# GSK EU REGULATION PAPER

The pharmaceutical industry is probably the most highly regulated sector of the economy. Much of this regulation is perfectly understandable and necessary – the safety, efficacy and quality of medicines is of paramount importance. But the way regulation is drafted, implemented and administered can be unnecessarily prescriptive which leads to unintended outcomes. When such issues arise industry stands ready to work with the Commission and Member States to find a way forward. The Commission has a key leadership role to play in this respect. GSK believes that greater focus is needed on:

- **How legislation/regulation is developed**. There is sometimes a lack of industry involvement, particularly at early stages, resulting in poor workability of legislation.

- **Overlap and duplication between regulations, particularly as new regulations come into force.** There is insufficient attention paid to conflicts and overlaps between new regulation and how it fits with existing regulation. This is particularly true of environmental legislation. The result is that business often has to deal with multiple regulations addressing the same issue, leading to misalignment and additional administration. Early stage impact assessments - with proper analysis of how the proposed new legislation would sit with the existing acquis communitair, and which measures will need to be amended and repealed in order to avoid any duplication – would help significantly.

- **How regulations are transposed and interpreted.** Uneven transposition and lack of harmonisation in the implementation of EU regulations or directives, and they way they are enforced, often reduces the main benefits of having EU legislation.

- **Some regulation simply becomes out of date as technology improves and business models evolve**. A continual process of legislative review to ensure that new technologies are not stifled by regulation is needed. Regulation should enable and stimulate innovation and continuous improvement.

- **Some regulation is simply excessive**. The EU Penalties Regulation which proposes that companies could be fined up to 5% of Community turnover for a regulatory infringement is an example of excessive regulation. The lack of a relationship between the size of an enterprise and the harm done by a violation makes it disproportionate to link fines to company size in the context of pharmaceutical regulation or other public health areas. It is clear that this regulation may be held by the European Court of Justice to be beyond the competence of EU legislative institutions. Working with industry to formulate an alternative a more proportionate approach could be developed.

This paper sets out 15 current EU regulatory issues, from across GSK's business, where rules could be simplified, amended or removed without undermining or altering the policy objectives underpinning the regulation.

The document sets out a number of examples (not in priority order), in the following fields:

- Environment, health and safety
- Genetically modified organisms
- Approval of medicines
- New Medicines Legislation
- Research and Development
- Penalties

The issues raised are not all new; many are already under active discussion with regulators. But we have brought these examples together to illustrate the cumulative burden on industry and the potential benefits of launching a process of regulatory simplification to reduce the burden on industry.

We hope this document is seen as a constructive contribution to this important debate. We are not trying to alter policy. We are simply trying to ensure the objectives of the EU are met in a way that does not unduly harm the competitiveness of Europe. We look forward to addressing the issues raised.

# ENVIRONMENT, HEALTH AND SAFETY

**1. REACH.** The proposed EU Chemicals Regulation (REACH) creates a comprehensive framework for the registration, evaluation, authorisation and control of chemicals. Many of the proposed new duties overlap with existing regulations. For example, the Chemical Agents Directive requires *users* of chemicals to assess the risks to their employees arising from the way a chemical is used in an industrial process, and to take appropriate risk management measures. Under REACH, there is now a duty on the *manufacturer* of a chemical to also assess the risks from using a chemical in a specific industrial process. Thus both the *manufacturer* and the *user* of a chemical have to carry out essentially the same process. Needless duplication of this sort is just one example of the overlapping problems associated with REACH. We therefore believe that, once the proposals are finalised, there will need to be a comprehensive review of all relevant legislation to determine overlaps and conflicts with REACH with a view to rationalising existing directives such as:

Legislation governing exposure of employees to chemicals in the workplace, eg.:

- Framework Directive 89/391/EEC
- Chemical Agents Directive 98/24/EC
- Carcinogens Directive 90/394/EEC
- Pregnant Workers Directive 92/85/EEC
- Indicative Occupational Exposure Limit Values Directive 2000/39/EC

Legislation covering the control of emissions and discharges from installations, eg.:

- Integrated Pollution Prevention and Control Directive 96/61/EC
- Solvent Emissions Directive 1999/13/EC
- Water Framework Directive 2000/60/EC

Legislation covering the supply and use of chemicals, eg.:

- Marketing and Use Directive 76/769/EEC
- Safety Data Sheets Directive 91/155/EEC
- Restriction of Hazardous Substances Directive 2002/95/EC
- Fluorinated Gases Regulation (proposed)

Legislation governing explosive atmospheres, eg.

- The Control of Major Accident Hazards (COMAH) Directive 96/82/EC
- The Explosive Atmospheres Directive 1999/92/EC

**2. Exposure to electromagnetic fields.** Maximum exposure limits for electromagnetic fields are set by Directive 2004/40/EC 29 April 2004 on the Minimum Health and Safety Requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (18th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). The limits that have been set have no scientific basis and consequently may compromise the future use of Magnetic Resonance Imaging (MRI) in medicine and biomedical research.. MRI and functional MRI (FMRI) represent significant breakthroughs in medical diagnostics

and research. This is an area in which the EU could relinquish its leadership to the US if regulation becomes too heavy. GSK believes that there should be further research into the safety of exposure to MRI based on analysis of existing exposure data from clinical MRI and basic research into biological effects. **Based on this research, Members States and the European Commission should re-examine the Directive and/or issue guidelines based on scientific evidence** that do not unnecessarily inhibit the use or development of MRI in medicine or biomedical research.

# GENETICALLY MODIFIED ORGANISMS

**3.** A large number of complex and overlapping regulations control the acquisition, transport, tracing, labelling, use and disclosure of Genetically Modified Organisms. **There is a need for a comprehensive review of all relevant regulations** to produce streamlined, integrated regulation proportionate to the risk of contained use of GMOs in the pharmaceutical industry and in the context of international competitiveness and intellectual property protection.

**4.** **UN Cartagena Protocol on Biosafety**. The objective of the Biosafety Protocol is to govern the safe transfer, handling and use of genetically modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, also taking into account risks to human health, and specifically focusing on transboundary movements. **EU regulation has gone beyond the international requirements of the Biosafety Protocol**. This has had the effect of bringing back into scope a number of matters which had been specifically excluded. The treatment of GMO material is inconsistent and not risk-based. For example, naturally-occurring organisms which are known to be hazardous can be shipped without any regulatory notification, but the same organisms which have been genetically modified have to be notified, whether hazardous or not. As part of the comprehensive review of GMO regulation GSK believes that this EU regulation should be revised with a view to meeting international requirements but not going beyond them.

# APPROVAL OF MEDICINES

**5. The Clinical Trials Directive (2001/20/EC)** has produced an increasing regulatory burden. Unnecessary administrative requirements introduced by Member States are undermining any advantage that should have been expected from harmonisation across the EU. There are a number of issues related to how different member states have implemented the directive:

- **Lack of standardisation** in administrative requirements, for example for notarisations, application forms, documentation formats, samples, product labelling, and quality declarations - few, if any, of these requirements contribute to patient safety.

- **Differing implementation** in the member states for:
  - Safety (adverse event) reporting,
  - Pharmaceutical data included in Clinical Trial Approval (CTA) applications,
  - Differing interpretations of what is an ***investigational*** medicinal product, and therefore differences in what types of products do or do not require approval if used in clinical trials,
  - Unnecessary requirements for good manufacturing practice certification.

- **Lack of harmonised pharmacy data requirements** (sometimes excessive) for approval of well- established medications imported from third countries – and intended to be used as comparator in EU clinical trials.

- **Inconsistent interpretation** of which types of protocol or product changes are substantial enough to require amendment to a Clinical Trial Application: the same change is being handled differently by different member states. The procedure to make amendments to clinical trials also takes too long, especially for clinical pharmacology studies.

GSK suggests that the Commission should take responsibility for ensuring that all the above issues are dealt with by the Clinical Trials Facilitation Group. The Group should focus on ensuring that harmonisation takes place to an optimal, rather than a maximal, level. In addition, it is important that implementation of change is carried out quickly, with full involvement of industry.

Making the EU a more competitive place to do clinical research, will increase the numbers of large studies done here and is a key part of developing the European lead in clinical science. The alternative would be for more of these studies to be done outside of Europe, which would not serve the long-term interest of the European economy.

**6. Current Variation Regulations (Commission Regulations (EC) Nos 1085/2003 & 1084/2003 and Guidelines).** The Variation regulations, relating to

registering changes to medicinal products authorised under the Centralised Procedure and Mutual Recognition Procedure in Europe, are creating an environment that imposes unnecessary regulatory burdens on industry and which often inhibits continual improvement and innovation. This is exacerbated by the fact that individual EU member states have not implemented the Community regulations in a harmonised manner for national variations.

The Commission should use the opportunity of the International Conference on Harmonisation (ICH) quality guidelines on ICH Q8 Pharmaceutical Development and Q9 Quality Risk Management, as well as the new ICH quality topic Q10 Quality Systems, to fundamentally rethink how post-approval changes should be managed in the EU. Any future post-approval system should incorporate a science and risk-based approach, initiated by the company, in assessing the need for prior approval by the authorities. There also needs to be a more concerted effort on behalf of appropriate competent authorities to harmonise national variation requirements.

**7. Electronic Submissions.** During 2005, some Medicines Agencies (Belgium and UK) started accepting electronic submissions (thereby removing the need for paper copies of the dossier). Other Agencies will adopt electronic submissions during 2006 and 2007 (e.g. Netherlands, EMEA). While these initiatives are to be encouraged, the transition from a paper-based regulatory system, to one that relies on electronic interactions, will be complex. The complexity of the transition from paper, and the associated inefficiencies and increase in regulatory burden, will be magnified by four factors, which can all be minimised:

- **Lack of common standards.** Individual Medicines Agencies are developing individual systems for e-submissions. To minimise confusion and bureaucracy, GSK suggests that the Commission should seek to ensure that all systems are based on the relevant ICH (e.g. Common Technical Dossier (CTD and electronic Common Technical Dossier (eCTD)) and EU (e.g. electronic Application Form (eAF) standards. Additionally, during the transition, individual Medicines Agencies should not require both old and new formats to be submitted, as this would represent a huge increase in regulatory burden. GSK suggests that the EMEA should take the lead on the development and implementation of EU-wide standards for e-submission. EMEA will implement eCTD as an optional submission format in the Centralised Procedure from 1 December 2006, but budget discussions with the Commission may jeopardise not only this date, but potentially the whole project. Since the EU Medicines Regulation and Directive does not specifically mention the use of electronic submissions, their use is being regarded as unnecessary and hence potentially unbudgeted. EMEA must be supported in their objective to implement eCTD on 1 December 2006 to maximise efficiency of business process. Lack of implementation by EMEA will encourage Member State Agencies to develop and implement their own approaches, systems and "national standards".

- **Staggered implementation across EEA countries**. The end of 2009 has been agreed as the target date by when each Medicines Agency will be ready to accept marketing authorisation applications in the eCTD electronic format

developed by ICH. Staggered implementation across EEA Agencies will occur until then. Differences in implementation dates, differences in transition timelines, and different requirements between Agencies, are already giving applicants a significant challenge to manage. We accept that this transition is inevitable. **However, the additional burden that it brings must be managed through the implementation of EU wide and ICH standards, not national approaches**.

- **Implementation of national Medicines Agency systems and portals.** National Medicines Agency systems are being implemented to meet the requirements of the individual Member State. Entry of data, e.g. in an application form, into one national Agency system does not allow re-use in another. **National portals should be engineered to accept the eCTD, and specific and unique approaches to e-submission should not be developed locally. Again, this is something the Commission should ensure happens.**

- **An uncoordinated and non-standardised approach to the implementation of <u>secure</u> e-regulatory interactions.** Digital credentials are required to provide a secure and reliable means of establishing identity within electronic interactions. Their use in electronic interactions between applicant and Agency provides greater security of information transmitted and received. A number of digital credentials are in use in the European Biopharmaceuticals sector, and there is a concern that these will proliferate as each Agency implements their own approach. The Commission should ensure that compatible standards and approaches should be adopted such that individuals are not required to manage multiple electronic identities.

**8. Increasing size and scope of clinical data required for submission to obtain Marketing Authorisations approvals.** The number and complexity of clinical trials, and the number of patients required to be included in trials, continues to increase. The clinical phase of drug development is now the most costly and time-consuming, especially for New Active Substances. It is recognised that there is a need to ensure a thorough scientific evaluation of risk/benefit balance for patients; however, there are a number of areas where this trend can lead to unnecessary clinical studies:

- Regulatory Agencies and Pricing and Reimbursement Authorities often require comparative studies with existing medication to "benchmark" efficacy and safety. Requirements for different comparator products may proliferate across the member states, making it difficult to set up a single development programme to satisfy all, and often resulting in duplicative studies. In one GSK case, a post-approval commitment study was requested with a new comparator that had become the "gold standard" but was not registered at the time the Phase III studies started - this is of concern, since a judgement as to what may be considered a "gold standard" could be subjective or even nationalistic.

- There is an increasing trend for agencies to request further clinical data as post-approval commitments. In Europe, according to one estimate, the total

number of NAS in each year with one or more post-approval commitments has increased from 82% in 2000 to 96% in 2004 (Anisha Chauhan, Poster Session during the 41st Annual DIA meeting in June 2005 - Centre for Medicines Research).

**A more flexible approach to drug comparator studies requirements is needed**. Much of the increased clinical data requirement may be justified if it genuinely better characterises risk benefit for patients, but where this is not the case it is unnecessarily driving up development costs. The introduction of **Risk Management Plans** in Marketing Authorisation Applications could be very positive if it increases confidence for Agencies in making approval decisions, and shifts some of the burden into the post-approval phase. However, this needs pragmatic implementation by Agencies, with good pre-submission dialogue with the company and agreement on plans.

## 9. Difficulties in setting up Global development programmes

Drug development is increasingly global in nature; however, there are barriers to overcome for companies wishing to implement a truly global programme:

- Co-ordinating agreement to the development plan from the various agencies without incurring unnecessary delay, or proliferation of data requirements - especially between the US and EU.

- Divergent approval decisions occur, for example between US and EU, resulting in different questions to resolve and further possibly duplicative studies to be completed. For example, between January 1995 and January 2000 for industry as a whole, the FDA had authorised 13 of the 38 applications (34% of applications) that had a negative outcome in the EU centralised procedure (internal GSK analysis of public domain information).

The introduction of parallel scientific advice between the EMEA and FDA is a good start. The Commission should ensure that we build on this success and extend and develop the process, with a view to creating a greater harmonisation between EMEA and the FDA.

# NEW MEDICINES LEGISLATION (NML)

NML introduces a significant degree of change in the EU regulatory framework, in terms of modification of the EU authorisation procedures, and operation of the EMEA and other regulatory bodies. It also introduces a number of new demands on industry, in terms of new requirements for applicants for Marketing Authorisations, and new obligations for Marketing Authorisation holders.

Many of these changes are welcomed by industry as rational, reasonable and appropriate developments to the regulatory framework. For example, the introduction of a requirement, where appropriate, for submission of details of the risk management system that the applicant will introduce for a new product, the increased frequency of Product Safety Update Reports (PSURs) to help strengthen the Pharmacovigilance system, and the focus on improving the Patient Information Leaflets via User Testing in defined circumstances, are all welcome developments.

However, some of the changes under NML introduce additional burdens whose value can be questioned. Some examples are briefly outlined below:

**10. Dossier Requirements for Renewals of Marketing Authorisations** *(EMEA guideline on processing of renewals in the Centralised Procedure - EMEA/CHMP/2990/00 rev. 3; Mutual Recognition facilitation group guideline on the Processing of Renewals in the MR and Decentralised Procedures).* The Commission's original legislative proposals abolished the concept of renewals, as they were considered unnecessary in the context of the proposed enhanced pharmacovigilance provisions. However, EU legislators insisted on the retention of the concept of renewals, and we now have a system of one renewal 5 years after the initial authorisation, with a potential for one further renewal after an additional 5 years. These mostly unnecessary requirements simply add to the amount of data and paperwork which have to be submitted.

Given that these renewal requirements were finally included in the legislation, the priority now is to ensure their regulatory burden is minimised. In particular, it should be made clear that a new updated version of the original dossier (often several hundred volumes of data) is not required. New implementing guidelines covering products approved via European procedures make it clear that a number of specified documents must be submitted with the application for renewal, but that a new updated version of the dossier (full or partial) ***is not required***. GSK believes that this guidance is pragmatic and fully meets the needs of the Competent Authorities in allowing them to fulfil their Public Health responsibilities. Consequently, GSK suggests that the Commission should ensure that EU Competent Authorities do not require full or partial new updated dossiers, and should accept the implementing guidelines. This would maintain a common approach across all products and procedures, and minimise unnecessary and burdensome requirements for the industry.

**11. Requirements for harmonisation of prescribing information across the Member States.** Article 30 of Directive 2001/27/EC as modified by Directive 2004/27/EC provides that each year the Mutual Recognition Coordination Group (CMDh) must lay down a list of medicinal products for which harmonised prescribing

Information (summary of product characteristics or SPC) should be drawn up. The CMDh has endorsed the following criteria for products for which a harmonised SPC should be drawn up:

- Significant differences in core parts of the SPC (Sections 4.1-4.4)
- Exclusivity/patent expiry dates
- Extent of the use of the product
- Number of Member States where the product is authorised

SPC harmonisation activities consume significant industry and agency resource. GSK believes such resource could be better directed to the development, submission, review and approval of new chemical entities or new indications that may bring a significant health benefit to the Community. In addition, GSK believes there is no evidence that the existing SPC differences between Member States have caused any public health concerns. Conversely, public health issues and patient concerns may result from new restrictions of existing indications based on established patient treatment in individual member states. The rationale for an extensive harmonisation exercise is therefore questionable, particularly as the issue of divergent SPCs will greatly decrease over time as a result of the use of European procedures
GSK accepts that the legislation now states that products can be selected for harmonisation on an ongoing basis. However, GSK believes that the selection of products by the CMDh should be based on the sound principle of genuine public health concerns, and that there should be a rigorous process put in place to ensure that the significant burden such harmonisation activities place on Marketing Authorisation Holders is minimised.

**12. Requirement for Certain Excipients to Comply with GMP.** The new legislation extends current Good Manufacturing Practices (GMP) requirements to mandate that GMP are applied to 'certain excipients'; these excipients will be defined and listed by the Commission. It is important that appropriate controls are applied otherwise this raises significant issues for the industry. Notably:

- Imposition of GMP standards on a broad list of excipients would place the EU at a competitive disadvantage relative to the rest of the world and would significantly add to the cost of the finished product manufactured in Europe.
- For those excipients where the pharmaceutical industry is a minority user, and therefore lacks the commercial pressure to impose such requirements on excipient manufacturers, the new requirements may cause some excipient manufacturers to abandon the relatively small pharmaceutical component of their business. This potentially could lead to shortages which could ultimately lead to the withdrawal of life-saving medicines, while the same materials would still be freely available, without the same controls, for foodstuffs.

In defining the proposed list of excipients for which GMP will apply, it is vital that the Commission limit the listed excipients only to those where a potential serious risk to patients can be envisaged, and after consultation with industry on the feasibility of

using this provision for the excipient proposed. Once the list of 'certain excipients ' is identified it is important that an appropriate GMP standard is applied i.e. one of the already existing guidelines for example from the International Pharmaceutical Excipients Council or the UK Pharmaceutical Quality Group. The full rigours of the EU GMP guidelines for drug products or active ingredients should not be applied.

# RESEARCH AND DEVELOPMENT

**13. Pharmacovigilance.** EU regulations setting out rules for adverse event monitoring and reporting are found throughout a range of legal texts. The sheer volume of regulations results in sometimes contradictory and often unclear procedures. The rules can be both complex and confusing, and they expose individuals responsible for pharmacovigilance in Europe to civil and criminal liability. Significant resources are spent on meeting these unclear and complex regulatory demands.

The legal framework can be greatly improved through the adoption of a single Council Regulation on pharmacovigilance. This single regulation would contain clear and concise provisions that would simplify, strengthen and provide legal certainty to the EU legislative framework for pharmacovigilance. It would:

- contain a single set of simplified rules for expedited and periodic reporting of adverse drug reactions ('ADR') in the EU.
- provide a single point for electronic reporting of all ADRs within the European Economic Area via EudraVigilance, with the facility for all Member States to access data in one central safety database.
- remove the "unexpected/expected" concept, and require the reporting of all serious cases when electronic reporting is implemented.
- contain clear and flexible provisions regarding Qualified Persons ('QPs') responsible for pharmacovigilance that allow individual companies to appoint the number of QPs best suited to their respective organisations.
- include consistent standards for inspections of company pharmacovigilance departments by the EMEA and EU Member State authorities

**14. Use of Animals in biomedical research.** The Commission is currently considering a review of the directive that regulates the use of animals in medical research in Europe (86/609). GSK supports initiatives at the EU level to enhance animal welfare in biomedical research. These should include reference to implementation of the 3Rs (refinement, reduction, replacement), harmonised and simplified statistics, and informative classification of pain and distress levels. GSK does, however, have significant concerns about the current approach to revision, based on technical reviews, which would only lead to increased bureaucracy without improving human health, animal welfare or animal research.

- GSK supports the addition of a locally based ethical review (ER) to the Directive, but notes that this is already very widely implemented with European regulation. GSK supports limiting regulation on ER to simple framework guidelines. Implementation should be local. This would provide continuity in such ethical considerations involving animal experimentation across the EU but avoid costly prescriptive rules that are likely with existing national structures and cultures.

- GSK does not believe that a central European database for animal experimentation is compatible with EU competitiveness. The burden would be very high, whilst benefit of such a database would be very limited. The academic grant review process and industry competitive awareness of research for novel and unique chemical entities causes no significant study duplications. Liability for any problem occurring in clinical use after relying on the data is unclear.

- There is no reason to include embryonic or larval forms in Directive. The amount of pain, harm and distress suffered by embryonic and larval forms remains unclear. The inclusion of embryonic and larval forms in the statistics would be difficult due to their sheer numbers, with questionable animal welfare benefit. Vaccine developers and manufacturers use large numbers of embryonated eggs. Fish larvae are used extensively for environmental toxicology. It would add to the reporting burden, distort the statistics, increase costs, and so reduce competitiveness.

- The Directive regulates the use of living animals in experiments. Tissues from animals killed for other reasons and the use of tissues from animal slaughterhouses have significantly reduced the need for live animal experimentation. Inclusion of all these animals in the provisions would greatly increase the number of overall animal experiments reported. Costs would increase from licensing and policing such a diverse group of animal slaughterhouses and university laboratories - for no animal welfare benefit. They should therefore be excluded from the Dircetive.

- The suggestions from the technical review on continued use or re-use of animals after pre-preparation (for example with catheters or implanted monitoring devices) would disallow subsequent mild interventions such as drug application, collection of blood and remote monitoring after a change of compound type or in study protocol, irrespective of the animals' total experience of distress. This approach is contrary to the principle of modern advanced scientific technique and the 3Rs. Review of clinical condition of the animals is determined by a veterinarian and local ethical review is an effective approach. Re-use of animals for other procedures under terminal anaesthesia should also be allowed.

- Further restrictions on the use of non-human primates, such as an irrevocable ban on the use of great apes, could dramatically compromise vital research programmes in Europe. GSK supports the current regulation ensuring that such animals are used only in strictly exceptional circumstances. GSK supports the use of purpose bred animals, but again, exceptions must be permitted with strong justification. Proposals to exclude the first generation born in captivity (F1) from experiments would be counterproductive as well would greatly increase the number of primates kept for breeding purposes.

- Accreditation of breeders and suppliers from third countries' establishments only after controls carried out by National Competent Authorities (NCA) could impact the import of transgenic animals (mostly rodents) which today are often available only from institutions in "3rd countries". These rodents are

essential for replacement of higher species in animal research. 3rd country breeders might stop supplying European markets, due to the administrative burden. The animal welfare benefit is again unclear.

Any increase in the overall regulatory and bureaucratic burden, without real animal welfare benefits, hinders the development of new medicines and vaccines for patients, undermines European competitiveness, and impairs investments in both academic and industrial research. Unnecessary bureaucracy also distracts animal care and welfare personnel from carrying out their core animal welfare functions. It is a basic principle of Better Regulation that regulators should always first consider alternatives to legislation. The European Partnership on Alternatives to Animal Testing is an example of a non-legislative approach that may well achieve the same objective as proposed legislative changes. GSK does not support the current prescriptive and burdensome approach to the revision of Directive 86/609. GSK suggests that a simple revision focusing on providing a framework for clarifying existing best practices is the most appropriate response to ensure health, animal welfare and competitiveness objectives are met.

# PENALTIES

**15. Second Draft Commission regulation concerning financial penalties for infringements of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004.** This draft Commission Regulation is not consistent with general principles of better regulation for two primary reasons.

First, nothing in Article 84(3) of Regulation (EC) No 726/2004 provides a legal basis for the attempt by the Commission of the European Communities to impose an obligation on the EU Member States to assist it in investigating alleged failures to fulfil obligations relating to grant of a marketing authorisation for a medicinal product in accordance with the centralised authorisation procedure.

Second, the fines that the Commission seeks, by its draft Regulation, to impose do not fulfil the criteria established by case law of the Court of Justice and are manifestly disproportionate to the objective pursued by the draft Regulation itself.

It would appear that, in establishing the level of fines and in developing the procedure for their imposition, the Commission has drawn inspiration from the Community policy governing breach of competition law provisions of the EC Treaty. Yet, the EMEA Regulation is not a competition law procedure intended to prevent breach of competition law provisions of the EC Treaty. Rather it provides a detailed and heavily regulated procedure for authorisation of medicinal products in accordance with the centralised procedure. Moreover, Article 84(1) of the Regulation provides EU Member States with the power to impose penalties for infringement of the provisions its provision as well as the provisions of other regulations adopted pursuant to it.

The intention of imposition of fines in the present case is to punish marketing authorisation holders who, although they have completed detailed obligations prior to grant of the authorisation, have either failed to fulfil obligations subsequent to the grant of authorisation, or whose pre-authorisation short-comings were recognised only after authorisation was granted. Imposition of fines of up to 5% of to marketing authorisation holder's Community turnover in the preceding business year must be considered to be an excessive means of achieving this desired end.

Moreover, imposition of fines up to this level is not, in the circumstances, necessary for achievement of the desired end. If it is concluded that a marketing authorisation holder has failed to fulfil obligations arising from the EMEA Regulation and, as a consequence, its product represents a threat to public health, the marketing authorisation holder faces the risk of having marketing authorisation for the product withdrawn, excluding the product entirely from the EU market.

Finally, the financial investment that the marketing authorisation holder must make in order to receive a marketing authorisation is commonly recognised. Moreover, the marketing authorisation holder will not profit from the authorisation until the product is accepted for reimbursement by the competent authorities of the EU Member States. In such circumstances, fines of the levels imposed by the draft Regulation are excessive in relation to the objective to be achieved.

The new enforcement powers will apply to a broad range of duties to which marketing authorisation holders are subject, including pharmacovigilance, labelling and package leaflet, compassionate use, manufacture, import and information and advertising.

There is a risk that the new enforcement powers in this regulation may be held by the European Court of Justice to be beyond the competence of EU legislative institutions. To minimise that risk the Commission should narrow the coverage of the legislation and the inclusion of more proportionate monetary limits rather than the high percentage limit in the current proposal. In establishing the levels of penalties, the redrafted proposal should prescribe gradations of offences as well as proportionate penalties to go with them. GSK believes that this is what the authorising legislation contemplated.