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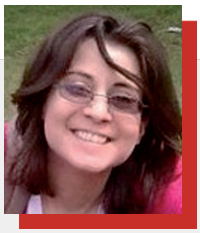

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Lead optimisation funnel diagrams

Visual aid to process improvement, realistic goal setting and resource management

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KEYWORDS

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ABSTRACT

This article discusses how Funnel Diagrams can be used to make a positive impact on your lead optimisation projects. Topics include: spotting process bottlenecks, confirming the successful impact of process changes, gaining insights into how achievable a goal is, taking a glance at how resources are split across multiple projects and assessing resource needs. Two example lead optimisation projects that are at different stages are used to illustrate the funnel applications. An error bar extension to the original visualisation is presented.

INTRODUCTION

There has been much discussion and debate on the exact cost of inventing a new drug, as highlighted by a recent article from Forbes (1). Although an exact figure cannot be agreed upon, it is clear that launching a drug is a very long and costly task. Lead optimisation has been estimated to be the most expensive phase within drug discovery and development when taking capitalised costs into account (2). Process improvement in lead optimisation therefore has the potential to have a large impact on the industry's productivity, as long as it is ensured that scientific innovation is not inhibited (3). The effect of process improvement work on people's motivation and therefore scientific creativity and innovation needs careful consideration (9-12). It is important to consider not only what is measured, but also how it is used.

Several successful applications of continuous improvement strategies to lead optimisation have been published (4-8). Here, we take a look at how the Funnel Diagrams (8), a previously developed process improvement tool, can be used to retrospectively review projects to help set realistic achievable goals and therefore impact motivation in a positive way. Another application of the funnels that will be presented is as an aid to resource management across active drug discovery projects within a company's portfolio.

THE FUNNEL DIAGRAMS

The analogy of a funnel can be applied to the research and development process. The broad opening at the top represents the vast number of compounds tested within research and the narrow neck represents the few compounds that make their way in to development and then hopefully on to the market. This analogy gave inspiration to the design of the Funnel Diagrams, which extend this funnel-like representation to simultaneously visualise attrition and timelines (8).

A Funnel Diagram is composed of several funnels. In each of the two Funnel Diagrams presented herein (Figures 1 and 2) a sequence of six funnels is used to represent a six month time shot of a lead optimisation project.

A single funnel represents how compounds newly synthesised within a particular month travel through the assay cascade. Note that the most recent month is shown on the left, in order to be able to see the most recent data first when viewing longer trellises of funnels. The top of each funnel starts with a red rectangle whose width represents the number of new compounds. The remaining rectangles represent other events being tracked through the cascade with their widths again representing quantity (also written to the right of each rectangle). For example in March for project A (Figure 1) 47 new compounds were synthesised. All of which went through assay 1, 44 through assay 2, and so on with just 2 going through assay 6.

The distance between a rectangle and the top of the funnel represents the average time from compound synthesis to that event (also written to the left of each rectangle in calendar days). Hence the y-axis represents time with a linear scale above the 3 month dashed border and no scale below the border.

For more details on this funnel architecture see the previous publication (8).

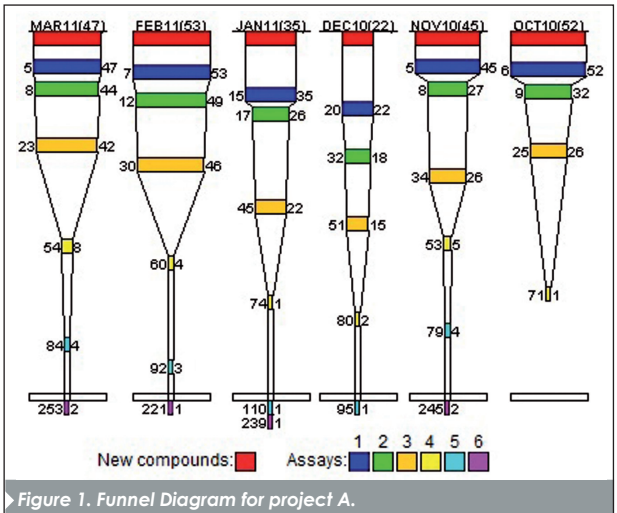

Figure 1. Funnel Diagram for project A.

Looking again at project A's March funnel, it took an average of 5 days from compound synthesis for assay 1 to be performed, 8 days for assay 2 and 23 days for assay 3.
In project B (Figure 2) notice the error bars that are displayed for assay 1, illustrating how the funnels can be extended to show variation in time.

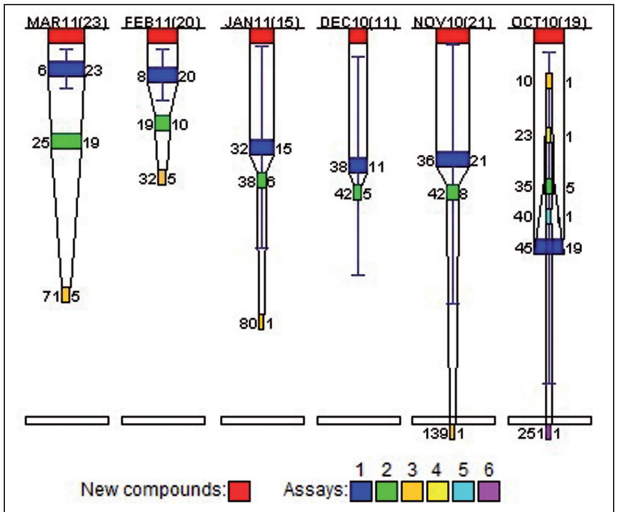

Figure 2. Funnel Diagram for project B with Assay 1 error bars.

PROCESS IMPROVEMENTS

Funnel Diagrams provide useful insights into process improvements. They can be used to identify bottlenecks and then later confirm whether these bottlenecks have been successfully removed after process changes have been made.
The diagrams were successfully used at Prosidion to make a positive impact on lead optimisation (8).

A potential process improvement can be seen for project A (Figure 1). The funnels show that the majority of compounds in February and March, 87 and 89 percent respectively, passed successfully through assays 1 and 2 into assay 3. This is an indication that the project has overcome a monitored selectivity issue. Due to the high success rate of assays 1 and 2, it makes sense to run assays 1, 2 and 3 in parallel, rather than keeping them in a sequential queue. This could reduce turnaround time by 2 to 3 weeks.
Project B's Funnel Diagram shows how a process improvement has already been made. Between October and January it took on average just over a month to get results from assay 1. This was because the assay was in its infancy and was still being optimised. By February assay optimisation was complete and this bottleneck was removed with results now being obtained within a week. Note the large error bars from October through to January, showing that the assay was still under development with infrequent runs and highly variable time. The error bars for February and March are much smaller due to the assay being consistently carried out within a week. Although the funnels would not have made a direct impact on the removal of this bottleneck, since assay optimisation is a natural process, they would hopefully have given the scientists involved in the optimisation a sense of pride in the importance of their work and the impact it has had.
A question highlighted for project B is: why does the time delay between assay 2 and 3 vary so much? October's funnel is an anomaly with assay 3 occurring 25 days before assay 2. The funnel folds back on itself due to assays being performed in a different order for one particular compound (a standard that was simultaneously entered into assays 1 to 5). The peaks and troughs in the time delays between November and March are caused by assay 3 only processing plates once they are full. Hence compounds in November and January's funnels had to wait until February's compounds were submitted. In March there was a delay again whilst waiting for further compounds to fill up empty wells. The process improvement suggestion here would be to not wait for plates to fill up and run the assay every month regardless.

Partially empty plates could also be filled with compounds that did not pass the previous assays, resulting in a greater understanding of the structure activity relationship around the third assay.

SETTING REALISTIC ACHIEVABLE GOALS

Setting and aligning goals correctly throughout all levels of a company's structure is pivotal to its success. A well-known acronym introduced in the 1980's, which is still commonly used as a checklist for setting useful objectives, is SMART (13). A SMART objective is: Specific, Measurable, Achievable, Relevant and Timely. Here we are concerned with the 'A' and how the funnels offer a way of checking if particular goals can be realistically achieved. If an out-of-reach goal is set then this will demotivate your team, crushing innovation. However, research has shown that challenging goals tend to led to higher performance than easy goals or no goals at all (14). A balance is clearly needed.

Consider the objective of selecting a pre-clinical candidate within the next 12 months. Funnel Diagrams can be used to estimate whether this is achievable by tracking back up the cascade of events to make projections on when prior gates will need to be passed. Let's assume that in both projects A and B if a compound performs successfully in assay 6 then it has passed all previous gates and is ready for selection as a suitable pre-clinical candidate. From the funnels we can see that it takes about 8 months after compound synthesis to obtain results from assay 6 regardless of which project. This transforms the objective into: the preclinical candidate must either have already been made or must be made within the next 4 months.

Looking across the top of the funnels at the red rectangles alone summarises the rate of synthesis of new compounds. When disregarding the Christmas period, the rate of synthesis is about 50 compounds per month for project A and about 20 for project B. Taking the 4 month synthesis deadline into account and assuming the preclinical candidate has not yet been synthesised, means the candidate must be present in the next 200 compounds for project A or the next 80 for project B. How reasonable this is can be partially determined by the attrition levels through the cascade.

In project B only one compound has been through assay 6. This single compound is a standard, so is not reflective of the project's chemistry. The majority of compounds are failing at assay 1 or 2 and not even reaching assay 3.

This reflects how the project is having issues with generating sufficiently selective compounds. At the current rate it is unlikely that project B will be selecting a clinical candidate in the next year unless a major scientific breakthrough is suddenly made or a major process improvement is put in place to drastically shorten cycle times and increase throughput. The 12 month objective seems much more realistic for project A than project B. Project A has a higher throughput into assay 6 of approximately 1 compound per month. Assuming this throughput is maintained, 12 further compounds are yet to be tested. What are the chances of assay 6 having at least one success in the next twelve runs? A retrospective look back at similar historical projects to see if any patterns emerge may hold the answer.

RESOURCE MANAGEMENT

The Funnel Diagrams also show how resources have been split across projects and whether it is time to reshuffle your project teams. If the 12 month deadline discussed in the previous section is non-movable for Project A and no rapid back up candidate selection is required then once the extrapolated 4 month synthesis deadline has passed, a shift in chemistry resources on to Project B may be worth considering. Shifting resource in this way will help ramp up the number of new compounds being synthesised with the knock on effect of solving the target selectivity issues more quickly, assuming the chemistry moves in the correct direction.

So far we have used the Funnel Diagrams to look at compound synthesis and the assay cascade. It may be useful to examine some pre-synthesis events. This would provide more detail about what sort of chemistry resources need to be shifted. For example the funnels could be extended to capture: the volume of compound ideas, how many of these ideas will be made and the time taken to decide this, how long it takes to assign a compound to a chemist and how long synthesis takes. We could then determine whether project B is short of ideas or short of resources in actually carrying out the synthesis work. Alternatively maybe the process of assigning compounds to chemists needs rethinking.

If project B's chemistry input is doubled then a check of whether the assay resources are likely to cope should be carried out. It is worth checking if the funnels highlight any sudden time lags due to an assay reaching its capacity. For example look at assay 2 in project B. The average time between assay 1 and 2 is less than a week during November to January. However in February and March, when the number of compounds increases to over eight, a time lag emerges. This is a clear warning signal that the current resource assigned to this assay will need to be increased with any increase in chemistry.

CONCLUSIONS

Funnel Diagrams offer a novel way of simultaneously visualising attrition and timelines. They are capable of making an impact on process improvement work and are an aid to realistic goal setting and resource management. They could also be used as a motivational tool to highlight the positive impact of assay development work or other process changes. An error bar extension to the original visualisation enables the variation in an event's time to be viewed and a more detailed analysis to be drawn whilst maintaining simplicity. This analysis technique is valuable in determining high level questions, which might be missed with the more traditional process maps. Funnel Diagrams are a complimentary visualisation that add to the richness of information obtained from your process data.

Historical lead optimisation projects within a company can be viewed retrospectively to examine any patterns in funnel shapes across projects. If patterns emerge then they could be used to make predictions about current active projects. ■

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