

The importance of good laboratory notebook practice

Take note. Poor laboratory notebook documentation could cost you! Your laboratory notebooks can be critical in establishing your rights to an invention.

The importance of a well-kept laboratory notebook will not be news to those who work in a highly regulated environment, such as the pharmaceutical industry where regulatory bodies, including the Therapeutic Goods Administration (TGA) or the United States Food and Drugs Administration (USFDA), require all aspects of research, development and manufacture of products to be fully documented for compliance with good laboratory and manufacturing practice. However, not all scientific environments expect such a high level of documentation and researchers in these areas have not always adhered to good laboratory notebook practice.

There are many reasons to accurately record the date and details of the formation and development of your research, one of the most important being that a laboratory notebook can be vital in establishing patent rights, particularly in the United States (US), where a laboratory notebook may be admitted as evidence of inventive activity. Any laboratory notebooks relied upon as evidence will be subject to thorough inspection and, if not appropriately kept or witnessed, will be given little or no weight in establishing rights to a patent.

In Australia, as in most countries, we have a 'first to file' system, which means that the right to the grant of a patent lies with the first person to file the patent application for protection of that invention, regardless of the date on which the invention was actually made.

In the US, there is a 'first to invent' system, where priority of invention is awarded to the person who can establish that they made the invention first according to a relatively complex priority of invention calculation. Essentially, in this system, the act of invention is considered to comprise two steps: 'conception' and 'reduction to practice'. The conception of the invention has been described as the formation in the mind of the inventor of a definite and permanent idea or concept of invention as it is to be applied in practice. The reduction to practice of the invention can consist of either actual reduction to practice of the invention, which involves building, performing or testing the invention and checking that it works for its intended use, or constructive reduction to practice, which is the filing of a patent application.

In the US, the question of who is the first to invent can arise during interference proceedings at the US Patent and Trademarks Office (USPTO). During interference proceedings a person can defeat another person's claim to an invention by establishing, through evidence, an earlier date of conception together with diligence* in reducing the invention to practice. Laboratory notebooks usually form part of the evidence, which can help establish the date of conception and diligence. Importantly, Australian applicants of a US patent have the same right to rely on the earlier date of invention in an interference proceeding and, therefore, it is critical that researchers ensure that their laboratory notebooks are sufficiently detailed and the details correctly recorded to support the date of conception, and diligence in reducing the invention to practice.

Essentially, to prove conception of the invention, the inventor should ensure that there is a full written description of the inventive concept. If the invention is a nucleic acid or a chemical compound, the doctrine of 'simultaneous conception and reduction to practice' is likely to apply in the US. This doctrine states that an inventor is unable to establish conception until the invention has been reduced to practice through a successful experiment. Therefore, for the purpose of proving conception and reduction to practice for biological and chemical inventions, the laboratory notebook will need to include details of the structure of the invention, and how to synthesise or isolate the substance.

There have been many instances in the US in which a patent was granted to an applicant who filed second because the second applicant was able to prove (with evidence, such as laboratory notebooks) that they had conceived the invention first and were diligent in reducing the invention to practice. A well-known and costly example is in the case of Yeda Research and Development Company Ltd. ('Yeda'), who sued ImClone Systems and Aventis Pharmaceuticals,† alleging that three scientists from Israel were the true inventors of ImClone Systems' cancer drug Erbitux. The court held that the three scientists from Israel were the real inventors, who should be named in the patent, and that there was no documentary evidence suggesting that any of the other named inventors had made inventive contributions. As a result, in December 2007 ImClone Systems signed a set-

tlement agreement with Yeda to end worldwide litigation related to the US patent in which Yeda received US\$120 million and ImClone Systems were granted a worldwide licence to the technology.

An example of where poorly kept records played a part was in the case of *MediChem S.A. v Rolabo S.L.*,[‡] in which the rights to a novel process for making loratadine (a tricyclic antihistamine) from two precursor chemicals by a chemical reaction that yielded diols and alkenes was disputed. Medichem's claimed process required that the reaction be carried out in the presence of a tertiary amine while Rolabo's process permits by not excluding, but does not require, the presence of a tertiary amine. In other words, the Medichem invention was a subset of the Rolabo invention. Rolabo filed its patent application prior to Medichem, and Medichem attempted to prove reduction to practice prior to their filing date. Initially, the judgment found in Medichem's favour but this was reversed by the US Federal Circuit who disagreed that Medichem had proved an earlier reduction to practice. Medichem sought to rely upon laboratory notebooks which were unsigned and therefore held to be of minimal value. Furthermore, Medichem did not help their cause as it was found that they had fraudulently backdated some of the documents relating to the reduction to practice. Specifically, it was held that although the NMR spectra of loratadine relied upon by Medichem may have been sufficient to support a claim to a compound, it was insufficient to substantiate a claim to a process of actually making that compound.

As a minimum, good laboratory notebook practice should include the following:

- To ensure entries cannot be inserted or removed, the laboratory notebook should be bound with printed consecutive page numbers.
- All entries should be recorded in chronological order and each experiment should be dated when started and when completed.
- Entries should always be in permanent ink and if a mistake is made the pages should not be ripped out or defaced; one line through the error is sufficient (no correction fluid should be used).
- If corrections are required, it is preferable to make the correction on the current page and reference the earlier page and indicate why the correction was required. No signatures should ever be backdated.
- Any attachments (e.g. instrument printouts or photos) should be stapled or stuck into the notebook and signed and dated across the attachment and the underlying page.
- There should be no blank space on any page; any blank space should be crossed out.

- Once the page is finished, it is important that it is signed and witnessed by a third party who is capable of understanding what has been written. It should then never be added to or amended. The witness should not be a co-inventor.
- Laboratory notebooks should be kept for the 20-year term of protection of the patent and for at least another five years, as some pharmaceutical and biotechnology patents are eligible for an extension of term of the patent, giving a total term of up to 25 years.

It is now theoretically possible to keep a laboratory notebook electronically; however, certain precautions are needed to increase the likelihood that such electronic records would be taken into account in a patent interference proceeding. As a minimum, any electronic system must reliably identify who created the record and the date the record was created, and have a means of ensuring that the record cannot be amended without electronically recording the fact. In other words, the electronic system must ensure that no one (not even the owner of the document) can modify it once it has been saved (e.g. using trusted time date stamping). Significantly, USPTO has not yet recognised electronic laboratory notebooks in patent interferences, and USFDA has not accepted electronic notebooks when applying for approval of a new drug or in other regulatory processes. Therefore, a hard copy of all electronic records should be kept until electronic data is accorded the same legal status.

In summary, good laboratory notebook practice will always be important regardless of industry or purpose. In the case of patent applications in the US, or at least in cases where the US is considered an important market for the invention, it is vital that good laboratory notebook practices are followed to ensure that during a dispute an inventor has the best possible chance of being awarded the right to their invention with the earliest possible date of conception.

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*Diligence of the inventor to reduce the invention to practice after conception is also important in determining who is the first to invent. For example, if the inventor who first conceives the invention does not reduce it to practice until after the second inventor, the second inventor may still be considered to have made the invention first if the inventor who conceived the invention first was not diligent in reducing the invention to practice following its conception. In addition, abandonment of an invention following conception or reduction to practice can also lead to loss of rights to the invention.

[†]*Yeda Research and Development Co v ImClone Systems Inc* (2006) 03 Civ 8484.

[‡]*MediChem SA v Rolabo SL* (2006) 437 F3d 1157 1169.