FROM THE ANALYST'S COUCH

Phase II and phase III failures: 2013–2015

Richard K. Harrison

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Understanding the reasons for clinical failure is essential for decreasing attrition in clinical development. With this in mind, we examined the reported causes of drug candidate attrition by clinical development phase and by therapeutic area for the period 2013–2015 (*Drugs Today* **52**, 131–163; 2016).

During this time period, there were 218 reported failures between phase II (including phase I/II) and submission (each drug indication combination is considered as a separate record and both new active substances and new indications of marketed drugs are included in the analysis). Of these failures, 174 had stated the reason for the failure and these were used in the subsequent analysis.

Reasons for failure

The majority of failures were due to a lack of either efficacy (52%) or safety (24%), where safety includes those failures that were due to an insufficient therapeutic index (FIG. 1a). Strategic (15%), commercial (6%) and operational (3%) reasons were cited for the remainder of the failures. The breakdown by therapeutic area (FIG. 1b) shows that the highest percentages of failure were in oncology (32%), central nervous system (CNS) diseases (17%) and musculoskeletal diseases (13%), with additional contributions from cardiovascular (7%), alimentary (7%) metabolic (6%) and infectious (5%) diseases.

The higher proportion of failed trials for oncology and CNS diseases may simply reflect the greater number of trials for these indications compared with other therapeutic areas. Data from Cortellis Clinical Trials Intelligence show that the numbers of phase II or phase III trials started in 2013–2015 for oncology (5,821) and CNS diseases (2,796) were substantially higher than the approximately 2,000 or fewer for all other therapeutic areas for the same time period. The high number of failures in both of these therapeutic areas might also reflect the complex and heterogeneous nature of the diseases.

Examining the data by stage of development (FIG. 1c,d) shows that the failures in phase II were primarily due to insufficient efficacy (48%) or safety (25%) and, combined, these represent 73% of all phase II failures. Similarly, insufficient efficacy was the primary reason for failure in phase III (55%), followed by safety (14%). Although the decrease in late-stage failures for safety is encouraging, one would hope that for an industry becoming better at 'failing early', the proportion of compounds failing owing to insufficient efficacy would have been lower for phase III than for phase II, but this was not observed.

Failures for strategic reasons such as a change in therapeutic focus or being dropped owing to mergers represent 21% of all phase II terminations and 14% of all

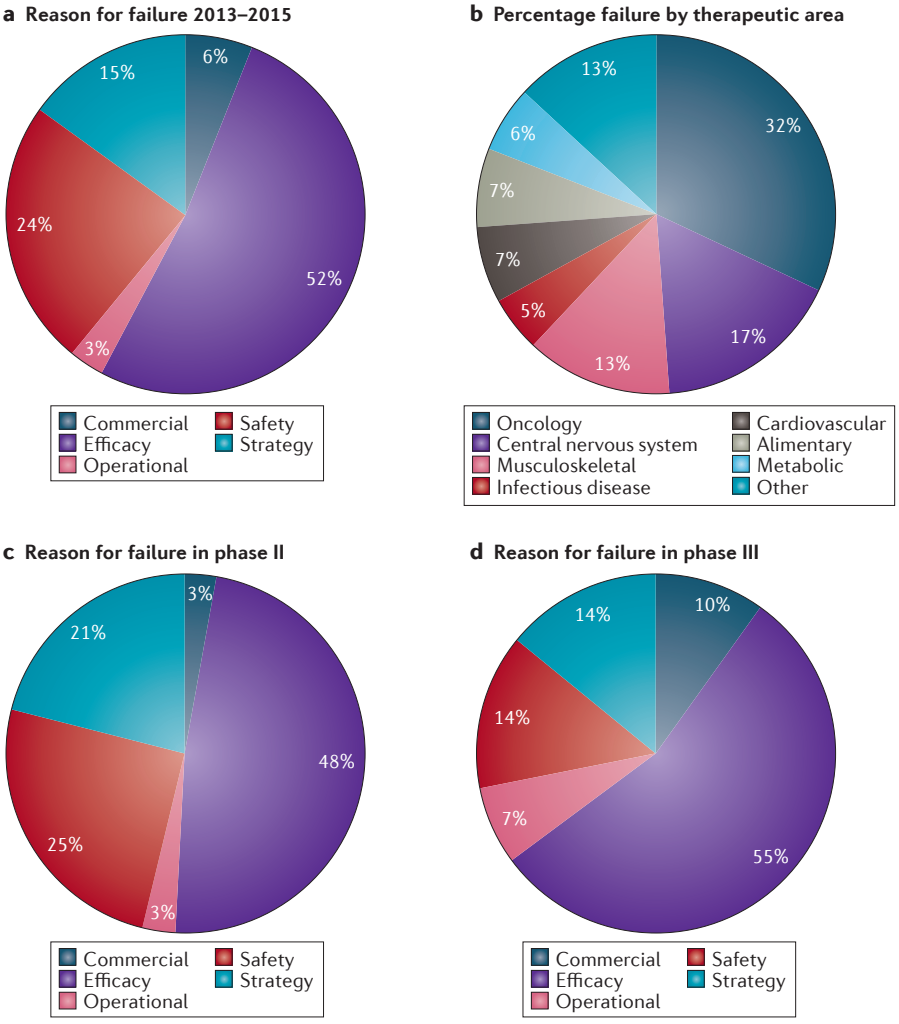

Figure 1 | **Reasons for clinical trial failures 2013–2015.** The pie charts illustrate the reason for failure for phase II and phase III trials for which a reason for failure was reported for all 174 clinical trials (part **a**), according to therapeutic area (part **b**), in all therapy areas for phase II only (part **c**) and in all therapy areas for phase III only (part **d**). Data are from Thomson Reuters and Drugs of Today (©Prous Science S.A.).

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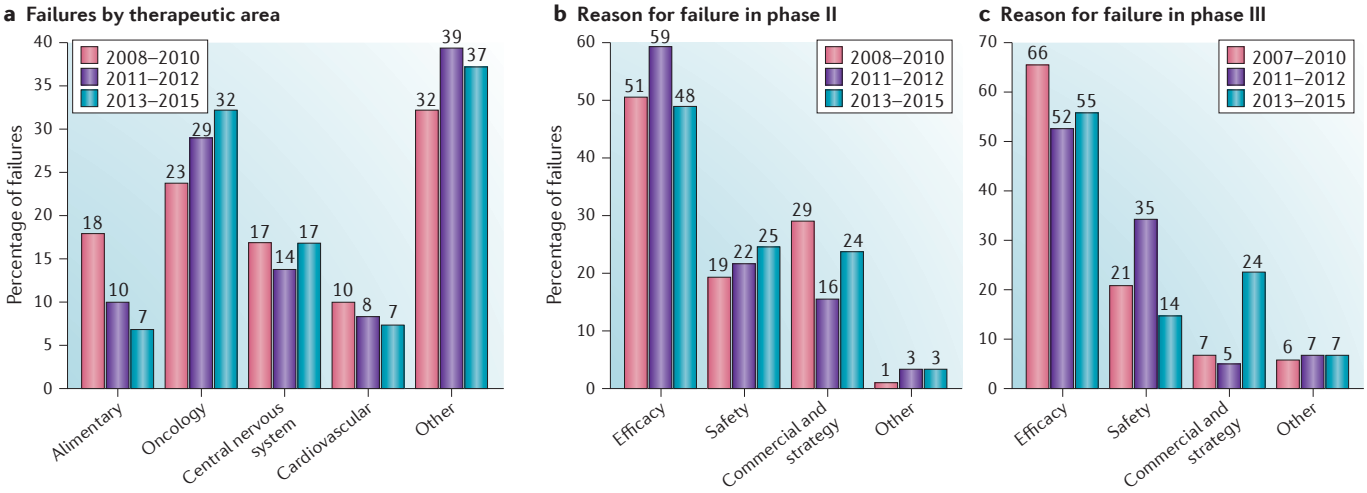

Figure 2 | **Recent trends in clinical trial failures. a** | The combined percentage of phase II and phase III clinical trial failures in the three periods indicated by the colour codes, subdivided according to therapeutic area. **b** | Reasons for failure in phase II clinical trials. **c** | Reasons for failure in phase III clinical trials. In each panel, the total data for each colour-coded time period represent 100% of the reported failures in that time period. Data are from Thomson Reuters and Drugs of Today (©Prous Science S.A.).

phase III terminations. This may reflect the increase in mergers and acquisitions occurring in the industry. Data from Recap (see Further information) show that the number of mergers and acquisitions has nearly doubled in the past 4 years (from 248 mergers and acquisitions in 2012 to 468 mergers and acquisitions in 2015) and it can be argued that as more mergers occur there would be a greater number of duplicate or competing projects that merging companies would be forced to drop, or that with these mergers comes a change in therapeutic area focus. In addition, the observation that only 3% of phase II failures as opposed to 10% of all phase III failures are for commercial reasons suggests that the lower cost of phase II trials outweighs the commercial risks, but the increased cost of phase III trials requires a more stringent cost-to-benefit analysis.

We compared these data with those from previous periods, using analyses that covered failure rates in 2008–2010 (*Nat. Rev. Drug Discov.* **12**, 328–329; 2011) and 2011–2012 (*Nat. Rev. Drug Discov.* **12**, 569; 2013) to identify trends in attrition by therapeutic area and stage of development. The percentage of failed trials is changing for each therapeutic area over time (FIG. 2a). Oncology had the greatest number of failures overall and the percentage of failures in oncology increased from 23% in 2008–2010 to 32% in 2013–2015. The greatest decrease was seen in the proportion of failures for alimentary diseases, which changed from 18% of all failures in 2008–2010 to only 7% in 2013–2015.

Looking at the historical trends by phase of development, insufficient efficacy has consistently been the most common reason for failure in phase II trials, accounting for around half of all reported failures in each period (FIG. 2b). Insufficient efficacy has also been the major reason for failure in phase III trials (FIG. 2c), and accounts for more than half of all reported failures in each period. Comparing the 2008–2010 period with 2013–2015, the proportion of efficacy failures in phase III trials decreased by 11%, and the proportion of safety failures decreased by 7%, while the proportion of failures for commercial and strategy reasons increased substantially from 7% to 24%.

Summary and outlook

We observed a number of changes in the frequency of reasons for termination of phase II and phase III clinical trials over the past 7 years. Efficacy is still the greatest reason for failure, but we are hopeful that this can change as trial populations are increasingly stratified using efficacy biomarkers and understanding of disease biology and target selection improve. Although the proportion of failures due to safety is increasing for phase II trials, it is decreasing for phase III trials, which suggests that efforts to remove unsafe agents earlier in the development cycle are paying off. Data from CMR International (see Further information) show that success rates for advancement to the next stage of development are slightly increasing. In 2010–2012, only 20% of compounds from a cohort of 40 large and mid-sized pharmaceutical companies advanced from phase II to phase III, whereas in 2013–2014 the proportion of compounds advancing from phase II had increased to 25%. The corresponding rates for progression from phase III also increased slightly, from 55% in 2010–2012 to 58% in 2013–2014. Finally, the rates of success at the regulatory review stage also increased, from 84% in 2010–2012 to 91% in 2013–2014. Overall, these trends are encouraging for the pharmaceutical industry and for patients.

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Competing interests statement
The author declares no competing interests.

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