TOLERANCE INTERVALS AS CONTROL CHART: COMPARISON TO CLASSIC SHEWHART $\overline{X}$-R CONTROL CHART

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Without the monitoring of a routine process, i.e., drug production, drug analysis…, one cannot guarantee the quality of results produced. Statistical Process Control techniques are set-up to allow an early detection of special (or assignable) causes of variations that are occurring in routine process in order to adjust this process and maintain it under statistical control. To achieve this, several tools are used: histogram, Pareto chart, cause/effect graph, XY graph, check sheets and control charts. The latter are considered as the most powerful ones. In the last few years, statistical tolerance intervals have shown their usefulness at several steps of the lifecycle of analytical methods, especially for methods validation and transfer [1,2]. Their adequate predictive behaviour has also been demonstrated [3]. This work aims at evaluating the usefulness of tolerance intervals as control chart during the routine application of analytical methods. To evaluate their efficiency as control chart, three analytical methods were first validated, namely the dosage of levonorgestrel (in an intra-uterine device by liquid chromatography (LC) (Method 1), the assay of ethanol in serum by gas chromatography (GC) (Method 2) and an immunoassay for the determination of ethanol in serum (Method 3). β-content γ-confidence tolerance intervals for ANOVA 1 random sampling scheme obtained from method validation data are used as control limits for monitoring the routine runs reliability. These intervals define a region where β=95% of the methods results will be included with a probability γ=99%. Secondly, during their routine application several quality control (QC) samples were analyzed at concentration levels corresponding to those studied during validation: 30-500 ng/mL (9 series, 4 repetitions per series) for Method 1; 0.5-1.0 g/L (2 repetitions per series during 11 months) for Method 2; 0.5-3.0 g/L (2 repetitions with alternating concentration/day during 4 months) for Method 3. For each concentration level at each routine run 95% β-expectation tolerance intervals were computed from the QC samples results. The analytical methods are declared under statistical control when the QC tolerance intervals are included within the control limits. Finally, these tolerance interval control charts are compared to Shewart $\overline{X}$-R control chart.

Rerefences

1) P. Hubert et *al*., *J. Pharm. Biomed. Anal.* 45 (2007) 82.
2) W. Dewé, B. Govaerts, B. Boulanger, E. Rozet, P. Chiap and Ph. Hubert, *Chemometr. Intell. Lab. Syst.* 85 (2007) 262.
3) E. Rozet, C. Hubert, A. Ceccato, W. Dewé, E. Ziemons, F. Moonen, K. Michail, R. Wintersteiger, B. Streel, B. Boulanger, Ph. Hubert, *J. Chromatogr. A*, 1158 (2007) 126.

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