Disappointing biotech

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Biotechnology offered the hope of cheaper and better drugs. Analysis of biotech products licensed in Europe shows the reality is somewhat different

The advent of DNA recombinant techniques and other biotechnologies has raised expectations for more selective drugs. The techniques promise "magic bullets" that are better tolerated because they are more similar to endogenous products and cheaper to make thanks to potential large scale production. Thus biotech products offer a good model for assessing the level of therapeutic innovation of drugs. We assessed the biotech medicines approved by the European Medicine Evaluation Agency from its inception in 1995 to 2003, when the European pharmaceutical law was revised.¹ The agency approved 87 biotech products, corresponding to 65 active ingredients, during this period. Four were approved for diagnostic purposes. How innovative were the 61 licensed with more therapeutic indications?

Innovation of biotech substances

The box shows the 61 active substances classified according to their type of benefit compared with existing treatment or placebo, as appropriate (see bmj.com for details of the indications). We obtained the information from the European public statements, available on the EMEA website (www.emea.eu.int/index/indexh1.htm). Only 15 products represented therapeutic innovation, that is, drugs for diseases without effective treatment, more effective than existing treatment, or active in patients resistant to current treatment. Twenty two offered limited non-therapeutic advantages over existing products (10 in terms of safety and 12 in terms of convenience), and 24 were copycat or me too products.

The products with improved safety include coagulation factors, insulins, and sex hormones, where DNA recombinant techniques theoretically reduce the risk of viral infection compared with old extraction procedures. Examples of drugs that have pharmacokinetic advantages include darbepoietin, peginterferon alfa, and pegfilgrastim, which can be taken once a week instead of three or five times a week like their parent compounds. However, the optimal doses are not well established. Multiple vaccines are also categorised as increasing convenience.

Evidence supporting innovation

Dose finding studies were done for only seven of the 15 innovative substances (figure). Only 11 had their efficacy and safety tested in randomised controlled

trials. Six of the substances were compared with placebo, even though an active comparator was available for three of these (mycophenolate mofetil for basiliximab; sulfasalazine and methotrexate for infliximab in Crohn's disease and rheumatoid arthritis respectively; and glucocorticoids for interferon beta 1b in multiple sclerosis). Four innovative substances were approved on the basis of superiority to active comparators in randomised controlled trials (becaplermin, desirudin, rasburicase, and trastuzumab). Hard end points were used for three drugs (basiliximab, infliximab, becaplermin), although the first two were tested against placebo. One trial of eptotermin alfa against an active comparator used soft end points (clinical healing of the tibia, in terms of stability, weight-bearing, and reduced pain).

The efficacy and safety of tasonermin were assessed in four open label, non-randomised trials and of alemtuzumab in three phase II non-comparative trials. No randomised trial to assess efficacy was done for rituximab, and the evidence for efficacy of pegvisomant came from post hoc subgroup analysis at the time of approval.

At the time the drugs were approved the trial results for only five out of 15 drugs had been published in peer reviewed journals.²⁻⁶ All four orphan drugs were approved on the basis of placebo controlled trials measuring soft end points (pain for algasidase alfa) or

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Methodological characteristics of clinical trials supporting licence application for biotechnological drugs. Numbers in square brackets indicate innovative drugs

surrogate end points (glycosphingolipid reduction for agalsidase beta, suppression of insulin-like growth factor 1 for pegvisomant, and change from baseline forced vital capacity for laronidase).

Poorly assessed poor innovation

These data suggest that biotech substances were often not assessed using rigorous methodological criteria. The small numbers of dose finding studies and controlled trials, especially comparing new drugs with an existing treatment, reflect more general deficiencies in the documentation supporting the applications for marketing authorisation. They give the impression that commercial priorities come before the sound development of drugs in the interest of patients. The licensed innovative drugs often had restricted therapeutic indications, either because they were orphan drugs or because they were tested in small, selected populations. Rituximab, trastuzumab, infliximab, anakinra, alemtuzumab, and tasonermin were all developed for second or third line indications.

The large proportion of drugs copying existing products suggests that market interests predominate in

Summary points

Biotechnology products are considered models of innovation in medical treatment

Only a small proportion of biotechnology products that have reached the European market are therapeutically innovative

Most of the new products were variations on existing drugs

Evaluation of these substances was not always based on rigorous methodological criteria

Biotechnology substances approved in European Union 1995-2003

Innovative

Agalsidase beta
Laronidase
Desirudin
Human protein C
Becaplermin
Pegvisomant
Alemtuzumab
Rituximab
Trastuzumab
Interferon beta 1b
Tasonermin
Basiliximab
Infliximab
Eptotermin alfa
Rasburicase

Me too

Insulin aspart
Agalsidase alfa
Lepirudin
Reteplase
Tenecteplase
Octocog alfa
Human coagulation factor IX
Epoietin beta
Epoietin delta
Follitropin beta
Somatropin
Teriparatide
Calcitonin
Pneumococcal vaccine
Inactivated hepatitis A virus + rDNA
Hepatitis B surface antigen

Safer

Insulin (human)
Imiglucerase
Drotregogin alfa
Eptacog alfa
Morococog alfa
Nonacog alfa
Choriongonadotropin alfa
Follitropin alfa
Lutropin alfa
Hepatitis B vaccine

Interferon beta1a
Interferon alfa 2b
Interferon alfacon 1
Peginterferon alfa 2a
Daclizumab
Adalimumab
Anakinra
Etanercept
Diboterminal alfa

More convenient

Insulin lispro
Insulin glargine
Darbepoietin alfa
Palivizumab
Hepatitis A, B vaccine (adults and children)
Haemophilus influenzae, hepatitis B vaccine
Diphtheria, tetanus, pertussis vaccine
Diphtheria, tetanus, pertussis, hepatitis B vaccine
Diphtheria, tetanus, pertussis, hepatitis B, polio vaccine
Diphtheria, tetanus, pertussis, hepatitis B, polio, haemophilus type B vaccine
Pegfilgrastim
Peginterferon alfa 2b

biotechnology as in other pharmaceutical research. Indeed, most such copies fail to offer new options for patients or public health, providing no advantage, even in terms of cost.⁷

The promises of good tolerability of biotechnology substances have not been met—most are no less toxic than conventional drugs. For example, trastuzumab, which is licensed for the treatment of metastatic breast cancer, is cardiotoxic, particularly in patients previously treated with doxorubicin.⁸ Alemtuzumab and rituximab cause a cytokine release syndrome with fever, chills, nausea, and vomiting.^{9 10} Infliximab may increase malignancies¹¹ and exacerbate tuberculosis¹² while tenecteplase and reteplase induce bleeding and haemorrhagic strokes no less than other available thrombolytics.^{13 14}

One clear difference between conventional and biotechnology drugs is cost. Those produced by biotechnology are generally more expensive, and this deserves evaluation.

In conclusion, the promises of biotechnology substances to be more effective and less toxic than conventional drugs have been only partially fulfilled. Many of the substances produced so far are analogues of existing drugs and have contributed little to innovation in medicine. Nevertheless, biotechnology has made it possible to make available drugs that would otherwise be impossible to obtain in large amounts or research tools that are useful for discovering new drugs. Let us hope that in future biotechnology will better live up to its promises.

Contributors and sources: SG served as a member and VB as an expert on the committee for proprietary medicinal products. VB is a member of the technical scientific committee of the Italian Drug Agency. SG and VB have long experience in pharmacology, clinical pharmacology, and clinical trials. They have collaborated on writing several papers on the evaluation of anti-cancer, cardiovascular, and central nervous system drugs as well as on policy of drug approval. SG had the original idea and proposed the subject; RJ searched and organised all the documentation; all the authors critically evaluated and discussed the data; RJ and VB drafted the manuscript; SG reviewed the paper and is guarantor.

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Simultaneous comparison of multiple treatments: combining direct and indirect evidence

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How can policy makers decide which of five treatments is the best? Standard meta-analysis provides little help but evidence based decisions are possible

Several possible treatments are often available to treat patients with the same condition. Decisions about optimal care, and the clinical practice guidelines that inform these decisions, rely on evidence based evaluation of the different treatment options.^{1 2} Systematic reviews and meta-analyses of randomised controlled trials are the main sources of evidence. However, most systematic reviews focus on pair-wise, direct comparisons of treatments (often with the comparator being a placebo or control group), which can make it difficult to determine the best treatment. In the absence of a collection of large, high quality, randomised trials comparing all eligible treatments (which is invariably the situation), we have to rely on indirect comparisons of multiple treatments. For example, an indirect estimate of the benefit of A over B can be obtained by comparing trials of A v C with trials of B v C,³⁻⁵ even though indirect comparisons produce relatively imprecise estimates.⁶ We describe comparisons of three or more treatments, based on pair-wise or multi-arm comparative studies, as a multiple treatment comparison evidence structure.

The need to combine direct and indirect evidence

Concerns have been expressed over the use of indirect comparisons of treatments.^{4 5} The Cochrane Collaboration's guidance to authors states that indirect comparisons are not randomised, but are "observational studies across trials, and may suffer the biases of observational studies, for example confounding."⁷ Some investigators believe that indirect comparisons may systematically overestimate the effects of treatments.³ When both indirect and direct comparisons are available, it has been recommended that the two approaches be considered separately and that direct

Angioplasty balloon device used to unblock and widen arteries

comparisons should take precedence as a basis for forming conclusions.^{5 7}

Difficulties arise, however, if the direct evidence is inconclusive but the indirect evidence, either alone or in combination with the direct evidence, is not. Furthermore, this approach becomes increasingly impractical as the number of treatments increases. If five treatments have been compared with each other,

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Further details of the method are on bmj.com