www.technologyreview.com/biomedicine/25591/

[58] http://www.opcw.org/fileadmin/OPCW/events/2011/IYC2011/Guidotti-OPCW-Hague11.pdf

[59] BWC/MSP/2008/MX/WP.11: Oversight of Emerging Technologies: Examples of UK Approaches to Responsible Development of Science.

[60] Bonin, S. (2011). Security Implications of Synthetic Biology and Nanobiotechnology: A Risk and Response Assessment of Advances in Biotechnology. Turin: UNICRI.

particular applications[61]. Its first report gives an overview of current developments in neuroscience and neurotechnology.

120. In this field, technologies for the discovery and development of compounds that act on the central nervous system (CNS) are of particular relevance to the BTWC. These include advances in molecular and genetic neuroscience, drug discovery technology, bioregulators and drug delivery to the brain.

121. Ion channels and neurotransmitter receptors are key components in many cellular processes, including the transmission of nerve impulses across synapses, and are frequently targeted in the search for new therapeutic drugs. Most natural biological toxins or venoms, that have evolved to attack the nervous systems of prey, affect the ion channels of nerve synapses. Ion channels have been extensively studied at molecular and genetic level, and hundreds of genes have now been identified that encode their constituent protein subunits. Synapse proteomics will be of increasing importance in genomic diagnostics of brain diseases as well as in providing a new set of potential drug targets. Such developments have been facilitated by advances in fields such as high-throughput DNA sequencing and proteomics. Mutations in the genes encoding receptor subunits have been shown to play a role in many human diseases, and this has stimulated the search for new drugs that act on these sites. However, recent developments have indicated that the discovery of new medicines will require a combination of molecular tools and the effectiveness of approaches that study biological systems as a whole.

122. In recent years, advances in drug discovery technology have included screening with high content systems (HCS), which is based on a bioassay approach, using automated digital microscopy and flow cytometry to evaluate multiple biochemical and morphological parameters in cellular systems. This has joined high throughput screening (HTS) as an approach to the selection of candidate drug compounds from large libraries produced by combinatorial chemistry. These and other recent developments, together with microfluidic reactors, offer significant improvements in energy efficiency, reaction speed and yield, safety, reliability, scalability, on-site/on-demand production and process control.

123. Bioregulators regulate vital cellular processes and a range of important physiological responses through reaction of a peptide ligand with cellular receptors. Peptide bioregulators and their synthetic derivatives continue to be of interest for their therapeutic potential, and also have potential applications in agriculture. The costs for peptide synthesis and production are likely to continue to fall, and be increasingly undertaken by specialist synthesis companies, obviating the need for in-house production capability. Phage and ribosomal display technologies and combinatorial chemistry, with HTS, will lead to new peptide drugs that target specific receptors.

124. Peripherally administered bioregulators, and analogous synthetic drugs, however, do not readily reach the brain due to the blood-brain barrier (BBB), leading to failure of many potential therapeutics. Computational *in silico* approaches have recently been used to predict BBB permeability, which may facilitate the identification of potentially suitable compounds. Large molecules can be re-engineered to cross the BBB as molecular 'Trojan horses' - endogenous peptides, or peptidomimetic monoclonal antibodies which enter the brain from the blood via receptor-mediated transport on endogenous BBB transporters. Liposomes and nanoparticles have also been used for drug delivery to the CNS.

125. Advances in technologies for drug development and delivery have many potential beneficial applications, including in the development of new compounds with potential medical countermeasures utility of relevance to biological defence. Such applications have

[61] http://royalsociety.org/brainwaves/

implications for the operation of the BTWC, for example, in the provision of assistance to mitigate the consequences of a violation of the Convention, as well as in deterring violations at the outset since more effective defensive measures could become available. Developments in this area could also result in the identification of compounds with potential for misuse as biological or toxin weapons agents since drugs acting on the brain to produce toxic or incapacitating effects could also have utility in a BW programme. Methods to facilitate delivery of such agents could also be exploited for harmful purposes, for example, to facilitate the entry of peptide neurotoxins across the BBB. However, the prohibitions of Article I of the BTWC fully cover all such biological agents and toxins, whether naturally occurring or artificially created, regardless of their origin or method of production. Since many of the benefits and risks of advances in neurosciences lie in the future, it is timely to consider issues related to governance of this dual-use technology area, balancing the obligation to take measures to prohibit misuse with the need to ensure that the beneficial development of science is not hampered. This is one of the reasons why we have proposed in our Working Paper on a new Intersessional Work Programme that a Task Group on science and technology address oversight issues for scientific and technological developments.

126. The third module of the Royal Society Brain Waves project, 'Neuroscience, conflict and security' has been addressing the dual use nature of advances and their implications for the BTWC and the CWC. The findings of this work have yet to publish; however, it is covering issues relevant for future consideration of this topic, such as:

(a) the impact of advances in areas such as neuropharmacology and drug delivery (by aerosol and across the blood-brain barrier), particularly on the ability to enhance, manipulate or degrade human performance;

(b) how misuse of associated physiologically-active compounds may be addressed under the CWC and the BTWC;

(c) governance of neuroscience, including current frameworks and policy recommendations.

6. Biological production technologies

127. Fermenters and bioreactors are key technologies in the production of microorganisms and microbial products (including toxins), and are commercially available from small scale (1 to 20 litres) to large scale (1000 to over 100000 litres). Design improvements in recent years have lead to an increase in yield, portability and safety of fermentation systems. Programmable, modular systems now allow for ease of on-line sample analysis and tighter control of process parameters. This and other developments, such as fed-batch and dialysis fermentation and increased computer control, have led to significant improvements in cell densities achieved during fermentation and improved set-up and control of large-scale fermentation. Magnetic agitator systems, contained sampling devices and leak test software have improved safety in the production of pathogens by reducing the risk of leakage.

128. Progress in single-use or disposable bioreactor systems has continued with working volumes up to 2000 litres now available. These are easily installed, reduce costs, streamline validation, increase product consistency and reduce overall turnaround times. These systems range from bag-lined, hard-walled fermenter systems suitable for growth of bacteria, to simpler rocked-bags more suited to cell culture, including for virus vaccine production, where there is a trend towards growth in mammalian and insect cell lines rather than traditional systems such as avian egg culture. Single-use or disposable components also increasingly feature in downstream processing equipment, such as filter cassettes for cross-flow filtration. At a much smaller scale, microfluidic bioreactors for virus production

have been developed which can provide a continuous supply of virus supernatant for further production or storage or for use in studies such as the evaluation of viral vectors for gene therapy applications.

129. Small peptides, including toxins, can be chemically synthesised – a service that is now readily available commercially. Many recombinant microbial products, including toxins, can also be produced in *E. coli*, and increasingly yeast; yeast expression systems are particularly suited to production of complex eukaryotic toxins and venoms, which may have therapeutic uses. Recombinant DNA technology is also predicted to revolutionise vaccine manufacturing, removing the need for both culture of pathogens, and parallel product streams in conjugated vaccine processes. Some recombinant vaccines have now been licensed, e.g., Hepatitis B.

130. Developments in transgenic plants and animals have continued since the Sixth Review Conference. The transgenic production of therapeutic biological agents in plants has recently progressed with the start of clinical trials of a monoclonal antibody against HIV produced in transgenic tobacco plants[62]. This is a potentially low-cost, scalable system, and it is hoped that widespread use of plant-based production may lead to cheaper vaccines and drugs for the developing world – however, the complications and costs of downstream processing are often underestimated. Similarly there are advantages and disadvantages in the exploitation of transgenic animals. However, a recombinant form of human antithrombin produced in the milk of transgenic goats was the first transgenically produced protein approved for human use. The expression of recombinant human lysozyme, a bactericidal protein, in the milk of transgenic cattle has been reported recently[63].

131. The potential benefits for such developments in biological production technologies are vast and include many of relevance to the BTWC, e.g., under Articles VII and X. They provide more rapid, flexible and cost effective methods for production of medical countermeasures to combat infectious disease, whether naturally occurring or deliberately caused, which will have impact globally. However, they also have the potential to be misused for the production of biological or toxin weapons agents. In particular, the trend towards simpler, single use or disposable systems and the availability of equipment and information on the internet will make the technology easier to access worldwide. However, the prohibitions of Article I would fully cover any biological or toxin agents produced by any of the described fermentation technologies as well as by chemical synthesis or in transgenic plants or animals.

132. A more recent issue to consider is that of so-called amateur, hobby, ‘garage’ or ‘DIY’ biology, which has attracted scrutiny from a safety, security and proliferation point of view, especially regarding unregulated culture of microorganisms, genetic engineering and synthetic biology undertaken outside recognised scientific institutions[64]. Currently, hobbyists may obtain cheap, second-hand laboratory equipment, or utilise microcentrifuges, PCR thermocyclers, etc, that are homemade from designs circulating on the World Wide Web. They may also band together to set-up ‘community’ laboratories, pooling resources to purchase more expensive equipment such as DNA synthesisers or analysers. In the future, existing or new supply companies may specifically target this growing amateur market. The implications of these developments for the operation of the BTWC also need to be considered given Article IV obligations to take the necessary national measures to implement the prohibitions of Article I, and Article III requirements not to transfer to others or assist anyone in the manufacture of biological or toxin weapons agents. As amateur

[62] http://www.in-pharmatechnologist.com/content/view/print/387675
[63] http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0017593
[64] http://www.nature.com/news/2010/101006/full/467650a.html

biology grows, States Parties must consider what measures might be most effective in preventing its misuse by individuals or groups. Outreach, education and awareness-raising activities have a role to play in preventing intentional or accidental misuse of biotechnology, but regulation and licensing are also possibilities to be considered.

7. Delivery and dispersal

133. Research in aerobiology has contributed to the development of alternative, inhalation-based methods of drug and vaccine delivery, with recent advances overcoming some of the earlier problems and achieving improved efficacy of inhalable biologics. Such developments draw upon advances in other disciplines and technologies - a particular example being recent development of nanomaterials with unique properties that allow targeted drug delivery[65].

134. Microencapsulation is a developing, dual-use technology used widely in the food and pharmaceutical industries, e.g., for isolating and protecting bioactive molecules and facilitating their controlled release. A range of chemical and mechanical methods are used for microencapsulation. Of the latter, modern approaches to rapid spray-drying have become less technically demanding and well-suited to use with thermosensitive compounds; they can also produce microparticles of controlled sizes and types appropriate for inhalation and intraocular delivery of drugs. A drawback of microencapsulated particle drug delivery can be the subsequent low penetration and diffusion into tissues. However, it has been shown recently that drug-containing nanoparticles, in the form of nanoemulsions, can be microencapsulated by spray-drying to form so-called "Trojan" particles[66]. These combine the manipulation and administration advantages of microparticles (e.g., as an aerosol) with the tissue penetration properties of nanoparticles, which are released after administration to the patient and penetrate tissues to reach the cells targeted for therapy. As knowledge of receptor targets for bioactive molecules increases, delivery of therapeutic drugs by this or similar technology is likely to become widespread. Such advances in nanomedicine are of relevance to the operation of the BTWC, with potential benefits for medical countermeasures provided in support of a response to a violation of the Convention, as well as in the application of scientific discoveries to the prevention of disease and other peaceful purposes.

135. Obviously there is also the potential for misuse of delivery and dispersal technologies for hostile purposes. Encapsulation of biological materials could be used to increase their stability, facilitate more efficient dissemination or allow evasion of detection or medical countermeasures. Advances in aerobiology could also have application in the dissemination of biological or toxin agents. Modelling systems, such as respiratory and inhalation models, developed to support beneficial advances in this field, could also provide information that could be misused for harmful purposes. However, such offensive applications are clearly prohibited by Article I of the BTWC, and States Parties have a commitment to take the necessary national measures to prohibit and prevent the misuse of science, including by promoting awareness-raising on the Convention and associated risks.

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[65] Trends in Science and Technology Relevant to the Biological and Toxin Weapons Convention: Summary of an International Workshop: October 31 to November 3, 2010, Beijing, China', pp. 16-19. http://www.nap.edu/catalog.php?record_id=13113

[66] Li, X., Anton, N., Ta, T.M.C., Zhao, M., Messaddeq, N. & Vandamme, T.F. (2011). Microencapsulation of nanoemulsions: novel Trojan particles for bioactive lipid molecule delivery. International Journal of Nanomedicine 6, 1313-1325.

8. Surveillance, detection, diagnosis, and bioforensics

136. Advances in technologies described earlier in this paper have assisted the development of applications in the surveillance, detection and diagnosis of infectious diseases of humans, animals and plants. New, sophisticated forms of information and communication technology, some utilising the internet, are playing an increasing role in detecting, tracking and responding to infectious disease outbreaks, such as the 2009 H1N1 influenza epidemic. Such developments have enabled the initiation of new regional and international disease monitoring networks. There have been recent notable advances in the development of epidemiological systems and statistical capabilities for estimating the location and extent of populations potentially exposed to biological agents, and the timing of such exposures, to assist in the targeting of countermeasures and other response activities. More sophisticated spatio-temporal statistical techniques are also under development that take such epidemiological data and apply algorithms to estimate such aspects as the time of release of a biological agent, the extent of its dispersal and hence the extent of the population that has been exposed. Syndromic surveillance could well provide real-time surveillance of patient data in the future; but to be effective internationally, capacity building in global public health, disease reporting and disease surveillance is necessary.

137. A major developing technology area that is relevant to disease surveillance, as well as detection, diagnosis and bioforensics/attribution is genome sequencing. In the last few years, the introduction of technologies like pyrosequencing and nanopore technology has allowed high throughput sequencing at markedly decreasing costs. The advent of bench-top instruments has also made the technology much more widespread and accessible, such that it is no longer the preserve of large research centres. Indeed, one of the latest commercial developments in rapid genome sequencing technology, which decodes DNA directly on a semiconductor chip and works by detecting a voltage change, allowed for rapid and early prospective whole genome characterisation of the virulent *E. coli* O104:H4 that caused a recent fatal outbreak in Germany[67]. Access to such information in the early stages of an outbreak helps in making important informed decisions regarding treatment, prevention and tracking of the source.

138. High throughput genome sequencing has also improved knowledge of the natural phylogeography and comparative genomics for some biological agents, through, for example, comparison of single-nucleotide polymorphisms (SNPs) in different isolates. This could provide vital knowledge for bioforensics and attribution following a BW attack; such data are already available for some possible threats.

139. Systems for rapid DNA detection, such as DNA biosensors and DNA microarrays, have applications in diagnostics, bioforensics and detection of BW agents. A range of technical approaches to sensing DNA binding have been developed in the last few years, and electrochemical detection of DNA has the potential to be miniaturised to produce portable systems for clinical testing and on-site environmental monitoring. Biosensors based on nanotechnology for the molecular detection of food-borne pathogens and potential bio-terrorism agents have also been reported recently; and the integration of nanofabrication with a microfluidics platform brings truly hand-held DNA detection and identification much closer. Sample preparation remains a key challenge in molecular

[67] Mellman et al (2011). Prospective Genomic Characterization of the German Enterohemorrhagic Escherichia coli O104:H4 Outbreak by Rapid Next Generation Sequencing Technology. PLoS One 6:e22751. http://www.plosone.org/article/info:doi/10.1371/journal.pone.0022751, http://www.nature.com/news/2011/110720/full/475278a.html

diagnostics and detection, as does the integration of various systems for sample collection, processing and analysis.

140. One concern for bioforensics is that, while the rapidly growing numbers of analytical methods available provide new opportunities and capabilities, they also create challenges for validation. Nevertheless, microbial forensics would be a vital tool in responding to suspected bioterrorism, deliberate, accidental and natural disease outbreaks, and investigations of alleged use of BW. In this regard establishment of international standards and cooperation would be beneficial.

141. Because the spread of infectious diseases, whether natural or deliberate, is not limited by national borders, there is a need for database systems to capture and integrate diagnostic systems on a national, regional and international scale, which will require capacity building for sampling, processing and data collection. Encouraging the sharing of clinical, diagnostic and pathogen data can also facilitate the implementation and impact of current and new technologies. Thus international cooperation in this field can make a key contribution to the development and application of scientific discoveries for the prevention of disease, or for other peaceful purposes. The 2008 meetings of the BTWC Intersessional Process addressed these issues, and recognised the fundamental importance of enhancing international cooperation and promoting capacity building in infectious disease control, in the context of Article X of the Convention as well as through the efforts of international organisations such as the WHO, OIE and FAO in enhancing capabilities and coordinating activities.

142. Such enhanced capabilities would also have implications for the operation of other Articles of the Convention, particularly Article VII in supporting assistance to a State Party exposed to danger as a result of a violation of the Convention. The application of advances in technologies, particularly in bioforensics, would be highly relevant in the support of investigations under Article VI. Although there is the potential for misuse of some technological advances described here, for example, epidemiological modelling systems could be misused in the design of BW attacks, the improved detection methodologies and the possibility of forensic attribution could also act as a deterrent factor, making BW less attractive. Improved surveillance, detection, diagnostic and forensic technologies also have a role to play in the enforcement of national measures to implement the prohibitions of the Convention, providing means for the detection and attribution of prohibited activities.

9. Medical countermeasures

143. Since the Sixth Review Conference, advances in several enabling technologies have enhanced progress in the development of therapeutic and prophylactic medical countermeasures against biological and toxin agents. The relentless rise of resistance to common antibacterial antibiotics has driven the search for new antibacterial therapies and several new antibiotic classes have recently entered clinical use, including: cyclic lipopeptides (one of many synthetic and natural antimicrobial peptides with therapeutic potential), glycylcyclines (derived from tetracycline but designed to overcome resistance) and new oxazolidinones (with greater antibacterial activity and less potential for resistance). Research is also underway on new approaches to antibiotic discovery by targeting alternative virulence aspects, such as the production and secretion of toxins, rather than the traditional targets of nucleic acids and protein and cell wall synthesis[68].

144. There are now more than 60 licensed antiviral drugs available, but most target human immunodeficiency virus (HIV) and various herpesviruses. Novel therapeutic

[68] e.g. http://www.sciencedaily.com/releases/2011/02/110208123640.htm

approaches against hepatitis C virus (HCV, an RNA virus), include candidates that block viral RNA replication by targeting the polymerase enzyme, inhibit viral protein cleavage by targeting the HCV protease, stimulate the immune response and exploit RNA interference (RNAi). Two protease-inhibitor antivirals against HCV have been approved recently. However, there is an urgent need for drugs to treat the numerous viral diseases caused by RNA viruses for which limited or no therapeutic options are currently available. Broad-spectrum antivirals would be highly desirable and may come from targeting host cell proteins rather than viral proteins. For example, a recently reported novel broad-spectrum anti-viral approach induces selective apoptosis (programmed cell death) in host cells containing viral RNA, without harming uninfected cells[69]. However, targeting host cell proteins may result in a higher risk of toxicity, which could lead to the identification of harmful compounds with the potential for misuse.

145. The therapeutic potential of using RNAi-mediated gene expression silencing for treatment of viral and genetic diseases, and cancer, has been recognised for some time and was reviewed in the UK contribution on advances in science and technology to the Sixth Review Conference. RNAi has an advantage over small-molecule drugs, because most genes are susceptible to targeting by short interfering RNA (siRNA). However, effective *in vivo* delivery to specific tissues and gene targets has been a significant challenge to realising RNAi as a therapy. Promising methods for delivery of siRNA include liposomes, polymers, protective chemical modifications, nanoparticles and antibodies. New technologies that combine siRNA molecules with aptamers (small DNA or RNA sequences that bind to target cellular receptors) have also shown promise, and therapies targeting the liver to treat metabolic diseases are in clinical trials[70]. RNAi undoubtedly has potential to influence markedly future medical countermeasures, but challenges related to targeted delivery have slowed progress to some extent, such that some pharmaceutical companies may be reducing investment in research and development in this area. The dual-use nature of RNAi technology is also recognised, with possible hostile applications including the enhancement of viral virulence or silencing of functional genes in humans. However, use of RNAi in BW agent development would face many of the same technical challenges as therapeutic development, and would demand significant technical know-how and financial investment with high potential for failure. Thus, until the technology matures, offensive use of RNAi remains largely theoretical rather than an imminent risk. However, any significant breakthrough that overcomes the existing challenges to therapeutic use of RNAi would also have implications for its potential for misuse. Thus regular monitoring of advances in this field is important, and again supports the need for more regular reviews of advances in science and technology.

146. Traditional approaches to vaccine development – that is, 'live-attenuated' and 'killed' vaccines – have been augmented by newer strategies, which start from microbial DNA or RNA. Amongst these are the use of recombinant vectors, plasmid and 'naked' DNA, reverse vaccinology and genetics, synthetic peptides and capsular polysaccharides, and identification of virulence factor genes using microarray analysis[71]. Rational vaccine design, although still largely at the stage of advanced research and development, draws on enabling technologies such as genomics, bioinformatics, systems biology and immunology, and also seeks to direct and optimise the immune response to vaccination by using new adjuvants such as CpG oligodeoxynucleotide, liposomes, Toll-like receptor agonists and

[69] http://www.plosone.org/article/info:doi/10.1371/journal.pone.0022572

[70] Czech M.P., Aouadi M & Tesz G. (2011) RNAi-based therapeutic strategies for metabolic disease. Nature Reviews Endocrinology 7:473-484. http://www.nature.com/nrendo/journal/v7/n8/pdf/nrendo.2011.57.pdf

[71] See, e.g., http://www.nature.com/nm/journal/v11/n4s/pdf/nm1209.pdf

cytokines. Recent developments in vaccine delivery have drawn on advances in nanotechnology and microencapsulation. Non-parenteral routes of administration, such as intranasal, aerosol, oral and transcutaneous, are also being exploited; addressing, for example, the need to stimulate mucosal immune responses and improve the efficacy of mass vaccination.

147. Such technological developments, and the widening focus of vaccinology to address non-infectious disease targets (such as autoimmunity, contraception, obesity and addiction), along with some unexpected severe adverse effects encountered in trials of certain new vaccine candidates, have highlighted the potential for an increased risk of misuse of rational vaccine design for harmful purposes. On the other hand, the rational design, genomic and proteomic approaches have reduced the timescale for vaccine development, and have in some cases reduced or removed the requirement for large-scale cultivation of pathogens in vaccine production. Indeed, the widening diversity of vaccine production methods now include: cell cultures and cell suspension bioreactors; recombinant DNA, metabolic engineering and synthetic biology; chemical peptide synthesis; and, transgenic animals or plants. Recent approaches are expected to lead to more rapid, increased and cheaper production of vaccines and encourage their wider use, especially in resource-limited countries. Global strategies to promote policies of advocating vaccine development and use are required to overcome lack of uptake for some vaccines.

148. Advances in the development of new vaccines and new vaccine technology, as well as improvements in the production of established vaccines, are highly relevant to the BTWC. Such advances should be taken into account in review of the current Confidence Building Measures (CBMs), particularly CBM G which requires the declaration of facilities licensed to produce vaccines for the protection of humans. Some developments described above have the potential to be exploited for hostile purposes; however, the scope of Article I prohibits all such misuse covering agents ‘whatever their origin or method of production’, and their means of delivery. National measures such as legislation and regulation are necessary to prevent prohibited activities related to Articles I and III of the Convention; such measures should be designed and implemented in a way to prevent adverse effects on legitimate activities.

149. Wider availability and timely administration of vaccines and therapeutics will reduce the likelihood of successful BW use, and will be a key factor in developing a global response to infectious disease outbreaks, whether natural, accidental or deliberate. Such capabilities would be important in implementation of Article VII of the BTWC, in providing assistance to any State Party exposed to danger as a result of a violation of the Convention. The development of cheaper and more readily available medical countermeasures is a significant issue for activities related to Article X, and for the wide range of other international initiatives for the development and application of scientific advances for the global prevention of disease.

10. Decontamination

150. Following a biological weapon attack, an effective decontamination response would involve removing or inactivating hazardous biological agents from contaminated environments or surfaces, including skin, clothing, buildings, water and air. A range of technologies may be employed, including: sampling, testing and analysis (both on-site and at a laboratory), to determine the extent and levels of contamination; containment and mitigation, which may include computer modelling and simulation; and decontamination itself, followed by confirmatory sampling and testing. Relevant recent research and development areas include:

(a) microbial and toxin detection technologies, including real-time, portable biological detectors, and detection of drinking water contamination;

(b) improved sampling and analysis methods;

(c) understanding infiltration of contaminants into buildings and reducing re-aerosolisation risks;

(d) persistence of biological agents and toxins on various types of surface materials or under certain environmental conditions;

(e) decontamination of personal protective equipment, common absorbent and non-absorbent surfaces, or buildings and other spaces (e.g., using UV light, irradiation, heat, ozone, aqueous solutions, gels or various gaseous and vapour-phase fumigants such as hydrogen peroxide and chlorine dioxide, as less corrosive alternatives to carcinogenic and persistent formaldehyde);

(f) improved biological indicators of fumigation efficacy;

(g) hazardous material disposal.

151. For fumigation and decontamination technologies, developments may relate not only to more effective, environmentally-friendly and safer decontaminants (including liquids, gases and even bioactive materials such as enzymes), but also to improvements in the delivery equipment, e.g., aerosolisation technologies. Evaluations of many commercially-available technologies and methodologies in these areas are openly available in the scientific literature and on government websites[72].

152. Development of decontamination applications is relevant to providing assistance to a State Party exposed to danger as a result of a violation of the Convention, in accordance with Article VII. However, many technical and policy challenges and deficiencies relating to decontamination remain to be addressed even for developed countries. International collaboration and cooperation, consistent with the provisions of Article X of the Convention, may be useful in addressing some gaps and in building global capacity. There is of course also potential for the misuse of developments in this field. For example, modelling capabilities developed to understand the distribution, deposition, re-aerosolisation and degradation of biological aerosols, or indoor dispersion could be used in planning and optimising biological or toxin weapons attacks. Equipment designed for the delivery of decontaminants or knowledge gained in its development might also have utility for an offensive BW programme. However, such misuse is clearly covered by the prohibitions of Article I of the BTWC, and Article III covers the issue of transfer of equipment, technology and information that might assist acquisition for activities prohibited by Article I. National oversight mechanisms for biological defence research and development programmes have an important role to play in ensuring compliance with the BTWC of work such as the development of decontamination capabilities, and help assuage concerns about its dual-use nature.

[72] For example: Wood, J.P., Choi, Y.W., Rogers, J.V., Kelly, T.J., Riggs, K.B. & Willenberg, Z.J. (2011). Efficacy of liquid spray decontaminants for inactivation of *Bacillus anthracis* spores on building and outdoor materials. Journal of Applied Microbiology 110, 1262–1273; and http://www.epa.gov/nhsrc/rhighlights.html.