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# Evolution of Continuous Chromatography: Moving Beyond Chiral Separations

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AMPAC FINE CHEMICALS

**Continuous chromatographic separations of intermediates and active pharmaceutical ingredients are an important part of drug production. Multicolumn processes such as simulated moving-bed (SMB) chromatography have evolved above and beyond simple chiral separations. The author presents recent developments in SMB chromatography as well as applications that benefit from the high performance of this process.**

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Continuous chromatography using the simulated moving bed (SMB) process has been used in the pharmaceutical industry for the past 15 years, mainly for the purification of enantiomers (1–3). This technique is well established and accepted as a unit operation to achieve high enantiomeric purity at a competitive price compared with other techniques such as classical resolution or dynamic kinetic resolution. The need for high purity at a low cost is a major reason for the pharmaceutical industry to evaluate new tools or apply existing tools in new applications for achieving an economical process. Continuous chromatography can provide economical solutions to a broad range of purification problems.

## In search of chiral purity

The US Food and Drug Administration and other regulatory agencies encourage the pharmaceutical industry to develop drugs with fewer side effects for the benefit of the end user. Better understanding of the mode of action of an active pharmaceutical ingredient (API), as well as tragedies such as the thalidomide-related birth defects in the 1960s, drove the need to achieve chiral purity. Enantiomeric purity can be achieved in two ways. The desired enantiomer can be synthesized directly by using either naturally occurring chiral building blocks as starting materials or by asymmetric synthesis through chemocatalytic or biocatalytic methods. Asymmetric synthesis is often considered the most elegant solution by chemists (4). It is an attractive option, but it may require large development efforts and associated costs.

Another method is to prepare the racemate and separate the desired enantiomer from the unwanted enantiomer. This approach has the advantage of producing both enantiomers during early development, which allows each enantiomer to be analyzed in toxicology studies and to be used to generate reference standards for analytical purposes. The chiral separation can be achieved either by salt resolution, enzymatic resolution, or chiral chromatography. Salt resolution is common, but it involves a three-step process: salt formation, resolution, and product recovery. This process requires large amounts of solvents and generates the equivalent amount of waste. Enzymatic resolution can be efficient, but its success relies on the identification of the best enzyme for the process. Sometimes several generations of enzymes need to be engineered before an optimal biocatalytic route can be developed. Chiral chromatography quickly provides a solution that can be cost

effective. In two to three weeks, several chiral stationary phases (CSPs) can be screened with various mobile-phase compositions to identify separation conditions. At this point, either a batch or a continuous chromatographic method can be used. Typically, for small quantities, a batch preparative column (1–8 cm in diameter) is easy to set up and can provide the desired amount of product in a short period of time with a minimum investment in CSPs and solvents. When quantity requirements are larger, a continuous process such an SMB can be considered. Only a few more data points are usually required to develop the SMB process. Ultimately, a demonstration can be performed on a benchtop unit equipped with small columns to obtain the actual productivity of the separation and generate data for the scale-up. The total development time for a SMB process is approximately six weeks. After this initial work, the process can be demonstrated at any scale without additional development.

**Figure 1:** A simulated moving-bed chromatography unit (5 x 1000 mm) at AMPAC Fine Chemicals' Rancho Cordova, California, facility.

## A scalable process

The scale-up of chromatographic processes follows a simple linear rule based on the square diameter of the columns. All the parameters gathered at small scale are sufficient to calculate the process throughput and quality at any other scale. As a result, the development time for an SMB process is short. In a matter of weeks, one can have an idea of the performance of the process. Scale-up to commercial scale is straightforward and usually limited only by the availability of the feed material to be separated or by the availability of the equipment. Because of the cost of the CSP as well as the quantity of solvent involved, small-scale separations can be relatively expensive even though they may not be the most efficient. These considerations are normally balanced by the short period of time needed for development compared with other methods. Once the process reaches commercial scale, the CSP is usually amortized over a large amount of product, so the contribution of the CSP to the final product is small. AMPAC Fine Chemicals (AFC, Rancho Cordova, CA) has operated two large-scale SMB units for the same product using the same packing material for more than 10 years in one unit and for five years for the second unit (see Figure 1). During that time, the amount of product processed was more than 2500 metric tons of racemic feed using only about 400 kg of CSP. Additionally, the solvent used for the process can be integrally recycled. SMB is an isocratic process that operates under mild conditions. Unless volatile impurities in the product build up in the solvent and eventually affect the process, typically more than 99% of the solvent is recycled without difficulties. In the first stage, 65–85% of the solvent is stripped from the product in falling-film evaporators. This solvent is directly recycled to the eluent tank. The remaining solvent is recovered from the drying process (see Figure 2). This solvent is returned after appropriate quality controls to the eluent tank or to a make-up tank. As a result, the solvent consumption at commercial scale is low. The 5 x 1000 mm SMB unit uses about 38,000 gallons of solvent per day, but only three to six 55-gallon drums of solvent per month are used to make up the inevitable losses from the process. In 2007, AFC received the Pollution Prevention Recognition Award from the Chemical Industry Council of California and the Department of Toxic Substance of California for implementing recycling in its commercial-scale SMB units.

The fate of the unwanted enantiomer is an important factor. Because 50% of the manufactured product is to be discarded, it is important to try to conduct the separation as early as possible in the synthetic scheme to avoid carrying the dead weight throughout the process. It may be more economical, however, to conduct the chiral separation at a further downstream intermediate stage where the unwanted enantiomer can be recycled (i.e., racemized or sold as a side product). Under these conditions, the economics of the process drastically improve.

## Continuous processes

During the past five years, interest in continuous processes for the pharmaceutical industry has increased. FDA is in favor of

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continuous processes because they are compatible with the agency's quality-by-design (QbD) principles and are amenable to process analytical technologies (PAT). The pharmaceutical industry is interested in continuous processes because they are more efficient, cleaner, and safer than batch processes. They are also less demanding in terms of a manufacturing footprint and manpower. In short, they are more cost effective (5). Because continuous processes are amenable to QbD and PAT, there is less batch-to-batch variability, which results in a lower risk of batch rejection for failure to meet specifications and therefore better process economics. Continuous processes have been used for many decades in other industries. Almost all of the batch-unit operations in pharmaceutical manufacturing can be performed continuously, and these processes can be easily applied to pharmaceutical manufacturing. To successfully implement continuous processes, however, the conventional approach to process development needs to change. Evaluation of the kinetics and mass transfer is required for successful modeling and simulation of any unit operation. This assessment results in a better definition and understanding of the design space. It allows for the identification of critical parameters and their effect on product quality. A better process can be developed and implemented, thereby resulting in a more economical manufacturing process.

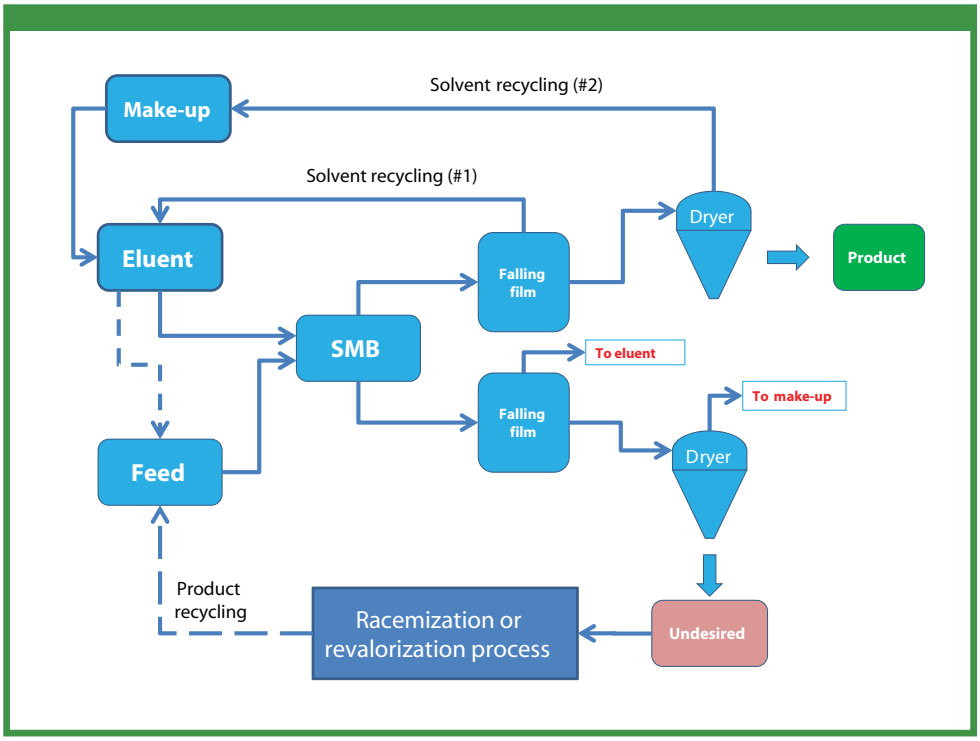


**Figure 2:** Simulated moving-bed (SMB) chromatographic process for a chiral separation with eluent recycling and unwanted enantiomer revalorization.

To design and operate an SMB unit, it is necessary to understand the process and how its output evolves with changes in flow rates, temperature, or solvent composition (6, 7). Once the critical process parameters are identified and studied, the process can be designed and controlled efficiently. During normal operations, all parameters involved in an SMB operation can be controlled accurately using modern instrumentation and analytical tools. If these parameters are maintained efficiently and accurately within their desired range, the output of the process will consistently be within specifications. Regular sampling or on-line testing is performed to monitor the SMB output and ensure compliance. Recently, the University of Zurich and the equipment manufacturing unit of Novasep (Pompey, France) developed a controller that can automatically adjust the SMB parameters to maintain the product quality and the optimum throughput based on a regular sampling of the SMB output streams (8). This kind of smart automation has not yet been implemented at a commercial scale, but it is an improvement that should find its way to the production floor soon.

## SMB in other applications

**Yield improvement.** SMB is well established as a binary process that combines the performance of chromatography with the economical benefits of a continuous process. This technique is successfully applied in the pharmaceutical industry for the chiral separation of APIs and intermediates. Chiral separations are only a few of the processes that can benefit from SMB. A few years ago, the purification of crude paclitaxel, a natural high-potency product, was implemented using an SMB process (9). The separation was complex due to a large number of impurities. This process was turned into a binary separation where the troublesome impurities such as impurities not efficiently removed by crystallizations were eluted together in one SMB stream while the purified product was eluted in the other stream. As a result, a crude product with overall purity of approximately 75% was increased to a purity of more than 95% with a recovery greater than 98% before the final crystallization.

**Large molecules.** The latest application of SMB is the purification of large molecules for the biopharmaceutical industry. Chromatography (i.e., ion exchange and size exclusion) is used to purify the expensive molecules produced from bioreactors and fermenters. These processes usually require large amounts of water-based mobile phases. An increasing number of scientific publications addresses the conversion of these inefficient batch processes into continuous processes (10, 11). Because these batch separations usually require several steps (i.e., loading, elution, and regeneration), the basic set-up of an SMB unit needs to be modified to apply this technique to these separations. SMB units with five zones or more have been designed. These design variations may make the process more complicated, but nevertheless improve throughput and solvent consumption. Other difficult separation problems can also be solved using SMB technology. A few examples, recently developed at AFC, are described below and show how SMB can be efficiently used in API manufacturing.

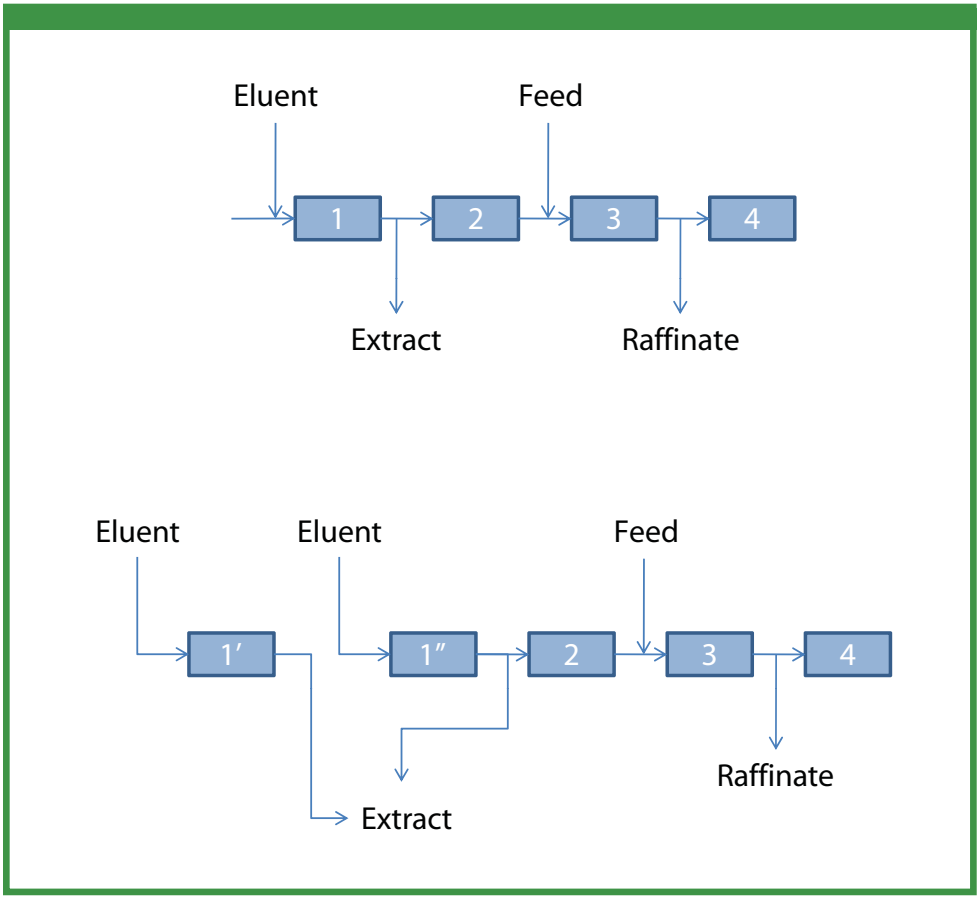


**Figure 3:** Comparison between traditional four-zone simulated moving-bed (SMB) and the modified SMB system for separations with large selectivity or increasing retention time.

**SMB modifications for increased throughput.** SMB provides a significant advantage over batch chromatography when the selectivity of the separation is rather low. In the case of high selectivity, batch chromatography may outperform SMB because of flow and operating pressure constraints. In an SMB unit, the flow rate in the first zone of columns pushes out the most retained product. For a long retention time, it takes a high flow rate to push everything out of the column before the column switch occurs. Because all the zones of the SMB are connected, if one zone is operated at a very high flow rate, then the other zones must be operated at a lower flow rate. This zone manipulation is necessary to manage operations below the maximum operating pressure of the system. As a result, the production rate is reduced. AFC developed a simple modification to the process (see Figure 3) that alleviates the pressure constraint by decoupling the first zone of the SMB from the other zones of the SMB unit (12). This additional zone allows for a rapid wash of the column with the mobile phase at maximum operating pressure without affecting the pressure in the other zone. As a result, the rest of the separation can be conducted at a higher flow rate and therefore at a higher throughput.

**SMB for chiral separations and impurity removal.** Ideally, racemic feeds only contain the two enantiomers. Unfortunately, in most cases, a few impurities that are closely related to the product also are present in the mixture. These impurities are usually either leftover starting material or side products from previous reactions. In either case, they might be difficult to remove during downstream processing without sacrificing yield. The chiral SMB separation can potentially be used to purify the product as the enantiomers are separated. Many publications describe the SMB process, but they rarely address impurities (6, 7, 13). If an impurity is present in the racemic product, it can potentially be doubled after the separation because approximately 50% of the mass of the feed is removed. Therefore, it is important to know the fate of the impurity during the SMB separation.

Five major cases can be identified, and Figure 4 shows some examples of the removal of an impurity with a chiral separation. The first case is when the impurity elutes with the desired compound (see Figure 4a). The only way to address this case is to change the separation conditions. The second case is when the impurity elutes with the unwanted enantiomer. This is a good case because the impurity will be completely removed (see Figure 4a). If the second enantiomer is to be recycled by racemization, one must ensure that the impurity is addressed in the recycle step to avoid accumulation over time. For the third case, the impurity is eluted between the two enantiomers (see Figure 4b). This case is more difficult but can usually be solved with the existing separation method. The fourth and fifth cases are when the impurity is eluted much later or earlier than the enantiomers (see Figure 4c). Under these conditions, the impurity is usually distributed evenly in both the extract and the raffinate streams. By adjusting certain flow rates, it is possible to control the ratio of the impurity in the outlet streams.

**Removal of a suspected toxic impurity.** During the past few years, there has been a lot of interest in the identification and removal of genotoxic or carcinogenic impurities to very low levels in APIs. This removal is usually difficult to do by traditional crystallization techniques without losing significant amounts of product in the mother liquor. Chromatography is one technique that can achieve very high purity while maintaining a high recovery of product (i.e., greater than 95%). The removal of a toxic impurity is a binary separation and can be done by SMB. These separations can normally be developed on normal-phase packing materials (i.e., bare silica or silica functionalized with a cyano or amino group, for example). These phases are not as expensive as chiral phases and provide larger loading capacity, thereby resulting in high throughput.

AFC recently developed an SMB process to solve an impurity problem that was originally performed using crystallization to

remove an impurity from about 1% to 10 ppm. The purification was performed using crystallization and required two to three crystallizations with an 85% yield for each step, thereby bringing the overall yield to 61–72%. As an example, the processing of 50 metric tons of this intermediate using crystallization would result in only 30.7 metric tons of pure product after three crystallizations. Assuming that each crystallization adds a cost of $30/kg to the product and that the crude feed costs $1000/kg, the crystallization process increased the pure-product cost to $53.3 million or $1736/kg. Despite a relatively cheap crystallization process, the overall cost of the product is drastically increased because a significant amount of product is lost to the mother liquors. Alternatively, if the purification is done by SMB and the estimated cost for the SMB separation is $50/kg, then the associated manufacturing cost for the pure product is only $52.4 million or $1104/kg with a total of 47.5 metric tons of pure product recovered. The lower cost of the SMB process is mostly due to the high recovery of product because it is not lost in the mother liquors as in the crystallization process. In this example, a 95% recovery was estimated; however, at commercial scale, typical yields of > 98% are realized. This difference in cost between the two methods can significantly increase when the price of the material to purify increases.

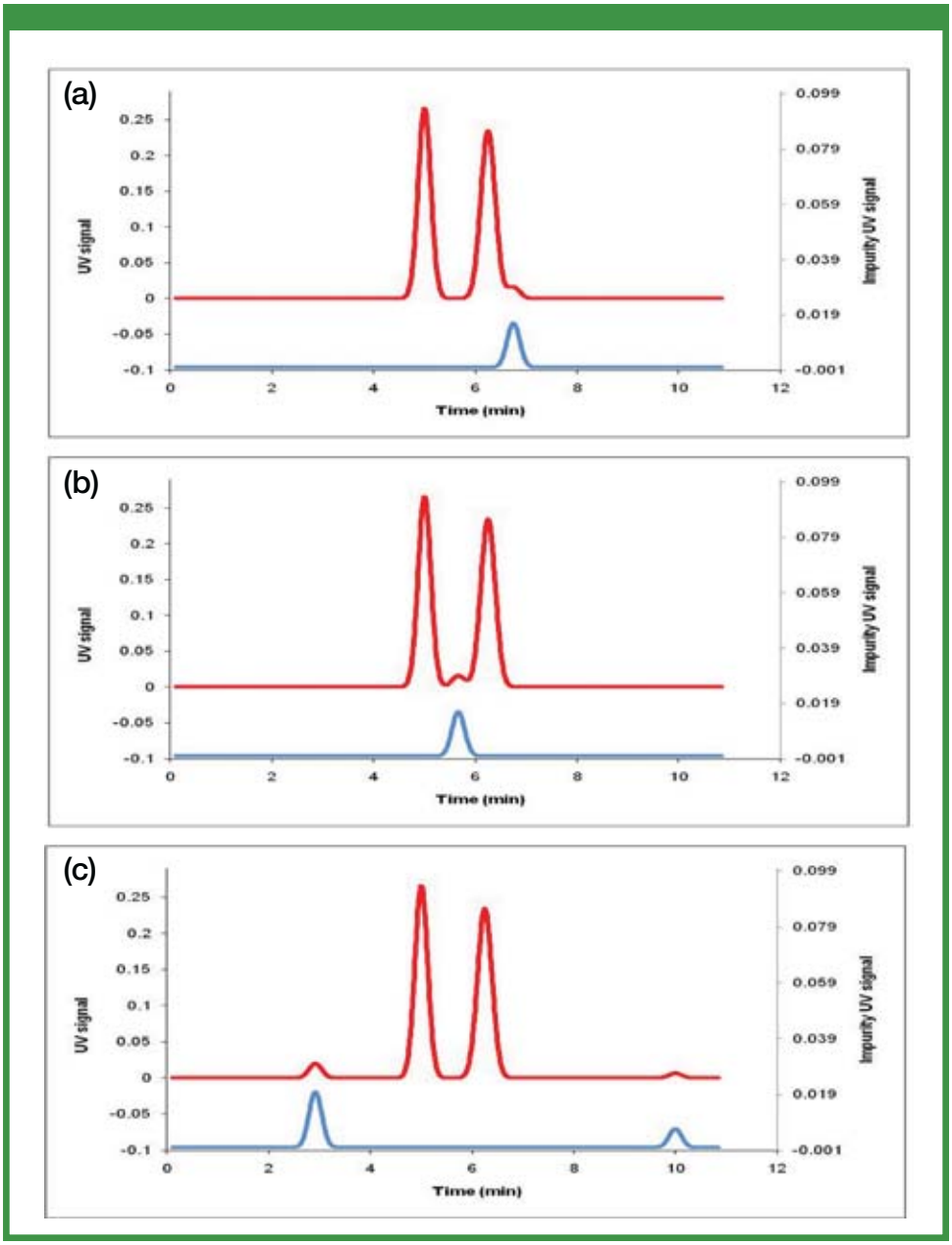


**Figure 4:** Separation of impurity(ies) during a chiral resolution by chromatography shown with simulated chromatograms. The red graphs represents an overall chromatogram, and the blue graph denotes the impurity(ies). Figure 4(a) is an impurity eluting with one of the enantiomers. Figure 4(b) is an impurity eluting between the two enantiomers. Figure 4(c) shows impurities eluting much earlier or later than the enantiomer.

**Reclaiming product from mother liquor**. It is not unusual for a chemical synthesis to require more than five steps of chemistry, and every manufacturer is looking to improve the overall yield as much as possible by fine-tuning every unit operation involved in the process. Once the chemistry has been optimized to provide the best possible conversion and the best yield, a major loss of product can happen during the final crystallization and subsequent product washes. Ideally, these steps (i.e., crystallization and washes ) are conducted with a solvent that can solubilize the impurities but not the product. Unfortunately, the product is always slightly soluble in the crystallization solvent and the wash solvent. As a result, 5-20% of the valuable product can be lost to the mother liquor and the cake washes. It is very difficult to recover the product from these effluents because of the level of impurities is significantly higher. Additional crystallization will only result in marginal product recovery and is usually not economical.

AFC recently developed a process to reclaim the product from these effluents by using continuous chromatography. In one specific case, the mother liquor contained about 30% of the desired product and two major impurities that prevented further product recovery by classical crystallization. AFC developed a chromatographic separation process that allows the product to elute away from the main impurities. This separation becomes a binary-like separation that can be processed on an SMB unit. Once the purified product is recovered from the SMB, it can be crystallized using the normal crystallization method. Because the crystallization process has an 87% recovery, the 13% product loss was reclaimed in the SMB with a 95% recovery. This material

is crystallized with an 85% yield, corresponding to a recovery of 10.5% of the original quantity. By adding these two steps, the total yield of the process increases from 87% to 97.5%. The additional SMB and crystallizations steps, however, add cost to the final product. In this example, however, the savings in the raw material were significant.

## Conclusion

Continuous chromatography can provide a step-change in process economics. SMB technology was developed more than 50 years ago and is intensively used in the food and petroleum industry to achieve low manufacturing costs. This technology also has been implemented successfully in highly regulated environments for the manufacturing of pure chiral APIs. The justified interest in continuous processes and the push by regulatory agencies for more efficient, controlled, and robust processes are major reasons to implement continuous chromatography in manufacturing operations. High purity with high yield at a low cost is achievable. The technology, the experience, and the know-how are available to perform these operations at all scales.

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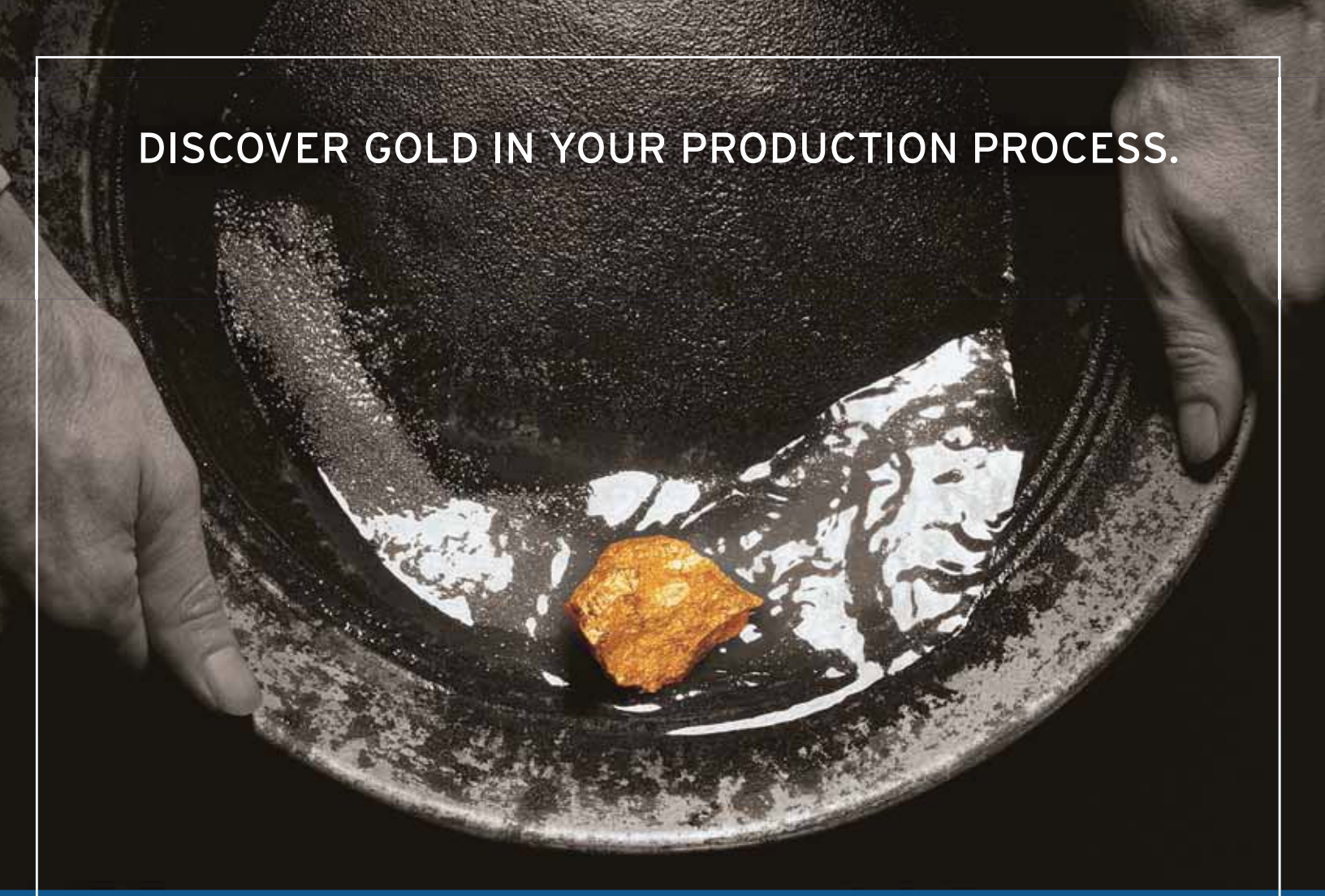

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