HMRC internal manual

Corporate Intangibles Research and Development Manual

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Back to contents

CIRD81920 - R&D tax relief: conditions to be satisfied: DSIT Guidelines - application to pharmaceuticals

Companies in the pharmaceutical industry that undertake research and development into potential new drugs have to conform to the regulatory processes of the countries in which they wish to market the drug. There are four basic stages in pharmaceutical R&D, these are summarised below.

The four basic stages

1. Drug Discovery

This is the earliest stage of the pharmaceutical research process, where potentially useful compounds (referred to as new chemical entities or NCE's) are identified. This stage involves drug synthesis, biological testing and toxicology studies. Developments such as 'high throughput screening' (robotic screening systems that check thousands of molecules per day for particular characteristics), have aided this process tremendously. The process may involve searching huge 'libraries' of compounds for any that might have helpful biological activity - researchers can then select compounds for further testing.

2. Preclinical Development

This stage involves the initial development of candidate NCE's. The NCE will be the subjects of further laboratory tests in vitro and on live animal subjects, to further establish its properties and effects. The company will be planning how it is to test and trial the NCE, how it is to source any substances it needs to produce sufficient quantities of the compound for trials, and how it is to approach the regulatory authorities. It will establish a structured and managed plan to test the compound and to present the compounds test data and report findings at the most optimal time and in the most appropriate format. At this point pharmaceutical companies usually give NCE's a code name prior to selecting a brand name.

3. Clinical Development

Clinical trials are initiated when an NCE identified from laboratory research shows promise as a therapeutic intervention. Such potential drugs are tested on human subjects. This takes place in three stages. Phase I to III clinical trials are necessary before a medicine can be licensed as safe, effective and of good quality by the relevant regulator, for example the MCA (Medicines Control Agency - UK), EMEA (European Medicines

Evaluation Agency - EU) or FDA (Food & Drugs Administration - USA).

- Phase I strategic work is often referred to as ‘situation analysis’. Investigations are conducted into how the drug is absorbed, how it is distributed to tissues, how it is metabolised and how it is excreted. This is assessed by administration to small numbers of healthy volunteers. This stage establishes the maximum non-toxic dose levels and the most common adverse events.
- Phase II intends to assess preliminary efficacy evaluations in small numbers of patients suffering from the target disease or condition. It establishes the dose-response effect, further common adverse events and a benefit/risk assessment. Key strategic marketing decisions and early branding work also commence at this point. Evaluation of data from the R&D, commercial and marketing teams culminates in the formulation of the product profile and strategic summary documents. Brand name research and logo development takes place towards the end of phase II and continues into Phase III.
- Phase III is the largest definitive investigation and involves comparative efficacy and tolerability studies in a large number of patients suffering from the target disease. Concurrent marketing analysis is conducted and concentrates around developing the brand character, the value proposition and early positioning work. Many other programmes, such as pricing, packaging and sales pitch, are decided at this time. Creative development strategy and concept testing is completed just prior to launch. As the largest of the pre-registration studies, Phase III trials consume the most resources, often employing armies of investigators and monitors.

It is largely on the results of Phase III studies that the efficacy and tolerability profile of a new drug is established. Regulatory dossiers are compiled containing chemical, pharmaceutical and

biological documentation, results from Phase I-III trials and special particulars relating to that drug. Once the dossier is filed with the licensing authority, a decision may take some time especially if the regulatory authorities request clarification, further data and/or an audit of investigational sites and procedures.

Between the time of filing and the granting of a product licence, further clinical trials may be required. These trials are sometimes described as 'Phase IIIb' (post-submission but pre-registration). When the product licence is granted, the drug can be launched and marketed to prescribers.

4. Post Launch

Phase IV trials occur once a product has been licensed. A medicine may cause as yet unknown side effects that are only recognised in such instances; similarly, a medicine may cause previously unknown effects by interaction with other medicines. Thus Phase IV involves post-marketing confirmatory studies; special interest studies in patient subgroups; longer-term efficacy, tolerability and safety profile assessment; further comparative studies; and monitoring of adverse events in widespread use.

Studies of a product will continue throughout its life, focusing on customer and prescriber issues such as positioning, behaviour, perception, satisfaction and loyalty.

Use of these stages in deciding whether R&D is taking place

It seems to be the case that the research activities of discovery, pre-clinical development and Phase I to III trials will usually be concerned with the resolution of scientific and technological uncertainty, but that Phase IV trials will not. Experience has shown that this is generally an appropriate starting point for examination of claims from pharmaceutical companies. But if there are unusual circumstances meaning R&D is done in Phase IV trials, or not done in some

elements of Phase I to III trials then this can be examined further.

Some of the work within the phases will not qualify for R&D tax relief. For example the brand name research and development work referred to in the description of the Phases above is clearly not a part of the resolution of the scientific uncertainty.

Companies can produce generic versions of existing drugs that are losing patent protection. They may only need to demonstrate that their product shows bio-equivalence and has equal clinical safety to the existing product. This will not therefore have the same uncertainties to resolve.

What is important with every claim is that the company claiming can demonstrate by reference to what it has actually done that the expenditure is incurred on research and development as defined by the DSIT guidelines.