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Drug safety and efficacy impaired by quality failure

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The three main pillars of drug evaluation are quality, safety and efficacy. Each marketing authorization dossier has to demonstrate conformity with quality, safety and efficacy requirements separately. While this is justifiable, it may nevertheless lead to some important problems being overlooked. The relationship between these three aspects of a medicinal product can be of great importance. Little is said about how quality can affect safety or even efficacy. It is worth discussing these connections in order to assess side-effects appropriately and to distinguish between quality failures and real pharmacovigilance problems. Not every side-effect is a result of the drug's pharmacodynamic or pharmacokinetic properties or other therapy-related issues such as interactions. Sometimes a patient complaint is caused by substandard quality of the drug. This possibility should never be ignored in any assessment of side-effects. This paper presents a useful check-list of quality failures that can endanger drug safety.

Not enough attention is paid to the problem of interactions between quality and safety, quality and efficacy, and safety and efficacy. Although these connections are of great importance, they have scarcely been mentioned until recently. The issue has been raised in a few papers (Figueras et al. 2002; Görög 2003, 2008; Pifferi and Mannucci 1999) where the authors have mentioned that quality defects may lead to undesirable safety implications. This question, however, was unfortunately not elaborated upon. The International Conference on Harmonization released two general guidelines focusing on impurities in new drug substances (ICH Q3A 2006) and new medicinal products (ICH Q3B 2006). The ICH takes this into consideration and recommends evaluation of the toxicity of suspected impurities. Organizations distinguish three types of thresholds: reporting, identification and qualification, depending on the level of impurity. The minimum toxicological screen should cover genotoxic potential; *in vitro* detection of point mutations and chromosomal aberrations. Extended tests, if required, should test the general toxicity on animals and may lead to different specific study endpoints. As a consequence of interest in the field of undesirable contaminants, one journal has devoted a whole issue to pharmaceutical impurities from analytical, toxicological and regulatory perspectives (Basak et al. 2007). This provides a comprehensive review of the current state of the art.

The quality of a drug can indeed affect its safety. Any medicine can undergo different unwanted degradation processes such as hydrolysis, oxidation, reduction, isomerization or radiation which can occur because of incorrect storage or transport conditions. Problems can arise also in the pharmacy where compounded formulations are prepared according to a physician's prescription. This leads to the formation of degradation products. The synthesis process is also where several types of impurities can occur, including reagents, catalysts, ligands, residual solvents, intermediates or by-products (including enantiomeric impurities and unintended polymorphic forms). Pharmaceutical forms can also contain – especially with products of natural origin - pesticides, heavy metals, ash (inorganic and/or organic moieties), polycyclic aromatic hydrocarbons and pathogenic microorganisms. Biotechnological engineering, gene therapy and stem cell technology are associated with the occurrence of highly reactive biological contaminants similar to physiological metabolites and cellular structures, including peptides, nucleotides, enzymes, or polysaccharides (Barnes et al. 2009). Another group of drugs of special concern are radiopharmaceuticals (Nandy et al. 2010). Radiochemical impurities are dangerous due to radiation and their unknown pharmacokinetic and pharmacodynamic profile.

As listed above, contaminants can come from degradation processes, manufacturing or other unpredictable sources. We can make many different divisions of impurities, e.g., into organic and inorganic. In view of the subject of this publication I wish to propose a novel classification, as follows:

1. Impurities that demonstrate neither pharmacological nor toxicological potential.
2. Impurities that demonstrate pharmacological potential:
   a) same action as undecomposed substance:
      - having the same strength of action,
      - weaker,
      - stronger,
   b) generating another effect.
3. Impurities that show toxicological potential:
   a) immediate, dose-independent,
   b) immediate, dose-dependent,
   c) delayed in time.
4. Impurities that demonstrate both pharmacological and toxicological potential.

The distinctions presented here need careful consideration and rationale. The presence of impurities of the first type does not equate to an immediate risk, but, nevertheless, contaminants should be managed with regard to both quality and quantity. The impurities listed in section 2.a) can affect the strength of a medicinal product and can lead to therapeutic inefficacy. If an undesirable substance exhibits a pharmacological effect different from that of the product, its mechanism of action and strength must be determined. There is a need to assess whether this effect is of clinical importance and how it interacts with the primary application of the pharmaceutical.

The impurities listed under section 3 demonstrate toxic effects. The most dangerous are those substances which exert an immediate action irrespective of the dose given. Even a small dose may provoke a severe intoxication, including anaphylactic shock. A lower hazard is associated with those contaminants which exert their adverse effects dose-dependently. The third group comprises substances which bring with them a hidden, delayed risk. The side-effects appear only after some time because sufficient accumulation in the body is necessary, an immune

response is not provoked until there have been successive contacts with the substance, a disease develops on the basis of prior genotoxic effects/mutagenic changes, or as a result of other circumstances. The role of drug contaminants is still not understood in rare, unpredictable immunological diseases like toxic epidermal necrolysis (TEN, Lyell's syndrome) or Stevens-Johnson Syndrome (SJS). Could the cause of the immunological response be a simultaneous infection, accumulation of toxic metabolites or perhaps the presence of contaminants?

The fourth case, when an impurity demonstrates both pharmacological and toxicological potential, is the hardest to assess properly. In such situations it is necessary to take into consideration all the problems previously listed and to estimate the effects of all possible interactions to identify the global final risk. Point-by-point analysis on the basis of the proposed classification will ensure an acceptable level of safety risk management.

Numerous types of impurities, as can easily be imagined, could cause safety problems. They may be, among others, allergic, pyrogenic, genotoxic, carcinogenic, cytotoxic, teratogenic, toxic to reproduction and development, phototoxic or radiotoxic. Side-effects can be limited to specific organs or tissues; we know of many substances that are hepatotoxic, nephrotoxic, cardiotoxic, neurotoxic, immunotoxic, ototoxic etc. Poisonous effects could be also a result of incorrect pH, moisure content, ionic strength, particle size or osmolarity adjustment and many other quality factors.

Substandard quality may concern both active substances and excipients. We cannot exclude interactions between the active pharmaceutical ingredient (API) and excipients, especially when the product is reconstituted before use, it is made in the pharmacy or it is in course of development. We should not ignore impurities which come from packaging or disinfectants - they can also exist in medicinal products. In extreme cases, counterfeit pharmaceuticals could contain anything, and there are, hopefully, very rare situations where the drug includes macroscopic impurities such as pieces of glass, human hair, flakes of paint from the ceiling, charcoal or filter aids. Despite the implementation of and attention to GMP, GLP and PAT (Process Analytical Technology) principles, specific quality problems are unpredictable, and so unavoidable.

Regulatory authorities have paid greatest attention to genotoxic impurities, as demonstrated by the issuing of detailed guideline documents (EMEA 2006, FDA 2008). Maximum daily exposure over lifetime has been established as 1.5 μg per person, compared with a level of several milligrams for other, non-genotoxic, impurities (depending on the drug dose). Examples of proven genotoxic/carcinogenic agents are easy to enumerate: alkylating agents, nitrosamines, azoxy compounds, 9-aminoanthracene, methyl methanesulfonate, ethylene oxide, etc. Investigation of genotoxic impurities is still a very hot topic that needs further evaluation (Robinson 2010).

Specific documents are also devoted to residual solvents (ICH Q3C 2009) and metal catalysts (EMEA 2007). This is justified by the known toxic effects of representatives of these groups of substances, together with their lack of therapeutic benefit. Benzene, carbon tetrachloride, and dichloroethane are proven human carcinogens. Such substances as acetonitrile, chloroform, cyclohexane, 1,4-dioxane, hexane, methanol, pyridine, toluene and many others should be avoided or limited due to their non-genotoxic hazardous potential. Metal catalysts that are known or suspect carcinogens are: platinum, palladium, iridium, rhodium, ruthenium, osmium, molybdenum, nickel, chromium and vanadium. Metal catalysts with a lower potential toxicity are copper and manganese. The elements listed above do not cover the spectrum of all possible toxic metal contaminants. Lead, mercury, cadmium, arsenic, aluminium, cobalt, tin, thallium, beryllium, antimony, and tungsten have known hazardous potential. Some metals like actinium, thorium, uranium or radium are radioactive.

Quality can impair efficacy in a direct manner. In most cases, unexpected degradation processes lead to the formation of therapeutically inactive products. Pharmaceutical formulations may also contain too little of the active substance due to manufacturing failure, leading to pharmacological ineffectiveness. At this point, it is also necessary to remember the possibility of counterfeit products and the suspected poor bioavailability of some generic medicines.

One should take into consideration the fact that there is also a connection between the safety of a drug and its efficacy or, more generally, between safety and effectiveness of therapy. The problem is generally associated with side-effects and interactions of clinical importance that lead to discontinuation of medication. There are also some interesting examples of medicines that have side-effects similar to their indications, e.g., antiarrhythmic agents may generate arrhythmias, cetirizine can be an allergen, and prolonged use of purgatives can lead to severe constipation as a result. In such cases withdrawal of therapy by the patient could be a result of safety concerns.

This provides a strong rationale for further characterization and control of impurities. More research is needed in this area to build up comprehensive knowledge. In rare situations, as has been stated, impurities can produce not only toxic effects but also unexpected pharmacological actions. Currently we possess very useful computational techniques enabling complex *in silico* evaluation based on qualitative structure-activity relationships (QSAR) and knowledge of pharmacofores and toxicofores (Basak et al. 2007). For example aromatic amines, alkylating electrophilic centers, aromatic nitro-groups, azo-structures, epoxides, and *N*-nitroso groups are chemicals known to have serious hazard potential. More detailed toxicological assessments of impurities must be done whenever reasonable, especially at the drug development stage. In this phase we need to know the risk and possibly modify the synthesis process to avoid formation of toxic impurities.

When considering safety issues there is a need to exclude quality problems as the cause of side-effects or interactions. The presence of unexpected, and sometimes unidentified, constituents could be the basis for many safety issues. The extent of the problem is probably not very great, but we cannot ignore it because of the many kinds of possible impurities. There is a need to estimate and manage the pharmaco-toxicological profile of any contaminant. The aim is not to attribute a side-effect incorrectly to the drug which can happen quite often. I hope that the listing presented in this publication will be helpful in assessing any safety event. The relationships between drug quality and safety, quality and efficacy and safety and effectiveness should be taken into consideration both by pharmacovigilance professionals and by the academic sector at every opportunity.

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