University of Strathclyde Glasgow

CANCER RESEARCH UK

# Cancer Research UK Formulation Unit

## Strathclyde Institute for Pharmacy and Biomedical Sciences

*Together we will beat cancer*

# Welcome and Introduction

Welcome to the Cancer Research UK Formulation Unit within Strathclyde Institute of Pharmacy and Biomedical Sciences at the University of Strathclyde. The Unit was established within the Department of Pharmaceutical Sciences in 1983. This initiative was based on the Department's experience in the manufacture of small volume injectable products, its established clean room facilities and pharmaceutical science research portfolio.

This unique move was designed to provide Cancer Research UK (previously Cancer Research Campaign) with facilities to formulate and manufacture experimental anti-cancer drugs for initial clinical trials in patients. In 2008 new facilities within the Strathclyde Institute for Pharmacy and Biomedical Sciences were licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) to manufacture and import investigational medicinal products for human use in accordance with European Union Clinical Trial Regulations.

For more information go to www.strath.ac.uk/cancerresearch

# Role

The Cancer Research UK Formulation Unit is a unique academic facility with an international reputation for the pharmaceutical research and development of new anti-cancer drugs.

Compounds are selected by the New Agents Committee of Cancer Research UK. Initial research is aimed at characterising the raw material then determining a suitable formulation for toxicity testing and clinical trial. A manufacturing method is established for the product, which is then subjected to stability tests, to allow shelf life determination and the initiation of toxicity testing. Further batches are then manufactured for use in clinical trial. The material is despatched to the participating clinical centres in the United Kingdom whilst stability studies continue. Since the compounds possess a diversity of properties, a wide range of formulations has been produced, ranging from injectable solutions and lyophilised materials to emulsions and liquid fill capsules.

Bench to Bedside

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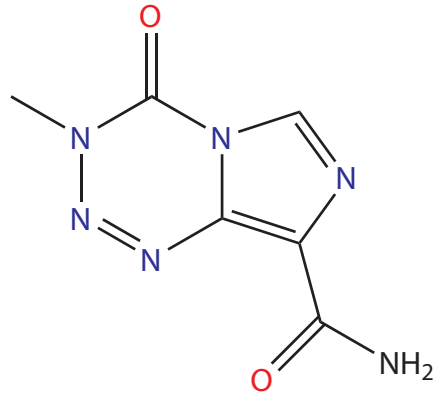
## Statistics

Since inception the Unit has handled around 100 compounds and manufactured over 1,000,000 product units. Several of the compounds have been passed on to international pharmaceutical companies for further development and are now available worldwide for the treatment of cancer, for example temozolomide marketed as Temodal™ by Schering Plough.

The Formulation Unit is entirely funded by Cancer Research UK, has a staff complement of 20, an annual budget around £1 million and performs pharmaceutical research on up to 8 compounds annually.



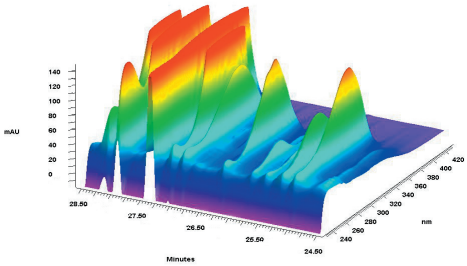

It is involved in the pharmaceutical control of up to 15-20 compounds in clinical trial and deals with Cancer Research UK Clinical Centres throughout the United Kingdom. In addition the Unit also liaises with the National Cancer Institute of USA in Bethesda and the European Organisation for Research into the Treatment of Cancer in Amsterdam, on the pharmaceutical development of putative anti-cancer agents.

# Analysis

Once a new drug substance arrives in the Unit it must undergo analytical testing. This involves the development of methods to confirm its identity, purity and quality. These tests include detection of possible impurities such as synthetic intermediates and manufacturing reagents (including solvents and heavy metal catalysts).

Through a series of tests designed to assess the suitability of the material for human use, a Certificate of Analysis for the raw drug is established. The assessment criteria are based upon the available pharmacopoeial guidelines, the route of administration and clinical requirements of the drug.

A similar testing regime is applied to (the final packaged) drug product to ensure consistency between manufactured batches.




Above shows an example of a PDA-HPLC trace which helps establish a drug's impurities.

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## Formulation

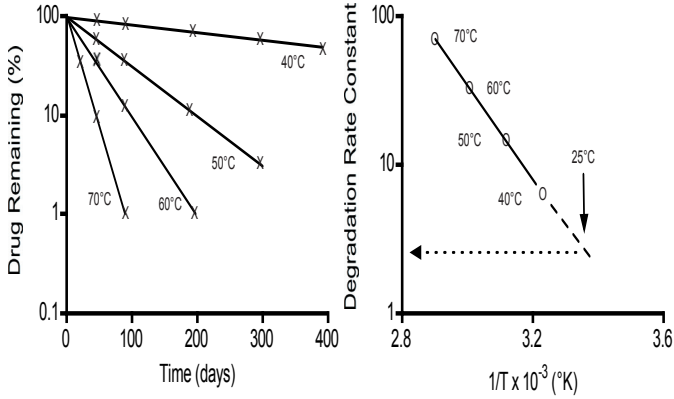
The formulation of a new drug is a key step in its conversion from the chemist's powder to clinical reality. There are two main stumbling blocks in this process: poor aqueous solubility and poor chemical stability. Unfortunately, the majority of new anti-cancer drugs possess one or usually both of these problems! Aqueous solubility can be improved by employing solubilising agents such as biocompatible solvents and surface active agents or through special formulations such as liposomes.

Chemical stability can be enhanced through careful examination of the degradation process to determine the route. Removal of the driving force for degradation leads to improved stability. For substances which undergo hydrolysis (i.e. degradation by water) freeze drying (lyophilisation) removes the water and greatly improves stability.

In one case formulation required the utilisation of two solvent systems and lyophilisation. One solvent was used to dissolve the drug initially, it was then lyophilised from this solvent and finally just before administration it was re-dissolved in a second solvent to provide the final formulation.

Every patient must receive the same medication and an important feature is the formulation's (new agent's) stability during storage. To ensure stability all formulations are subjected to accelerated and real time stability testing.

Current EU guidelines recommend testing at 25°C (50% relative humidity) equivalent to real time and 40°C (75% relative humidity) equivalent to accelerated or stressed conditions. To simplify testing the Unit excludes light unless the molecule is known to exhibit photostability problems. Conditions are modified however to suit the properties of individual formulations.




Real time cannot be accelerated nor recaptured! Stability testing is therefore an important stage, product instability could delay entry into clinical trial. In addition the small scale nature of early formulations necessitates that each batch may be different, requiring at least real time monitoring of every batch to ensure stability.

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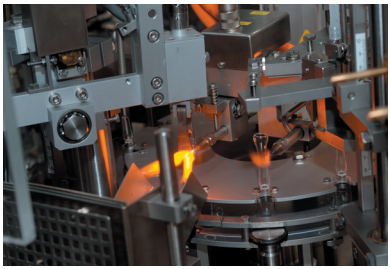
# Manufacture

After analysis and formulation, drugs handled by the Unit have to be manufactured on a suitable scale. For stability studies and early clinical trials the quantity required is low at no more than 100-1000 units per batch.

At the lower end of the scale, automated equipment is not available so all manufacturing steps are conducted manually. This ranges from the initial washing of glassware and re-usable items through to the filling and sealing of the formulation in its final container. Once the needs of the batch become greater the Formulation Unit have the facility using semi-automated equipment to prepare ampoules, vials and capsules.



On average the Unit manufactures over 25 batches of product per annum.
Once prepared each batch of product is then quarantined until it has passed various quality control tests.

# Regulatory

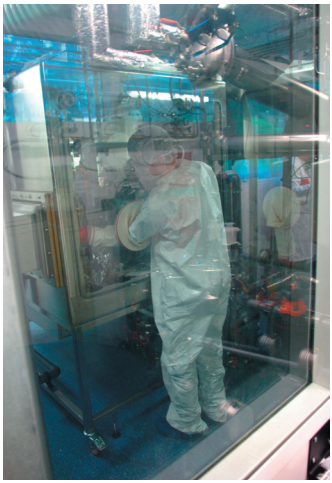
The Formulation Unit is licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) to manufacture and import investigational medicinal products for human use.

The regulations that the Unit must comply with are uniform throughout all manufacturers of medicines for human use. The same regulations must be followed by small manufacturing facilities like the Formulation Unit, to large pharmaceutical manufacturers.

The Formulation Unit is inspected every two years by the MHRA to certify that all work carried out complies with Good Manufacturing Practice (GMP). The objective of GMP is to ensure that products are consistently produced and controlled to particular quality standards.

The Formulation Unit has staff trained in Quality Assurance and Regulatory Affairs, and these staff members ensure that current regulations in manufacture are employed.

# Clean Rooms



The Formulation Unit specialises in the preparation of small volume parenteral (injection) products. These products have demanding quality parameters and for example must be sterile to protect the patient.

To ensure stability the products are manufactured in specialised "Clean Rooms". These rooms are supplied with filtered air to remove any micro-organisms and the operators wear protective clothing to prevent human contamination of the atmosphere.

In addition manipulations are conducted in cabinets in a continuous stream of filtered air to provide further product protection.

The atmosphere inside the rooms is continuously monitored and cleaned to ensure freedom from contamination.

# Distribution

The Formulation Unit does not treat patients, therefore all products must be delivered to Cancer Research UK Clinical Centres spread throughout the United Kingdom.

Cancer Research UK has around 20 clinical oncology centres, ranging from the Beatson in Glasgow to Queen Elizabeth in Birmingham and the Marsden in Surrey. Drugs are therefore despatched to all parts of the UK and even in one case as far afield as Auckland in New Zealand.


On average the Unit despatches product to a clinical centre every two to three days. This requires close control to ensure that all products are monitored, stored and correctly transported. In addition product in the field must be supported to ensure that expired product is recalled or destroyed.

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# Facility Plan