Biosimilars hurdles in safety monitoring

Biological products (BP), or biologics, is a class of heterogeneous medical products derived from different natural source materials (mammalian, insect and plant cell cultures, yeast, etc.) intended to treat, cure, prevent or diagnose diseases and medical conditions (1, 5). BP introduction to pharmaceutical market has revolutionized treatment strategy for many therapeutic areas such as oncology (2), dermatology, rheumatology, etc. helping to fight with rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis (5). In spite of diversity these products may be divided into different groups according to, for instance, following features – origin (plant, mammalian, bacterium, etc.), indication (antirheumatic, antipsoriatic, etc.), and molecular size. If classified by latter parameter one of the most notable and not only by high molecular weight and structure complexity are monoclonal antibodies (mAb). Although mAb present comparatively new drug class patent protection for some of them has already expired (e.g. adalimumab, abciximab, bevacizumab, etanercept, infliximab, omalizumab, ranibizumab, rituximab) (4) or expires in the nearest future causing plenty of opportunities for production of follow-on biologics (more commonly called "biosimilars") (3).

Biosimilars are "copies" of original drugs that are just similar, not identical to them. Such difference may be explained by inability to exactly copy manufacturing process of original biologics, which in terms results from lack of available information published by developer of the original product, necessity for reversed engineering, absence of reliable analytical methods allowing original product and biosimilar comparison, molecule complexity and some other factors. Unfortunately, it seems rather complicated to increase likeness of follow-on and original biologics and change status quo not only due to described reasons, but because of variability in regulatory requirements as well.

General guidelines for the approval of biosimilars have been developed or are being drafted by a large number of countries. However, up to this moment in clinical and post-marketing requirements are diverse and sometimes rather vague for follow-on biologics in different countries (table 1).

Table 1

Authority	Description
FDA	FDA approach to biosimilars and biologics investigation is very deep – the administration followed WHO recommendations to include EMA/WHO biosimilars related guidelines only after several years of their publication. However, those few follow-on approved within this time period biologics vary in number of safety and efficacy tests and therefore may have different safety profiles.
EMA	EMA provided piloting universal guidelines for similar biological medicinal products. Nevertheless, great variety in requirements within EU countries for biosimilars substitution reflects difference in understanding of drugs safety profile potentially causing risk increase for certain products.
Roszdravnadzor	Russian biologics and biosimilars market is rapidly developing and characterized by such safety related several issues, as constantly improving pharmacovigilance system on state as well as regional levels, which does not always provide required access to local and global safety data. Alongside with disharmonized definitions of "biologics", "biosimilars" and "non-innovators" in Russian and foreign legislation potentially jeopardizing registration process.
CFDA	Chinese biologics and biosimilars market is also rapidly developing. Nevertheless, no universal guideline of biosimilars or biologics was issued by CFDA till now. But in aspects of in-vitro diagnosis reagents, stem cell and vaccine, there are some specific guidelines separate. Therefore, the regulations and guidelines of drug are the current guidelines for biologics and biosimilars.

Bearing in mind that mAb represent one of the most structurally complex and heavy biologics available on the market described manufacturing related issues have great impact on product quality (purity, homogeneity, etc.) (5). Therefore to ensure such products safety and efficacy even more thoroughly prepared pharmacovigilance plan as well as more detailed investigation during pre-clinical and clinical phases is required.

However, during second decade of 21st century EMA has already published separate "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" and approved biosimilars for monoclonal antibody drugs. These facts emphasize high importance of making quick decisions regarding these drugs making obvious requirement for **following global upgrades:**

Effective and standardized safety information exchange between local PV systems during clinical trials and post marketing

Cumulative registered biosimilars specific global database

Corresponding registration procedures for different types of biosimilars around the world

Consistent approach to drug withdrawal from the market

Requirement for developers of original biologics to publish minimal data on manufacturing process after patent protection expiration

Considering global trends for discussions and enhanced information exchange within global biologics society there is a hope that European experience will be improved and (like EMA/WHO guidelines for biosimilars) translated to all other countries resulting in increase of mAb and other biosimilars likeness, safety and efficacy.

References:

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