Policy on

Recombinant Live Biotherapeutic Products

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Introduction

As synthetic biology shifts from in vitro studies to possible therapeutic products, the necessity of a regulation that determines whether a developed organism is optimal for human use arises.

There are presently no international-wide regulations governing the topic.
A suggestion of how Live Biotherapeutic Products (LBP) can be regulated is highly demanded and this policy tries to implement a strategy to follow when developing this regulation, basing it on the current information available for the market authorization for GMOs, probiotics, drug delivery systems and drugs.

Background of the current regime

What is a Genetically Modified Organism (GMO)

A GMO is an entity whose genome has been altered, in a way not possible through mating or natural recombination.

Today, new genes are incorporated from one species into an unrelated species through genetic engineering, which optimizes the production of valuable pharmaceutical substances and the agricultural performance. Crops, farm animals, and soil bacteria are some of the examples of organisms that have been subject to genetic engineering.[1]

Regulations for GMO

GMO in the environment, such as foods are regulated by the European Commission together with the European Food Safety Authority.
This regulation serves mainly to protect human and animal health and the environment by using safety assessments. There is a need to submit a notification including an environmental risk assessment and to ensure traceability of the GMO before being placed on the market.

Another important factor of the regulation is also to establish clear labelling to enable consumers as well as professionals (e.g farmers) to make an informed choice and to be advised how the GMO interacts with the environment.
It's important to take into consideration that the laws on GMO vary in the different European countries.

1 Phillips, T. (2008) Genetically modified organisms (GMOs): Transgenic crops and recombinant DNA technology, Nature Education, 1(1), p.213

Separate applications should be submitted in each Member State in order to apply for market authorization for genetically-modified products, when granted by each Member States it gives the right to object to such marketing within their borders.

From this point of view, if a medicinal product would consist of GMO, the legislation would be different and divided into two parts. The first one covering the environmental regulation stated above and the second one governing the pharmaceutical legislation.

In the pharmaceutical legislation, the applicant must submit to the European Medicines Agency a dossier which includes all the necessary administrative, quality, non-clinical and clinical data for the medicinal product. This data is assessed in accordance with the centralised procedure.

Together they regulate GMOs for medicinal products in Europe.[2]

Regulation in the United States is known to have higher approval of GMO compared to Europe. Regulation of GM crops in the US is divided among three regulatory agencies: the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA). Each of these agencies regulates transgenic crops from a different perspective. According to a policy established in 1992, FDA considers most GM crops as "substantially equivalent" to non-GM crops and if they are designated as "Generally Recognized as Safe" under the Federal Food, Drug, and Cosmetic Act (FFDCA), they do not require pre-market approval. Although there is a need for pre-market approval if the insertion of a transgene into a food crop results in the expression of foreign proteins that differ significantly in structure, function or quality from natural plant proteins.[3]

2 Committee for the Medicinal Product For Human Use (CHMP), European Medicines Agency, (2008), Guideline on Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products

3 Federation of American Scientists, U.S. Regulation of Genetically Modified Crops, Available at: https://fas.org/biosecurity/education/dualuse-agriculture/2.-agricultural-biotechnology/us-regulation-of-genetically-engineered-crops.html [Accessed 19 Oct. 2017].

Drug delivery systems (DDS) and combinational products

DDS are engineered technologies that control the rate at which a drug is released and/or the location in the body where it is released. Inside the range of DDS, we focus our interest on combinational products. A combination product is a product comprised of any combination of a drug and a device, a biological product and a device, a drug and a biological product, or a drug, device, and a biological product.[4]

Regulations for DDS

The regulation of combinational products has raised several debates in Europe. The most widely-discussed one involves the classification of these products. A medicine usually acts through a pharmacological, immunological or metabolic action, while a medical device does it through physical or chemical means.

The mechanism of action determines whether the product should be viewed as a medicine or a medical device. A combinational product incorporates elements of both, and because of this, makes the work of the regulatory agencies even harder. European authorities have adopted a case-by-case assessment approach, where this determination is taken at a national level. However, this classification does not impede other member states to chose differently.

With regards to product development (chemistry, non-clinical and clinical studies), for a DDS where that will be authorised as a drug, the product would be expected to satisfy the same standards of quality, safety and efficacy as required of any other drug by the European Medicines Agency. The same happens if it is considered as a medical device, namely it would have to satisfy the requirements established by the European Commision.

Apart from these requirements, the nature of the delivery system will entail consideration of safety assessments such as biodistribution, cell distribution, effects on immune system function and requirements/methodology for genotoxicity testing.

4 National Institute of Biomedical Imaging and Bioengineering (2016). Drug Delivery Systems: Getting Drugs to Their Targets in a Controlled Manner. Bethesda, Maryland: National Institute of Biomedical Imaging and Bioengineering. Available at: https://www.nibib.nih.gov/science-education/science-topics/drug-delivery-systems-getting-drugs-their-targets-controlled-manner [Accessed 19th October 2017]

With regards to post-marketing surveillance, pharmacovigilance (PV) and risk management plans (RMPs) there might need to be a focus on areas of potential concern such as biodegradability/bioaccumulation, immunogenicity, tumorigenicity, and pro-inflammatory effects.[5]

In the USA, the FDA's Office of Combination Products (OCP) is in charge of the combinational products, by coordinating their reviews, that involve more than one agency centre. The OCP is also in charge of the post-market regulation and of disputes regarding the timeliness of combination product reviews.

The combination product is assigned to a lead centre, that will be responsible for the oversight of the review and regulation of the combination product. The lead centre is determined depending on the primary mode of action (PMOA) of the product. The PMOA provides the most important therapeutic action of the combination product.[6]

The product development analysed by the different centres focuses on the scientific and technical issues raised by the particular product being developed, both as a unit and all its constituent parts alone.

Therefore, when the constituent parts are a new medical device, some safety and/or effectiveness testing is necessary for the part itself and the product as a whole. In case the constituent parts have already been approved for another indication, preclinical testing would only be to be undertaken for the new use of the device as a part of the combinational product.[7]

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5 Regulatory Rapporteur (2016). Advances and challenges in the development of drug delivery systems – A European perspective: Regulatory Rapporteur - Vol 13, No 6, June 2016. Available at: https://embed.topra.org/sites/default/files/regrapart/1/6354/2016-6_regulatory-rapporteur_drug-delivery-systems.pdf [Accessed 19th October 2017]

6 Regulatory Rapporteur (2016). Advances and challenges in the development of drug delivery systems – A European perspective: Regulatory Rapporteur - Vol 13, No 6, June 2016. Available at: https://embed.topra.org/sites/default/files/regrapart/1/6354/2016-6_regulatory-rapporteur_drug-delivery-systems.pdf [Accessed 19th October 2017]

7 Food and Drugs Administration (2016). FDA developing improved methodology for determining purity of probiotic products. Silver Spring, Maryland: Food and Drugs Administration. Available at: https://www.fda.gov/biologicsbloodvaccines/sciencereresearch/ucm493702.htm [Accessed 19th October 2017]

Similarly, when the constituent parts are new molecular entities (NME) a critical characterization of its safety and effectiveness would be required. For this, preclinical (pharmacokinetic, dose ranging or dose finding, local/regional toxicity...) and clinical studies would need to be undertaken. On the other hand, regardless of the approval status of the drug/biologic constituent, data proving the overall safety and effectiveness of the drug under the new dosing regimen or indication would be required for a marketing application.[8]

What are Probiotics?

Probiotics are live microorganisms (e.g. bacteria) that are either the same as or similar to microorganisms found naturally in the human body and may be beneficial to health. The body, especially the lower gastrointestinal tract (the gut), contains a complex and diverse community of bacteria. Although people often think of bacteria and other microorganisms as harmful "germs," many microorganisms help our bodies function properly. In fact, microorganisms in the human body outnumber human cells by 10 to 1[9] [10].

Regulation of Probiotics

The regulation of probiotics differs depending on the area where the product is set to enter the market. The current European regulation regards probiotics only as food. Most live microbial strains used in EU foods and food supplements do not require a pre-market safety assessment, due to traditional and safe use in fermented foods. However, EU regulators look to EFSA (European Food Safety Authority) for guidance on strain safety, particularly for food supplements, since these must be notified prior to marketing in most Member States.

Because of this, the EFSA is the organization in charge of evaluating probiotics and giving market approval. All live micro-organisms used in animal nutrition must pass EFSA on strain safety prior to marketing and face a stringent safety assessment, including measuring the strain identity, QPS – EFSA (lists absence of

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8 Food and Drugs Administration (2016). Guidance for Industryand FDA Staff: Early Development Considerations for Innovative Combination Products Silver Spring, Maryland: Food and Drugs Administration. Available at: https://www.fda.gov/downloads/Regulatoryinformation/Guidances/ucm126054.pdf [Accessed 19th October 2017]

9 National Center for Complementary and Integrative Health (2016). Probiotics: In Depth. Bethesda, Maryland: National Institute of Biomedical Imaging and Bioengineering. Available at: https://nccih.nih.gov/health/probiotics/introduction.htm [Accessed 19th October 2017]

10 Cleveland Clinic (2015). Probiotics. Cleveland, Ohio: Cleveland Clinic. Available at: https://my.clevelandclinic.org/health/articles/probiotics [Accessed 19th October 2017]

toxin and virulence factors and antimicrobial resistance (AMR) as key qualifiers for strain safety) and full genome.

The health claims for probiotics are also analysed by this organization, with little involvement from the EMA or the European Commission. EFSA heavily insisted that probiotic efficiency is strain-specific, making the approval process even longer and tougher. Up to this day, only one probiotic has been approved to have a health claim in Europe. The product, Winclove probiotics, Propionibacterium freudenreichii W200 which contains adequate amounts of vitamin B12 to satisfy the granting of a health claim.[11]

In the US, the Food and Drugs Agency (FDA), is responsible for the regulation of probiotics, referred to as live biotherapeutic products (LBP), independently of its intended use (medical or food supplement). However, the regulatory requirements differ greatly depending on this intended use. For dietary supplements, premarketing demonstration of safety and efficacy and approval by the Food and Drug Administration are not required; only premarket notification is required.[12]

On the other hand, if a probiotic is intended for use as a drug, an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, then it must undergo the regulatory process as a drug. For this intended use, the probiotic has to go through the new therapeutic agent approval process before marketing approval can be granted. The probiotic drug must be proven safe and effective for its intended use before marketing.

The guideline for Early Clinical Trials with LBP includes the FDA's current views on this topic and provides applicants with recommendations regarding Investigational New Drug Application for early clinical trials with LBP in the US, on topics such as Chemistry, Manufacturing, and Control Information. The proposed clinical trials to evaluate LBP vary in design, depending on the product, proposed use, and intended population for enrollment.[13]

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11 European Food Safety Authority (2017). Nutrition and health claims. Parma, Italy: European Food Safety Authority. Available at: https://www.efsa.europa.eu/en/topics/topic/nutrition-and-health-claims [Accessed 19th October 2017]

12 Venugopalan, V., Shriner, K.A. and Wong-Beringer, A., 2010. Regulatory oversight and safety of probiotic use. Emerging infectious diseases, 16(11), p.1661.

13 Wright, A.V., 2005. Regulating the safety of probiotics-the European approach. Current pharmaceutical design, 11(1), pp.17-23.

Even if the current US regulation provides a more advanced solution for the topic of LBP, there is a long way to go. The FDA is continuously challenged by companies in the area of probiotics, that believe that the current regulations seek to limit what qualifies as a probiotic.

The restrictions in the area of probiotics are perceived as less stringent in the US, and the laws that regulate approval are better defined than in another area, like in Europe. The previously mentioned guideline contains segments regarding recombinant LBP, a live biotherapeutic product composed of microorganisms that have been genetically modified through the purposeful addition, deletion, or modification of genetic material.

A recombinant LBP, which is a GMO, is likely to raise additional considerations and thus would require additional information to be submitted in an IND. Potential sponsors of an IND for a recombinant LBP are encouraged to contact FDA to obtain additional guidance prior to submission of their IND, as no regulation is currently available in this area. The concept of recombinant LBP and GMO has been inconceivable in Europe outside the production of crops until now. However, the issue should be given more publicity in order to catch up with the FDA work.[14]

A global standardisation of the requirements for the evaluation would be highly useful for the improvement and acceleration of the production and marketing process of probiotics in the future. In 2001, the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics developed guidelines for evaluating probiotics in food that could lead to the substantiation of health claims. However, since the development of these guidelines, only a few manufacturers have conducted small, randomized, controlled studies with humans to prove efficacy and safety of their products.[15]

14 Venugopalan, V., Shriner, K.A. and Wong-Beringer, A., 2010. Regulatory oversight and safety of probiotic use. Emerging infectious diseases, 16(11), p.1661.

15 Joint FAO/WHO Working Group and Joint FAO/WHO Working Group, 2002. Guidelines for the evaluation of probiotics in food. London: World Health Organization, ON, Canada: Food and Agriculture Organization.

The problem

The overall issue arising for applicants wishing to enter the market of a recombinant LBP is the grey zone in regulations. Europe compared to the US, does not regard LBP as a drug, and therefore there are no regulations for such purpose. There are also grey zones in the definition of GMO as a pharmaceutical product, which complicates it for companies wishing to enter this market.

Therefore this policy aims to clarify and suggest a proposal for how to bring a recombinant LBP/ medicinal GMO into the market through drug development.

Solution

After reviewing the lacking and inadequate current regulations, reading about similar cases and discussing with experts in the industry, different stakeholders and the public, a solution has been developed for a combinational product using LBP as a drug delivery system. One that takes into consideration the different key steps that would most likely need to be considered in order to receive support from the federal agencies and succeed to put LBP in the market.

The developed solution has been divided into Human Safety, Environmental Safety and risk assessment with several final considerations on how clinical studies should be performed.

Human Safety

To prove that the LBP delivery systems are safe, different species and strains should be tested via inhalation of the used bacteria, having previously undergone vigorous in vitro analysis of the bacteria.

The global standardisation of the guidelines for the evaluation of probiotics that could lead to the substantiation of health claims, proposed in 2001 by the Joint Food and Agriculture Organization of the United Nations and World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics are considered gold standard towards the evaluation of these drug-delivery systems.

The proposed guidelines recommend **1)** identification of the genus and species of the probiotic strain by using a combination of phenotypic and genotypic tests as clinical evidence suggesting that the health benefits of probiotics may be strain specific **2)** in vitro and in vivo testing to delineate the mechanism of the

probiotic effect, the safety and the efficacy **3)** substantiation of the clinical health benefit of probiotic agents with human trials.

Additionally, safety assessment of the probiotic strain should at a minimum determine **1)** patterns of antimicrobial drug resistance, **2)** metabolic activities, **3)** adverse effects noted in humans during clinical trials and after marketing, **4)** toxin production and hemolytic potential if the probiotic strain is known to possess those properties, and **5)** lack of infectivity in model organisms.[16]

One of the main responsibilities of regulatory agencies is to ensure that new medicines are safe and effective when reaching the patient. However, it is extremely difficult to introduce a novel pharmaceutical intervention without any adversities, as it is almost impossible to guarantee 100% safety. Any medical intervention carries risks as well as benefits, and the aim of drug safety assessment is to ensure, as far as possible, that the risks are outweighed by the benefits of exposing anyone to that product.[17]

In particular with LBP, the potential inherent risks are the incidence of opportunistic infections, the spreading of organisms into other compartments of the host and the cross-talk/interplay between the commensal bacteria and LBP.

Because of this, it is suggested to:

- Conduct a proper risk-benefit ratio where the benefit of using a specific solution should be large enough to exceed the risk of not taking any action. The next step in the development of LBP is to provide proof of product efficacy and if possible, a positive correlation of benefit and efficacy.[18]

- Conduct Laboratory toxicology studies including 28-day repeated-dose toxicology studies in two species, in vitro and in vivo genotoxicity tests, safety pharmacology and reproductive toxicity assessment [19]
- Develop and validate a sophisticated bio-containment strategy limiting the growth of LBP to defined environments. A three-layered strategy has

16 Joint FAO/WHO Working Group and Joint FAO/WHO Working Group, 2002. Guidelines for the evaluation of probiotics in food. London: World Health Organization, ON, Canada: Food and Agriculture Organization.
17 Scalia, A., 1987. Responsibilities of regulatory agencies under environmental laws. Hous. L. Rev., 24, p.97.
18 L J. Frewer, J Scholderer, L Bredahl, (2003), Communicating about the Risks and Benefits of Genetically Modified Foods: The Mediating Role of Trust, Risk Analysis
19 H P. Rang, R G Hill, (2012), Assessing drug safety, Drug Discovery and Development, 2nd edition

previously been described which holds promise but still needs to further be improved. Thymineless death (TLD), the fatal process which thymine auxotrophic microorganisms undergo in reaction to thymine starvation and it has previously been used as a biosafety strategy in for example GM-L. lactis strains11. It was first discovered in E. coli12 and exists in many other organisms.[20]

Environmental Safety

As GMOs are increasingly deployed at large scales and in open environments, genetic biocontainment strategies are needed to prevent the unintended proliferation of GMOs in natural ecosystems, affecting the ecological diversity and the natural gene flow. Therefore environmental safety concerns are of paramount importance and need to be addressed.[21]

The aforementioned sophisticated biocontainment strategy should take into consideration these concerns and subsequently it should be properly designed ensuring human safety and the environmental safety as well.

Risk assessment

The concept of risk entails a double identity, which is the probability of an adverse outcome to occur and the degree of its adversity (hazard).

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), the following steps work as guidelines for the risk assessment of new synthetic drugs:

- *Dose and frequency of use*
- *Short-term and especially long-term effects*
- *Interactions with other substances (including alcohol and medicaments)*
- *Individual characteristics*
- *Characteristics of the social environment*[22]

20 Wegmann,U, Carvalho, A, Stocks, M, Carding, S, (2017), Use of genetically modified bacteria for drug delivery in humans: Revisiting the safety aspect, Scientific Reports 7, Article number: 2294

21 Mandell DJ, Lajoie MJ, Mee MT, Takeuchi R, Kuznetsov G, Norville JE, Gregg CJ, Stoddard BL, Church GM, (2015), Biocontainment of genetically modified organisms by synthetic protein design, Nature

22 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), (1999), Guidelines for the risk assessment of new synthetic drugs

Another important factor to consider is that certain patients with incurable diseases (cystic fibrosis) or diseases with a high probability of mortality (cancer) or where available treatment is insufficient, may tolerate certain risks and they should be taken into consideration in the risk-benefit analysis.[23]

A Failure Mode Effects Analysis (FMEA) is recommended in order to analyse all the factors considered before, this system will also need from the creation of a tolerability matrix that would help determine the level of risk, low enough to maintain the processing of a product.[24]

Clinical considerations

Once in vivo studies in different model organisms have been performed, clinical research would be the final step to execute before obtaining marketing approval from any regulatory authority. Clinical trials must be extremely well structured and regulated and the profiles of the individuals taking part in the trials should be well-assessed and documented.

Even when the product has been proven safe for healthy individuals, the outcomes for patients may differ significantly. For example, it is well-known that healthy individuals do not have similar lung microbiome compared to patients with CF, asthma and COPD. Thus, it is essential to assess the safety and efficacy in the diseased individuals.[25]

Because of this, during clinical research, each individual has to be accounted for separately when administering LBP. In addition, every reaction caused by the introduction of LBP will need to be accounted for and documented, as they could determine the final step for submission for marketing approval or most likely provide with a list of all the possible side effects the LBP can cause in individuals.

The great amount of documentation and individual assessment needed before regulatory approval is granted have been some of the problems that have caused the biotech industry to reduce its growth rate, not being able to fulfill the expectations of many, who had predicted that the sector would outrun the pharma field in every aspect by now.

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23 H P. Rang, R G Hill, (2012), Drug Discovery and Development, 2nd edition

24 Yock, P.G., Zenios, S., Makower, J., Brinton, T.J., Kumar, U.N., Watkins, F.J., Denend, L. and Krummel, T.M., 2015. Biodesign. Cambridge University Press.

25 Blaser, M.J., 2016. Antibiotic use and its consequences for the normal microbiome. Science, 352(6285), pp.544-545.

Ethics

Ethics are defined as norms for conduct that distinguish between acceptable and unacceptable behaviour. These norms promote the fair aims behind any research project, such as knowledge, truth, and avoidance of error. Not only this helps in the image a research project can have with respect to the public, but it also helps in building support from the society.

Ethics also help in the development of trust, accountability, mutual respect, and fairness, that are much needed for any research project involving a great deal of cooperation and coordination between individuals with different backgrounds, coming from diverse disciplines and institutions.[26]

Because of this, throughout the process of discovery and development, every product must comply with different ethical principles. These principles differ depending on the stage of development the product is on. During the Research period, the product must comply to Good Laboratory Practices (GLP) and general research ethics. While the drug is being manufactured, it must comply with the Good Manufacturing Practices (GMP) system. Once the drug has been tested and is ready to enter Clinical Trials, the Good Clinical Practice (GCP) standard should be satisfied, as well as the Basic Principles of Medical Ethics.

The principles of GLP promote the quality and validity of data generated in the testing of chemicals and prevent fraudulent practices. By fulfilling GLP, duplicative testing is avoided, as mutual acceptance of the data obtained is achieved.

GLP covers all the stages of the production of a drug/product inside a research facility. From the structure and responsibilities of the test facility organisation and personnel to the quality assurance programme facilities including waste disposal and apparatus, material, and reagents used and storage and retention of records and materials.[27]

On the other hand, research ethics cover honesty, objectivity, integrity, responsible publication, openness, respect for intellectual property, confidentiality, non-discrimination and much more.

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26 Beauchamp, T.L. and Childress, J.F., 2001. Principles of biomedical ethics. Oxford University Press, USA.

27 US Food and Drug Administration, 1978. Good laboratory practice regulations for nonclinical laboratory studies. Federal Regulations, 43(247), pp.60015-60019.

A GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to reduce the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.[28]

GMP covers all aspects of production from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product.

GCP is an international ethical and scientific quality standard for designing, recording and reporting trials which involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected and that clinical-trial data are credible.

GCP indicate that a risk-benefit assessment should be performed before the start of the trial and the rights, safety and well-being of the subjects are the most important considerations and should always prevail. The participants should give their informed consent after foreseeing the risk-benefit of the trial. The privacy and confidentiality of the subjects need to be always respected. GMP are to be followed and there need to be systems with procedures assuring the quality of every aspect.[29]

The trial should be scientifically sound, well described and in accordance with the available non-clinical and clinical information. All the information from the trial should be recorded, handled, and stored for reporting, interpretation and verification. Any decision taken and medical care given should always be the responsibility of a qualified physician. Every individual performing a task in the trial needs to be qualified by education, training, and experience for this position.

28 Ahmed, A., 2009. Good manufacturing practices. ISBT Science Series, 4(1), pp.6-10.

29 Grimes, D.A., Hubacher, D., Nanda, K., Schulz, K.F., Moher, D. and Altman, D.G., 2005. The Good Clinical Practice guideline: a bronze standard for clinical research. The Lancet, 366(9480), pp.172-174.

For a medical practice to be considered “ethical”, it must respect the four principles of medical ethics. These principles include autonomy (informed consent), justice (uphold the spirit of existing laws and be fair to all players involved), beneficence (with the intent of doing good for the patient), and non-maleficence (to not harm the patient involved or others in society). [30]

Conclusion

Recombinant LBP used as therapeutics are currently in the pipeline and may soon reach the ordinary patients. Thus, the necessity of novel and robust regulation comes into place to evaluate whether this developed organism is beneficial for humans arises.

This policy attempts to propose a strategy to follow when developing this regulation, basing it on the current information available for the market authorization for GMOs, probiotics, drug delivery systems and drugs.

There is still a grey zone in regulation which needs to be further addressed and assessed by stakeholders and regulatory agencies. All the issues surrounding the area must be understood before any international harmonization can be achieved. However, this policy aims to trigger a chain of discussions on how these newly developed organisms should be evaluated.

With the collaboration of different regulatory agencies, experts in the field of synthetic biology and always taking the public opinion into consideration, the future of science could be determined by the success of regulations targeting this area.

Even if the developed products have been proven safe and effective, there might be different barriers before any product with these characteristics could be accepted by the public. New marketing strategies and education should be provided to potential users in order to succeed in the development of a new era for the biotech and pharmaceutical industries.

30 World Medical Association, 2008. Declaration of Helsinki. Ethical principles for medical research involving human subjects. http://www. wma. net/e/policy/b3. htm.