GENOTOXIC IMPURITIES IN MEDICINAL PRODUCTS – REGULATORY REQUIREMENTS

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Most chemical syntheses use highly reactive molecules, which are often DNA-reactive (mutagens). They may be present in the active substance (AS) or in the drug product as genotoxic impurities (GI). The mechanism of action of most GIs is based on DNA modification by direct binding (electrophilic - alkylating agents), insertion into the DNA chain (topoisomerase inhibitors) and antimetabolites (purine/pyrimidine analogs). Structural alerts (SA) for carcinogenic activity are defined as functional groups or substructures of compounds associated with carcinogenic activity (1). SA indicates a chemical group that causes toxic effects through one or several common mechanisms of action. GIs can bind directly to DNA or after metabolic transformations (oxidation and reduction), thus the SA structure may indicate the formation of several toxic metabolites. The risk assessment for the presence of GIs is a mandatory part in the module 3 (AS/DP impurity profile) submitted in the marketing authorization procedure, also in the approval of clinical trials. Guideline ICHM7(2) provides recommendations for identification, categorization, qualification and control strategy of mutagenic impurities in order to limit the potential carcinogenic risk. According to ICHM7, the classification (class 1-5) of all impurities is performed on the basis of data on carcinogenicity and bacterial mutagenicity (BM) from databases/scientific literature. If data are not available, computational toxicological assessment (QSAR) is performed and BM is predicted with two independent models. If any of model shows SA structures, a BM assay (*Ames* test) is performed. The high potent mutagenic carcinogens (aflatoxins, nitrosamines, alkyl-azoxy compounds) referred to as "cohort of concern".

References

1. Muller L. et all. A rationale for determing, testing and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity. *Regul. Toxicol. Pharmacol.* 2006, 44, 198–211.
2. ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, February 2018.

GENOTOKSIČNE NEČISTOĆE U LEKOVIMA - REGULATORNI ZAHTEVI

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U većini hemijskih sinteza se koriste veoma reaktivni molekuli koji su često i DNK – reaktivni (mutageni). Oni mogu biti prisutni u aktivnoj supstanci (AS) ili gotovom proizvodu (GP) kao genotoksične nečistoće (GN). Mehanizam dejstva većine GN se zasniva na modifikaciji DNK i to direktnim vezivanjem (elektrofili - alkilujući agensi), umetanjem u lanac DNK (inhibitori topoizomeraze) i antimetaboliti (purinski/pirimidinski analozi). Upozoravajuće strukture (SA) za kancerogenu aktivnost se definišu kao funkcionalne grupe ili delovi strukture jedinjenja koje su povezane sa kancerogenom aktivnošću (1). SA ukazuje na hemijsku grupu jedinjenja koja izaziva toksične efekte kroz jedan ili nekoliko obično zajedničkih mehanizama delovanja. GN mogu direktno da se vezuju za DNK ili nakon metaboličkih transformacija (oksidacija i redukcija) pa SA struktura može da ukaže na nastanak nekoliko toksičnih metabolita. Procena rizika na prisustvo GN u delu koji se odnosi na profil nečistoća AS/GP je obavezan deo dokumentacije o kvalitetu leka koji se podnosi u postupku registracije leka, kao i odobravanja kliničkih ispitivanja. U smernici ICHM7(2) su date preporuke za identifikaciju, kategorizaciju, kvalifikaciju i kontrolnu strategiju mutagenih nečistoća kako bi se ograničio potencijalni kancerogeni rizik. Prema ICHM7 se vrši klasifikacija (klase 1-5) svih nečistoća na osnovu podataka o kancerogenosti i bakterijskoj mutagenosti iz baza i naučne literature. Ako podaci nisu dostupni sprovodi se *in silico* toksikološka procena (QSAR) i predviđa se bakterijska mutagenost sa dva nezavisna modela. Ako jedan od modela pokaže SA strukture, radi se test povratne mutacije na bakterijama (*Ames* test). Posebno se razmatraju visoko potentni mutageni kancerogeni (aflatoksini, nitrozamini, alkil-azoksi jedinjenja).

Literatura

1. Muller L. et al. A rationale for determing, testing and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity. *Regul. Toxicol. Pharmacol.* 2006, 44, 198–211.
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