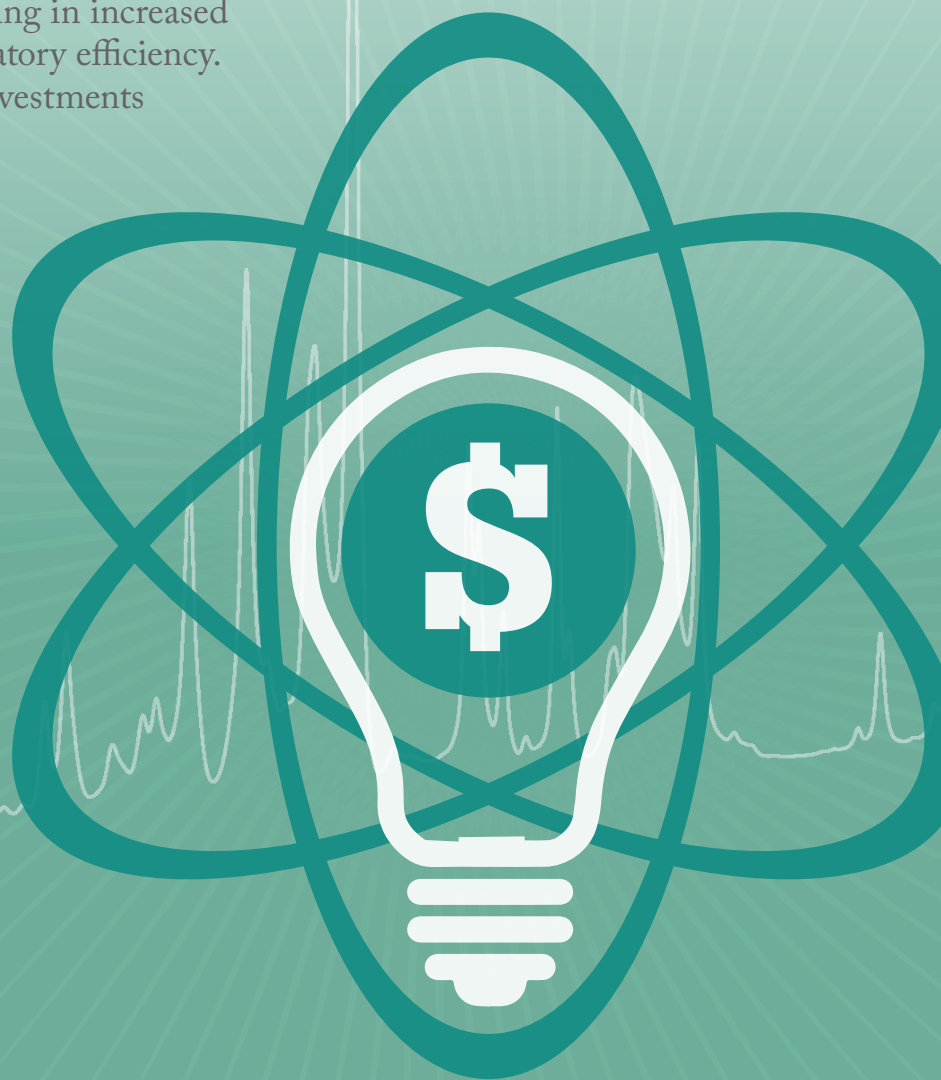


Exploring the Economics of Innovation

Continual advances in liquid chromatography have raised the bar from high performance to ultra-high performance, resulting in increased analytical, instrument, and laboratory efficiency. What's holding you back from investments in UHPLC technology?



MORE EFFICIENCY MORE FREE TIME

The new Agilent 1290 Infinity II LC

All you expect, and more. Setting new benchmarks in analytical, instrument and laboratory efficiency. You may find yourself with extra time on your hands.

Meet the next generation UHPLC

EfficientUHPLC.agilent.com

What would you do with extra time?
Join the [#EfficientUHPLC](https://twitter.com/EfficientUHPLC) talk.



© Agilent Technologies, Inc. 2015

Introducing the Economics of Innovation

Some of you may remember the HPLC Symposium in Nice, France, back in 2003; I've been told that even the stairs were crowded in the conference hall when Ron Majors talked about a new generation of sub-2 μ m and superficially porous column technology. Soon after, various vendors – along with a great deal of hype – introduced UHPLC systems. We've now had 12 years to learn all about the technical benefits of ultra-high performance (whether we wanted to or not). The big question: does UHPLC live up to the hype?

Let's consider a few points:

- The majority of LC systems are still running good old HPLC methods from the end of the last century. But instruments are aging and change is coming.
- The second generation of UHPLC systems are designed for routine laboratories, offering gains in efficiency that allow scientists to rapidly develop better methods, technical operators to cope with ever-increasing numbers of samples, and lab managers to meet calls for higher output with fewer resources.
- Researchers with a strong need for increased peak capacity, higher sensitivity, higher throughput or faster turnarounds have already technically justified the new generation of instruments.
- Lab managers are typically outside of their comfort zone when it comes to justifying the economic value of a technological refresh for their laboratory (for example, the switch to UHPLC) – but they are aware that a number of factors must be taken into account.

The following compendium offers wisdom from fearless leaders in the field, who share their experiences, personal views and tips & tricks on the UHPLC transition. Wolfgang Kreiss brings economic science to the laboratory. Dwight Stoll covers the challenges – and innovations required – to push technology from academia into a more regulated environment. Michael Dong offers tips and tricks gained from many years' experience in the biopharmaceutical industry. Matthias Pursch shares a successful move to UHPLC for routine analysis in the fine chemicals industry. Hiroshi Iwase jumped on the UHPLC bandwagon early on and also successfully jumped over any hurdles in his way. And Adrian Clarke offers his personal view after mastering the transition at two different pharmaceutical companies, confirming both the technical and economic benefits.

Change is never easy, but good science and experienced leaders can help you make an easy transition to ultra-high performance.

Rich Whitworth

Editor, The Analytical Scientist



Contents

04	The Analytical Economist by Wolfgang Kreiss
06	Ten Years of UHPLC an interview with Dwight Stoll
07	Resolving Inefficiencies
10	The Chromatographic Consultant by Michael Dong
12	Measuring UHPLC Investment
14	The Early Adopter by Hiroshi Iwase
16	Defining UHPLC an interview with Matthias Pursch
18	The Voice of Experience by Adrian Clarke
20	Appendix Models & Scenarios, Results in Detail

The Analytical Economist

Justifying investments is never easy, especially when assumptions about an uncertain future must be made. Fortunately, model systems allow deeper scrutiny of economic impact and can help mitigate the guesswork in your decision-making process.

By Wolfgang Kreiss

I started at Bayer as an analytical chemist about 30 years ago, gaining experience in separation techniques and general analytics. As head of an analytical R&D department I got to know the rather diverse practical aspects of laboratory operations. And working for five years as Sales Director on the business management of analytical and other industry services helped me to better understand the business side of analytical laboratories. Afterwards, such economic insights combined with analytical and operational experience proved to be very valuable for managing a large group of analytical departments. Today, I'm an independent consultant and specialize in the field of laboratory management.

Laboratory managers are often faced with making difficult decisions when it comes to investing in new laboratory equipment, especially given the expense of modern day analytical instrumentation and the diversity of options available. But by applying economic principles to the decision making process, it's possible to make a more objective decision, in many cases – but only if the full picture is taken into account. Instrumentation investments have a cost impact over and above the purchase price, and certainly affect laboratory output.



To buy or not to buy

For many years, I was responsible for making such investment decisions – and I've been able to use much of what I learnt about the application of holistic economic analyses to assess the financial implications of UHPLC investment on a number of levels. My work in that area forms the scaffold on which this compendium is built.

It's natural for laboratories operating in a commercial environment to deeply consider the economic aspects of investments – but analytical chemists

(who have also become managers) are not always fully trained in the art of researching the implications of a potential investments. Nevertheless, in today's highly competitive environment, most laboratories must make a concerted effort to be more efficient and drive down the cost-per-analysis.

When comparing standard HPLC versus UHPLC, it's clear that there is a difference in the price of the laboratory equipment, but even if you take this into account along with the productivity of each system, comparisons tend to be too

simplistic. Indeed, such straightforward calculations don't allow you to make a fully considered decision as there are many other influences at play (see page 7). A good laboratory manager must look at the total cost of a laboratory and must assess the impact of an investment on the big picture. For example, if a manager is considering replacement of several LC systems, maintenance, personnel (often the main cost of a laboratory), space, and other factors must all be taken into account.

A model system

With that in mind, we were able to create a complete calculation model for a typical analytical laboratory, including all the economic factors that contribute to the total operating cost. In the model, we can adjust a large number of parameters to fully investigate the economic impact of investments or price changes; for example, we can alter the price of acetonitrile (the main consumable in HPLC) and see the effect on total cost. You may remember a shortage in acetonitrile a couple of years ago – the price increased tremendously (in Germany at least) to the point where pharmaceutical companies developed crisis plans. In terms of HPLC versus UHPLC, the latter consumes significantly less solvent per analysis and is therefore less sensitive to price changes in acetonitrile. Indeed, with such a complete model, you can not only investigate linear changes over the estimated lifetime of an instrument, but also tweak the model to allow exploration of unexpected changes; for example, a non-linear or dramatic increase in employee salaries – or an unexpected acetonitrile shortage.

Developing assumptions for the future is always the tricky aspect of making an investment decision but, by using a calculation model, it is possible to assess the sensitivity of a given scenario to

economic changes (financial risk), which reduces some of the guesswork.

Is the glass half empty or half full?

Clearly, when investing in new equipment, it's traditional to focus only on the negative aspects – the outgoing expenses – commonly referred to as cost-comparative or static methods. But, of course, analytical data has real value. And so we used a net present value method (a very well accepted method that economists refer to as "dynamic"), which takes into account the earnings – the positive aspects – of operating an analytical laboratory. As a dynamic method, the net present value factors in future cash flows. By using both static and dynamic calculation methods, we can gain an even fuller picture.

We consider scenarios involving both conservative projections (where the demand for analytical services remains stable) and also expansive growth projections that take full advantage of more capable instrumentation; for example, the higher throughput of UHPLC. In simple terms, if you have an instrument that produces results in half the time, you have the potential to double the number of analyses – but only if additional work exists. Likewise, offering higher precision, increased resolution or a substantial gain in analysis speed could increase demand for your analytical data.

Surprising impact

As an analytical chemist (with an keen eye on economics) I am very careful not to make predictions ahead of analysis in case I reduce my impartiality or introduce bias. However, I must say I was very surprised by the dramatic effect of making full use of an upgrade to UHPLC in a lab in the case of an expanding market (see page 13). I think it would be hard to anticipate such a tremendous impact – but at the end of

"We were able to create a complete calculation model for a typical analytical laboratory, including all the economic factors that contribute to the total operating cost."

the day, it's just mathematics. Notably in our lab model, even the conservative scenario calculations showed that return on investment increases in line with investment in UHPLC technology. With aging instrumentation, higher maintenance costs will become a heavy burden. Replacement without technology upgrade and without a gain in capacity provides assurance that operating costs will stay predictable. You can view the higher depreciation rate like an insurance fee to secure stable maintenance costs.

Ultimately, the project has led to the creation of a powerful calculation model that can be used by most analytical laboratories to evaluate the economic outcome of potential investment scenarios. Here, we use it to explore eight scenarios of UHPLC investment – one of which may mirror your own situation. We hope you find it as informative as we did.

Wolfgang Kreiss is an independent consultant based in Germany.

Ten Years of UHPLC

Discussing the past, present and future of UHPLC with Dwight Stoll, Associate Professor of analytical chemistry at Gustavus Adolphus College.



What are your views on early UHPLC development?

Back in the late 1990s, I think a lot of academics were observing Jim Jorgenson's work on higher pressures in HPLC from a distance and wondering how practical it was (1). To his credit, UHPLC became a commercially viable product pretty quickly (2004). But even going back to the late 1960s, academics were discussing the potential of higher pressures (2), so it seems strange to me that we were stuck on an upper limit of 400 bar for the intervening 30 years or so. There appeared to be no incremental increase in pressures, and then suddenly, we were at maximum pressures of 1000 bar in commercial instruments. In any case, Jorgenson was truly a pioneering experimentalist in this area.

By about 2012, most of the major instrument vendors had at least one UHPLC system in their portfolio. And while the marketing efforts of some manufacturers have over-promised over the years, I don't think anyone can argue that UHPLC has not been a big step forward.

Where is UHPLC today?

The transformation in technology that has brought us to UHPLC has been impressive. Among the general consumer base, there seems to be a perception that UHPLC is all about pressure – but the reality is that the commercial implementation of UHPLC was born out of a complete redesign and reengineering of the instrumentation – even down to the connection technology, which is completely different to what we had ten years ago. And so UHPLC really represents the sum of many innovations – and that has been extremely beneficial to the field.

I recently gave a talk at an Environmental Protection Agency quality assurance conference in Texas – and they wanted me to focus on UHPLC. I put up a slide that asked, “Why should you care?” – and there were only three bullet points:

- Analysis speed
- Reduced solvent consumption
- Improved detection sensitivity.

What are the main hurdles holding UHPLC adoption back?

For me, the advantages of UHPLC speak for themselves, so I think one of the barriers to adoption must be that some potential users don't understand enough about the fundamentals to recognize a good thing when they see it. UHPLC gives access to the upper limits of single-dimension liquid chromatography performance (“ultra” is a clue!) and perhaps some of the discussions on – and skills required for – the optimization required are simply beyond some of those who could stand to gain.

When it comes to highly regulated environments, the inability (or at least difficulty) to change methods over from standard HPLC is another challenge. But that's got a lot more to do with

bureaucracy than science.

Finally, legacy equipment just keeps on running – and I think many laboratories would rather run old instruments into the ground before considering something new, irrespective of advantages – economic or otherwise. And there is something reassuringly rugged about old-school HPLC systems...

And the death of standard HPLC?

I think regular HPLC has got a good few years (maybe even decades) in it yet – especially in some parts of the world. I think the majority of academics in separation science have already recognized the benefits of UHPLC – and many made the transition early on. In routine laboratories, the transition will be slower for the aforementioned reasons. I would say that anyone wanting (or needing) to benefit seriously from any of the bullet points I mentioned earlier, should at least consider UHPLC. There's a solid basis for the idea that you can achieve higher throughput and/or reduce costs so that you can more than recoup the extra capital costs over a defined period, given certain assumptions. And in a very high-throughput environment where there is a real focus on productivity and efficiency, and a genuine attempt to maximize the capabilities of the instrumentation, UHPLC is a no-brainer – the reality is likely to follow the theory closely. But I would urge each laboratory to assess its needs using a holistic approach that takes into account all aspects, from analytical to economic.

References

1. JE MacNair, KC Lewis, and JW Jorgenson, “Ultrahigh-pressure reversed-phase liquid chromatography in packed capillary columns”, *Anal Chem*, 69(6), 983–989 (1997).
2. JH Knox, MJ Saleem, “Kinetic conditions for optimum speed and resolution in column chromatography”, *J Chromatogr Sci*, 1969; Vol. 7, pp 614–622.

Resolving Inefficiencies

High performance liquid chromatography (HPLC) is one of the workhorses of analytical laboratories all over the world. The big question: is it time to retire your old workhorse for an ultra-high performance racehorse?

In addition to faster separations, UHPLC is able to provide increased chromatographic resolution, peak capacity, and retention time precision. UHPLC systems can also reduce carryover and offer greater detection potential. No surprise then that UHPLC has become the method of choice for some of the most challenging LC problems.

But is UHPLC unnecessarily sophisticated for standard separation procedures, where HPLC is still the preferred technique? Certainly, the improved speed (and efficiency) of UHPLC methods suggests greater productivity, which is important for increasing numbers analytical laboratories in an increasingly competitive world. Furthermore, specific features associated with advanced UHPLC systems can deliver additional cost-savings, for example, with regard to solvent consumption and space. But is it possible to quantify the economic advantage of UHPLC? And are the savings sufficient to trigger use of UHPLC even in standard operations?

Running costs

Answering such questions requires an assessment of the costs and returns associated with HPLC and UHPLC procedures in an analytical laboratory – information that is not always readily available. However, we can derive reasonable estimates using assumptions

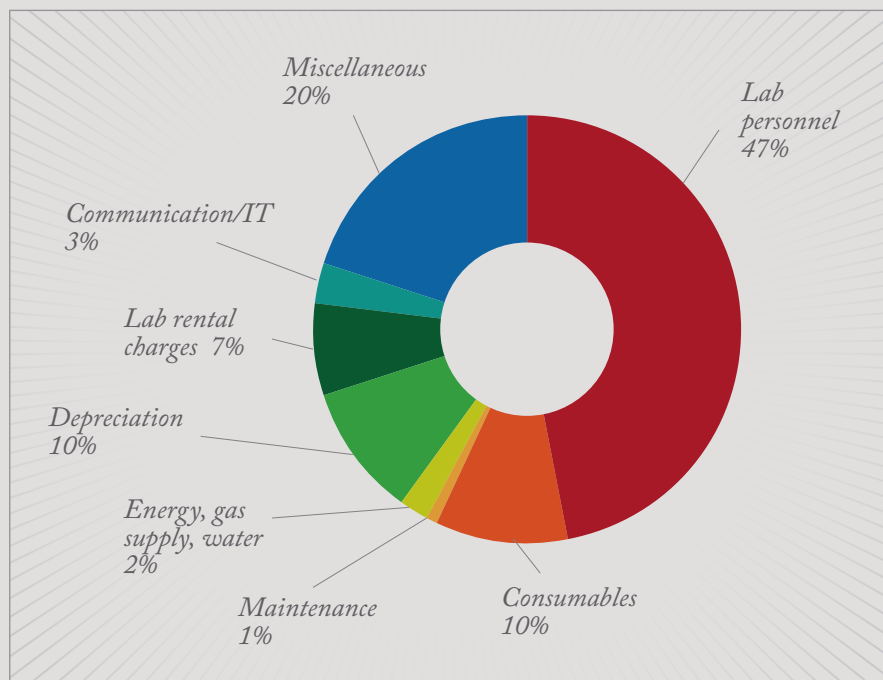


Figure 1. Breakdown of costs in an average analytical laboratory.

based on publicly available information (such as wage reports, product price lists for instruments, services and consumables, public tender information, and so on). Figure 1 shows that over 80 percent of the costs of our average chromatography laboratory (see page 20 - appendix) comprise, labor, lab space, depreciation, energy, consumables and maintenance. So how might a conversion from HPLC to UHPLC systems modulate these costs?

Labor

In the model HPLC lab we used to assess economic aspects of UHPLC (see Measuring UHPLC Investment on page 12), labor accounts for 47 percent of costs. If we assume that staff levels remain constant, upgrading from HPLC to UHPLC won't decrease the costs of labor. It should, however, increase the productivity of labor. In other words, transitioning to UHPLC should allow the laboratory to produce more and better results per unit time with the same number of staff.

UHPLC could achieve this in a number of ways. Most significantly, the speed of UHPLC allows it to run more samples in a given time period. For example, for the same sample, a 150 mm HPLC column using 5 μ m particles has an 8 min run time, whereas a 50 mm UHPLC column

using 1.8 μ m particles has a 3 min run time – and offers superior resolution. In other words, some aspects of productivity may be doubled by switching to UHPLC. In commercial labs where revenues are limited by capacity, this is an attractive increase. It is also relevant to non-commercial labs, as it will allow them to provide results more quickly, whether for academic research, clinical analysis or some other function.

Similarly, advanced features associated with modern UHPLC systems may decrease the time per analytical procedure in other ways, for example automation and dedicated software are designed to reduce set-up time. The automation of steps such as solvent purging and column equilibration are significant labor-saving devices. And, in the sample loading stage, the Agilent OpenLAB CDS Drag&Drop sample entry system is said to reduce set-up time by 50 percent when compared with traditional single entry methods, thus freeing up operator time for other activities, including additional analytical procedures.

Furthermore, advanced UHPLC systems not only make the existing working day more productive, they may actually extend the working day, at no additional labor cost, by offering automation features. For example, the

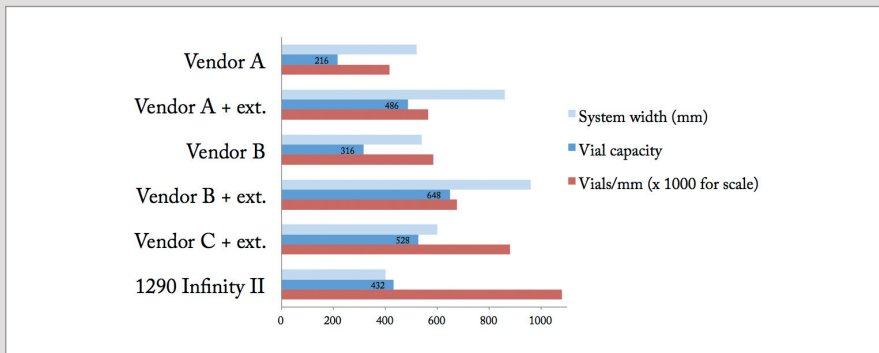


Figure 2. Comparative footprint of UHPLC systems. Within the footprint of the Agilent LC stack, the 1290 Infinity II Multisampler takes a maximum load of 16 microtiter plates for a total capacity of 6144 samples or up to eight 2-ml vial trays for a total sample capacity of 432.

Agilent 1290 Infinity II Multisampler's capacity can be scaled up to hold enough samples for continuous 24/7 operation so that analysis can continue outside normal working hours with minimal operator impact. These types of autosamplers have sufficient sample capacity even if runtimes per sample are reduced to a few minutes. Again, this would permit a step up in terms of productivity and measurable outputs for the lab.

Another route to improved labor productivity is ensure that less time is spent on unproductive activities, so that more time is spent on activities that are directly revenue-generating. Error elimination is a very important feature of advanced UHPLC systems. Errors lead to rework and missed timelines. Again, the dedicated software and automated set-up systems that come with UHPLC systems are intended to reduce set-up errors, including errors at the sample loading stage.

Advanced UHPLC systems also greatly accelerate the speed of method development (as noted by Michael Dong, page 10; and Matthias Pursch, page 17), which once again offers a real and noticeable boost to productivity. Clearly, if less time is taken to develop faster methods, one can spend more time executing those faster methods and generating results – and revenue.

Additional automation can help to prevent new bottlenecks in sample preparation or data analysis when the volume of samples is increased. This underlines the importance of new software associated with advanced UHPLC systems that is designed to make analysis and subsequent data processing faster and easier. Examples include Agilent PeakExplorer functionality, which is intended to speed up data analysis, such as identification of outliers, and the associated database, which has been designed to simplify data storage, management and retrieval.

Many of the advantages brought by UHPLC innovations may be lost if new systems are difficult to integrate or use. Manufacturers are aware of this barrier to uptake, and have supported many of the above innovations with tools to facilitate operator learning and familiarization. In particular, there have been efforts to maintain key historic features with which operators are familiar, and to enable integration with standard software. Making the move from legacy systems to modern UHPLC systems should be fast and easy – though as Adrian Clarke notes (see page 18), good training is essential to bring out the best of UHPLC. Agilent E-familiarization helps you to learn what you need, when you need it – and you can document the new skills acquired.

In summary, though UHPLC systems may not reduce staff costs per se, staff can not only be more productive but also generate higher quality analytical results. And in an environment where we are all measured by our output in some form, that has to be a good thing.

Lab space

The space taken up by the instrumentation required to perform a particular procedure is another aspect of its cost. Therefore, reducing the footprint of analytical instrumentation is important. Of course, if you reduce the size of an instrument too far, you also reduce its capacity – or functionality – so a more meaningful measure of space-associated cost is not just footprint, but sample capacity in that footprint. Figure 2 expresses this measurement as sample vials/cm bench length (according to published specifications) and suggests that some systems give you more bangs for your buck than others in terms of sample capacity. The UHPLC 1290 Infinity II Multisampler comes out top in this measure of efficiency.

Depreciation

Depreciation is an accounting charge relating to the cost of the instrumentation and its allocation occurs during an instrument's lifetime. Depreciation may be accounted for as part of the fixed overheads, i.e. the costs of running the laboratory that do not vary with laboratory activity. Fixed overheads are normally allocated among units of output to help a business accurately estimate a price at which the units could be profitably sold. Therefore, the size of the fixed cost allocation per production unit decreases with an increase in the volume of production. As a consequence, an increase in the output of the laboratory should be associated with greater profitability at the same product price, or the same profitability at a lower price. Therefore, mechanisms that increase the rate of utilization of laboratory assets – for

example, the throughput per instrument, and/or the hours per day an instrument can be used – would be economically advantageous.

Advanced UHPLC systems can support increased instrument utilization through faster analysis times, increases in the intrinsic sample loadability of the instruments (see Figure 2), and the high degree of automation. Modern UHPLC systems allow solvent replacement and column switching functions to be performed without human intervention and can be run for 20 hours a day as compared with the 8 hours typically associated with most of today's laboratories. And though such increases in productivity demand new ways of working (as Clarke notes on page 19), the increase in utilization allows depreciation charges to be spread over an equivalently greater number of units of output, representing a significant increase in the economic efficiency of the lab early on.

Finally, newer UHPLC systems are flexible in terms of their precise application, meaning that a single instrument can be leveraged for a broader range of tasks, which also increases the utilization rate of the asset. By contrast, older HPLC machines are less flexible, requiring two machines for tasks which could be fulfilled by one UHPLC unit, resulting in one machine often being idle while a given task is executed by the other.

Some UHPLC systems can be flexible enough to run HPLC methods. And the Agilent 1290 Infinity II LC System is unique in its ability to emulate the behavior of multiple HPLC or UHPLC systems, thus enabling higher utilization. This is of particular interest when UHPLC methods need to be trimmed down to check the fit for low-budget environments without UHPLC capabilities.

For the purposes of our model lab, depreciation is set such that after eight years, instruments are 'written off' such

that a value of zero is assumed, which is unlikely in a real world example, but suitably conservative for our purposes here.

Energy

The energy costs of an analytical lab represent about two percent of its total costs. Modern UHPLC systems have been designed to be energy efficient and some modules consume significantly lower energy. For example, a compressor-based chiller saves significantly compared with a Peltier-based cooler. In addition, energy cost per sample is less just because UHPLC analysis takes shorter time. Most modern LC systems have shutdown routines to reduce consumption in idle mode.

Consumables

The consumables costs in an HPLC lab may represent 5 percent of total costs. Nevertheless, they comprise an important part of the variable costs of the lab, i.e. those costs that increase with increasing output. A sustained cut in consumables use may deliver significant cost savings if it is consistently applied over a reasonable period of time.

Here too, modern UHPLC systems may be associated with economic benefits. In particular, UHPLC uses less solvent per analysis. Shortening runtimes by a factor of 3-5 reduces the solvent cost accordingly per run and is fairly easy to achieve. UHPLC is typically implemented with smaller column IDs, which further decreases solvent consumption.

If sufficient resolution has been achieved with HPLC columns in the past, a much shorter (typically one third the length) UHPLC column will achieve the same resolution, which means that HPLC and UHPLC column costs are actually comparable – and the same goes for pre-columns in HPLC and UHPLC applications. Finally, with necessary care (during sample and solvent preparation), UHPLC columns have excellent longevity.

Maintenance

Maintenance-associated costs only represent one percent of the total costs of our HPLC lab. But if machines cannot be used because of faults or breakdowns, the output of the laboratory will suffer. In addition, there are costs associated with system clean-up and repair, and obviously the more often these actions are required, the greater the associated expense. Unplanned downtime can be very disruptive, and damaging to a laboratory's reputation and income. Not only is revenue not being generated, but timelines are not being met. Therefore, mechanisms to reduce maintenance and to increase uptime are welcome.

Hence, advanced UHPLC systems have features which are intended to allow operators to track the system's maintenance needs; these include records showing the instrument's utilization history and maintenance logs; systems can send alerts or allow remote monitoring for the operator as necessary; and mechanisms to track instrument wear. The idea is to notify the operator about early maintenance needs well before the system efficiency degrades or damage is incurred, which helps to minimize costly unplanned downtimes and optimize lab planning and operations. It also addresses the issue of staff being more familiar with the hardware or chemistry, but not necessarily both (a common consequence of specialization). Indeed, advanced lab diagnostic advisors and support tools that guide machine repair are welcome additions to advanced UHPLC systems. Service contracts can include remote diagnostics and maintenance wizards further guide users.

Finally, the advances in engineering and process technology that have gone into the design of modern UHPLC systems make them significantly more reliable than HPLC systems. Instead of tens of thousands of injections, now hundreds of thousands of injections per year are considered to be normal for a high capacity autosampler.

The Chromatographic Consultant

I've worked with HPLC since its early days, and I've witnessed first hand the transition to UHPLC. Here, I share my experience and offer a few tips and tricks of the trade.



By Michael Dong

My very chromatography-centric career began at graduate school, at a time when HPLC was quite new and exciting. Even then, economics came into play for me – I was told I could easily get a job as an analytical chemist! And so for my PhD, I studied chromatography at the City University of New York focusing on the characterization of polycyclic aromatic hydrocarbons in the environment, and because of the novelty of HPLC back then, it was actually pretty easy to get published. My post-doctoral fellowship took me to the Naylor Dana Institute for Disease Prevention in the department of Environmental Carcinogenesis, and then industry called and I became section head of a separation lab at a chemical company in New Jersey. I then decided that it would be advantageous to gain experience of cutting-edge chromatography instrumentation and joined an HPLC manufacturer in Connecticut, where I

pioneered “fast LC” using short 3- μ m columns. Finally, I transitioned into the pharmaceutical industry for 16 years – eight as a senior scientist at Genentech, in research and early-stage development of new small molecule oncology drugs.

Very recently, I decided to relocate back to my adopted hometown in Connecticut and put my many years of LC experience to good use as a consultant and trainer – in both HPLC and pharmaceutical analysis (www.mwd-consulting.com).

An evolution in LC

HPLC debuted in the late 1960s, but the equipment remained pretty stagnant for four decades as people were generally not unhappy with the limits of 400 bar, and there seemed to be no real need for higher system pressures... until the birth of UHPLC. In the mid-2000s, many people were touting the benefits of UHPLC, but I was also interested in its challenges and potential issues, particularly in a regulated environment. If you work in the academic world, you're constantly trying to push the limits. But the pharmaceutical world is much more conservative. In brief, my questions were: is it GMP compatible and does it have the right precision, sensitivity (mixing efficiency) and robustness? It's fair to say that over the years, the instrumentation has evolved to respond to my initial concerns.

At Genentech, UHPLC implementation started in 2008 when we bought our first system. In 2010, we made the decision to purchase only UHPLC systems with a view to eventually transition all our equipment to the newer platform. That's not to say it was a decision that was taken lightly – there was a very detailed evaluation period for every new model. At the time we were expanding very rapidly – indeed, the lab grew from about 10 HPLC to 40 systems of mixed vintages in the next five years. The primary driving force for the UHPLC transition was speed – and what that means in a busy lab. A 3–5-fold

increase in productivity is a big gain, and I think the majority of people who have jumped onto the UHPLC bandwagon have been attracted by this feature. Who doesn't want the ability to do more with less – or a great deal more with the same! After all, you could replace two or three HPLC systems with one UHPLC system and maintain the same level of productivity. But if you replaced three for three, then you could potentially do nine times more work...

Beyond speed – a superior LC system

But speed isn't the only advantage. As the UHPLC market has matured, I can think of a couple of other important areas. First, you have the ability to go to high resolution; when working with combination drug products with multiple active pharmaceutical ingredients (APIs) or molecules with multiple chiral centers, sample complexity is a huge issue – and resolution is key to accurate assays and drug quality. The second important benefit is in rapid method development; most pharmaceutical labs have to develop a large number of methods rapidly – with confidence – and UHPLC offers a tremendous advantage here. In method development, you want to be able to switch columns and mobile phases quickly, so the use of smaller columns with rapid system equilibration is a clear benefit. Here, it's not just about the increase in pressure, it's the reduced dwell volumes, lower system dispersion or lower extra column band broadening. It's this combination that makes UHPLC a superior LC system.

As scientists, it's no surprise that we are attracted to the technical aspects of UHPLC – speed, precision, sensitivity, high resolution... But in most laboratories, there are economic realities to balance our excitement. There's no doubt that UHPLC systems are currently more expensive than their HPLC equivalents. But when you look at a laboratory, the

cost of the equipment is only half the story. You have to hire people – and in many parts of the world, employees are the biggest expenditure. Therefore, if you can make those people more productive – for example, by making method development or sample analysis three times as fast – you're getting more value for your money – it's simple math.

Of course, if you work for a pharmaceutical company with deep pockets, such justification may be less essential, but even then, good management will not be disappointed when being told about productivity gains or the ability to handle very complex samples with higher confidence.

Transition tips and tricks

The transition from HPLC to UHPLC is certainly easier today than in the mid-2000s, but I think the majority of chromatographers will still seriously benefit from a deeper knowledge of the chromatographic process, which is the key to unlocking the true capabilities of UHPLC. As an example, column choice (including particle size and inner diameter) is of paramount importance to fully utilize the "ultra" performance. Indeed, UHPLC by itself does not give you an instant productivity gain without an appropriate column choice.

Newcomers could be confused by a number of other factors; much lower injection volumes and smaller columns mean that system dispersion becomes much more important in UHPLC, for example. Or you might experience much noisier baseline than expected in impurity testing, which could be caused by an incorrect choice of mixer. Indeed, what tend to be more minor considerations in HPLC can become accentuated in UHPLC, demanding extra attention.

The good news is that in the last ten years, our understanding of many of the challenges has grown significantly. We're not dealing with brand-new technology any

more, and the instrument manufacturers have done a lot to address some of the pain points. That said, complacency is never recommended – one should not enter into UHPLC blindly, especially in industries where the level of experience is lower.

Time to go ultra?

I'll echo the scenarios in these pages when I offer my recommendations on stepping up to ultra performance. Those companies not necessarily concerned with gains in chromatographic productivity (because no increase in analytical workload is expected) are still likely interested in another important resource: time. HPLC productivity may not be a constraining factor, but there could be a bottleneck elsewhere in your lab. Could the extra time gained (from not doing chromatographic analyses) be used for another important task? Alternatively, the extra time gained could be used to perform higher quality analyses or repeat analyses for confirmation. In either case, perhaps equally important is the flexibility that UHPLC systems offer. What if there is a need to react to an urgent request for results or to develop a new method more rapidly than usual? With UHPLC you can go to high speed and high resolution – if you need to. Consider it a super HPLC – you pay a little bit more, gain a lot of flexibility – and there seems to be very little downside.

What about companies in an expanding environment, with an interest in gaining productivity and throughput? The answer is even more straightforward. Just from an economic point of view, without stretching a UHPLC system too much you can gain increases of 2–3 fold in productivity. You can run more projects, analyze more samples – and if you're a contract research organization (CRO), you can generate more income. The economic argument is very much in favor of UHPLC.

For most pharmaceutical companies, method transfer is a serious consideration.

Software simulation can certainly help – Agilent Technologies' ISET system, for example, allows you to mimic other LC systems. But I think it's important to remember that when transitioning to UHPLC, you don't have to jump in at the deep end with sub-2 μm particles and 2.1 mm ID columns – in fact, I think that's perhaps a less prudent approach for pharmaceutical labs, especially those concerned about method transfer. If I could give one piece of advice for laboratories that want to adopt UHPLC technology (and once again it comes back to the importance of the column), it is to use 3-mm ID columns (and sub-3 μm porous particles or superficially porous particles) – and that's what I've been advising my lab mates in recent years. Why? Because it is a more QC-friendly approach that gives you the flexibility to swing backwards and forwards between using HPLC and UHPLC equipment.

My final piece of advice is about the mixer in the UHPLC system. A small mixer is can be great if you want to change solvents instantaneously, but it comes at a cost: mixing efficiency. If you want to mix acetonitrile with a buffer that is mass spectrometry compatible but also want to do UV detection below 230 nm (which is essential in many cases for ICH-compliant impurity testing) you may find that your baseline noise is in no way optimal. The choice of mixer is therefore more critical than people realize in pharmaceutical analysis.

To conclude, even if you're not quite ready to make the transition to UHPLC now (and note that at some point in the near future, it could be challenging to even purchase a "standard" HPLC system) it might be time to at least familiarize yourself with the promises and nuances of UHPLC.

Michael Dong is principal consultant at MWD Consulting (www.mwd-consulting.com), Norwalk, Connecticut, USA.

Measuring UHPLC Investment

Advanced UHPLC systems have the potential to both save costs and increase productivity in a standard laboratory. But talk is cheap – can we quantify the UHPLC advantage?

Calculating the economic advantage of replacing HPLC with UHPLC in an analytical laboratory is not straightforward. Ideally, costs and revenues would be measured both before and after replacement, but this kind of data is not readily available. Furthermore, non-commercial labs don't have revenues as such, so directly calculating the benefits for not-for-profit labs may be problematic. One way around this is to develop a theoretical model based on reasonable assumptions. By inputting likely costs and economies associated with investing in UHPLC instrumentation, and by allowing for the time value of money, we can arrive at a net present value (NPV) for the investment. Any positive NPV, no matter how small, indicates that the investment has more benefit than cost.

Details of the model are provided in “Models and Scenarios” on page 20. In brief, the model is intended to represent a typical analytical lab, and was used to project the possible effect on laboratory output and cost profile of investing in UHPLC instruments. We postulated an analytical lab with seven legacy HPLC instruments, and investigated the effect of replacing one or more HPLC instruments with some combination of UHPLC instruments. We also modeled the effect of two conditions: growing output and unchanged output. In total, eight scenarios, including the reference scenario, were modeled (see Table 2). Note that the reference situation is replacement of each legacy HPLC instrument with a 1220 Infinity LC, which can use UHPLC

<i>Scenario</i>	<i>New instrument combination</i>	<i>Market conditions</i>
1	7 x 1220 Infinity LC	Static
2	6 x 1220 Infinity LC 1 x 1290 Infinity II LC	Static
3	6 x 1220 Infinity LC 1 x 1290 Infinity II LC	Growth
4	3 x 1220 Infinity LC 2 x 1290 Infinity II LC	Static
5	3 x 1260 Infinity LC 2 x 1290 Infinity II LC	Static
6	3 x 1260 Infinity LC 2 x 1290 Infinity II LC	Growth
7	3 x 1290 Infinity II LC	Static
8	7 x 1290 Infinity II LC	Growth

Table 1. Model scenarios (see page 21 for graphical representation).

columns if necessary, but which is assumed to be used for standard HPLC operations as before.

Interestingly, the model shows that all scenarios bar one give a positive NPV, indicating that the benefits of upgrading outweigh the costs in most modeled situations (see Figure 3). Indeed, only Scenario 2 shows a negative NPV; however, it would only take a small increase in revenues of the order of 2-2.5 percent – that is to say, a very slightly expanding market – for this scenario too to deliver a positive return. And gaining a few percent higher efficiency from state-of-the-art instrumentation (or a slight improvement in uptime) and 2-3 percent more lab capacity also leads to a positive NPV. Viewing this as an insurance fee to sustain the service quality over time would also be a valid perspective.

Figure 3 shows that NPVs are particularly large under growth scenarios. “Growth” assumes that all of the increased capacity resulting from switching to UHPLC instruments is taken up by increased demand from the internal or external market. The results suggest that the upgrade to UHPLC will be particularly beneficial for labs that foresee an increased demand for their services.

The economic benefits of switching to

UHPLC in growth scenarios is further emphasized when we consider the reduction in costs per sample analyzed (see Figure 4). In an extreme case, by replacing seven HPLC instruments with seven fully-utilized Agilent 1290 Infinity II instruments, the cost per sample can be reduced by up to 32 percent.

Of course, an increased workload also increases other costs. Therefore, it is also important to note that the model assumes an up to 60 percent increase in operational costs under growth scenarios, the majority of which is accounted for by labor costs (for example, the increased sample preparation, data analysis, and reporting that are associated with higher laboratory output). That said, some modern UHPLC systems are able to reduce the assumed increase in labor costs by virtue of automation; for example, with regard to sample preparation and reporting. These additional benefits, though difficult to quantify, would be expected to further reduce the cost per sample. Thus, the positive effects of UHPLC investment under growth scenarios, as shown in Figure 3, may be overly prudent.

Conversely, the model allows for costs increasing in line with increased output, for example, additional personnel, additional IT cost, maintenance and miscellaneous

expenses. In reality, however, there could be additional market-driven changes that would have an impact on the revenues or costs. These could include a reduction of prices, reduced budgets, increasing competition, or customer self-service. Similarly, there could be additional expenses associated with achieving full output, for example, if more sales and marketing effort is required to sell the additional capacity. Finally, there could be a delay in the acquisition of new contracts. Clearly, there are limitations to any model system versus real-world scenario.

As expected, under conservative conditions (a non-expanding market), the costs per analysis are not decreased as significantly as under the growth scenarios.

In summary, switching from HPLC to UHPLC systems seems likely to deliver benefits not only in terms of quality of analysis and technological sophistication, but also in terms of the economics of the analytical laboratory. The economic advantages seem greatest in scenarios where the switch involves both an increase in capacity and the full utilization of that increased capacity. The largest NPV is provided by upgrading to seven new state-of-the-art instruments in a market that has sufficient demand for the machines to be fully utilized; full-capacity operation is typically associated with 1600 operating hours per year.

Where a laboratory is considering investing in new instrumentation, either due to redundancy of older systems or due to growth in demand for its services, switching to UHPLC could be an economically sound decision. Often, however, it is difficult for a laboratory to update all of its machines at once, due to the disruptive effect of the changeover, and the budget effect of such a big capital outlay in one year. Accordingly, there are advantages in adopting a flexible approach by which new instrumentation can be integrated with legacy systems in a stepwise approach that permits full transition over an extended period.

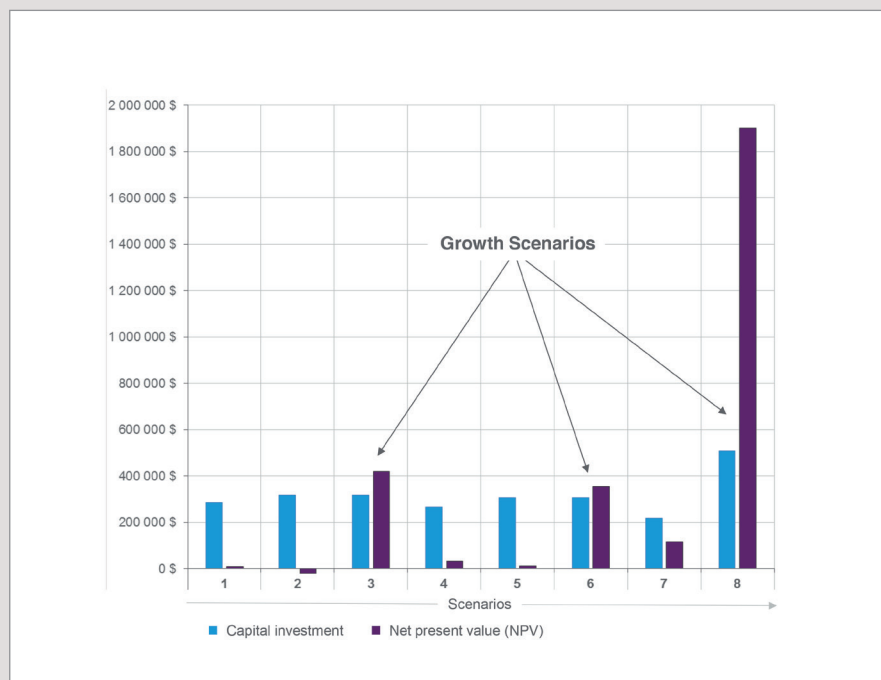


Figure 3. NPVs and capital investment per scenario. All scenarios are based on invested capital and respective net present values. Growth scenarios separate themselves due to the high NPV numbers. Scenario 5 is the most attractive when we review the conservative scenarios.

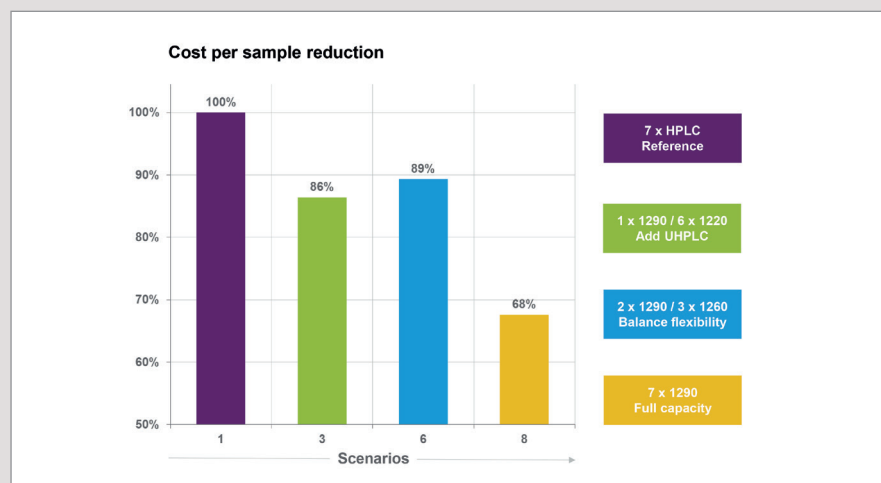


Figure 4. Cost per sample reduction achieved by upgrading to UHPLC under growth scenarios.

Much of this analysis is written from the perspective of a commercial laboratory; however, UHPLC also offers advantages for labs that are more interested in reducing costs than in boosting output. Indeed, such labs may prefer investment options that offer low running cost and low purchase costs, such as in scenarios 4 and 7 (see Figure 3).

Other labs may be assessed by criteria such as volume, speed and quality of services, for example analytical laboratories in research centers, where technical

capabilities may be ranked above purely economic considerations. In these cases, investment decisions may be constrained by relatively limited budgets, and targeted at increasing their technical capabilities. For these labs, scenarios 5 and 8 may be of particular interest.

Commercial laboratories are operated according to strict economic criteria, and often seek to maximize their productivity by controlling costs and increasing revenues and profits. For these labs, scenarios 6 and 7 are likely to be most relevant.

The Early Adopter

We made the decision to invest in UHPLC when it was in its infancy. Why? Because the potential increase in throughput was compelling. Today, UHPLC systems are less expensive, more robust, and better understood, making the investment decision even easier when it comes to high-throughput environments.

By Hiroshi Iwase

Cokey has been manufacturing glycyrrhizin from *Glycyrrhiza* root (licorice) since 1964, and is now the number one supplier of pharmaceutical monoammonium glycyrrhizinate in Japan. However, we also import and sell active pharmaceutical ingredients (APIs) and

“Our initial interest in UHPLC (around 10 years ago) stemmed from having far too many samples (perhaps 1000 per month) and not enough time.”

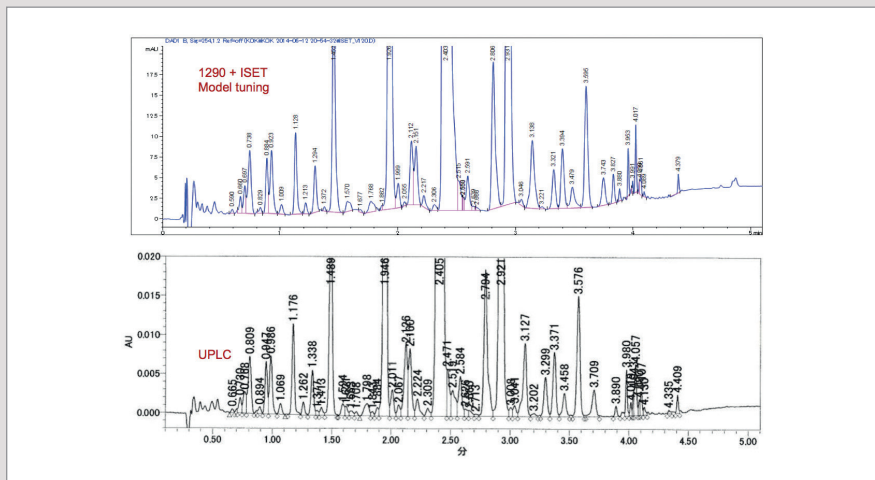


Figure 5. Comparison of chromatograms for the same sample of Glycyrrhiza extract on a Waters Acquity UPLC® System and an Agilent 1290 Infinity II LC System with Intelligent System Emulation Technology (ISET).

intermediates to generic pharmaceutical manufacturers; importantly, adding value by providing analytical data to guarantee quality. In both aspects of the business, advanced analytical capability is of great importance. As general manager of quality control, I am responsible for selecting the best analytical instrumentation for our laboratories and, therefore, must also seek out cutting-edge technology that may be applicable to our work. I also think it is important to consider the educational value of new techniques and methodologies, because up-to-date knowledge can help us stay ahead.

My first consideration when it comes to new technology is the potential impact on analytical data in terms of accuracy and precision; reproducibility and robustness are both key for us – and we do not want to introduce a new source of potential error with new instrumentation. Once I am sure that results are assured, I begin to think more carefully about other important aspects, such as throughput (increased productivity) and cost reduction (reduced consumables expenditure), which have more to do with laboratory efficiency than analytical integrity.

Too many samples

Our initial interest in UHPLC (around 10 years ago) stemmed from having far too many samples (perhaps 1000 per month) and not enough time. Despite the relative expense of UHPLC back then, it essentially allowed me to take control of time – the resource that was in the shortest supply. Of course, there was an option to simply increase the number of HPLC systems and perhaps the number of analysts, but on balance, the additional investment in UHPLC was more than matched by the gains in productivity.

I am sure I am not alone in being bombarded with samples and a simple request – “as soon as possible, please!” – UHPLC allows us to process samples faster and offer next day results. As quality control manager, I am responsible for adhering to deadlines, but also ensuring that data quality is not affected, which can be a tough balancing act. UHPLC ticks two important but often-conflicting boxes: quality and quantity.

When we made our leap of faith into UHPLC, I have to say I was surprised that we were able to reduce analysis time



by a factor of nine while maintaining the same analytical accuracy and precision. Another efficiency gain came in the form of short column equilibration times. But the transition wasn't without some perplexing problems – after all, we were early adopters. In particular, there are significant differences between UHPLC and HPLC dwell and dead volumes,

which can affect retention times and selectivity (because of discrepancies between expected and observed solvent gradients – and our assumptions based on HPLC). The reality is that methods must be adapted for UHPLC – and we had to learn a number of tips and tricks to get the most out of our new system. Needless to say, over the last

10 years, many of our initial challenges and questions have been addressed, and today, the specific behavior of UHPLC is well understood.

Intelligent emulation

Migration of methods from HPLC to UHPLC does take time, but once fixed they allow us to benefit from the speed

“The reality is that methods must be adapted for UHPLC – and we had to learn a number of tips and tricks to get the most out of our new system.”

of UHPLC, which is clearly beneficial for urgent results or for routine, high-

throughput scenarios.

Agilent Technologies’ Intelligent System Emulation Technology (ISET) eases the method transfer path by offering a powerful and reproducible way to match retention times from modern instrumentation to historical data. For example, glycyrrhizin is obtained from a natural product, so the source may vary – China, other central Asian countries, Russia, and Spain are all possible locations. Importantly, different regions have characteristic chromatograms, which we have collected over many years, forming a bank of valuable data. ISET gives us the ability to run (and fine tune) legacy methods, so that the same retention times and peak resolution are delivered. An example of the actual utility of this technology can be seen in Figure 5, where chromatograms obtained from our 10-year-old UHPLC

system are emulated by ISET and the 1290 Infinity II LC – I am sure you will agree the results are surprising.

We purchased our first UHPLC system 10 years ago to gain a much-needed increase in productivity. Today, UHPLC is not only more mature and consequently better understood, but software tools, such as ISET, exist to make the transition from HPLC to UHPLC (and from old UHPLC to new UHPLC) easier and smarter. And although it will take time for UHPLC to be accepted in regulated environments (where legacy HPLC methods remain the norm), ISET takes us one step closer to more widespread UHPLC adoption – and means that I can consider saying “sayonara” to my old 1100s in manufacturing.

Hiroshi Iwase is Quality Control General Manager at Cokey, Japan.

Defining UHPLC

To gain further industry perspective on UHPLC, we speak with Matthias Pursch, Technical Leader for LC at The Dow Chemical Company in Stade, Germany.

Could you give us a little personal background?

I have about 20 years of practical experience in using liquid chromatography, and for the last 16 years I’ve been at Dow. As technical leader for LC, I’m responsible for assessing new technologies, identifying future needs across the company, and collaborating with colleagues on LC method development. You might say, I’m the “LC guy”! I would say the main drivers for much of my efforts echo many chromatographers. I’m usually trying



to not only do analysis faster, but also better – especially in terms of resolution and selectivity.

How do you define UHPLC?

When UHPLC first arrived on the scene, the area was really defined by

the capabilities of the technology, and though that is still partly true today, I think the definition of UHPLC is now

“Indeed, UHPLC instrumentation is now starting to differentiate itself in terms of reduced dwell and dispersion volume, which also have an impact on “ultra” performance.”

much broader – and a little more blurred – with the introduction of superficially porous particles. As a result, “ultra high pressure” has certainly become “ultra high performance”, whether conferred by an increase in system pressure, advances in column technology – or both. Whatever the definition, what’s clear is that UHPLC offers users much improved separation when compared with traditional HPLC 3.5 or 5 μm particles.

In other words, pressure is only one consideration. Indeed, UHPLC instrumentation is now starting to differentiate itself in terms of reduced dwell and dispersion volume, which also have an impact on “ultra” performance. And at the detector level, faster scan rates are also becoming more important.

What are the major benefits of UHPLC?

When I think of UHPLC, the first benefit that springs to mind is the increase in productivity – after all, analysis times can be reduced substantially. The second is higher information content – the result of better peak resolution. Sometimes this is more important than speed. Of course, benefits should match needs. At Dow, getting results faster is a key consideration factor when it comes to investing in new technology. Improved resolution has helped us develop improved methods for impurity analysis, for example. Also, an increased speed now allows 2D-LC methods to be run much faster than before.

How easy was the transition from HPLC to UHPLC?

When using sub-2 μm columns in the early days, there was a bit of a learning curve! For example, we sometimes experienced column clogging, which we addressed using better sample filtration. We also learnt that water quality played a big role. Today, the

major concern is ensuring that the system configuration is appropriate for running at UHPLC conditions, including capillary connections and so on. For the novice user, there are a couple of areas to trip up on.

“Though there will likely be a few specialized application areas where standard HPLC remains, UHPLC methods will become more and more prevalent.”

Any positive surprises?

Absolutely. We’ve seen a substantial decrease in the time needed for method development when using shorter columns and column screening tools; UHPLC allows us to vary parameters much faster than standard HPLC and really facilitates the process. And while we were expecting improvements, another positive surprise was the speed at which we can generate data – and that goes both for R&D and quality control. Of course, this is directly linked to the increase in analytical speed that UHPLC offers, but it’s interesting to note the consequent effect in other departments.

How does Dow use the productivity gain?

It really depends on the application. In

certain areas, we want a higher throughput. In other applications, the shorter analysis time allows the analyst to work on other projects, so the gain in time resource is used in a different way. In essence, you can either do more work or free up human resources for other important tasks.

What advice would you give to a lab that has not explored UHPLC?

First, I would say that it is very worthwhile considering the transition! From a technical point of view, you first have to make sure that you have (or can acquire) the appropriate instrumentation. And then it really comes down to the needs of the individual lab. In general, if the laboratory is working with complex samples or needs higher productivity, I would strongly recommend UHPLC. Over the years, the transition from HPLC to UHPLC has been made much easier. Vendors (of columns and instrumentation) have been proactive in offering practical tips, application notes and solid documentation. Also, there is a wealth of user information in scientific magazines. But the increased availability of UHPLC-compatible instrumentation is a real milestone. Today, “standard” HPLC is very similar to UHPLC in its infancy; 600 bar is now a standard pressure limit for many systems. High-end instrumentation can go up to 1500 bar, but even at 600 bar you can gain “ultra” performance.

Where do you see the future of LC?

I don’t think it’s too bold for me to say that there appears to be a general trend towards UHPLC. As with any technology, what is cutting-edge today is standard tomorrow. And though there will likely be a few specialized application areas where standard HPLC remains, UHPLC methods will become more and more prevalent. In addition we’ll likely see a growing use of multi-dimensional separation methods.

The Voice of Experience

I've been involved in managing the transition from HPLC to UHPLC in two Big Pharma companies. Here, I share some of the lessons we learnt along the way.

By Adrian Clarke

My PhD in analytical chemistry focused on chromatography – and I've been heavily involved in liquid chromatography in its various guises ever since. I worked for AstraZeneca R&D for 12 years, where I was involved in local and global chromatography user groups, and spearheaded a local implementation of UHPLC. As part of the process, we had to evaluate the cutting-edge instrumentation of the time but also prepare an investment proposal that detailed how we would use and implement UHPLC in practice. About five years ago, I moved to Novartis Pharma AG in Switzerland who were also in the early stages of UHPLC implementation. Right now, I'm the leader of a Global Analytical Network, which connects and supports all analytical groups in the Pharmaceutical and Chemical development functions – about 500 analytical scientists globally. I'm very much involved in the continued purchase and utilization of UHPLC technology as we continue to roll it out across the company.

Proving performance

At AstraZeneca, we conducted a number of coordinated evaluations at different levels ahead of making any investment decisions. Our initial evaluation was driven by the high potential of UHPLC particularly in terms of speed

(productivity), but also resolution. But I have to say, our first attempts with the first generation of instruments were not quite as successful as we had hoped (at least in our R&D labs). Nevertheless, we saw promise and decided to conduct more detailed global evaluations that sought to ascertain whether UHPLC could live up to the hype.

We weren't only interested in the improved analytical performance of UHPLC; we also needed to be confident that it was robust enough to be routinely used in all global analytical development departments. We had a number of questions: is precision and accuracy where it needs to be? Will the instrument fail when used by multiple users with different knowledge of LC? Can we run thousands of samples and demonstrate that downtime is equal to or better than HPLC? Is it suitable for routine use in QC groups in commercial operations?

Certainly, the perception of UHPLC in the early days was that ultra performance may come at the cost of ultra fragility. And as I mentioned, first generation instruments did have some issues. However, over the course of a significant evaluation period, we

were able to demonstrate that several UHPLC systems were truly up to the task. Other instruments on the market at that time were simply not good enough.

We recognized that the move to UHPLC should be accompanied with a focus on method development to improve standardization. To that end, we assigned dedicated instruments for method development screening on a defined set of columns and with MS-friendly mobile phases. The speed of UHPLC allows us to develop methods faster, and the improved MS data quality (from sharper peaks) and increased resolution allows us to develop better methods.

Evaluating economics

We had proven the productivity and robustness of UHPLC in an analytical development environment – but some sort of financial justification is also needed. In fact, we needed to prove that it was possible to run our laboratories with fewer instruments, if UHPLC was adopted. When it comes to a long-term instrument replacement strategy, the ability to replace two or three HPLC systems with one UHPLC system in certain applications is clearly a benefit,



despite the higher initial investment required. Fewer instruments means less bench space and reduced maintenance, qualification and associated compliance costs. UHPLC also reduces solvent consumption, so is greener than HPLC! All of these elements were factored into the assessment.

Fifteen years ago or so, cost was not a serious driver in big pharma – investment in new instrumentation was less critically appraised. But today that has changed, and like-for-like replacement plans are no longer seen as a strategic investment or even feasible in some cases.

We looked at our inventory of HPLC systems across the departments, focusing on instruments that were coming to the end of their useful life (for example, 12 years old or over) and would probably need replacing over a defined period. We then compared a like-for-like replacement plan with a scenario in which they were replaced with fewer UHPLC instruments. In fact, it's easier to justify a switch to UHPLC, if you can demonstrate higher efficiency and better utilization of fewer instruments.

New ways of working

Increases in speed and productivity can only be realized if instruments are actually being used. That sounds obvious, but to gain the true advantages of UHPLC, it's worth considering the way your lab works and consider "lean principles". For example, an instrument booking system can help maximize usage, and you might want to centralize UHPLC instruments and make sure columns, mobile phases, buffer stocks and spare parts are all easily accessible.

It's also important to have 'super users' on hand to facilitate the transition and provide training and guidance. UHPLC is less forgiving of 'school-boy errors' made by less experienced analysts or chemists. With HPLC, you might not encounter any problems when you find

microbial growth in mobile phase that hasn't been changed for a couple of months; in UHPLC, you'll end up with a blocked column or you'll see artifact peaks. Samples that contain particulates also cause problems, so they also need filtering. In some ways, UHPLC demands that we address some of our bad habits – modern (almost black-box) HPLC has led to a little complacency.

Top three reasons to switch

To conclude, here are three good reasons to consider investing in UHPLC:

1. Increased productivity. Faster method development, faster analysis times, and increased flexibility can all boost lab efficiency. UHPLC also opens the door to time-critical analyses; for example, cleaning verification or unstable analytes.
2. Improved quality. Higher resolving power and higher quality data (especially MS data) boosts knowledge and confidence in your analyses – and your products.
3. In the long term, the first two advantages can come at a lower cost. If you can reduce instrument numbers and implement changes that increase utilization of the systems available, UHPLC makes financial sense.

Finally, I'd like to point out that UHPLC is not a completely different technique or something that should be feared – it's just another format of liquid chromatography!

Adrian Clarke is a Senior Fellow and the Technical R&D Analytical Network leader at Novartis Pharma AG, Basel, Switzerland and a committee member of The Chromatographic Society (www.chromsoc.com).

Tips for the Transition

1. In a routine environment, you make the transition with a 'critical mass' of instruments; you're unlikely to change the world with a single UHPLC system.
2. Where are the UHPLC methods going to be used? If your (internal or external) customers don't have access to UHPLC, transfer of methods back to HPLC will be an important consideration. Method translation tools are important here!
3. Consider your long-term needs. You need to plan several years ahead and look at instruments across company before investigating the economics of a replacement strategy.
4. Discuss the transition with other departments; could others benefit from a joint and aligned effort to make the switch?
5. To support the ample literature on the topic of UHPLC, ask vendors to help you assess the benefits of UHPLC with your "real" samples – it could prove very persuasive for upper management.
6. Consider changing the way you work – harmonized and standardized ways of working, including booking systems and centralized UHPLC systems can maximize usage.
7. Make sure experts are on hand to support the transition. Tips and tricks training – and a refresher on good chromatography practice – will make the transition much smoother and increase instrument up-time.

APPENDIX

Models and Scenarios

The lab

Our model postulates a liquid chromatography lab that provides standard-type HPLC analysis. Typical tasks include sample analysis (single samples and/or series of samples) and method development. The lab routinely follows DIN/EN/ISO/IEC 17025.

We assume that the lab is part of an enterprise that has incurred fixed wage, asset and consumables costs based on the following:

- three technical team members
- 90 m² lab space, including desks for results review and documentation
- 7x HPLC systems (ready for replacement)
- Other lab equipment for weighing, dilution and sample preparation
- Chromatography data system, computers, printers
- Storage room for solvents, reagents, samples.

The plan is to replace existing HPLC systems at the end of year 0, so that at the start of year 1 all instruments are productively used in the model. We assume that the lifetime of the new instruments is 8 years, after which they are fully written off (thus no returns are expected from selling these assets). Depreciation is on a straight-line basis following legal and internal company guidelines.

Annual laboratory costs are divided up by type: labor, material, maintenance, energy & infrastructure, depreciation, lab space rental, communication & IT, miscellaneous. All data were derived from public sources, and are considered typical for analytical laboratories operated in the medium size enterprises of the chemical industry in Germany.

<i>Type of cost</i>	<i>Annual cost (\$)</i>	<i>Percentage of total cost</i>
Lab personnel	179935	47
Consumables	38713	10
Maintenance	5453	1
Utilities	5453	2
Depreciation	39823	10
Lab space	26172	7
Communication/IT	9815	3
Miscellaneous/indirect	76336	20
Total Operating Costs	384425	100

Table 2. Breakdown of costs in our model laboratory.

For laboratories with a different focus or in different geographies these master data may need to be adapted.

Using the above information, and taking year 0 as the reference year, the breakdown of costs in our model laboratory is shown in Table 2.

The revenues

Laboratory revenues were calculated under market growth or market stasis conditions. Market stasis assumes a stable market, where revenues are constant and are independent of the labs' investment decision. Market growth assumes an expanding market, where the increased lab capacity obtained from the investment is fully utilized and results in additional revenues.

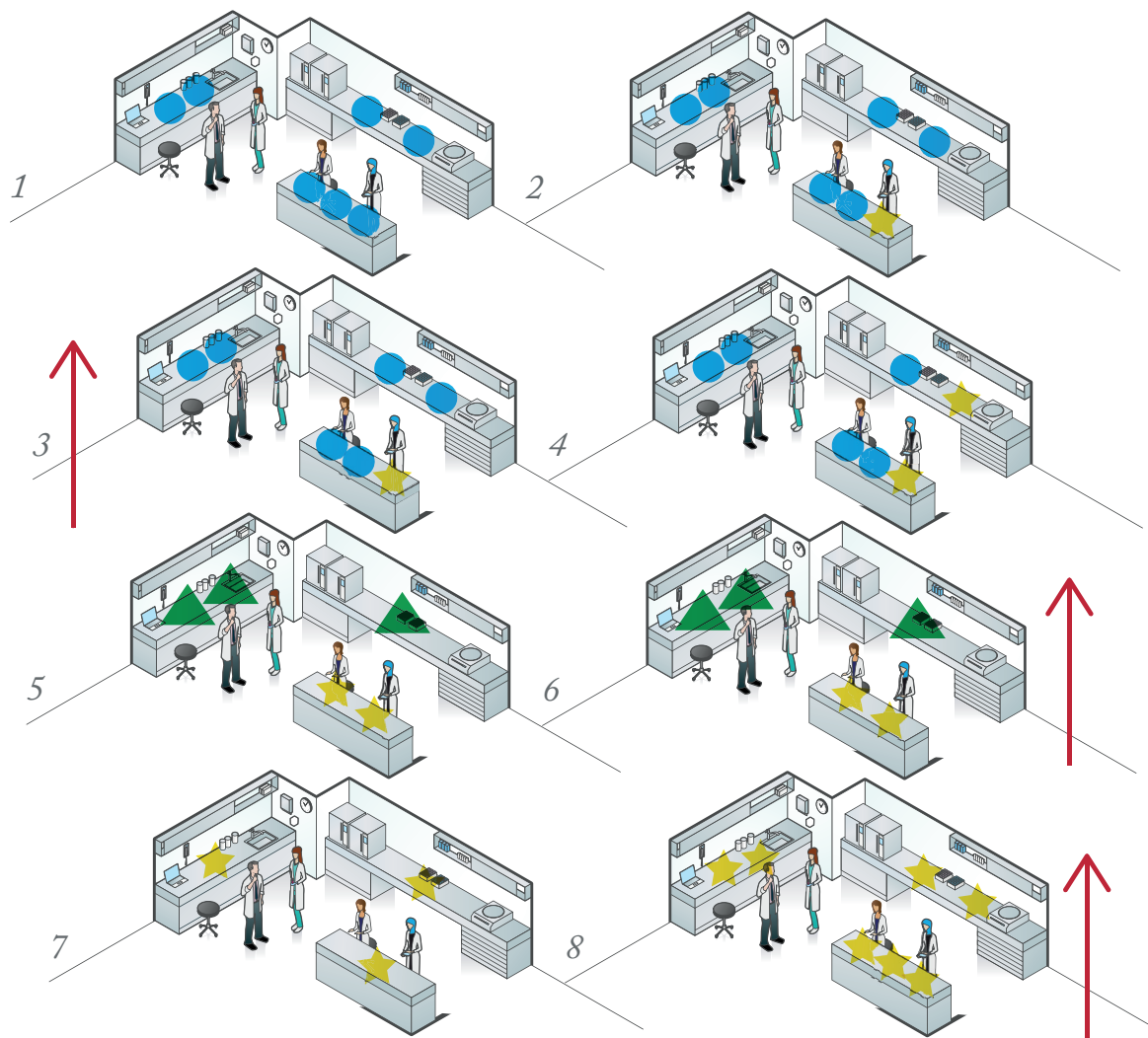
In all growth scenarios, the additional output is assumed to be provided at the same price per unit as before the switch. Unit costs are based on lab capacity and operational costs including depreciation charges relating to the cost of the new equipment. Cost reduction is compared to the reference scenario, where the current HPLC systems are due to be replaced with seven Agilent 1220 Infinity LC systems that reflect a suitable price/performance point.

The instruments and scenarios

To assess the economic return on

investment in UHPLC systems, we modeled eight scenarios in which the seven legacy HPLC instruments were replaced with one or more systems from the Agilent LC portfolio (1220 Infinity LC, 1260 Infinity LC, 1290 Infinity II LC).

- Scenario 1 – The 'reference' scenario. All seven old instruments are replaced with a 1220 Infinity LC (which can use UHPLC columns if necessary). Work is expected to continue based on standard HPLC-type operations.
- Scenario 2 – Static; exploratory stage. As scenario 1, except that one instrument is replaced with a 1290 Infinity II LC. Most work is expected to continue based mainly on standard HPLC-type operations with some use of the 1290 Infinity II LC on a case-by-case basis. The additional capacity gained is not used in this conservative scenario.
- Scenario 3 – Growth; testing the market. As scenario 2, but there is sufficient market demand for the lab to utilize all of the extra capacity.
- Scenario 4 – Static; staged conversion 1. Three old instruments are replaced with 1220 Infinity LC systems, and the remaining four



Key - ↑ Growth scenario ● Agilent 1220 Infinity ▲ Agilent 1260 Infinity ★ Agilent 1290 Infinity II

are replaced with two 1290 Infinity II systems. This scenario assumes about half the demand can be met using faster UHPLC technology. No change in output or revenues.

- Scenario 5 – Static; converted & flexible. Three old instruments are replaced with three 1260 infinity LC, and the remaining four are replaced with two 1290 Infinity II LC systems. A very flexible arrangement, but once again no change in output or revenues is assumed.
- Scenario 6 – Growth; converted & growing. As scenario 5, but there

is sufficient market demand for the lab to utilize all of the extra capacity.

- Scenario 7– Static; budget-focused but converted. Seven old instruments are replaced with three 1290 Infinity II LC systems. No demand for higher output, but productivity is used to reduce instrument numbers.
- Scenario 8 – Growth; fully converted & fast growing. Seven old instruments are replaced with seven 1290 Infinity II LC systems, and the extra productivity gains are fully realized.

Results in Detail

By setting the unit cost in the reference scenario to 100 percent we can compare the relative unit cost for each scenario (see Figure 6). The model suggests significant unit cost reduction in all growth scenarios, down to as low as 68 percent for scenario 8. Most of the conservative scenarios, with the exception of 2, show minor improvements. Among the conservative scenarios, scenario 7 has the largest unit cost reduction; we attribute this to investment in a smaller number of UHPLC instruments that are then fully utilized in meeting the existing demand.

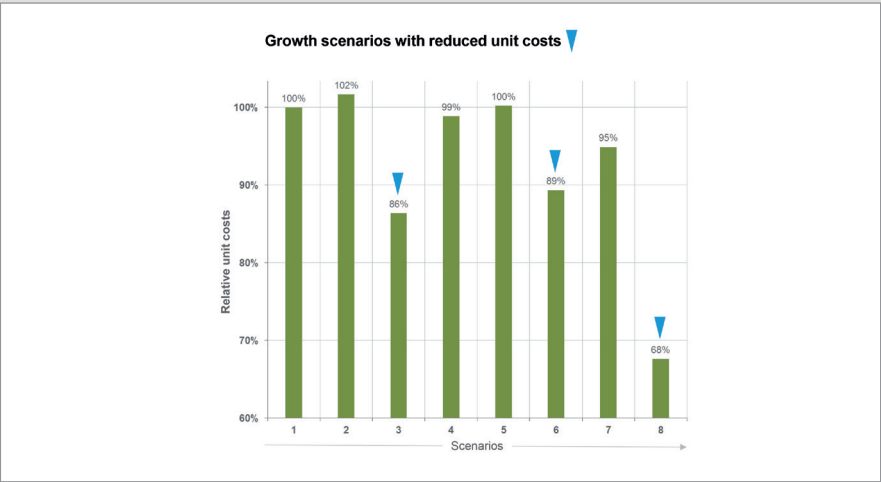


Figure 6. Unit cost relative to the reference scenario (set at 100 percent unit cost). Blue arrows represent “growth scenarios”.

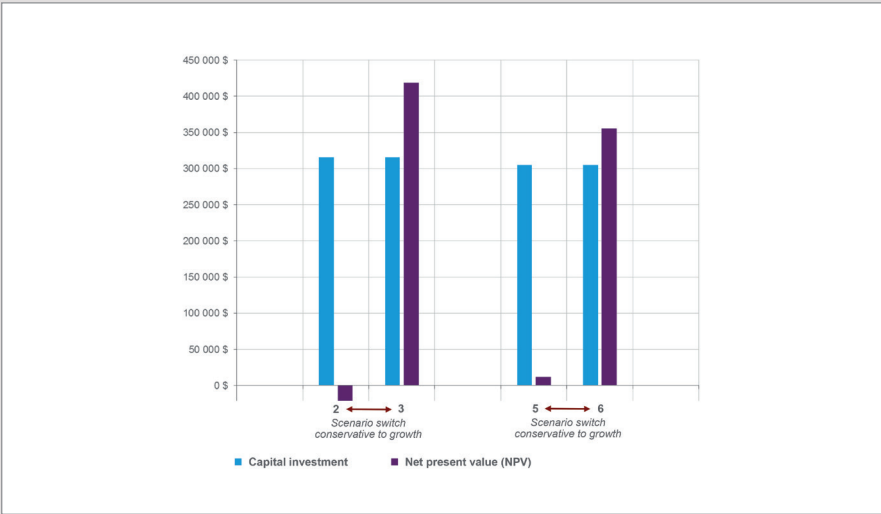


Figure 7. Effect of switching from static to growth conditions on net present value NPV.

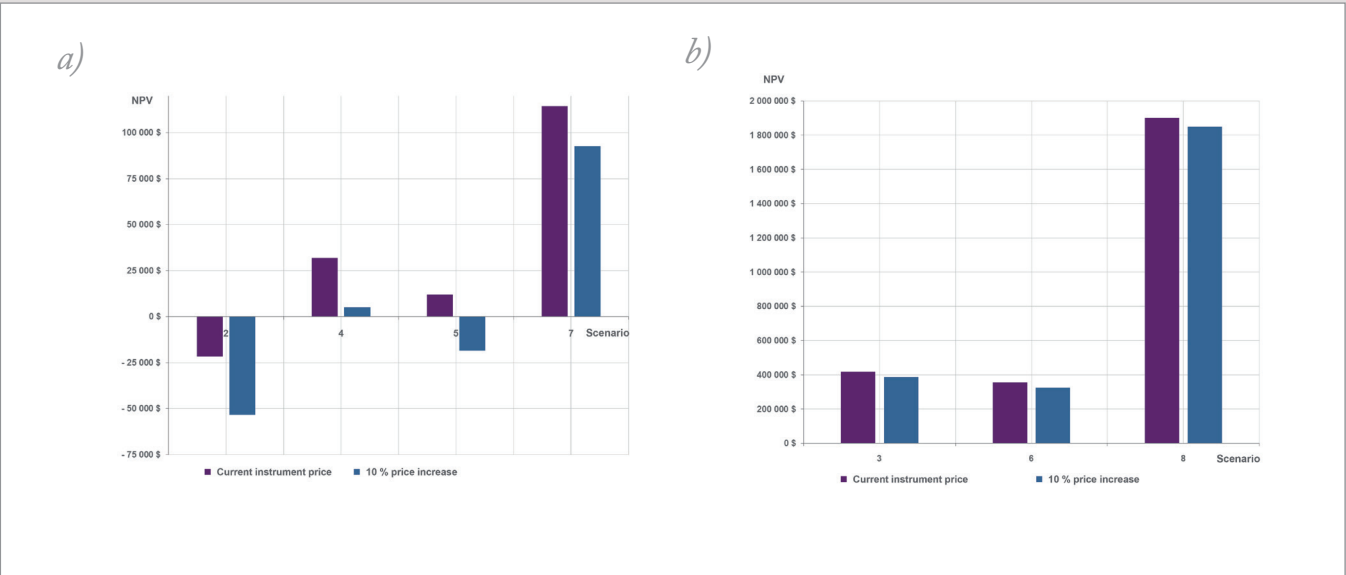


Figure 8. The impact of increased (10 percent) instrument purchase price on net present value (NPV) in a) conservative scenarios and b) growth scenarios.

Figure 7 illustrates the tremendous NPV increase when we move from conservative to growth scenarios; we compare two pairs (scenarios 2 and 3; and scenarios 5 and 6) where the level of invested capital is equivalent.

Sensitivity analysis

Our sensitivity analysis investigated the effect of various key inputs on the NPVs. The results (see Table 3 for details) show a strong impact of changes in personnel costs on the return on investment. However, under growth conditions, the sensitivities are much reduced; thus, the growth scenarios 6 and 8 are very robust. For example, in scenario 8 the personnel cost can be doubled before the model generates a negative NPV.

The price of consumables does not seem to be important for investment decisions.

For both growth and static scenarios an extension of depreciation periods leads to higher profits and increased NPV values.

The instrument purchase price is obviously an important factor in assessing the economic return on investments in

new UHPLC systems. The addition of an instrument contributes to operational costs, in particular via increased depreciation charges. In Figures 8a and 8b, we show the impact of instrument purchase prices on NPV values. Again, the model suggests that under conservative conditions, the scenarios are fairly sensitive to changes in instrument price. Scenario 2 in particular develops a significantly negative NPV, because the increased capacity provided by the investment is not giving any return in terms of increased revenue. The only scenario that retains a positive NPV under conditions of market stasis and a 10 percent increased instrument price is scenario 7. We conclude that in cases where the increased capacity represented by the new UHPLC instruments cannot be absorbed by the market, the increased instrument prices have a significant influence on the NPV of the investment.

Conversely, under growth conditions, the NPVs remain positive despite an increase in instrument price. Figure 8b shows the minimal impact of 10 percent price increases on scenarios 3, 6 and 8.

The lifetime of the instruments may also affect the NPV value. The anticipated lifetime depends on the application and usage. On average, LC instruments are used for 8–10 years. Lifetime may be reduced in a high-throughput environment, where wear and tear is expected to be higher.

In Figure 9, we show the effect of reduced instrument lifetime on the NPV of the optimal investment scenario (scenario 8, where all seven instruments are replaced with 1290 Infinity II systems, in a growing market where the full capacity of the machines is utilized). The model indicates that the NPV will be negative if the instruments last less than four years, which emphasizes the need for reliability and regular maintenance.

a)

	Operating profit (\$)							
Scenario	1	2	3	4	5	6	7	8
Labor cost +10%	-19679	-19679	-19679	-19679	-19679	-26239	-19679	-32799
Instrument price +10%	-5674	-6317	-6317	-5338	-6102	-6102	-4360	-10173
Solvent cost +10%	-1503	-1342	-1395	-859	-644	-644	-322	-751
Operational hours +10%	-2254	-2013	-2093	-1288	-966	-966	-483	-1127
Depreciation period +1 year	5693	6769	7071	5151	6473	5151	3610	12723
Critical labor cost (monthly wages)	3928	3808	5350	4015	3928	4844	4322	7863

b)

	NVP (\$)							
Scenario	1	2	3	4	5	6	7	8
Labor cost +10%	-112513	-112513	-112513	-112513	-112513	-150017	-112513	-187521
Instrument price +10%	-28369	-31583	-31583	-26691	-30511	-30511	-2800	-50866
Solvent cost +10%	-8592	-7671	-7978	-4910	-3682	-3682	-1841	-4296
Operational hours +10%	-12888	-11507	-11967	-7364	-5523	-5523	-2762	-6444
Depreciation period +1 year	5859	6006	44034	6449	8217	32618	9691	179186
Critical labor cost (monthly wages)	3875	3770	5275	3953	3885	4756	4236	7740

Table 3. a) Sensitivity analysis for results from static investment calculations. b) Sensitivity analysis for results from dynamic investment calculations.

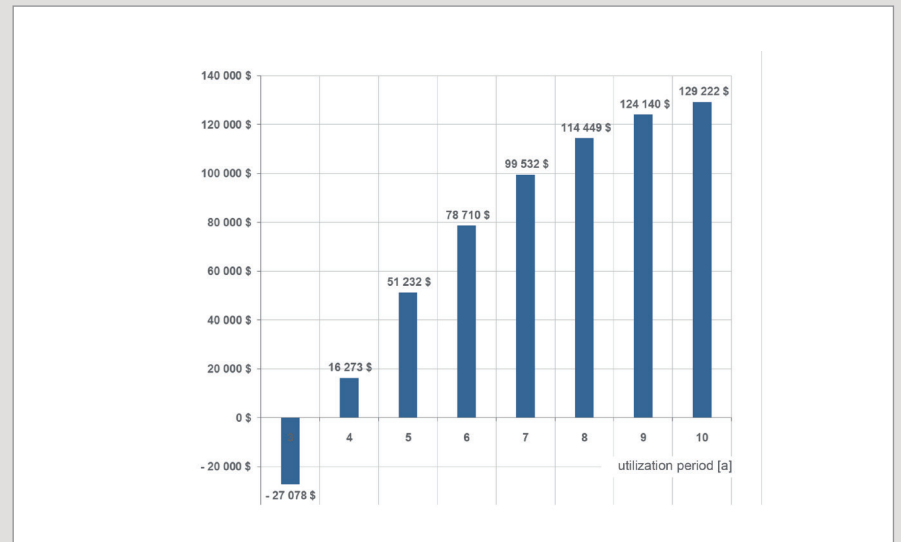


Figure 9. The effect of instrument lifetime on the net present value (NPV) in scenario 7.

