

ASTRAZENECA LECTURE

Moving drug delivery beyond the “bakery in a pharmacy” stage

The AstraZeneca Industrial Achievement Award lecture was given by Dr Harry Ferres. He described how the manufacturing of drug delivery systems would have to improve in order to bring greater benefits to patients

Manufacturing of drug delivery systems in the 19th century applied cookery techniques like mixing, milling and compression in a pharmacy setting. Current manufacturing applies cookery techniques in a factory. For the 21st century there needs to be a move towards individualised manufacturing from identical components, Dr Harry Ferres, senior vice-president for research and development, GlaxoSmithKline, said during his lecture.

Dr Ferres said that drug delivery systems (DDSs) had to go beyond simply transporting the drug into the body. They were a way of adding value for customers, intellectual property for pharmaceutical companies and showing real benefits to the organisations or governments paying for them. However, he said, there has been a lot of hype about DDSs that has not yet translated into reality.

Many existing DDSs are not target specific. He said that they had been described as being “like flooding a skyscraper in order to put out a fire in a waste paper basket on the 25th floor”.

“Of the two components in a medicine — the molecule and the DDS — it is often the delivery system that is the weakest link,” Dr Ferres added.

He believes that during the latter half of the 20th century only four delivery systems were invented that were real advances and which delivered significant benefits for patients. These were pressurised aerosol devices, modified-release oral tablets, transdermal patches and “stealth liposomes”. “We need to get into customisation of DDSs, achieving cellular targeting and programmed tailored drug release.”

FORMULATION CHANGES

Changing the formulation of a drug could, occasionally, bring benefits for pharmaceutical companies. He cited the example of Cardizem (diltiazem). Moving to modified-release preparations had brought in \$4bn (£2.66bn) of sales after the initial patent expiry. This was not typical for product line extensions and, he said, Cardizem had succeeded because it was in a major chronic therapeutic area (cardiovascular disease), there was a big opportunity for improving compliance by reducing the number of daily



Current manufacturing applies cookery techniques in a factory

doses, the formulations used had been patent protected, there was good timing of the new product's introduction followed by aggressive marketing and there had been demonstrated outcome benefits for patients.

Dr Ferres said that there are currently many restraints on producing better DDSs. These include inconsistent drug substances and excipients (when viewed at a microscopic level), poor correlation between a drug's pharmacokinetic and pharmacodynamic behaviour, outdated tablet designs and gaps in the knowledge of biological targets.

“We are moving towards particle engineering,” he said. This was necessary to overcome inconsistencies in drug substances which are a major problem in formulation and manufacturing. “The solution is to get consistent particles with the same surface properties each time.” A number of techniques are being used for this, including supercritical fluids, nano-milling and power fluidics, “but none of them are as well developed as we need for routine use”.

Drug delivery areas which continue to need development were identified by Dr Ferres as gastro-retention systems (“not there yet”), absorption of proteins and peptides, absorption enhancers, organ and site targeting (“still largely molecule dependent”), and programmed release (“currently physicochemical not pathophysiological”).

In terms of drug release, Dr Ferres said

that systems had moved from immediate-release to controlled-release with some work on chrono-release. Further moves were needed to cascade-release, because some systems such as cytokines have multiple cellular interactions, and finally to tailored-release, optimising pharmacokinetics to pharmacodynamics. The so-called “pharmacy-on-a-chip” systems, which can deliver precise amounts of drug substance on command, have been demonstrated in laboratories, Dr Ferres said, but have yet to be shown to be effective in practice.

In order to be more successful, the manufacturing of pharmaceutical products needs to move in the same direction as the manufacturing of motor cars, Dr Ferres said. At present pharmaceuticals are made by mixing large amounts of substances which may differ in their physicochemical properties from batch to batch. They contain lots of excipients, most of which are

only there to smooth the manufacturing process and do not benefit the patient. Cars are assembled from standardised components, each of which can be tracked through the manufacturing process.

“Individually engineered drug delivery systems will give us tailored-release patterns, multiple therapies in a single tablet and fewer excipients and will require less manufacturing infrastructure. We can adopt techniques from other manufacturing industries to help us with this,” he said.

DIFFICULT ENVIRONMENT

Drug delivery systems need to make a contribution to companies' ability to sell their medicines, Dr Ferres said. The selling environment has become more difficult with downward pressures from governments on the prices of medicines and upward pressures from increased research and development costs.

“Improved delivery systems will be needed for the customised medicines that may result from genomics. These offer the possibility of charging premium prices in what are likely to be individualised and segmented markets.”

In conclusion, Dr Ferres said that future DDSs would need to be “PILLS”: “They will need to be programmed, individualised, localised, lower cost and safer.”