Conference Paper

QUALITY ASSURANCE AND STANDARDISATION OF PATCH TESTS FOR CONTACT ALLERGENS SKIN TESTING

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The misbranding of raw materials used in the manufacturing of patch tests and the counterfeiting of the final product of these test materials have gained increasing importance in the last decade with respect to the production process in the pharmaceutical industry. To guarantee the performance and safety of a semi-solid pharmaceutical testing form, it is important to make oneself acquainted with the different quality standards and official requirements demanded by the national and international regulations.Moreover it will be necessary to get an idea about the major factors which influence the quality of patch tests and therefore finally the quality of the medical allergic diagnosis.

KEY WORDS: *contact dermatitis, corporate culture, manufacturing process, patch test substances, pharmaceutical standard, pharmacokinetics, process validation, quality assurance system, regulatory authorities*

The quality of patch tests mainly depends on three factors. The first is the quality of the manufacturing process according to the regulations of the World Health Organization (WHO) the binding instructions of the Pharmaceutical Instruction Convention (PIC) and the EU Guide to Good Manufacturing Practice (EU GMP Guide) which consist of very precise instructions how to manufacture in every possible case.

The second factor influencing the test quality in those pharmaceutical and technical parameters of pharmaceutical preparation is connected with obtaining the right diagnosis. When considering the above mentioned aspects the right test concentration will be the final result.

The quality of the staff members with their value systems and personal beliefs and the way how they put the philosophy of their company into action is the third factor to ensure a good pharmaceutical quality. Apart from these facts, which can be described as progress in personality development, technical training and scientific education have to be taken into consideration (1-8).

Quality of the manufacturing processes and related regulations

Patch tests have to be of the highest quality; correct diagnosis of an allergy depends on it. It is no longer sufficient to test the quality of the final product, but it is absolutely necessary to monitor each step of the manufacturing process in accordance with the latest EU regulations known as Annex 15 to the GMP Guidelines (9).

Regulations which govern the manufacturing process are steadily enlarged. Originally based on the best practice in the industry, they have been updated, as technology and practice have further been developed. In order to get a manufacturing licence, pharmaceutical companies have to pass several inspections by regional government authorities. In

addition, they are controlled by the Paul-Ehrlich-Institute (PEI), the highest authority in the EU for immunological affairs. These examinations and revisions have the aim to guarantee the compliance with the GMP Guidelines.

Today, an EU GMP Guide has a statutory authority and defines GMP as that part of any Quality Assurance (QA) System which ensures that patch tests are consistently produced and controlled with respect to the quality standards appropriate for their intended use and product specifications.

The final version of Annex 15 to the EU GMP Guide describes the principles of qualification and validation which are applicable to the manufacturing of patch tests. The main argument of the Guide is that the mode of production determines the kind of validation which is necessary to guarantee control over operations (10).

What does validation mean? Validation is defined as the "Action of proving, in accordance to the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results" (11). The key elements of a qualification and validation programme should be defined and documented. This documentation may be considered as a Validation Master Plan (VMP).

Process validation is the means of ensuring and providing documentary evidence that processes are capable of consistently producing a finished product of the required quality within their specified design parameters. The requirements and principles outlined in the Annex 15 are applicable to the manufacture and packing of pharmaceutical dosage forms. They take into account the initial validation of new processes, the subsequent validation of modified processes and re-validation (12).

Every manufacturing process contains a number of factors that may affect product quality. These factors are identified during the development of a product and influence process optimisation studies. Process validation should normally be completed prior to the distribution and sale of a medicinal product. The technical term for this is prospective validation. There where this is not possible, it may be necessary to validate processes during routine production; this is called concurrent validation. Processes which have been in use for some time are validated through a retrospective validation.

In theory, it takes only one validation for any given process. In reality, a process never takes place under the same conditions. Changes occur in components like raw and packing materials; equipment is modified; technical production is improved. In addition, it cannot be assumed that the process environment has remained the same as it was during the initial validation.

Last, risk assessment is necessary to determine the scope and extent of the validation process. When all this information has been collected and generated, it is submitted to a regulatory authority as a licence application with all development, manufacturing and stability data,. The regulatory authority reviews all the evidence and decides whether to grant a licence or not. It requires a huge investment on the part of pharmaceutical companies to bring a new patch test on the market.

Qualification of patch testing against the background of pharmacokinetic parameters

The development of patch tests was for a long time based on experience. Relevant diagnostic aspects are the variables of an antigen which are substance-specific and concentration-dependent. On the other hand, physicochemical properties of a diagnostic drug may influence the rate of its release from the ointment base.

The diagnostic relevance of a patch test depends on the rate of dissolution of the antigen, the rate of diffusion in the matrix, and on the distribution behaviour between ointment and skin (13).

The knowledge of these factors will help to select a suitable test concentration and to understand interdependencies between physicochemical properties of the diagnostic drug and the immunologic reaction.

Without the understanding of pharmacokinetic properties of the allergen it is impossible to make a reasonable and reliable diagnosis. The task of pharmaceutical technology is to conduct the pharmacokinetic studies to understanding better and optimise the manufacture of patch tests with regard to their chemical composition and skin application.

Patch tests mainly consist of suspended antigens stored in an appropriate fatty matrix which is normally white vaseline. The antigen's dissolution rate from the ointment base and its transport through the matrix are decisive for the time required for the allergic reaction on the skin to take place. Therefore, the knowledge of the dissolving behaviour, the lipid/hydro distribution coefficient and the particle size are vital for technological research. It is the release rate from the ointment base that determines the beginning,

duration, intensity and end of an allergic reaction (14).

This can clearly be demonstrated when one uses suspension ointments because their dissolution takes longer than the subsequent absorption into the skin. The knowledge of these fundamental physicochemical processes and respective pharmacokinetic speed parameters is vital for further qualification of existing patch tests and for better understanding of immunologic processes.

Mathematical models serve to describe variables which are important for the ongoing processes and to validate the results found. Numerous mathematical models have been developed on the basis of the above mentioned interdependence in order to comprehend the absorption process and the passage through biological membranes (15).

The main question is the practicability of such abstract models which can be made even more complex by adding more parameters to a reasonable extent. The knowledge of the basic molecular processes which take place in patch tests enables us to predict the subsequent immunologic steps in the human organism. The recurring question about the antigen's correct test concentration - which is still of highest importance for test quality - has got a new meaning and even greater importance in the light of the before mentioned interdependencies. Our main objective is to improve the quality of allergy diagnostics by optimising patch tests on the basis of a better knowledge of these laws, including all parameters relevant to the rapidity and validity of an allergic reaction.

In vivo trials are needed to determine certain unknown correlations between applied antigen and biological effect by describing blood level data of an antigen using appropriate mathematical function. Thus the functional relationship between molecular processes in the suspension ointment - such as the degree of saturation, rate of dissolution in the vehicle, and the permeation coefficient - can help to improve the quality of patch testing.

Standard for the "qualified person"

A "qualified person" plays one of the leading roles in manufacturing pharmaceuticals. No batch of a pharmaceutical product may be released for sale or supply unless a qualified person issues a certificate that all specifications meet the GMP Guide requirements.

The production of patch tests is highly controlled; the study and research of pharmaceutical factors is thorough and continuous, and the level of technical and scientific training is high.

The final decision regarding the handling of any pharmaceutical process is based on the competence, understanding and decision-making of people working in this field.

One's attitude toward economic, personal, technical, social and environmental issues is often driven by one's individual interests, wishes and needs. Moreover, people mainly focus on those pieces of information which are in accordance with their personal situation which in turn may be determined by their education, training and lifestyle. These lead to individual differences in the assessment of a given situation, people and processes in a pharmaceutical company.

This philosophy has to take into consideration the needs of the company, those of the employees and customers as well as possible negative consequences and effects for our environment.

In the "brial allergen company" we have come to the conclusion based on long-term experience that material and technical standards highly correlate with the development of the personality and character of our employees (16). Our professional activities, human resources management and company philosophy are founded on the *biophilia* postulate of the Jesuit Rupert Lay (17). Hence, corporate responsibility and responsible leadership are the manifestation of our principle "management by participation". We therefore pride ourselves on having developed a corporate culture dealing with inner and outer environment. Our corporate image that has arisen from this culture over the years corresponds with the theory of a "self-learning organisation" (18-20).

The realisation of a "self-organising company" with respect to the above mentioned theory requires the introduction of a series of restructuring measures. This process takes several years with both the management and the staff being involved in it. The implemented measures comprise, among others, support between the staff. This includes the introduction of perception training and behaviour analysis related to aspects of leadership. This means communication and presentation training, conflict management, team work training and social ethics.

To my mind, the faculty of lifelong learning and the ability and necessity to take decisions weigh heavily in a globalising world. The basis for personal

development of our team members are clear and transparent working and operation processes in accordance with the requirements of the TQM (Total Quality Management) (21) quality concept and DIN EN ISO standards (22).

The reduction of our hierarchical organisational structures which has automatically resulted from the above mentioned issues has brought about notable changes with regard to our company culture. The internal decision-making has become faster and a management team which performs all management tasks and represents our company was formed. Thanks to the self-control within our management team, several, formerly necessary control measures have become needless and could be abolished.

The decisive factor for successful implementation of all these measures is the development of the communication ability and social behaviour between our staff members. In addition, we carry out communication trainings in order to promote self-critical analysis of organisational processes within our team.

Our company philosophy is shaped by common norms and values which form the basis for dealing with each other within and outside our company. In this way, corporate identity is created in which the uniqueness of every single staff member finds its expression.

Due to this way of working and learning together in an atmosphere of confidence and safety, both the staff and the management have got more freedom to concentrate their attention and activities on the quality of our goods with regard to our of customers' and patients' contentment.

In this field of management studies and development of leadership qualities we are exploring a new theory of organisation with the intention to create a self-organising company. Our model are those structures of nature which are analogical to immunologic patterns and behaviour of our body defence system and the corresponding cell interaction and communication structures in our organism (23).

REFERENCES

1. WHO Drug Information 2001;15:2-5.
2. International Federation of Pharmaceutical Manufactures Associations (IFPMA). Counterfeiting. Available from: URL:http://www.ifpma.org
3. World Health Organization (WHO). Quality Assurance of Pharmaceuticals. Volume 2. Good Manufacturing Practices and Inspection. Geneva: WHO; 1999.
4. World Health Organization (WHO). GMP: Supplementary Guidelines for the Manufacture of Pharmaceutical Excipients. WHO Technical Report Series No. 885;1999.
5. PIC/S Committee. Draft: Internationally Harmonised Guide for Active Pharmaceutical Ingredients. Good Manufacturing Practice (API Guide). Brussels: EFPIA; 1997.
6. International Pharmaceutical Excipients Council. GMP Audit Guideline for Distributors of Bulk Pharmaceutical; 2000.
7. Amico LA, Caricofe RB, English JD, Goodson GW, Lewis LD, Franz RM. Pilot Plant Operation. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. New York (NY): Marcel Decker Inc.; 1995;12:187-207.
8. Lay R. Über die Kultur des Unternehmens [Corporate culture, in German]. Düsseldorf, Vienna, New York (NY): Econ Verlag; 1994.
9. GMP Guidelines. Available from: URL: http://eudrams1.is.eudra.org/F2/eudralex/vol-4/pdfs-en/v4an.15.pdf
10. US Food and Drug Administration. Guideline on General Principles of Process Validation. Division of Manufacturing and Product Quality. Office of Compliance. Rockville (MD); 1987.
11. Auterhoff G. EG-Leitfaden einer Guten Herstellungspraxis für Arzneimittel [EU Guide to Good Manufacturing Practice, in German]. 5th edition. Aulendorf: Editio Cantor Verlag; 1998.
12. Bias-Imhoff U, Glanzmann G, Woiwode W. Annual Product Review, ein Verfahren der retrospektiven Produkt- und Prozeßvalidierung [Annual Product Review, a procedure of retrospective product and process validation, in German]. Pharm. Ind. 1992;54: 177-82.
13. Brinkmann J. About the reliability of allergy tests. 2000. Available from: URL: http://www.brial.com/en/unternehmen/veroeffentlichung_en.asp
14. Martin AN, Leuenberger H. Physikalische Pharmazie [Physical pharmacy, in German]. 4th edition. Stuttgart: Wissenschaftliche Verlags-Gesellschaft; 2002.
15. Brinkmann J. In-vivo-Untersuchungen zur Freisetzungskinetik in Arzneiformen [In-vivo trials referring to release behaviours in ointments, in German] [dissertation]. Bonn: Rheinische Friedrich-Wilhelms-Universität; 1975.
16. Brinkmann J. QMS und Firmenphilosophie [QMS and corporate philosophy, in German]. Available from: URL: http://www.brial.com/funternehmen.asp
17. Lay R. Kommunikation für Manager [Communication for manager, in German]. Düsseldorf, Vienna, New York (NY): Econ Verlag; 1991.

18. Seiffert H, Rodnitzky H, editors. Handlexikon zur Wissenschaftstheorie [Philosophy of science, in German]. 2nd edition. Munich: Ehrenwirth; 1994.
19. Gouillart FJ, Kelly JN. Business transformation. Vienna: Ueberreuther Verlag; 1995.
20. Puschmann NO. Systemtheorie [System theory, in German]. Unna; 2000.
21. Töpfer A, Mehdorn H. Total Quality Management. 4th edition. Neuwied, Kriftel, Berlin: Luchterhand-Verlag; 1995.
22. Deutsches Institut für Normung (DIN). DIN EN ISO Norm 9000-1. Qualitätsmanagement und Elemente eines Qualitätsmanagementsystems, Teil 1: Leitfaden [DIN EN ISO Standard 9000-1. Quality management and elements of a quality management system, Part 1: Guidelines, in German]. Berlin: Beuth Verlag; 1994.
23. Brinkmann J. Allergie im Quantensprung [Quantum leaps in allergies, in German]. Landsberg: Ecomed; 1999.

Sažetak

PRIKLADNOST I STANDARDIZACIJA PATCH TESTA ZA TESTIRANJE KONTAKTNIM ALERGENIMA

Pogrešan izbor sirovina za izradu pripravaka za *patch* testove, što rezultira neprikladnim finalnim proizvodom takvih test-materijala, dobiva tijekom zadnjeg desetljeća sve veću važnost u odnosu na proizvodni proces u industriji lijekova.

Da bi se garantirala izvedba i sigurnost polukrutoga farmaceutskog oblika za testiranje, važno je biti upoznat s različitim standardima kvalitete i službenim zahtjevima sadržanim u nacionalnim i međunarodnim propisima. Nužno je i saznanje o glavnim čimbenicima koji mogu utjecati na kvalitetu *patch* testova te u krajnjoj konzekvenciji na kvalitetu medicinske dijagnoze alergije.

Vrijednost *patch* testa ovisi uglavnom o tri faktora. Kvaliteta proizvodnog procesa mora biti u skladu s pravilima Svjetske zdravstvene organizacije, s uputama PIC-a (Konvencija farmaceutskih uputa) te EU-GMP vodičem koji se sastoji od vrlo preciznih instrukcija o tome kako proizvoditi u svakom od mogućih slučajeva. Drugi faktor koji utječe na kvalitetu testa odnosi se na farmaceutske i tehničke parametre farmaceutskog proizvoda povezano s točnošću dijagnoze. Krajnji je rezultat točna koncentracija materijala za testiranje. Kvaliteta osoblja koje sudjeluje u proizvodnji i njegovo osobno shvaćanje vrijednosnih kriterija koji moraju vladati kod proizvođača, treća je nužna pretpostavka za osiguranje vrijednosti proizvoda.

Osim razmatranja navedenih ključnih pretpostavki u vezi s osiguranjem prikladnosti i standardizacije *patch* testa za testiranje kontaktnim alergenima raspravlja se i o ulozi kliničke izobrazbe i znanstvene edukacije osoba uključenih u izradu pripravaka za testiranje.

KLJUČNE RIJEČI: *edukacija osoblja u proizvodnji, farmakokinetika, kontaktni dermatitis, kultura odnosa, međunarodni standardi i propisi, ocjena kvalitete testa, proces proizvodnje pripravaka za testiranje*

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