DUBAI HEALTH AUTHORITY (DHA) WORKSHOP – BIO THERAPEUTICS

Wednesday, 12th July 2017

12:00 pm - 14:00 pm
The Oberoi Hotel
Dubai - UAE

WORKSHOP REPORT

BACKGROUND

A bio therapeutics workshop was conducted for the Dubai Health Authority (DHA), UAE and PhRMAG members on July 12, 2017 from 12 PM to 2 PM at Hotel Oberoi, Dubai.

ATTENDEES

SPEAKER

Peter J. Pitts

DHA TEAM

Sara Al Dallal - Health Service Specialist, Health Funding Department, DHA

Mohamed Farghaly - Senior Specialist, Head of Insurance Medical Regulation HFD, DHA

Ashraf Reda – Consultant – Dermatology, Welcare Hospital

Faisal Albadawi – Senior Specialist – Rheumatology, Dubai Hospital

Samir Alawadi – Consultant Gastroenterology and Head of Department, Rashid Hospital

Jameel Alakhras – Consultant – Gastroenterology, City Hospital

INDUSTRY REPRESENTATIVES FROM PHRMAG

Eyad Abualfateh (AbbVie)

Tamer Aly (AbbVie)

Nancy Toema (Abbvie)

Shereen Hammad (AbbVie)

Shereen Abdalla (AbbVie)

Nadia Issad (AstraZeneca)

Nadia Younis (AstraZeneca)

Jose Castellote (Janssen)

Sami Al Hegawi (Janssen)

Jeffrey P. Kemprecos (Merck)

Ibrahim Agel (Novartis)

Mazen Gamal (Roche)

MINUTES

THE TRUTH ABOUT BIOSIMILARS - DEVELOPMENT SCIENCE IS DIFFICULT, CLINICAL OUTCOMES COUNT, REGULATORY SCIENCE IS EVOLVING

DR. PETER J. PITTS – (FORMER ASSOCIATE COMMISSIONER, US FOOD AND DRUG ADMINISTRATION)

Dr. Peter began his discussion by highlighting that biosimilars are an incredibly important part of modern medicine. He mentioned that clinical outcomes count, but at the same time there is a tremendous amount of political pressure to control costs. There is a difference between saving money from a tendering perspective, and maintaining positive clinical outcomes.

Dr. Peter mentioned that biologics is evolving science, and a complex one. It is important to understand the existing clinical and pharmacoeconomic evidence of biologics in order to make some smart choices and decisions. Biosimilarity is a complex science and has profound clinical implications. While issues related to bioequivalence can be fixed and the therapeutic balance can thus be regained; biologics can pose a critical problem and is entirely different and complicated. To think that the terms bioequivalent and biosimilar can be used synonymously with the term 'identical' may not be true; this is a misconception that is believed by physicians too. Biosimilars are not the same as innovator products. Dr. Peter provided an example of a patient with epilepsy, well-controlled on treatment. The patient had a sudden episode of seizure, and on further questioning it was revealed that the drug had been switched at the pharmacy from brand to generic. This does not imply that generics are poor in efficacy. If the patient is on a particular drug, it is important to keep him on the same drug and not switch. It is essential that the PK/PD equilibrium is maintained. The same concept is applicable to biologics and biosimilars. Patients should not be switched from brand to generic or biologics to biosimilars. In every country across the world, and without exception – patients do not want to be treated with generics. This mindset necessitates the need for education.

Dr. Peter discussed the development of biosimilar products and highlighted a quote by Dr. Janet Woodcock (Director, Center for Drug Evaluation & Research, USFDA), "the amount of clinical evidence needed is related to the amount of residual uncertainty that remains after you've done the less costly, more quantitative, and less time-consuming analytical and functional studies". He emphasized that the two key words here are 'residual uncertainty'. Dr. Peter added that we cannot predict an exact outcome and that there will always be a variation in terms of the molecule, manufacturer, and patient outcomes. From the pricing and access perspective, it is critical to ascertain how these products actually work in the real-world. Most regulators from different countries are actively assessing real-world outcomes data to judge the effectiveness of medicines, as there is an obvious difference between a product's efficacy in a randomized, controlled trial and its effectiveness in the real-world.

Dr. Peter then discussed 'medication management', and explained that its main purpose is not limited to healthcare savings alone, but to ensure that the products that patients are provided access to have a place within a therapeutic, patient-focused environment. He listed down key discussion points related to medication management, and briefly described each of them:

- What does "similar" mean?
- Interchangeability
- Non-medical substitution
- Indication extrapolations
- Multiple brand biosimilarity

The definition of 'similar' is not the same across all products. All regulatory authorities are assessing molecules from an innovator perspective. This knowledge is then used to assess biosimilars. As the biosimilar marketplace evolves to include more complicated monoclonal antibodies, this acquired knowledge and understanding just becomes a foundation to move forward in an attempt to unravel the complexities associated with evolving biologics.

Interchangeability – In USA and Europe, interchangeability means that the products are close enough that they can be used interchangeably, there will not be any apparent therapeutic difference between the innovator and biosimilar. He provided an example of having a biosimilar A, B, and C of the same reference product. The questions that would arise in such scenarios are (1) would they all be

interchangeable to the reference product, and (2) would they all be interchangeable to each other. He explained about similar scenarios with more complicated chemical molecules wherein the molecule was a biosimilar of the reference product, but the various generics were not bioequivalent to each other. Due to this, physicians now demand to know not only about the molecule they are prescribing, but also the manufacturer of the product. Dr. Peter emphasized that it is important to think how we can begin to help the broader public health community understand what manufacturer is being provided to their patient. Providing access to medication is not just restricted to price but also to educate physicians, pharmacists, and patients.

Non-medical substitution – This refers to switching of a patient's medicine for reasons other than the patient's health and safety. A common question that arises is – should a well- maintained patient on an innovator biologic with positive therapeutic outcomes be switched to a biosimilar for economic reasons? If the biosimilar is not interchangeable to the reference product, the switching is not recommended. If it is interchangeable, the decision should be taken in collaboration with a physician. These are critical decisions to be made, as even from a health spending perspective, it is futile to invest in products that do not provide the best therapeutic benefit.

Indication extrapolations – A vital concern is whether a biosimilar, by definition, be approved for all the indications of the reference product. In USA, depending on FDA's knowledge about the innovator molecule, some molecules are seen to have generous indication extrapolations, others not as much. Interestingly, some companies that are submitting biosimilar applications to FDA are not requesting indication extrapolations. Companies recognize that the clinical work done is indication-specific and are aware of risks of indication extrapolations. The fact that in actual medical practice physicians prescribe a product for a broad range of indications is a practice of medicine issue.

Multiple brand biosimilarity – The binary innovator biosimilar discussion is not going to remain 'binary' for very long. Newer biosimilars for the same reference product will begin to hit the market in the near future. This must be taken into consideration.

Dr. Peter then discussed the importance of nomenclature from a post-marketing surveillance perspective. Naming of biosimilars has been a topic of discussion for long now: whether they should have the same name as the innovator product or should they be mandated to have a separate name. Dr. Peter believes that

biosimilars should have separate names, so it is easy for the physician to understand what is being prescribed. This helps when therapeutic outcomes shift, or when brands are switched. A differential nomenclature is important to differentiate between brands. Thus, after a huge debate, FDA, EMEA and WHO mandated on the importance of differential nomenclature. If the therapeutic outcomes or issues related to a product cannot be measured manufacturer–wise, then resources are not being as precisely spent as they might otherwise be. For example, if an oncology medicine goes off-patent and generic drugs come on the market, the adverse event reporting for the innovator products shoot up. Since all AE-related issues are targeted to the innovator product, this does not help regulators ascertain what is happening in the real-world, both from the regulatory science and reimbursement perspectives. Drug nomenclature enables better safety monitoring, promote timeliness in managing adverse events if they occur, and provide physicians with more information to understand which products are likely to be more effective in specific patient subpopulations.

Dr. Peter elaborated on the urgency of post-marketing surveillance and cited a quote from the British Journal of Clinical Pharmacology, “the most expensive drug is the one that doesn’t work”. Dr. Peter highlighted that the quote is of relevance to the MOHAP team, as being a health authority/ regulator they would want to pay for products that deliver the best therapeutic outcomes.

Dr. Peter then discussed a quote from his article from Lancet, “at a time when the number of biological agents due to come off patent is increasing, and in the face of a market fuelled by escalating drug prices and pressure from pharmaceutical companies and patient groups alike for expedited drug approval, issues surrounding the safety and efficacy of agents such as biosimilars and generics are paramount.” He mentioned that all issues of small molecule drugs, pricing, access, generics, and interchangeability will only get more complex with time.

Dr. Peter believes in the concept of regulatory convergence rather than regulatory harmonization. The former entails bringing all regulatory and reimbursement bodies’ closer together to learn from best practices. Adapting practices from a specific region would not be the right approach, rather it would be beneficial to understand best practices from different countries and implement a unified approach.

Dr. Peter then elaborated on some procurement challenges. He highlighted an example of Ranbaxy providing fake data of bioequivalence studies for atorvastatin, and the testing of their molecule against Pfizer’s Lipitor product. This leads to a

question specific to biosimilars, is paperwork enough for clinical evidence? The answer is that apart from reliable clinical data, more planned robust inspections are required, and trust is of paramount importance. Other criteria include whether drugs are approved in country of manufacture, API and excipient sourcing (Heparin), as well as packaging, labelling, and storage data. These measures must be taken to ensure the quality of products on which money is being spent. Evaluation teams must be comfortable with the clinical evidence and data presented and assess whether the products are worthy of consideration for reimbursement.

Thus, assessing the value of biosimilars becomes a 360 degree concept and involves tendering, quality and real-world evidence. Most critical is to monitor the real-world evidence and it is a continuous process even after the drug hits the market. Most countries do not have the technology to capture real-world data; however, Dubai has the ability to capture such data using technology as an enabler.

Dr. Peter quoted from the US National Institutes of Health (NIH), “as stewards of appropriate medication use, pharmacists must take the initiative to educate themselves, physicians, other clinicians and patients on these products to ensure an accurate understanding of this new category of drugs and to assure the safe and optimal use of biosimilars”. He added that biosimilars lower prices and are here to stay. However, it is the responsibility of the regulatory authority such as MOHAP to reach out to other members of the public healthcare community and educate them on the aspects of biosimilars. The way to make any medicine “safer” is to ensure it is used appropriately. We must embrace the “responsibility of risk”, and educate physicians, pharmacists and patients as a critical objective.

He then highlighted a quote by USFDA Interchangeability Guidance, “pharmaceutical interchangeability is as much a scientific as an educational enterprise that requires close coordination with many stakeholders over the effective lifecycle of the product. This won’t come easily or inexpensively and will require a substantial shift in agency, manufacturer, and healthcare provider engagement”.

Dr. Peter then elaborated on a clinical efficacy results of a generic form of imatinib at King Hussein Cancer Center (Amman). While the product did not create an adverse event, it did not provide any beneficial or positive therapeutic outcome; in order words, there was an absence of therapeutic benefit. The center began to collect data and made changes to their AE reporting system as well to call out for such pharmaceutical events.

He also discussed a study by Mercy University Hospital, University College Cork, Centre for Gastroenterology that studied the clinical impact of both the innovator product (Remicade) and its EMA-approved biosimilar (Inflectra). 80% of the Inflectra group required hospital readmission versus 5% of the infliximab (Remicade) group. (p=0.00004). Sixty percent of patients in the Inflectra group needed steroid augmentation of standard steroid tapering protocol with 50% requiring multiple increases in steroid dose versus 8% of patients in the Infliximab (p-value = 0.0007). Over the course of 8 weeks, 93% of patients in the Inflectra group had an increase in CRP with 7% remaining unchanged whereas 100% of patients in the infliximab group had a decrease in CRP (p=<0.001). This is an example of the need of continuous monitoring of biosimilars in the real-world.

Dr. Peter concluded by highlighting the mantra of the Office of Pharmaceutical Quality, FDA, "one quality standard" for all medicines. Quality must be standard and include effectiveness in the real world, clinical evidence, and adverse events.

Reference to the study comparing Remicade and Inflectra; such results that are submitted to FDA or EMA should have comparisons with a gold standard and not placebo.

One of the issues with this study in EMA was that the clinical data was based on one indication. However, the product is used for multiple indications. This raises the question of efficacy within the labelled indication. Data capturing is of vital importance; it is incorrect to say that a drug is bad or ineffective. Drugs are good, provided used based on clinical evidence.

There should be some coordinated effort between clinicians, procurement heads and the regulators so that clinicians are at least aware of what goes into the application files of drugs. Such data may otherwise not be available to the clinician community. The information that goes out from the regulatory bodies is minimal, and clinicians find difficulties in interpreting such approvals.

As mentioned earlier, education is critical in updating stakeholders about the specifics of a drug. This is a collaborative effort and means more work for everyone.

If biosimilars are not exactly similar or interchangeable, why does FDA or EMA not treat them as new medications? This is not the role of procurement or clinicians to segregate one from the other, and should be initiated by the regulatory bodies. As a clinician, if I trust the innovator, then I trust the biosimilar as it has been endorsed and approved by the regulatory body.

Let's take an example of generic drugs. In 1985, it was agreed that generics can be approved based on bioequivalence and clinical studies are not required. That proved to be hugely successful; in USA about 85% of drugs prescribed are generics. However, physicians and patients always prefer the brand when compared to generics. This is because the brand is trusted due to its quality. Quality, in this context denotes predictable, positive therapeutic outcomes. When it comes to biologics, FDA did not even have the authority for many years to allow biosimilars to exist. Guidelines are now changing and evolving, and FDA wants to educate physicians on the broader aspects of biologics versus biosimilars, interchangeability, switching etc. in order to define the best treatment option for patients. If the product is indeed interchangeable, the patient should be monitored closely. All this required a vast re-education of physicians through educational forums, continuing medical education etc. We are not collecting real-world evidence data to understand and increase our knowledge relative to whether drugs should be continued. There are no mechanisms in place to collect and analyze what is happening in the real world. Such issues need to be addressed.

How many biosimilars are approved in USA? With reference to the Ireland study, were the results picked up by analyzing data that the Irish health ministry collected?

There are 6 biosimilars approved in USA; it is interesting to note that for a number of these biosimilars the sponsoring company has not requested indication extrapolation. The Ireland study was conducted as the hospital recognized there was a problem and it began to collect cohort data. Companies want to go ahead with the strongest label possible, and keep the therapeutic indication as focused as possible.

Do oncologists require a checklist while ascertaining which biosimilar would be most suitable for their patients?

A more important question would be what information physicians have about the product. A basic understanding of what a biosimilar is, what manufacturer is being dispensed to the patient, and is that changeable.

With reference to the interchangeability designation drug policy that was announced this year by USFDA, to what extent will this help patient safety? What are the criteria?

Theoretically, this should help a lot. Prior to the guidance, there wasn't even the ability in US for a biosimilar to be interchangeable. The designation did not exist. What is changing now is that if a sponsor wants an interchangeable designation for a specific product, it has to be backed by strong and robust clinical data. In theory, every biosimilar approved by USFDA should seek an interchangeable designation. This is a start towards understanding what biosimilarity means in the marketplace. FDA is trying to drive better science for registration.

ADJOURNMENT

On behalf of PhRMAG, Nancy Toema (AbbVie) thanked Dr. Pitts for the educational session, and members of DHA for showing an interest in working towards the biosimilar guidelines and consensus. She then adjourned the meeting.