POVZETEK

Raziskovalno vprašanje (RV): Za vzpostavitev in ocenjevanje sistemov kakovosti v farmacevtski industriji obstaja več vrst standardov. S kakovostjo lahko povežemo tudi standarde za ugotavljanje skladnosti ISO 17000. Eden od standardov na področju ugotavljanja skladnosti je standard ISO/IEC 17025 Splošne zahteve za usposobljenost preskuševalnih in kalibracijskih laboratorijev. Standard zahteva, da laboratoriji pri navajanju rezultatov podajajo tudi merilno negotovost. Do zdaj je bil ta termin uporabljen le v primeru kalibracij in uporabe referenčnih substanc. Glede na zgodovino podajanja rezultatov kemijskih meritev lahko pričakujemo, da bo takšen način podajanja, tj. rezultat +/- merilna negotovost, kmalu uveljavljen tudi na področju farmacevtske industrije.

Namen: Namen magistrske naloge je v teoretičnem delu opredeliti kakovost, kontrolo kakovosti, zagotavljanje kakovosti, celovito obvladovanje kakovosti, odličnost, pomen standardizacije kot način izboljševanja procesov, zaposlene kot vir inovacij in stalnih izboljšav ter merilno negotovost. Namen praktičnega dela je ovrednotiti merilno negotovost posameznih merilnih veličin in preveriti njihov vpliv na merilno negotovost rezultata. Cilji raziskave so določiti merilno negotovost rezultatov analiz, izvedenih s tehniko tekočinske kromatografije visoke ločljivosti v farmacevtskem laboratoriju, ugotoviti, kateri izvori merilne negotovosti obstajajo in ključno prispevajo k merilni negotovosti rezultata, in ugotoviti, katera od možnih napak izvajalca (analitika) v merilnem postopku ključno vpliva na rezultat, ter na osnovi ugotovitev postaviti model, s katerim bomo izboljševali proces vrednotenja rezultatov v farmacevtskih laboratorijih v smislu zmanjševanja merilnih negotovosti posameznih merilnih veličin ter zmanjševanja napak izvajalcev analiz.

Metoda: V magistrski nalogi smo ovrednotili merilno negotovost rezultatov, dobljenih z metodo tekočinske kromatografije. Merilno negotovost smo izračunali v sladu s priporočili Vodila za podajanje negotovosti pri meritvah (angl. *Guide to the expression of uncertainty in measurement* – GUM). Merilno negotovost smo izračunali tudi s t. i. Kragtenovim načinom. Posamezne prispevke k merilni negotovosti končnega rezultata smo analizirali in s tortnimi diagrami prikazali, kateri od posameznih prispevkov največ prispeva k merilni negotovosti končnega rezultata.

Rezultati: Ugotovili smo, da uporaba večje volumetrične steklovine signifikantno vpliva na zmanjšanje skupne merilne negotovosti končnega rezultata. Ugotovili smo tudi, da je izobraževanje in usposabljanje strokovnega kadra ključno pri zmanjšanju napak v laboratoriju.

Organizacija: Določili smo, kateri parametri ključno vplivajo na zmanjšanje merilne negotovosti, in postavili model, s katerim bomo izboljševali proces vrednotenja rezultatov.

Družba: Pri vrednotenju rezultatov v farmacevtskem laboratoriju imamo lahko dva skrajna načina vrednotenja; rezultat ocenimo kot neustrezen, dejansko pa je ustrezen, in rezultat ocenimo kot ustrezen, dejansko pa je neustrezen. V prvem primeru je posledica nepravilnega vrednotenja rezultatov uničenje serije zdravil, ki so sicer ustrezne. S tem povzročimo organizaciji izgube. V drugem primeru pa lahko resno ogrozimo zdravje pacientov.

Originalnost: Originalnost raziskave je v vrednotenju merilne negotovosti v farmacevtskem laboratoriju.

Omejitve/nadaljnje raziskovanje: Pri raziskavi smo se omejili na vrednotenje merilne negotovosti rezultatov, dobljenih z metodo tekočinske kromatografije.

Ključne besede: kontrola kakovosti, zagotavljanje kakovosti, celovito obvladovanje kakovosti, odličnost, standardizacija, merilna negotovost.

ABSTRACT

MEASUREMENT UNCERTAINTY ESTIMATION IN PHARMACEUTICAL LABORATORIES – A STEP TOWARDS BUSINESS EXCELLENCE

Research Question (RQ): The quality system in the pharmaceutical industry can be established and controlled by using different quality standards. Quality can be linked also to the group of standards ISO 17000. One of the standards from this group is standard ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories. This standard requires that laboratory reports the results together with measurement uncertainties. So far, this term was used in pharmaceutical laboratories only in regards of calibrations and usage of reference substances. Looking back to the history of the way of reporting the results of chemical measurements, we may predict that such a way of reporting, e.g. result +/- measurement uncertainty, will be soon implemented also in the pharmaceutical laboratories.

Purpose: The purpose of the master thesis is to define the terms such as quality, quality control, quality assurance, total quality management, excellence, standardization as the way to improve the processes, employees as source of innovation and improvements and measurement uncertainty. The main objective of the practical work of this thesis is to evaluate measurement uncertainty of each input quantity and to determine their influence on the measurement uncertainty of the final result. The objectives of this investigation are: to evaluate measurement uncertainty of the results obtained by High performance liquid chromatography in pharmaceutical laboratory, to identify all sources of measurement uncertainty which contribute to the measurement uncertainty of the final result; and to identify which of possible analyst errors during the measurement procedure have major impact on the final result. The results of this investigation will be used to establish a model which will serve for process improvements in pharmaceutical laboratories in the way to improve measurement uncertainties of input quantities, as well to reduce analyst errors made during measurement procedure.

Method: In this master thesis measurement uncertainty of the results obtained by high performance liquid chromatograpy was evaluated. Measurement uncertainty was evaluated using Guide to the expression of uncertainty in measurement (GUM) as well using so called Kragten appoach. Individual uncertainty contributions were analysed and their contributions to the uncertainty of the final result were presented using pie chart.

Results: One of our findings is that the usage of volumetric labware of bigger volumes significantly reduces measurement uncertainty of the final result. Additionally, we found out that education and periodic training of analytical staff significantly contribute to reduction of analysts' errors made during the measurement procedure.

Organization: The contributions of measurement uncertainty of the final result were determined and the model for process improvement was established.

Society: The results obtained in pharmaceutical laboratory must be evaluated according to the specification. There can be two different wrong ways of evaluation; it is said that the result doesn't confirm with the specification, but actually it confirms, or it is said that the result confirms, but it doesn't. Such wrong decisions/evaluations may lead to drastic consequences; such as the company discards the whole batch of drug, which leads to the financial loss or with placing the drug on the market which doesn't confirm with the specification, patients' health may be in danger.

Originality: Evaluation of measurement uncertainty of the result obtained in pharmaceutical laboratory gives originality to this investigation.

Limitations/Future Research: This investigation was limited to evaluation of measurement uncertainty of the result obtained by high performance liquid chromatography.

Keywords: quality control, quality assurance, total quality management, excellence, standardization, measurement uncertainty.