Comments on
the consultation paper

Directive 2001/83/EC as regards Advanced Therapy Medicinal Products

"**IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION;**
Regulation (EC) No 1394/2007"

UNIVERSITY OF Southampton
School of Medicine

THE CLINICAL BIOTECHNOLOGY CENTRE BRISTOL

inovio
BIOMEDICAL CORPORATION

Genvax

We are writing in response to the Public consultation paper "**IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION;** *Regulation (EC) No 1394/2007*"

We greatly appreciate the clarity this document will provide for the regulation of gene therapeutic approaches to the community, and equally applaud the effort to ensure careful preclinical evaluation of new concepts prior to their testing in human.

The paper identifies medicinal products 'aimed at regulating, repairing or replacing a targeted genetic sequence; and whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence' to fall under the remit of the regulation according to the definition as stated in version 8 April 2008.
While our understanding of this document is that therapeutic vaccines using nucleic acids (DNA vaccines) are **not** included in the proposed regulation we are concerned that the regulations and guidelines covering DNA vaccines **will most likely refer to** this directive extensively and will therefore cover DNA vaccines indirectly.

We argue that therapeutic DNA vaccines should be treated as separate sub-group of Advanced Therapy Medicinal Products and as such **be specifically excluded** from "IMPLEMENTATION OF THE 'ADVANCED THERAPIES' REGULATION; *Regulation (EC) No 1394/2007*" and addressed in separate regulation. **The same considerations apply to RNA vaccines.**

Gene therapeutic treatments intended to provide long-term stable expression of the vector insert and/or stable integration into the host gene requires stringent regulation to ensure safety. However application of the proposed regulation **to nucleic acid vaccines, which do not integrate,** would hamper the timely clinical testing and will impose an unnecessary burden on developers of DNA based therapeutic vaccines. The result of this would be to stall or stop development of this safe and promising treatment strategy, which is highly attractive for both patients and physicians.

Please find below specific comments to support our proposal:

2.4.2 Specific requirements for GTMP - Non-Clinical data
Comment:
Extensive biodistribution studies have been undertaken and published for plasmid DNA (pDNA) vaccines. For intra muscular injection, even after few hours post injection less than 1-10% of the injected DNA remains at the injection site. Circulating DNA can be detected in other organs for a short period after injection but after 1-2 weeks plasmid DNA can only be detected at the site of injection. Integration in germline cells has never been observed. Additional safety is generated by the intended mode of action: immune cells attack transfected cells, terminate expression of antigen and eliminate vector DNA.
In line with this embryo-foetal and perinatal toxicity studies are not appropriate for DNA vaccines

2.5.2 Specific requirements for GTMP - Clinical data
Comment:

Requirements regarding shedding, biodistribution to gonads, reassortment of existing genomic sequences as well as neoplastic proliferation due to insertional mutagenicity are not applicable for plasmid based therapeutic DNA vaccines given the extensive literature from animal studies but more importantly from a growing number of clinical studies.

Importantly, there are several clinical trials of DNA vaccination in infectious diseases and in cancer which have reported no significant side effects. A typical example is our own trial of DNA vaccination against prostate cancer in 30 patients, which has almost been completed. The vaccine was very well received by the patients and minimal side effects have been observed. There is strong induction of the desired cytotoxic Tcells which are highly specific for the target cancer antigen. Clinical effects on the cancer are now being assessed. There is no evidence for any deleterious effect of this molecularly defined approach to inducing immunity, with investigators and patients equally keen to proceed with further development and testing. There seems to be no reason for introducing further shackles on an evidently safe procedure which has the promise of suppressing cancer.

If however, therapeutic DNA vaccines should be covered by this directive, there should be stated requirements separate from those for gene therapy. Therapeutic DNA vaccination and gene therapy are opposites in goal and design and, in our view, it is inappropriate to consider them together.

Stakeholders - Academic

Professor Christian Ottensmeier
Professor Freda Stevenson
Cancer Sciences Division, University of Southampton
Tremona Road, Southampton SO16 6YD, UK
+44-2380796184

Professor David Anstee
Clinical Biotechnology Centre,
Bristol Institute for Transfusion Science and University of Bristol
Southmead Road, Bristol, BS10 5ND, UK

Dr Olivier Lantz
Head of Immunotherapy Department
Institut Curie, 26 rue d'Ulm
75005, Pari, France
+33 1 44324218

Stakeholders – Commercial

Dr. Iacob Mathiesen
Inovio AS
Forskningsveien 2a; Oslo 0349, Norway

Dr. Mark Burton
Genvax
Bioscience Innovation Centre, Cowley Road, Cambridge CB4 0DS,
UK