The economics of residue analysis

H.F. De Brabander, J. Vanden Bussche, W. Verbeke, L. Vanhaecke

Since the onset of residue analysis some 40 years ago, much attention has been paid to several analytical aspects [e.g., the fight to achieve lower limits of detection (LODs), the gain in specificity, and quality assurance]. In recent years, ''omic approaches'' have also been introduced to accomplish these purposes. However, when reviewing the literature, one ''omic'' of residue analysis is not represented: the econ*omic*.

Residue analysis covers a broad working area, including banned (group A) substances and registered veterinary drugs (group B). Some 40 years ago, only thin-layer chromatography and gas chromatography with electron-capture detection were used for A substances, in combination with laborious sample clean-up and thus small sample throughput. The nominal or money price of such an analysis remained relatively stable from 1970 to 2010. However, the operational costs of analysis increased considerably over the years, in particular, personnel and equipment costs. But, higher operational costs were countered by much greater sample throughput, although this phenomenon remains limited.

For B substances, the strategy of screening with microbiological inhibition tests at a very low price competes with sophisticated ultra-high-performance liquid chromatography with (high-resolution) mass spectrometry systems, where the number of analytes/run can theoretically reach 122,500.

The question that we address in this contribution from an economics point of view is: ''How do laboratories keep the balance between price of analysis, specificity, LOD, number of analytes, quantification and quality assurance?''

Keywords: Analyte; Cost; Economics; Limit of detection; Price; Quality assurance; Quantification; Residue analysis; Sample throughput; Specificity

H.F. De Brabander*, J. Vanden Bussche, L. Vanhaecke
Ghent University, Faculty of Veterinary Medicine, Department of Veterinary Public Health and Food Safety, Laboratory of Chemical Analysis, Salisburylaan 133, B-9820 Merelbeke, Belgium

W. Verbeke
Ghent University, Faculty of Bioscience Engineering, Department of Agricultural Economics, Coupure Links 653, B-9000 Ghent, Belgium

*Corresponding author.
Tel.: +32 9 264 74 60;
Fax: +32 9 264 74 92;
E-mail: Hubert.DeBrabander@ugent.be

1. Introduction

Residue analysis covers a broad working area, including banned (group A) substances and registered veterinary drugs (group B) [1]. Since its onset some 40 years ago, much attention has been paid to several analytical aspects: the fight for lower limits of detection (LODs), the gains in selectivity and specificity, the measurement of uncertainty, increasing the number of analytes, quality assurance, accreditation and certification. In related areas (e.g., human doping analysis or pesticides and contaminants analysis), an analogous evolution is ongoing [2,3]. In recent years, omic approaches (e.g., metabolomics and proteomics) have also been introduced as a tool for the detection of the illegal use of drugs [4,5]. However, when executing a literature search, one ''omic'' of residue analysis could not be detected: the econ*omic*.

Some 40 years ago, only thin layer chromatography (TLC) and gas chromatography with electron-capture detection (GC-ECD) in combination with a very laborious sample clean-up could be used for A substances [6]. For data handling, no personal computers were available at that time: the analytical output of the instruments comprised only a black and white photograph of a TLC plate or a single response chromatogram of a detector as a function of time written on a strip chart recorder. Nevertheless, methods with a very low LOD (ca. 1 μg/kg) were developed, but at a very small sample throughput (e.g., 6 samples/analyst/week) [7,8].

Nowadays, sophisticated instruments controlled by computers are used, allowing low LODs and high sample throughputs [9]. For A substances, it should also be noted that the number of analytes is theoretically unlimited (e.g., new steroids, new β-agonists or even new classes of substances) and the number of matrices to be analyzed is high (e.g., meat, fat, urine, feces, bile, retina, and animal feed). For B substances, the situation is different, as the number of substances and matrices to be monitored is limited. The substances and their maximum residue limits (MRLs) are well known {with ~120 substances in the European Medicines Agency (EMA) list [10]}. Moreover, the MRL values are mostly $10–10^3$ times greater than the minimum required performance limits (MRPLs) or reference points of action

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(RPAs) of A substances (e.g., 0.3 μg/kg for chloramphenicol to 100 μg/kg for sulfonamides) [11]. For this purpose, screening methods based on inhibition assays are well known and widely used. These methods are relatively cheap (e.g., 30–50 €/sample) and require less sophisticated equipment [12,13]. Besides, a large number of TLC and high-performance liquid chromatography (HPLC) methods with ultraviolet (UV) detection or post-column derivatization have been published [2,3]. However, since 2000, liquid chromatography-mass spectrometric (LC-MS) analyses have been introduced increasingly for screening and confirmation of certain groups of B substances [14]. The strategy of screening with microbiological inhibition tests at a (very) low price is nowadays in competition with sophisticated ultra-HPLC-(high resolution) MS (U-HPLC-(HR)MS) systems, for which the number of analytes/run is very high (theoretically up to 122,500, but in practice already 300–500 substances in one run of ca. 5 min) [9].

However, the nominal or money price of a residue analysis has remained relatively stable over a period of 40 years (1970–2010). In contrast, the operational costs per analysis have increased considerably over the years, in particular personnel and equipment costs. These higher operational costs need to be countered by the laboratories through better productivity (i.e. a much higher sample-throughput/analyst/time). The objective of this study was therefore to address, from an economics point of view, the question: ''How did laboratories manage to keep the balance between operational costs and analysis price, given the evolutions with respect to specificity, LOD, number of analytes, quantification, quality assurance and accreditation in the past 40 years?'' We present a descriptive analysis of the evolutions of prices and costs over time (1970–2010) and provide a qualitative descriptive comparison and conclusion based on these evolutions.

2. Materials and methods

Primary economic data pertaining to market prices of analyses and instruments, and operational cost components are data collected during 1970–2010 by the Laboratory of Chemical Analysis at Ghent University. The operational costs for performing a residue analysis by the laboratory comprised multiple items: personnel, apparatus, consumables, accommodation, quality assurance and accreditation. Except for the costs of consumables, these cost components are mostly fixed in a university-laboratory setting. Moreover, overhead and/or taxes (Value Added Tax, VAT) and unpaid invoices are taken into account. Although these data mostly originate from routine analysis, they can be extrapolated to research, since research and routine analysis are very closely linked in residue analysis. The source of these numbers comprised internal accounts as presented in the proceedings of the EURORESIDUE and VDRA conferences (Hormone and Veterinary Drugs Residue Analysis or Ghent Conference) over the years 1986–2010 and our own experiences in Belgium.

Secondary data include unpublished data from reports and studies from other residue laboratories and national government statistics pertaining to economic indices [15]. An important index is the Consumer Price Index (CPI), which expresses the nominal cost of a specific market basket of goods at one point in time relative to the same cost at another point in time [16]. The CPI is the official measure of the rate of inflation for consumer prices. In Belgium, the CPI is based on 144,000 price quotations [17]; 126,000 prices for the 507 products are observed in 10,000 outlets, and 18,000 prices are followed centrally. The sample technique comprises 62% of the price observations made in 65 localities (cities, towns and smaller communities) and 38% collected centrally (mainly for rents, prices for cars, tariffs for postal services, trains and buses, banking, travel abroad, camping, insurance, electricity, gas, medicines, and water supply). In most countries, there are analogous systems.

3. Results and discussion

3.1. Evolution of price of analysis

The price of an analysis can be expressed as the nominal or money price (actual price at a certain time on an invoice) or the real price (price related to the money value at that time). The evolution of the nominal prices of group A substances in Belgium is depicted in Fig 1.

In 1970, the nominal price of an analysis of estrogens, gestagens and androgens (EGAs) with TLC amounted ~250 € and only 6 analyses in kidney fat or meat samples could be performed by one analyst in one week [8].

In 2010, the nominal price of a multi-residue analysis on EGAs with GC-MS^n or LC-MS^n or MS^2 amounted ~200 € but with a much higher sample throughput (~40–60 samples in a week with GC-MS^n) [18]. For thyreostats (TSs), a slight increase in nominal price could be noticed upon the introduction of LC-MS^n as detection technique (125 € in 1970 to 150 € from 2000 on). β-agonists (BAs) and corticosteroids (CoSTs) were introduced later in the residue-control plans of European Union (EU) Member States, and their prices are comparable to those of TSs and EGAs, respectively. Apart from slight changes, it may be stated that the nominal or money price of a residue analysis has remained relatively stable over a period of 40 years (1970–2010).

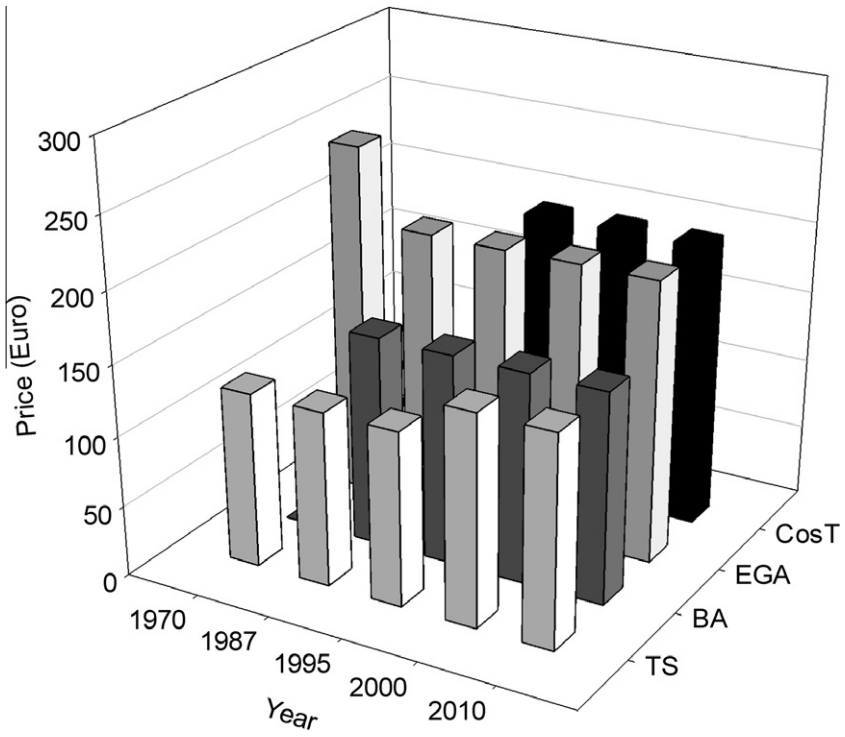

Figure 1. Nominal prices of analyses (in €) as a function of time (1970–2010) (TS, Thyreostats; EGA, Anabolic steroids; BA, β-agonists; CoST, Corticosteroids).

Table 1. Number of group A and annex IV substances as a function of time

	1970	1986	1995	2000	2010
Thyreostats	**3**	5	6	6	6
EGAs	**12**	16	20	22	36
BAs	–	**3**	16	16	22
CoSTs	–	–	**3**	11	12
Annex IV	–	–	**1**	5	7
Sum of analytes	**15**	**24**	**46**	**60**	**83**

In addition, we note that the number of banned substances (group A and Annex IV substances) to be screened and confirmed increased considerably during the same period (from ~15 in 1970 to ~83 in 2010) [2,3]. Table 1 shows this evolution. In Table 1, only the parent substances are counted (and not the potential precursors, metabolites or esters of the substances of interest).

Besides the individual parameters presented in Fig. 1 and Table 1, the ''nominal price/analyte'' may be considered an essential parameter for economic analysis and comparison of prices and costs as well (Fig. 2).

Indeed, the nominal price per analyte of a sophisticated LC-MS method for 30 analytes, which amounts 200 € (6.7 €/analyte), is much lower than the price for a (cheap and simple) enzyme-linked immunosorbent assay (ELISA) for one substance (e.g., chloramphenicol) at 35 €/analyte. From Fig. 2, it may be deduced that, in 2010, the price/analyte varies between ~5 €/analyte and 25 €/analyte (all with GC-MS^n or LC-MS^n or MS^2 methods). Moreover, the number of matrices to be mastered for group A and Annex IV substances increased considerably during this period. Next to the classical (edible) matrices (e.g., meat and fat), multiple target tissues (e.g., thyroid and hair), body fluids (e.g., urine) and, in some countries (e.g., Belgium), even feces need to be analyzed. An example of a special target matrix for monitoring β-agonists is the retina, in which these substances are concentrated [19].

3.2. Evolution of analysis costs

The cost of a residue analysis comprises several components – personnel, the purchase and maintenance of the apparatus, consumables, accommodation (e.g., buildings and utilities) and quality assurance. Moreover, most universities and public institutions charge an overhead (e.g., 17–21% in the case of flat-rate overheads and up to 65% in the case of real calculated overheads). Also taxes (e.g., 21% VAT) and unpaid bills (~5%) have to be taken into account. Table 2 presents the composition of costs of a GC-MS analysis for EGAs in kidney fat [20].

As can be deduced from Table 2, the personnel costs add up to ~50% of the total costs of an analysis, while

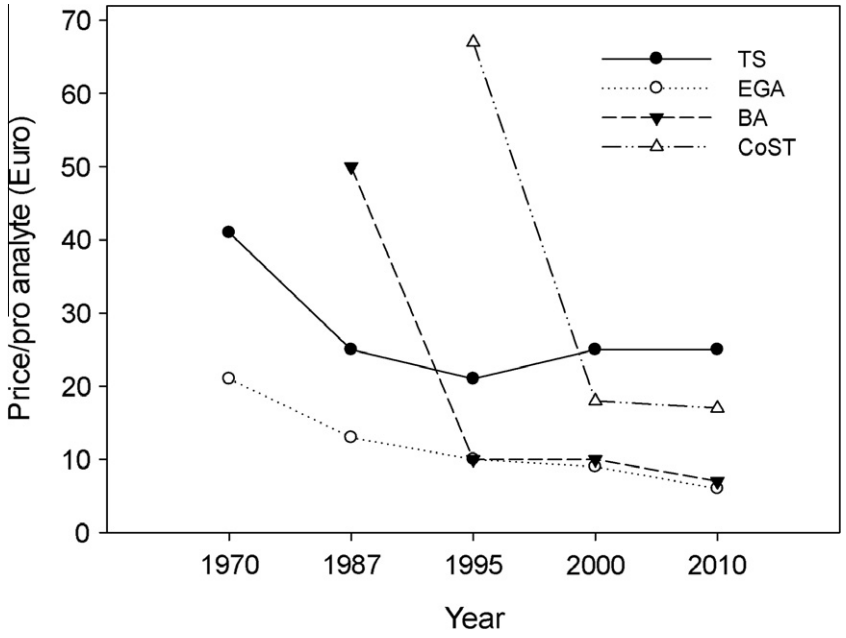

Figure 2. Nominal prices of analyses (in €)) per analyte as a function of time (1970–2010) (TS, Thyreostats; EGA, Anabolic steroids; BA, β-agonists; CoST, Corticosteroids).

Table 2. Relative composition of costs (%) of a GC-MS analysis for estrogens, androgens and gestagens in kidney fat [20]

	Personnel	Apparatus	Consumables	Total (%)
Clean-up	40	7	17	64
GC-MS	12	12	12	36
Total (%)	52	19	29	100

apparatus and consumables account for ~20% and 30%, respectively.

3.2.1. Personnel costs. The evolution of personnel costs in residue analysis is best represented by the consumer price index (CPI). Fig. 3 shows the evolution of the Belgian CPI, which increased by a factor 4.2 over the period of 40 years. This increase is in agreement with the increase in starting salary of scientific personnel at Ghent University, which also increased with a factor of ~4 in the same period.

Indeed, in Belgium, personnel costs are linked to the CPI. If we relate the analysis prices to the CPI or inflation, the ''real'' price of an analysis decreased with a factor of ~4 while the nominal prices remained stable. This implies that a nominal (and real baseline) price of 120 € in 1970 for a thyreostat analysis corresponds to a real price of 30 € in 2010.

3.2.2. Instrument costs. In line with the other cost components, the costs of most instruments needed for residue analysis also increased considerably over the years. For small instruments, the evolution approximately followed the CPI. Of course, the performance of these modern instruments (e.g., a fully electronic balance) cannot be compared with that of older versions from 1970.

The first GC instrument with an ECD detector at our laboratory was priced ~8000 € (1973). Some years later (1976), an HPLC instrument with UV detection was purchased for ~25,000 €. The market price of our first GC-MS system (1990) was ~100,000 €. LC-MS^2 or MS^n systems came on the market around 1994, and our first system was valued at ~250,000 €. Nowadays (2010), a modern quadrupole time-of-flight tandem mass spectrometer (Q-TOF) or Orbitrap system coupled to a modern U-HPLC [21] will easily have a market value of 400,000 €. The only significant decrease in instrument costs over the years is the cost of computers due to their widespread adoption and mass production.

3.2.3. Costs of consumables and accommodation. The evolution of the costs of consumables may also be represented by the CPI index. Solvent prices increased gradually over the years, but this increase was compensated by the environmentally-driven trend to use less solvent for extraction, clean-up and HPLC applications. In particular cases (e.g., acetonitrile), the costs may increase suddenly and considerably [22].

For accommodation, the evolution of the ''building index'' is important. Based on the evolution of building and construction costs and office rent rates [15],

accommodation costs and cost of installing laboratories can be reasonably estimated to have increased with a minimum factor of 10 over the period 1970–2010.

3.2.4. Costs of quality assurance and accreditation. Until the 1990s, laboratories could operate freely in Belgium. Only when a laboratory wanted to carry out official work for the government (e.g., Ministry of Public Health) did official ''recognition'' have to be obtained.

In 1990, definitions of quality were published and a Belgian accreditation board was established. The accreditation boards in Belgium were later merged into one system called BELAC (Belgian Accreditation) [23].

Besides accreditation of the establishment of a laboratory, the maintenance of quality in residue analysis in Europe is assured by a system of European Community Reference Laboratories (CRLs) and National Reference Laboratories (NRLs), while routine analyses themselves are carried out by field laboratories. The costs for this system can be divided into four parts:

(1) the regular audit of the laboratory by BELAC (cost around 2000–5000 €/year);
(2) the cost for a quality manager [one part-time equivalent (e.g., 20–40% part-time) with a university degree] (~10,000 €/year);
(3) the cost for regular calibrations and ring tests; and,
(4) the time devoted to quality assurance by the personnel themselves.

The last two items are very difficult to estimate in monetary value.

When research is considered, please note that the costs of undertaking an animal-drug-administration experiment have increased significantly over the years due to increasingly demanding regulatory requirements with a substantial impact on procedures, equipment and accommodation, for example.

3.3. Evolution of laboratory productivity

Laboratories are confronted with increasing operational costs and decreasing real analysis prices over the years. The only way to stay in financial balance and to survive in a competitive market is to increase labor productivity in analysis. This increase can result from an increase in the speed of the analysis and/or an increase in the number of analytes measured per run. In addition, a reduction of the number of repeat analyses has been achieved by decreasing the number of analyses failing at the first attempt. Such productivity increases are feasible due to improvements in physical capital (e.g., modern equipment), human capital (personal skills and training) and technology.

The speed of an analysis can be increased in all three phases of the residue-analysis process:

(1) extraction;
(2) clean-up; and,
(3) final identification and quantification.

In the extraction procedure, a crude extract of the matrix (e.g., meat) is made, and is freed, as much as possible, from interfering substances during clean-up. In modern analysis, extraction and clean-up are mostly combined and scaled down in sample size due to the improved detection capabilities of current instruments. An example is the 25,000-fold pre-concentration in a single step with liquid-phase microextraction (LPME)

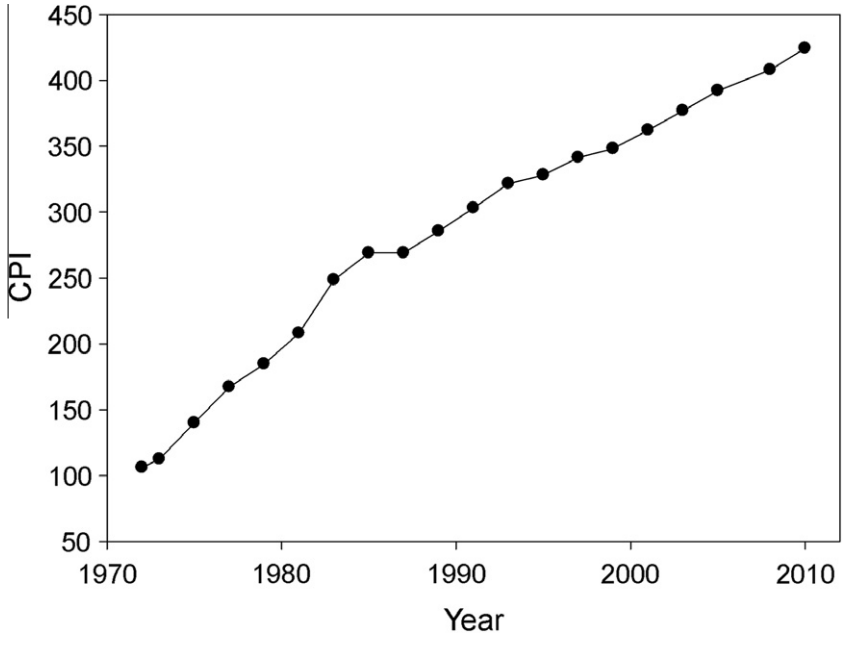

Figure 3. Evolution of the consumer price index (CPI) as a function of time (1970–2010) [15].

[24]. This results in consumption of less solvent and speeds up the procedure. As well as classical liquid-liquid extraction (LLE), modern alternatives can be used to speed up the analysis (e.g., accelerated solvent extraction (ASE) [25], single-drop micro extraction (SDME) [26], solid drop-based liquid-phase microextraction (SDLPME) [27] or cloud-point extraction (CPE) [28]). Other possibilities are the use of a very specific clean-up e.g., with molecular-imprinted polymers (MIPs) [29] or, more generally, a quick, easy, cheap, effective, rugged and safe (QuEChERS) approach [30].

For the increase of speed of analysis in the detection and quantification phase, especially, the introduction of U-HPLC was important [9,31]. By using sub-2-μm columns, classical HPLC runs may be reduced from ~20–40 min to ~5–10 min. One U-HPLC-QqQ-MS^2 system can replace at least two LC-MS systems from the previous generation; the result is a serious reduction in operational costs and an increase in productivity.

Moreover, in recent years, process automation for extraction, clean-up, detection and quantification has increased considerably. The impact of this increasing automation on the laboratory economics is reflected in the increasing relative contribution of instrument costs, compared to personnel costs (e.g., as in Table 2). Evolution in terms of process automation has a greater impact in those countries where staff, personnel or labor costs are high (relative to capital costs) as opposed to countries where labor costs are cheaper (e.g., developing countries).

Another very important parameter in the determination of the price of an analysis is the number of analytes determined in one run (or within one method). While most radio immunoassay (RIA) or ELISA screening methods are designed for one substance (e.g., chloramphenicol [32]) or a very limited group of substances (e.g., an ELISA for salbutamol with a limited number of cross-reactions [33]), most methods based on chromatography are, by nature, multi-residue. In the literature, a very large number of methods for a small number (5–20) of analytes can be found (e.g., 12 sulfonamides, 8 NSAIDs, 11 quinolones, or 12 coccidiostats). However, in pesticide analysis, a related area, larger numbers of analytes (more than 300 in one run by LC-MS^2 [34]) have been able to be measured for some time. This can be achieved using QqQ MS^2, but, more and more, high-resolution accurate-mass-based instruments (e.g., time of flight (ToF) or Orbitrap) are employed to this end.

In residue analysis, a similar trend towards an increase in the number of analytes that are determined in one run can be observed (e.g., more than 100 veterinary drugs in milk [35], and about 100 veterinary drugs in meat [36]).

Theoretically, the number of substances that could be determined by a U-HPLC-Orbitrap system is very high (e.g., 122,500). However, the number of group A and Annex IV substances to be monitored is (only) 83 and the number of B substances from the EMA list (only) 123, so they are small in comparison with that theoretical figure.

Suppose that a method could be developed able to screen, to identify and to quantify all group A and Annex IV substances in one run of 5–10 min. The nominal price/analyte of such a method would amount 250 € (the highest nominal price ever for EGAs) divided by 83 (the number of analytes) and thus ~3 €/analyte. This is much lower than the nominal price for an ELISA for an individual substance (e.g., 35 € for an ELISA for chloramphenicol). For the 123 B substances, the same calculation can be done – starting from a nominal price of 150 € (common nominal price for a LC-MS analysis), a nominal price per analyte of ~1.2 € could be realized.

4. Conclusions

The nominal prices of residue analysis have remained relatively stable over the period of 40 years (1970–2010). Due to inflation, the real prices of residue analysis decreased by at least a factor 4, while operational costs increased. As a result, laboratories had to counter this continual decrease in real prices with a continual increase in labor productivity, which was mainly realized by decreasing the time needed for one analysis, and thus an increase in sample throughput.

Greater sample throughput is very important in a university-based laboratory, for both research and routine purposes, but, undoubtedly, extremely important for commercial laboratories, which may face slightly different pressures in terms of targets for economic profit and competitiveness.

The decrease in time for one analysis resulted from a combination of the decreases in extraction and clean-up times required for a sample and the use of fast chromatographic separations coupled to very powerful detectors. Moreover, by combining better separation and detection (e.g., by measuring exact mass), the number of analytes that can be analyzed in one run is increasing from classical sub-group separation (~10 substances; e.g., 11 quinolones) to large group separation and detection (~100 substances). In this context, partial automation of data analysis is of increasing interest, although the analyst must be alerted to check manually data that are considered suspicious by the software.

Further improvements with respect to technology and physical capital are crucial to keep pace with the market situation of decreasing real analysis prices. In the future, it may be foreseen that this evolution will result in the use of more and more sophisticated and expensive instruments, which represent substantial fixed costs,

whose average costs decline as long as output expands. In order to sustain economic efficiency, laboratories will have to manage to take advantage of decreasing average fixed costs through volume. Hence, these instruments and the necessary human resources for their use will only be affordable for laboratories that have sufficient financial resources and have a guarantee of sufficient throughput of samples in the future.

Acknowledgements

The authors wish to thank Martine Anaf, Mieke Naessens and Dirk Stockx for their technical contribution to this manuscript.

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Hubert De Brabander is senior full Professor and Head of the Department of Veterinary Public Health and Food Safety. He is also Director of the Laboratory of Chemical Analysis and Dean of the Faculty of Veterinary Medicine, Ghent University. His main working area is the chemical analyses of food with, as major object of research, the analysis of residues and contaminants in biological material.

Julie Vanden Bussche is Assistant at the Department of Veterinary Public Health and Food Safety (Laboratory of Chemical Analysis). Her PhD thesis includes the analysis of thyreostats in various matrices and is focused on the search for the source of the natural occurrence of thiouracil.

Wim Verbeke is Associate Professor and Chairman of the Department of Agricultural Economics at the Faculty of Bio-science Engineering, Ghent University. His main research areas are economics, marketing and consumer behavior in relation to agriculture, food production and processing, food quality and safety, and food choices.

Lynn Vanhaecke is a postdoctoral fellow from the Flemish Science Foundation (FWO-Vlaanderen) at the Laboratory of Chemical Analysis within the Department of Veterinary Public Health and Food Safety at Ghent University. The chemical analyses of food, the metabolism and biological activity of food constituents and the analysis of residues and contaminants in biological matrices in relation to human health belong to her major research objectives.