Development of Veterinary Immunological and Biological Products – Now and Then?

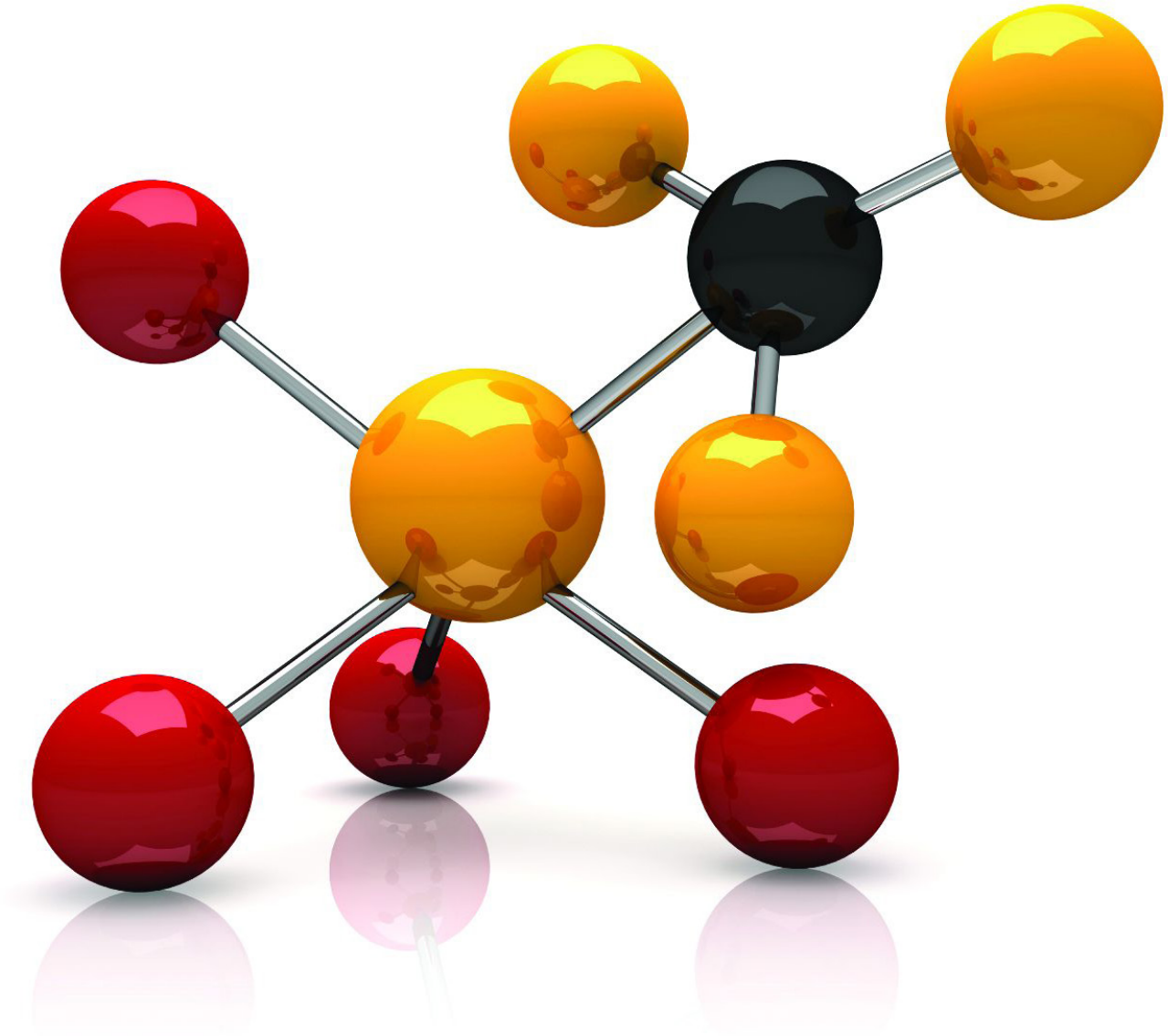
The requirements for the registration of immunological and biological products for veterinary use are currently defined by Directive 2001/82/EC as amended. According to the new proposal for a regulation for veterinary medicinal products (VMPs), COM (2014) 558 final 2014/0257 (COD), the Directive will be revoked and, more importantly, Regulation (EC) No 726/2004 regarding marketing authorisation procedures will be decoupled from the human medicinal product (HMP) one. The goal is that there will be a drive for more harmonised interpretation of the current Directive and fewer country-specific rules that may apply, reducing the freedom for manoeuvre and interpretation of national competent authorities (NCAs). This is emphasised also by replacing the current Directive with a Regulation. What are the consequences for veterinary immunological products and how may this impact on their development for registration if the regulation would be applied as currently proposed?

General provisions: In contrast to the current Directive 2001/82EC as amended, the new regulation added to the definition of an immunological product those for biological products and biological substances. Products that have to be registered under the centralised procedure will include also biological VMPs, which contain or consist of engineered allogenic tissues or cells (Article 38). This will be, for example, any stem cell-derived products that undergo *in-vitro* manipulation/engineering (e.g. by adding certain stimulating or inhibiting factors or genetic modification) and/or are derived from a different animal of the same species (allogenic). Guidance for new therapies, immunologicals and biologicals is still not very clear and remains open for discussion and interpretation, e.g. when should a product be developed under the immunological product guidance for quality, but under pharmaceutical product guidance with regard to safety and/or efficacy? Currently one can get a good idea about the approach that may be used when looking at the respective guidance available for HMPs, e.g. for monoclonal antibodies. Also one has seen different interpretations thereof, depending on the regions where the product is marketed, e.g. for Improvac® (a synthetic peptide analogue of GnRF conjugated to diphtheria toxoid), that has been considered a vaccine in Europe but a pharmaceutical product in the USA. International harmonisation of the classification and requirements of such products via VICH may further reduce the need for additional studies.

As to the proposed new regulation, the NCAs have the obligation to verify the quality of the product and batch-to-batch consistency (Article 127), whereas the current Directive 2001/82EC merely states that the manufacturing has to comply with GMP. This may be interpreted as a call for more emphasis on inspection and control of the manufacturing process, the control tests for intermediate, bulk and final product, and active substance providers for any single VMP by the NCAs within the scope of an application for a MA. Currently inspections of manufacturing sites are performed at least every three years (risk-based) and include any new products that the manufacturer is producing (new MAs) since the last visit. Will this mean that the NCAs will have to assure themselves of quality and batch-to-batch consistency of the manufacturing of a new VMP in the future, before an MA has been granted? If so, this may be a challenge for the inspectorates of the NCAs to comply within given timelines of a registration.

The current directive includes details regarding applications under MUMS (minor use minor species) while the new proposed regulation simply describes limited markets as well as applications in exceptional circumstances, either of them allowing for reduced dossier requirements. The new regulation defines that an authorisation for limited markets will be valid for three years and a market authorisation granted in exceptional circumstances for one year only before it has to be re-assessed. This indicates that for any of these specific authorisations, where reduced data packages would be provided, a "renewal" application would have to be performed and/or the dossier to be updated with further data by that time, whereas renewals will not be required for full marketing authorisations (MAs) any more. As to date some of these products are handled in the first instance in a similar way by NCAs for national applications (e.g. see Veterinary Medicines Guidance Note 2 for limited or provisional MAs) and subsequently on a European level with the new regulation the registration of these products will be more harmonised and, as a consequence, easily recognised throughout the European Union. This will further facilitate the development of vaccines as well as other immunological or biological products for limited markets or emergency use, and reduce the administrative burden of national MA applications for these types of products. Specifically for immunological/biological products, it appears that there is the possibility (Annex II of the proposed new regulation) to conduct pivotal field studies and sell a product whilst a full authorisation application is ongoing. An application for an MA may therefore be made without pivotal field data available at the time of submission further facilitating a faster route to market, especially for vaccines against emerging diseases from other regions; this has been seen previously for bluetongue, new strains of influenza viruses, Schmallenberg virus and possibly the new highly pathogenic porcine epidemic diarrhea virus (PEDv) that has emerged in Europe (e.g. Ukraine).

The new proposed regulation offers the possibility for CAs to require renewals exceptionally. Where this may be applied is not explicitly stated, but any products which bear a certain risk to either the animal, the user, the consumer or the environment (e.g. GMOs or new therapies) may be affected. One would assume that a renewal might be linked also to post-marketing obligations (e.g. surveillance measures).



Variations are currently classed by default as IB unless stated in Regulation 1234/2008 otherwise. However, the intention is to repeal this regulation when the new proposed regulation comes into force, and a related act listing the variations that need assessment has to be provided (Section 4, Article 58). To date there are provisions for vaccines where Type II variations are required, mostly in the area of quality of a product, sometimes also requiring additional efficacy and/or safety data. The intention is to change this to a system of administrative variations that do not require prior approval and variations that may affect efficacy and safety, and will require assessment and approval prior to implementation by the competent authorities (CAs) or the Commission. It is difficult to assess if any real change in the requirements will result from this for immunological or biological products, as currently insufficient information on any changes is available and only the basic principles are laid out in the proposed new regulation. However, due to the complexity of the quality of immunological or biological products, it is likely that most applications for variations that are currently dealt with under type IB (with the exception of minor type IB variations) and all of those dealt with under type II or as extensions of an MA may be listed in the related act of the new proposed regulation as requiring an assessment. For example, this would include any change of starting materials and for any biological starting materials, also the change of the supplier thereof, change or addition of a manufacturing site, and any change in manufacturing that concerns inactivation of a product.

With regard to distribution and sale, the reasons for prohibition of such are detailed in the regulation proposal and the NCAs are obliged to inform the Commission of any prohibitions in their territory. This is specifically relevant to immunologicals/biologicals in relation to Directive 2003/99/EC, and is currently applied in a similar way during the application procedure for an MA.

Administrative: Amongst other documents, the GMP certification of the manufacturer, the expert reports for

quality, safety and efficacy and the detailed description of the pharmacovigilance (PhV) system have to be included. Although the PhV system is usually the same for several products of a company, currently any change to the system, e.g. change of QPPV, requires a variation for each product dossier of the company. This can be quite a laborious and expensive exercise. The new regulation proposal proposes a pharmacovigilance master file independent of the dossier for one or more products of a company, similar to that already required in human pharma. In addition, any cases notified to the MAH will have to be included in a database at Union level directly. It will need to be observed whether the proposed changes will provide for a reduction in administrative burden in the long run. It appears that PSURs (periodic safety update reports) are no longer required by the MAH, but a sophisticated system for signal detection will be included in the central database and the MAH will always have to report AEs within three weeks. How this will be handled for immunological or biological products, where the active may be from the same class of pathogen but still different products, is not clear. In addition, for inactivated vaccines there is also the impact of adjuvants on the efficacy and safety profile. Further clarification in this area will be needed in order to ensure that, for example, not all immunologicals or biologicals for a specific indication may be impacted by one specific active of that class. An example in the area of a vaccine would be the case of Pregsure® BVD, where bleeding calf syndrome was associated with the vaccine; however this was not seen with any other vaccine against bovine viral disease virus to date.

Quality: Currently a detailed description of the starting materials used, the quality of the containers and closures, the quality of the active(s), diluents and excipients, the manufacturing process, the starting materials used with a respective risk-assessment of any biological starting materials are required. Data on consistency batches and stability data for three consecutive batches need to be provided. Specific attention would need to be given to GMOs (genetically modified organisms). In-process and final product controls must be detailed with the respective methods validated and used. The new regulation proposal (Annex II) does not state any differences to the current requirements. However, not much detailed information is given. Interestingly, the new proposed regulation appears to emphasise immunological homeopathics, biosimilars, hybrid and engineered allogeneic cell-based products, which may indicate that by the time the regulation will be in place there may also be guidance that is more specific available for these types of products, either in the regulation or accompanying respective guidance. Specifically one could expect additional guidance for engineered allogeneic cell-based products, as these were additionally included to the proposed regulation. This is even more interesting as the first stem cell product for human medicine has obtained a positive opinion recently under a conditional licence. In line with the possibilities for limited markets, the application of this approach currently seen for human medical products (HMPs) may, if applied to VMPs, encourage further development of advanced therapies (including engineered allogeneic tissues or cells) using limited data packages. For veterinary vaccines, specifically this could mean that more variability during production and for quality release requirements may be acceptable. Otherwise, will this also be allowed for products authorised under a full MA? Nevertheless, fundamental safety and efficacy requirements would still have to be fulfilled, such as demonstration of complete inactivation and a validated potency test.

Safety: Currently, apart from the immunological function, all laboratory safety tests have to be performed under GLP (good laboratory practice) at the maximum recommended dose (one dose, overdose, repeat dose administration, reproductive safety). For live vaccines, additional studies (dissemination, reversion to virulence, recombination or re-assortment and biological properties of the vaccine strain) have to be performed. In addition, based on the active and/or the adjuvant and excipients used, the user safety has to be assessed and mitigated by respective warnings or measures in place. Tests regarding MRL (maximum residue limit) and respective withdrawal period may be required, especially if novel adjuvants or excipients are used. In addition, interactions with other immunological VMPs may need to be investigated if respective warnings may not be acceptable. Any safety data should be complemented with respective data from field studies performed under GCP (good clinical practice). If the product is based on a GMO then a complete range of extra tests, such as the stability of the GMO, and specifically regarding the environmental safety, are required. It appears that the new proposed regulation does not foresee any changes to the safety part of the dossier (proposed Annex II). It can therefore be concluded that guidance documents for specific products currently in place will also be relevant in future, although maybe in a revised version. New guidance with regard to the safety of engineered allogeneic cell-based products may be needed if not available by the time the new regulation will come into force. There may, however, be one difference due to the introduction of a temporary marketing authorisation for products for limited markets (former MUMS) or under exceptional circumstances. For either, the data package does not require to be complete, however as currently for MUMS with regard to safety the basic safety package may need to be provided, although studies combining efficacy and safety, i.e. using batches at an average dose, may be acceptable. This will put more emphasis on PhV and post-authorisation surveillance measures, especially with the changes envisaged for the PhV Master File System and handling for the CAs. As before, there may be a risk of commercial batches at higher dose levels produced for which no or few equivalent safety data are available.

Efficacy:

Directive 2001/82EC requires laboratory efficacy tests to be performed to good controlled standards at the minimum dose. Specific details for the batches used for these studies have to be provided. For vaccines, this refers specifically to the studies to determine the onset and duration of immunity, as well as booster activity. Any analytic tests to determine the efficacy (e.g. ELISA) should be validated. The efficacy as determined here has to be linked to the potency test used for the batch release of the product. This is specifically relevant as the current Directive 2010/63/EC requires the use

where possible of in-vitro tests for batch release. In addition, where possible (exceptions, e.g., would be any diseases that fall under Directive 2003/99/EC for zoonoses) field studies under GCP are required to confirm the efficacy (and safety) observed in laboratory studies. It appears that for the demonstration of efficacy there are no changes to dossier requirements intended in the proposed new regulation. As for safety, additional guidance with regard to the efficacy of engineered allogeneic cell-based products may be drafted by the time the new regulation will come into force. The provision, however, of authorisations for limited markets with reduced data may allow for quite limited data sets on efficacy as long as there is no concern with regard to safety. This may increase the number of products that may not be of any safety concern but with limited efficacy to come to the market. As mentioned above, this will increase the reliance on the PhV system in place for safety evaluation of any new product.

Other specifics: Currently immunological homeopathics (Article 20) are excluded from the chapter of homeopathics (Article 17); however, the titles for distribution and pharmacovigilance still apply for these products (Title VI and VII). In principle, it appears that there is no fundamental change for immunological homeopathics foreseen in the new proposed regulation. Unfortunately, to date there is not much further guidance on immunological homeopathics, and it appears that no additional guidance is intended in connection with the new proposed regulation.

Worth mentioning are the products classed under hybrid applications, which are products that do not meet all the characteristics of a generic, but are similar (see Art. 18 of the proposed new regulation). These include the similar biological VMPs for which additional pre-clinical and clinical data are required when there are differences in biological raw materials. This means that unless a biological product is produced using the same raw materials and/or manufacturing process, a "generic" product of a biological product (similar biological VMP) may require a data package similar to that for a new application. This is further confirmed by Annex III of the new proposed regulation for reduced abridged dossiers, where similar biological VMPs refer back to the requirements of generics and specifically state that further data on safety and efficacy may be required. Bioequivalence and bioavailability data may not be sufficient in these cases.

Conclusion: With regard to the development and the dossier requirements, it appears that currently no major changes are foreseen in the new proposed regulation for vaccines. However, the new proposed regulation is not very explicit with regard to the requirements for immunological and biological products and has merely added new product definitions for VMPs. It specifically mentions engineered allogeneic cell-based products for which further guidance may be required by the time the new regulation comes into force. Hence, guidance for new therapies, immunologicals and biologicals is not very clear and open for discussion and interpretation. In addition, for some immunological and/or biological products, further harmonisation across regions (further VICH guidance) would reduce the burden on additional studies to be performed.

The administrative reduction of the burden regarding renewals and PhV (PhV system master file) will also apply to immunologicals and biologicals.

It therefore appears that the overall impact on the development and registration of new immunological or biological products will be minor, and apart from reduction of administrative burden, mainly lies in the area of MAs for limited markets or under emergency circumstances. The new regulation does, however, not open the door for conditional licences as is available for human medicinal products. It is currently not possible to estimate the full impact on variations to immunological and biological products, as no proposed list of variations under the new regulation that require assessments is available to date. Some new classifications may allow for faster processing of variations that have no major impact on safety or efficacy of a product.

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