The long road of biopharmaceutical drug development: from inception to marketing

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Summary
The development of therapeutics is costly, time-consuming and has high attrition rates. Biopharmaceutical medications differ from traditional agents in their discovery, design, structure and formulation. Prior to marketing a drug must show efficacy and acceptable toxicity in both preclinical and clinical trials. Regulatory bodies have a pivotal role in the licensing, naming and marketing of an agent.

Introduction
The voyage a novel therapeutic agent travels from inception to commercial availability is long and arduous. The development process may last up to 15 years at an estimated cost of over £700 million. Over the last two decades, medicine has witnessed the rise of biopharmaceutical agents, such as monoclonal antibodies, which have revolutionized the treatment of multiple conditions, especially autoimmune disease. Biopharmaceuticals differ considerably from traditional medications in relation to their discovery, structure and formulation. The aim of this article is to familiarize the clinician with the development process and review how a novel therapy eventually becomes marketable.

Drug discovery
History
Ancient civilizations the world over understood the benefits of nature in alleviating ailments, which almost certainly occurred as a consequence of serendipitous discovery. Willow bark, for example, was mentioned in texts from Egypt, Assyria, Sumer and Greece as being helpful for fever and aches; however, it was not until the 19th century that scientists exploited this knowledge to synthesize the active compound. Alexander Fleming himself inadvertently discovered penicillin after observing fungal destruction of staphylococcal colonies. As our understanding of the pathophysiology of disease has increased, a refined approach to drug development has occurred leading to targeted therapies at the molecular level.

Monoclonal antibodies
The production of monoclonal antibodies was first described by Jerrold Schwaber in 1973. The process commences by immunizing mice with the antigen of interest (Figure 1). Splenic cells removed from the animals are then fused to myeloma cells of mouse or rabbit origin which have lost the ability to secrete pathogenic antibody. The resulting hybridoma is diluted and cloned to produce the desired antibody which is tested for its affinity and activity and then finally cultured in high volume.
**Monoclonal antibodies as therapy**

The original therapeutic monoclonal antibodies were murine in nature resulting in a high frequency of allergic reactions. This coupled with suboptimal efficacy led researchers to develop more human friendly chimeric, humanised and fully human antibodies. Chimeric antibodies (60–70% human) consist of a mouse immunoglobulin (Ig) variable region coupled with a human constant zone. Humanized antibodies are 90–95% human with only the residues in the Ig variable region of mouse origin (Figure 2). Production of these antibodies involves merging human DNA, coding for the Ig constant region, with mouse DNA, coding for the Ig variable region. This combined DNA is then placed in expression vectors and inserted into mammalian systems such as the Chinese hamster ovary or mouse myeloma cell lines. Whole antibody molecules can then be produced in a similar fashion to their naturally occurring equivalents.\(^1\),\(^3\),\(^8\) The antibodies are then purified and tested for microbial contamination prior to packaging.\(^8\),\(^9\)

Inherent difficulties exist in biopharmaceutical formulation as the molecules have large molecular weights, are heterogenous mixtures, may be unstable following temperature changes or light exposure and have complex properties (e.g. tertiary structures).\(^2\) In addition, natural variability exists as they are produced in living cells.\(^3\) Large scale production of commercially viable quantities of drug is therefore challenging.

**Pharmaceutical trials**

**Preclinical phase**

Once a compound has been formulated and manufactured, preclinical testing commences. The aim of this phase is to define and analyse the pharmacokinetic and pharmacodynamic properties of the
proposed therapeutic agent as well as its dose effects and toxicity. Given that biopharmaceuticals are highly specific for the target molecule in humans, an equivalent system in an animal model needs to be identified. Thus, initial proof of therapeutic principle is obtained in lower species such as rodents or mice and if successful the agent is then trialled in non-human primates (NHP) such as rhesus or cynomolgus monkeys. Due to the greater immunological homology of NHP with humans, the efficacy and toxicity of therapeutic interventions may be more predictable.

Clinical phase

Once the preclinical phase has been completed, a pharmaceutical agent enters the clinical phase of development which involves testing in human subjects under controlled conditions (see Table 1). All clinical research must be conducted according to guidelines as part of Good Clinical Practice (GCP), which are internationally accepted and provide a scientific and ethical quality standard for conducting research.

Phase I trials

Phase I trials explore the safety, tolerability and pharmacokinetics of a compound, usually in a small number of healthy subjects (40–60 people), to support the progression to patient studies. As this is ‘first use in man’ administration, incremental single doses of drug are used in consecutive cohorts of individuals. If this proves safe, repeated dosing protocols are explored to determine the maximum tolerated dose.

Phase IIa trials

Phase IIa trials are exploratory and are used to obtain preliminary safety and efficacy data in patients which supports the ‘proof of concept’ of a medication. The immunogenicity of the agent is also elucidated at this stage which may not have been apparent in animal models. Results from phase I and IIa trials are critical in deciding whether a drug should be developed further.

Phase IIb trials

Phase IIb trials are dose finding as well as confirmatory studies. Selected doses and regimens are compared to placebo, or standard treatment, in a randomized, double-blind manner. The information gathered is analysed for dose–response relationships, efficacy and tolerability. Confirmation of the appropriate dose is then used to support drug registration.

Table 1 Clinical phases of drug trials in humans

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
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<tr>
<td>Phase 1</td>
<td>Small numbers of healthy volunteers (20–50)</td>
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<td>Safety</td>
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<td>Tolerability</td>
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<td>Pharmacokinetics</td>
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<td>First in man</td>
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<td>Phase 2</td>
<td>Proof of concept (efficacy)</td>
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<td></td>
<td>Larger groups (20–300)</td>
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<td></td>
<td>Safety</td>
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<td>Tolerability</td>
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<td>Immunogenicity</td>
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<td>Dose finding</td>
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<td>Phase 3</td>
<td>Confirmatory</td>
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<td>Multi-centre</td>
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<td>Large numbers (300–3000)</td>
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<td>Compared to gold standard treatment</td>
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<td></td>
<td>Randomized, double-blind trials</td>
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<td>Phase 4</td>
<td>Postmarketing surveillance</td>
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<td></td>
<td>Ongoing safety</td>
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Phase III trials

Phase III trials, extensions of phase IIb studies, help to confirm the efficacy and safety of an agent in larger numbers of subjects. Up to 1000 patients are administered the selected dose, which is compared to placebo or standard of care, in a randomized, double-blind fashion.

Phase IV trials

This stage involves postmarketing surveillance in order to capture any unexpected adverse events or toxicity the medication may have caused.

In total, up to 15 years may be required for a new medication to pass through all four phases of clinical assessment. High rates of attrition exist at each point and for every 10 000 compounds formulated, ~250 enter preclinical testing, and only five enter clinical trials, with approval ultimately being granted to only one agent.

Regulation

Following the successful trial phase of a medication, regulatory approval is mandatory. The Food and Drug Administration (FDA) in the United States is the government authority responsible for this with the equivalent group in Europe being the European Medicines Evaluation Agency (EMEA) (see below). In addition, these bodies play an important role in monitoring the marketing and safety of newly licensed agents.

Based on the data from preclinical studies, an Investigational New Drug Application (IND) must
be submitted to the FDA. In the case of biological agents, a Biologics License Application (BLA) is submitted which includes information regarding preclinical studies, manufacturing information, trial protocols and investigator details. Once the sponsor is ready to market the drug as a therapeutic agent, a New Drug Application (NDA) is submitted to the FDA with an independent expert advisory panel reviewing the data. Once approval has been granted, the agent may be marked only for that sole indication. A new BLA application is required if the medication is to be used in a different clinical context or for a different medical condition.

In Europe, biopharmaceuticals are approved by a centralized process which involves sponsors applying for single marketing authorization. Once granted, it is valid in all European Union states. All medicinal products for human and animal use derived from biotechnology and other high technology processes must be approved this way.

**Naming of agent**

A pivotal step in the development pathway is the naming of the agent. Each compound will end up with three names: the chemical name, derived from its molecular structure; the generic name created prior to the commencement of preclinical studies; and the brand name, for marketing purposes. The manufacturer of the medication requests the generic name which must be approved by the World Health Organisation International Nonproprietary Name (WHO–INN) expert committee. Established guidelines exist for this with high priority given to a name that is suitable for routine use. The sponsoring pharmaceutical company does not own the generic name; however, it does have the right of manufacture until the patent expires (usually 17 years).

The brand name (trademark) is chosen and owned by the manufacturer. The FDA/EMEA must approve this as well as approve the labelling, product and prescribing information and drug advertisements. An appropriate, clear brand name is critical to the success of a pharmaceutical agent.

**The future**

With the mapping of the human genome, the options for therapeutic manipulation have multiplied with up to 120,000 genes coding for myriad proteins. A greater understanding of the genetic basis of disease provides the rationale for individually tailored treatment which in turn, may minimize side effects and maximize efficacy.

**Conclusion**

The process of drug discovery and development has dramatically altered over the last few years. As our understanding of disease pathogenesis evolves and molecular tools advance, we also see the development in the refined approach to therapeutic intervention. This has fashioned in the era of biopharmaceuticals to treat a host of conditions. The development process, however, from inception to marketing, is lengthy requiring substantial infrastructure incurring great cost. In spite of this, research is burgeoning which holds great promise for individualized therapeutic intervention.

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**References**


