

LUNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

HANGSEN INTERNATIONAL GROUP LTD.,

Petitioner

v.

ZANOPRIMA LIFESCIENCES, LTD.,

Patent Owner.

IPR _____

U.S. Patent No. 10,913,962

DECLARATION OF ANDREW WARMINGTON, PH.D.

I, Andrew Warmington, declare as follows:

1. I am over the age of 18 and am competent to make this declaration.
2. I am the Editor of *Speciality Chemicals Magazine*, a chemical industry magazine that has been in publication for 38 years covering topics including pharmaceuticals, agrochemicals, cosmetics and personal care, bio-based chemicals, regulation and compliance, sustainability, and supply chain management.
3. The articles in *Speciality Chemicals Magazine* are technical and business-focused and center on the life sciences. They are not peer-reviewed. *Speciality Chemicals Magazine* accepts articles from both industry and academia.
4. I have been the Editor at *Speciality Chemicals Magazine* since December 2018. I had previously been Editor at *Speciality Chemicals Magazine* before 2018; my earlier tenure as Editor ended in September 2016. Between 2015 and 2021, there were repeated ownership changes of *Speciality Chemicals Magazine*.
5. Attached as Exhibit 1 is an article titled “Biocatalysis: Genes to GMP.” The article indicates that it was authored by Tom Moody of the Almac Group, a company active in the life sciences chemicals industry and a prominent funder of cancer research. The footer of the article indicates that it was published in the January 2016 issue of *Speciality Chemicals Magazine* beginning at page 12.

The footer also bears the name “Speciality Chemicals Magazine” and our website, www.specchemonline.com.

6. On information and belief, the article attached as Exhibit 1 appeared in *Speciality Chemicals Magazine* in the January 2016 issue. I cannot specifically recall this article having been published in the January 2016 issue and cannot independently confirm the contents of that issue. Over the course of the aforementioned ownership changes, numerous archives and files were lost.

7. However, the article attached as Exhibit 1 has the layout that an article in *Speciality Chemicals Magazine* would have had in January 2016. The article is the type of article *Speciality Chemicals Magazine* would have published, and the Almac Group was a regular contributor. The article also appears complete and readable without gaps between pages. As such, on information and belief, the article attached as Exhibit 1 appeared in the January 2016 issue of *Speciality Chemicals Magazine*, as indicated on the face of the article.

8. On information and belief, the document attached as Exhibit 2 appears to be a copy of the cover, table of contents, and editor’s letter from the January 2016 issue of *Speciality Chemicals Magazine*. The look and layout of the magazine reflects that of *Speciality Chemicals Magazine*, and the copies appear to be an accurate reflection of the publication. I note that the table of contents lists an article titled “Biocatalysis: Genes to GMP” by Tom Moody of Almac Group beginning on page 12, which is consistent with the article attached as Exhibit 1. Additionally, I

wrote the editor's letter in the document attached as Exhibit 2, and my photograph appears in the letter. On information and belief, Exhibit 2 is an accurate copy of a portion of the January 2016 issue of *Speciality Chemicals Magazine*.

9. *Speciality Chemicals Magazine* is published under controlled circulation. The vast majority of readers receive the publication for free and do not pay subscription fees. While the exact circulation oscillates over the months and years, *Speciality Chemicals Magazine* is and has historically been distributed to about 30,000-40,000 readers. On information and belief, this is a fair approximation of the circulation of the January 2016 issue.

10. The readers of *Speciality Chemicals Magazine* are typically senior managers in the fine and Speciality chemicals industry.

11. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that perjury or a willful false statement and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the paper with which this declaration is being submitted.

Executed on: 23 December 2022

/Andrew Warmington/

Andrew Warmington, Ph.D.,

Ledbury, England, United Kingdom

EXHIBIT 1

Biocatalysis: Genes to GMP

Tom Moody, head of biocatalysis and radiolabelling at the **Almac Group**, discusses how API manufacturing processes are increasingly applying biocatalysis

Biocatalysis has been involved with some of the oldest chemical transformations. Brewing fermentations were commonplace well before recorded history.

Lactic acid was probably the first optically active compound to be produced industrially using fermentation in 1880.¹ In 1921, Neuberg and Hirsch discovered that the condensation of benzaldehyde with acetaldehyde in the presence of yeast forms optically active 1-hydroxy-1-phenyl-2-propanone.² Nine years later, Knoll patented the conversion of this compound into L-(-)-ephedrine in Ludwigshafen.³

Biocatalysis is thus by no means a new technology, but its application in chemical processing has seen a massive uptake for the synthesis of chiral molecules. The phrase 'paradigm shift' has been used erroneously in relation to many technological advances in recent years, but this is certainly not the case here. The paradigm shift for the acceptance of biocatalysis is persistent and at the forefront of research within the fine chemicals and pharmaceuticals industries.

The concept of 'genes to GMP' in relation to chemical processing has truly become a reality at Almac, enabling the firm to meet timelines that are acceptable with clinical development and chemical processing. Off-the-shelf and specifically designed enzymes can be accessed within days and weeks respectively. These timelines allow synthetic chemists to include enzyme processing in their synthetic toolbox.

Bioprocessing is now the norm rather than the exception at Almac and has resulted in significant cost reductions for the production of GMP and non-GMP APIs, intermediates and fine chemicals. This article, through actual case studies, will highlight how Almac is developing viable cost-effective bioprocesses from gene identification and manipulation through to intermediate supply and to GMP processing.

Biocatalysis has become the workhorse of the chemists' toolbox for chiral chemistry. Enzyme processes are now at the epicentre of key drivers in process design, scale-up and economics, including:

- Route scouting
- Identification & prioritisation of routes to be investigated
- Determination of key cost contributors
- Key reaction optimisation methodology & DoE
- Investigation into waste stream management

The application of biocatalysis to organic synthesis has grown rapidly in the last decade. A Scifinder search of the terms 'biocatalysis' or 'biocatalyst' gave 1,325 references to articles published from 1995-2005, growing to 11,001 in 2005-15.

In part, the growth in the use of biocatalysis is due to the wide range of chemical transformations that may now be achieved biocatalytically. More importantly, biocatalysis now has all the support technologies to make it a viable option for chemical processing. The synthetic power of enzymes is their unequalled selectivity for the chemical reactions they catalyse. This is illustrated in Figure 1 using a hypothetical molecule.

The reason for the surge in the application of this green technology, in our view, is simply that success breeds success. Unlike ten years ago, we now have all the supporting technologies that can really make a difference in enzyme development, such as bioinformatics, enzyme evolution and high throughput screening, substrate engineering and process engineering.

Figure 2 highlights the options for driving bioprocessing from enzyme selection (enzymes are derived from metagenomics, bioinformatics, protein engineering and in silico design), process optimisation (process and substrate

engineering, DoE, the use of ultrasound for process intensification and enzyme immobilisation) and actual delivery of APIs, advanced intermediates or fine chemicals.

Another key advantage of running these processes is the timeline required for implementation. From the selection of a catalyst to the actual manufacture of product, timelines are similar to those of conventional chemistry optimisation and scale-up. The following highlights selected processes performed at Almac from enzyme design and engineering through to GMP product isolation.

In silico enzyme design & screening

Using in house built Gene-Informed Diversity Screening (GIDS) technology, Almac can rapidly access specifically built enzyme libraries for specific customer substrates. Using this technology, it can take customer substrates and by performing complex dockings studies can build tailored catalysts for the customer substrate. Figure 3 shows a recent example involved an imine reductase (IRED) project where Almac specifically designed 50 IREDs for the enantioselective reduction of the imine.

In silico rational protein engineering can provide crucial insight for the design of tailored enzymes. Starting with an in house Almac IRED, we constructed a list of in silico-designed mutants. This approach required the use of comprehensive methodologies like homology modelling, molecular docking and molecular dynamics simulations, in combination with information about correlated mutation networks within the protein sequences.

The computational scientists designed the enzymes, molecular biologists cloned and prepared the enzymes and finally the chemists screened the enzymes, resulting in the identification of an active and selective IRED

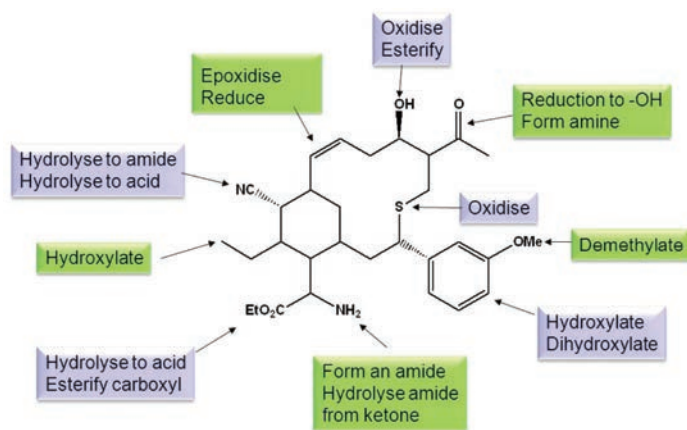


Figure 1 – Range of possible biotransformations

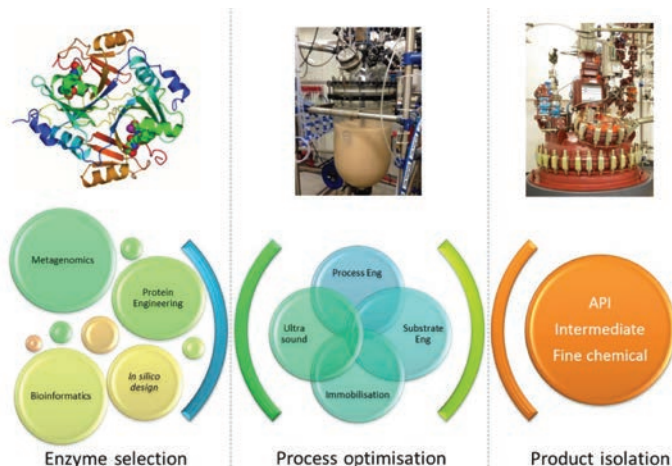
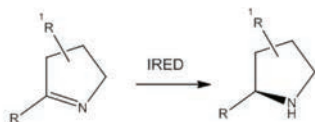


Figure 2 – Enzyme selection to product isolation



- *In silico* design of 50 IRED enzyme library
- Gene synthesised, cloned & expressed
- Screened against customer substrate – hits found

IRED no.	% HPLC peak area @ 260 nm		% HPLC peak area of product enantiomers		ee
	Product	SM	(S)	(R)	
3	9	91	54	46	8
5	2	98	0	100	100
8	77	23	89	11	78
9	2	98	13	87	74
12	3	97	100	0	100
16	3	97	77	23	54
20	100	0	100	0	100
25	1	99	89	11	78
27	31	69	92	8	84
28	8	92	0	100	100

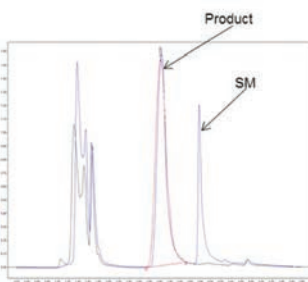


Figure 3 – IRED enzyme application

catalyst. The development of the enzyme panel building took less than eight weeks and we intend to reduce this timeline further still.

Rational & random enzyme evolution

An alternative to IRED-mediated chiral amine production is the application of transaminase (TAm) enzymes. A chiral amine project involved the screening of Almac's TAm library (400 enzymes) to identify a TAm for the transamination of a sterically hindered prochiral ketone.

The project was initiated via a simple and routine enzyme screen and a TAm enzyme was identified, which Almac had to hand. We then performed an in-depth cost analysis of the process and, due to tight cost demands on the product, the process required further optimisation to reduce the cost.

This was not possible via substrate and/or process engineering and the enzyme required evolving. This was done using both rational and random evolution methodologies. The first round of evolution involved *in silico* mutant design and verification through complex algorithms to build a focused and smart library using Almac's REACT (Rational Evolution Accelerated bioCatalyst Technology).

This first round of evolution resulted in a 25-fold increase in activity through synergistic mutational coupling using REACT technology (Figure 4). Further rounds of evolution have seen a 200-fold uplift in less than six months. This new enzyme is currently being evaluated in process optimisation.

Process intensification

A third case study involved process intensification using ultrasound technology with a lipase-mediated desymmetrisation process. Having identified a lipase using GIDs technology, it was evident very early on in the process optimisation that mass transfer between substrate and enzyme was becoming a problem. The team quickly evaluated the problem and implemented a rapid and scalable ultrasound solution.

Having expertise in the application of ultrasound for bioprocessing has resulted in a step change for rapid scale-up, without having to commit to enzyme engineering when timelines are extremely tight. Using ultrasound in a recirculated loop, reaction kinetics were recovered in processable timelines, as shown in Figure 5.

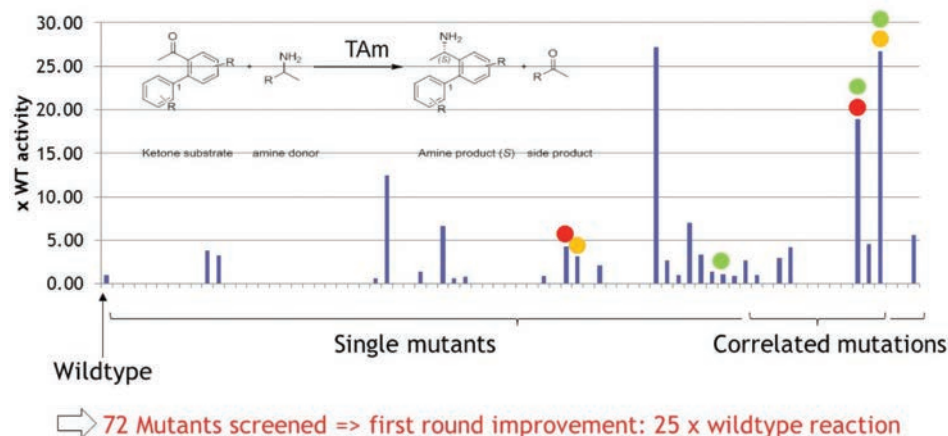


Figure 4 – TAm evolution using REACT technology

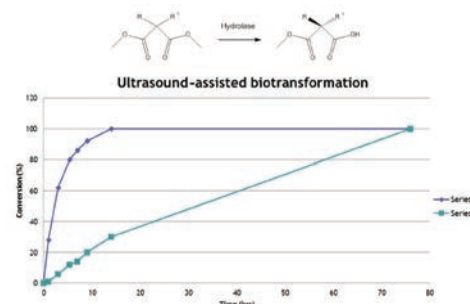


Figure 5 – Recovery of reaction timelines using ultrasound

GMP processing

A carbonyl reductase (CRED) GMP bioreduction process was developed from the metagenomic screening of novel CRED enzymes. Using metagenomic data, we retrieved a CRED enzyme that was able to accept a bulky ketone to deliver a chiral alcohol.

The project progressed through enzyme supply (including enzyme expression optimisation and fermentation) and bioreduction process development to deliver a GMP process. In parallel to process optimisation, analytical method development and phase appropriate validation were conducted.

Phase-appropriate testing for residual enzyme should be consistent with testing for normal organic impurities when conducting bioprocesses for API synthesis. Early in development, the synthesis of pre-clinical batches does require specific residual enzyme testing. Considerations of the overall purity of the API would be sufficient to support pre-clinical studies.

As the material advances in development and the GMP material is being produced for early clinical trials, the residual enzyme content as a potential impurity in the drug substance should be considered. The placement of the enzymatic process within the overall synthesis and its proximity to the final API would need to be considered for potential control strategies.

As the API advances to later stage clinical trials and approaching the registration batches, the final enzyme would have been developed with appropriate residual enzyme control strategies to ensure API quality.

Advanced intermediate supply

A typical project at Almac includes, for example, a Phase IIb compound where nine steps of chemistry resulted in the formation of three chiral centres from a registered starting material with a global yield of 7.4%. Key to winning the project was the marriage of Almac's synthetic, analytical and solid state chemistry and the introduction of green SelectAZyme** chemistry for the induction of chirality. The project was initiated with clear objectives to:

- Increase the productivity of the process to >50% kg/litre/day
- Achieve a >20% reduction in waste
- Reduce expensive and toxic solvents
- Reduce heavy metals and subsequent contamination

- Remove the need for specialised equipment (currently high pressure hydrogenation)
- Develop a process with consistent quality of product
- Reduce the cost/kg of the product

The original chemistry involved multiple steps including a late stage classical resolution using an expensive amine-resolving agent and high pressure hydrogenation using metal catalysis. The late stage resolution resulted in huge volumes having to be processed until Step 7.

Almac's challenge was to design a scalable, lower volume route that had green and cost incentives for change. We completed route invention and proof of concept demonstration followed by hundreds of kilos scale-up prior to tonne manufacture. The revised route consisted of five steps using three different SelectAZyme enzymes with a global yield of 23.4%.

Innovation was achieved by delivering a green process that was scalable, derived from readily available feed stocks, and used off-the-shelf SelectAZyme enzymes with no 'strings' attached. From retrosynthetic analysis, it was demonstrated that the registered starting material could be made from feedstocks that would not have any long-term supply issues and could be sourced readily from India and China.

Having the proposed route on paper, the next step was to synthesise the key intermediates and begin enzyme screening. The project involved an early stage bioresolution that resulted in a monoacid product with >96% ee. From this, a bioreduction step introduced another chiral centre.

Key to this enzyme screening was to find a CRED enzyme that was able to reduce the ketone of the desired enantiomer feedstock stereospecifically, not the undesired (2%) enantiomer left over from the bioresolution step. The CRED identified resulted in a diastereoselective reduction and simultaneous biopolish of the diastereomeric mixture.

	Chemical Route	SelectAZyme Route
No. of steps	9	5
Catalyst type	Rhodium-based Natural product amine	1x liquid enzyme 2x powdered enzymes
Volume efficiency	83 g/L	151 g/L
Solvent usage	DCM, MeTHF, EtOAc, DMF	EtOAc, Toluene
Global yield	7.4%	23.4%

Table 1 – Advantages of green enzyme process

The remaining undesired ketone was easily removed using conventional work-up at the next step. The process ran from start to finish using two solvent combinations. Having developed the process, all stereoisomers (seven different products) were synthesised readily from other SelectAZyme enzymes so that analytical development could be undertaken to determine the fate of these potential impurities. Table 1 summarise the advantages of the process.

Conclusion

The proven ability of biocatalytic technology to produce hard cost savings for pre-existing processes or to provide economical access to NCEs in the industrial sector is ensuring increased investment year on year in this area.

The key difference between biocatalysis today and ten years ago is that we now have excellent supporting technologies that greatly simplify enzyme identification and development. For this reason, traditional chemical technologies will surely find it increasingly difficult to compete in the coming decade with biocatalysis, which, we must remember, is even still in its infancy.

Almac's continued investment into evolution technologies and metagenomic programmes further confirm its commitment to green technologies. This is being driven by market needs and stresses and the key to future success is flexibility and rapid response to change.

Biocatalysis is a maturing technology and is certainly aiding future success stories for the rapid supply and delivery of chiral intermediates, fine chemicals and APIs. 'Genes to GMP' is now a reality. It's time to give it a go!

**Also contributing to this article were Stefan Mix and Scott Whary, biocatalysis team leaders, and Derek Quinn, biology team leader*
***selectAZyme is a registered trademark of the Almac Group*

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EXHIBIT 2



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13 December 2022

Dear Kevin

Biocatalysis: Genes to GMP by Tom Moody
Speciality Chemicals Magazine Vol. 36, Issue 1
January 2016 pp.12-14
Shelf mark: (P) LT 00 – E(45)

According to our records, one copy of this item was receipted by The British Library on January 29th 2016, and it would have been available for public use from that date.

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Yours sincerely

Tony Corsini



Speciality Chemicals Magazine

January 2016
Volume 36 No. 01

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for APIs

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■ Peptides & proteins ■ Chemspec India preview



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Plus ça change...

Will the DuPont-Dow mega-merger go ahead and what are the implications?

It has certainly been an interesting few months in the chemicals industry and downstream, with some of the most intensive M&A activity in many years. As so often, when companies cannot grow through the marketplace, at least not enough to shine on Wall Street, they grow by buying each other.

In oilfield services, three may become two when Halliburton acquires Baker Hughes (page 6) while in pharma, Pfizer is poised to acquire Allergan in a staggering \$160 billion deal. In agrochemicals, the long anticipated consolidation among the six remaining R&D-based giants was finally kick-started by the announcement in early December that DuPont and Dow were planning to merge into a single company with a market capitalisation of \$130 billion. And agro is not even close to being the half of it.

DuPont and Dow, lest we forget, are two of the US's oldest chemicals companies as well as the largest. For all that Dow CEO Liveris Andrew Liveris portrays this as something that was many years in the making – I personally doubt that a defunct collaboration in elastomers really counts and it is hardly surprising that there were existing connections between them – this comes as a seismic shock.

What came next, though, was entirely predictable. DuPont had already announced a \$700 million global cost saving and restructuring plan that will be implemented in parallel, with some 10% of the 54,000-strong workforce likely to go. Its home state of Delaware, inevitably, will bear the brunt.

Shortly afterwards, news leaked out that the historic DuPont Central Research & Development organisation will shortly pass into history (page 42). Whilst details are still sketchy, there seems no doubt that there will be an impact on the laboratories at Chestnut Run and Experimental Station in Wilmington, which have delivered many of the innovations on which the company's fortune was built over the last century.

There is also no doubt, whatever PR clichés are spouted about 'synergies' and 'innovation', that this merger was driven first and last by financial considerations. And if you won't take that from a cynical British left-winger, take it from the *Wall Street Journal*, which described the announcement of the merger as "the sound of corporate America giving up" or *Fortune's* Adam Murray who said "Unless you are an investment banker, it's hard to feel good about the deal".

Both firms had been labouring under pressure from 'activist' shareholders trying to force through short-term, shareholder-pleasing changes to the board and strategy over the past years. Both seemed to win the battle but lose the war, particularly at DuPont, where Ellen Kullmann saw off Trian Partners' attempts to foist their nominees onto the board at the shareholder AGM but still had to retire abruptly a few months later ahead of bad news on the dividend.

Predictably, neither 'activist' was that gracious about the end result. Third Point's Daniel Loeb



complained that the announcement came a day before the end of a standstill agreement preventing him buying more shares or criticising the firm and called Liveris's appointment as chairman of the combined firm "a slap and an insult to Dow shareholders". Clearly he didn't like a taste of his own medicine...

More depressing, however, was the response of Trian's Nelson Peltz, who said that DuPont's "strategy to

leverage 'integrated science' capabilities has, in our view, led to speculative corporate R&D investments and lacklustre return on invested capital". Um, Nelson, that's the nature of research. You really should know that by now.

Most of the analysis, inevitably too, has been from a financial point of view, with analysts arguing about what the upside is for shareholders. The rest has mostly been about whether the deal will get the go-ahead at all. Certainly regulators will want to take a very close look at it. Shareholders – or to be more precise, those who claim to speak in their name – may also shape the process.

What is genuinely new and interesting is the plan to split 'DowDuPont' into three separate firms focused on material science, agriculture and speciality products (in order of size). Assuming all this proceeds, will they, as Dow and DuPont stated (and as their nemeses said, albeit in a somewhat different context), be able to operate better outside a corporate structure?

The claim is that each new company will be more 'streamlined' and 'focused', yet with a higher market share in the specific areas in which they operate, meaning greater purchasing power and higher margins. They would also have a better financial position, which would enable them to grow and innovate. Assuming, of course, another 'activist' doesn't latch onto them...

What is also certain, it seems, is that the proposed merger will have a big knock-on effect among competitors seeking comfort in size. In agro, a sector troubled by the recent brake on its impressive growth and shedding jobs rapidly, it was already only seemingly a question of who-buys-who.

Will Monsanto finally do a deal with Syngenta which rebuffed it several times already, as noisily advocated by a group claiming to represent the shareholders? The Syngenta chairman admitted in late December that they were in touch and that "going it alone is hardly possible". Or will ChemChina, flush with cash, return to up the ante?

And, as and when that happens, what about BASF and Bayer? And, on a wider scale, will BASF, itself rather quiet after an uncharacteristically aggressive shopping spree a few years ago, seek a major acquisition to bolster its still world-leading position in chemicals? It's going to be a wild ride.

Dr Andrew Warmington
 Editor – Speciality Chemicals Magazine