WHITE PAPER

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THE UPCOMING CROWDED PIPELINE CRISIS AND WHAT TO DO ABOUT IT

A Forecaster's Perspective

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Recent analysis suggests that the number of pharmaceutical drugs in development has doubled over the last 10 years . Although the overall market has grown during this period, sales have not kept pace with this increase. Additionally, prospective evaluations of anticipated rates of return on drug development, based on consensus forecasts, have significantly decreased. As a result, many manufacturers are now revisiting their pipelines and portfolio strategies in response to increased competition and expected pressure on prices.

Markets with crowded pipelines are complex and notoriously difficult to forecast, and traditional tools for demand research and forecasting are poorly suited for these situations. As these markets become more and more prevalent, forecasters will need to up their game to accurately assess values for pipeline products and new opportunities. This white paper reviews the upcoming crowded market crisis and highlights some promising new approaches available for fine tuning demand estimates and forecasts in these situations.

Crowded Pipelines—the New Norm?

The number of drugs in development (globally) over the past 20 years is displayed in Figure 1.The data include preclinical and clinical stage assets plus any approved products still under development for additional indications and suggest that the number of drugs in development has roughly doubled in the past 10 years. Figure 2 shows the same data by therapeutic category; most categories have experienced significant growth, with oncology leading the pack with almost 3-fold growth.[1]

Figure 1. Total R&D Pipeline, 2004-2024[1]

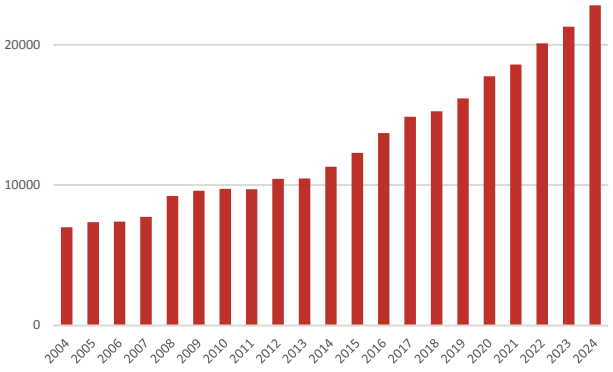
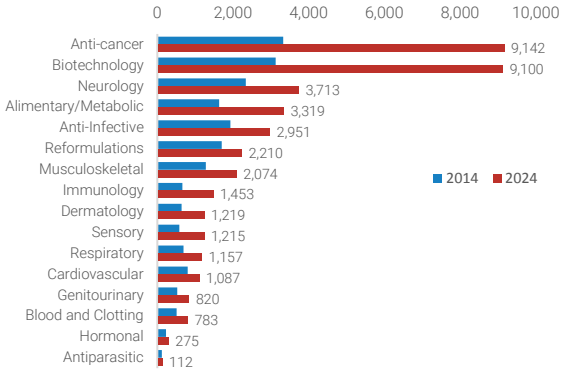


Figure 2. R&D Pipeline by Therapeutic Area[1]



Overall global pharmaceutical sales have also grown over the same time period, but not nearly as much.[2] Perhaps more importantly, when looking at prospects for later-stage pipeline products, estimated rates of return on drug development dropped from 7.2% in 2014 to under 2% in 2022, and peak sales forecasts for late-stage assets have also dropped dramatically.[3]

In many of these markets it is now unclear if investments in late-entrant assets will yield significant patient benefits and commercial success.[4] Increased rates of competition and pricing pressures in crowded markets have not gone unnoticed by manufacturers and other industry executives. Former Roche CEO Severin Schwan expects "an enormous drop-out" in oncology. According to Aiman Shalabi, chief medical officer at the nonprofit Cancer Research Institute, "The cycle of innovation has been shortened significantly. There is no doubt we are seeing fast follow-on and many identical agents hitting the same targets." Paul Major at BB Healthcare Trust remarked, "You're either first or you're best, or you're nowhere because it has become such a race." [5,6]

A Crowded Pipeline Example

It is useful to consider a current example to really get a handle on the issues associated with demand research and forecasting in markets with crowded pipelines. Ulcerative colitis (UC) is a chronic inflammatory bowel disease in which abnormal reactions of the immune system cause inflammation and ulcers on the inner lining of the large intestine. In the 1950s, 30 to 40% of patients with UC died from colorectal cancer, and many of the surviving patients lived their lives with a colectomy bag after removal of their colon.[7] Beginning in the late 1990s and the early part of this century, TNF inhibitors including Remicade and Humira revolutionized the treatment of UC, vastly improving prospects for long-term survival and limiting the need for removal of the colon.

However, UC is a therapeutic category where there is still a high degree of unmet need. Even with recently launched therapies, while a majority of patients experience some clinical response in the first 8 to 12 weeks, 80% do not achieve clinical remission in this time period, and only ≈50% achieve complete clinical remission after a year.[8] While newer therapies offer convenience advantages, efficacy is often similar or only slightly better than the original TNF inhibitors/biosimilars that most patients with moderate and severe disease receive as their first advanced/biologic therapy. Figure 3 describes currently approved and pipeline products for UC in the United States, EU4 and UK markets in 2024. For the pipeline, we have highlighted a select group of late-stage candidates with high likelihoods of approval as measured by Evaluate and Biomedtracker.

Figure 3. The UC Pipeline, 2024

Marketed Advanced Therapies

Remicade (infliximab)	Janssen	Stelara (ustekinumab)	Janssen
Humira (adalimumab)	AbbVie	Zeposia (ozanimod)	Bristol Myers Squibb
Entyvio (vedolizumab)	Takeda	Rinvoq (upadacitinib)	AbbVie
Simponi (golimumab)	Janssen	Omvoh (mirikizumab-mrkz)	Lilly
Xeljanz (tofacitinib)	Pfizer	Velsipity (etrasimod) tablets	Pfizer
Jyseleca (filgotinib)	Alfasigma		

Advanced Therapies in Development[1]

risankizumab BLA	AbbVie	guselkumab BLA	J&J
alicaforsen Phase III	Atlantic Health System	spesolimab Phase III	Boehringer Ingelheim
MK-7240 Phase III	Merck	ivarmacitinib Phase I	Reistone Biopharma
obefazimod Phase III	abivax	+ many more in Ph I/II + Biosimilars	

Approved in EU/UK

Approved in US, EU and UK

There are many challenges in developing a forecast for new products in markets like this, including:

- Complicated current market dynamics, where several products (eg, Zeposia, Rinvoq, Omvoh, Velcipity) have recently launched, and where the forecast will need to capture their adoption and uptake over time.
- A large number of potential new entrants.
- Variations in timing and order of entry.
- Uncertain future clinical performance, where many pipeline drugs are undergoing Phase III trials and go-to-market clinical performance is currently unknown.
- Significant pricing and regulatory uncertainty—it is unclear how payers will evaluate new entrants with marginal improvements over the SOC, and how the Inflation Reduction Act (IRA) will influence pricing and payer management strategies in the United States.
- Several products have novel mechanisms of action (MOAs), where there is limited knowledge amongst HCPs.

In the next sections, we discuss tools for demand research and forecasting in these complicated markets.

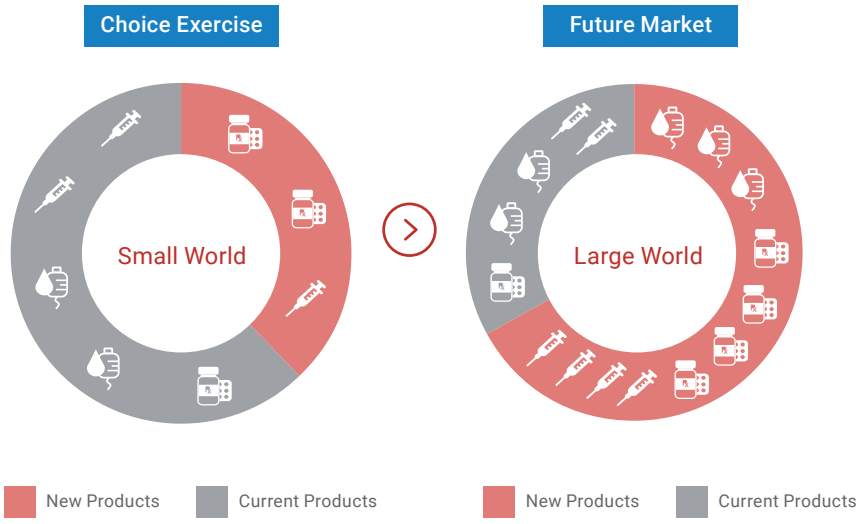
Demand Research in Markets With Crowded Pipelines

Many demand researchers will begin by considering an approach using fixed product profiles. This is certainly appropriate for products that have completed Phase III clinical trials like risankizumab (Skyrizi) and guselkumab (Tremfya). However, clinical profiles for drugs at earlier stages of development are not known, and taking a best guess at profiles for these drugs is risky, since there is a strong chance of missing the mark (perhaps significantly) on many of these products. The fixed profile approach also breaks down when we would like to include a larger number of new products in the forecast, simply because survey respondents quickly become overwhelmed and fatigued with the sheer volume of information they are required to evaluate in the research. Accordingly, traditional fixed profile research is ill-suited for these markets and rarely used.

An approach that is easier for HCP survey respondents and also captures clinical uncertainty is a straightforward product conjoint, where the new products are defined by product attributes and associated levels of performance. In the UC market, common attributes would include performance on efficacy measures like clinical and endoscopic remission, rates for certain adverse events, onset of action, dosing and administration, and MOA. In this research, survey respondents review and report on their anticipated prescribing for a series of market scenarios (generated by experimental design) for a small number of hypothetical new products. The conjoint survey data are then used to develop a choice model and simulator that in theory will provide share estimates for any combination of new products and associated levels of performance. The key simplification in the conjoint—defining the new products on a common set of product attributes—allows us to learn about the underlying preferences for the product "building blocks"; the methodology allows us value and then estimate market shares for any new product that can be defined by the attributes and levels in the conjoint, and to conduct sensitivity and "what if" analysis by varying product profiles and market composition.

Unfortunately, these traditional conjoint models perform quite poorly when asked to generalize to the larger markets associated with crowded pipelines.[9] To understand where the traditional models break down it is instructive to consider two different markets: 1) The market evaluated by respondents in the survey research, which typically contains a small number of new products (eg, 3) to ensure the choice exercises are not too complicated; and 2) The future market with a larger number of new products available. The difficulty arises when trying to extrapolate from the "small world" in the survey research to the "large world" associated with the crowded future market (Figure 4).

Figure 4. Survey Choice Exercises Versus Future Market



Traditional choice models perform poorly when asked to generalize to the larger markets associated with crowded pipelines

These traditional models generate implausible predicted shares and substitution patterns when a larger number of new products enter the market. For example, adding a new product to the market that is an exact clone of another product will increase total new product share when the clones should obviously just split the original share. More generally, these models fail to properly deal with product similarity in a way that extends to larger markets. This characteristic is familiar to choice modelers and is known as the independence of irrelevant alternatives (IIA) or the "red-bus blue-bus" problem; practical solutions have often involved ad hoc adjustments and use of different types of models, all with limited success.

However, a new class of choice models has recently been developed, called share of volume (SOV) models, which require no changes to the actual survey format and provide realistic market share simulations in crowded markets.[10] The approach modifies the underlying choice model to incorporate "similarity-structured covariances" – code for incorporating product similarity measured by the attributes and levels for the new products in modeled choices, resulting in more realistic substitution patterns and sources of business. When a new product launches that is very similar to another product in the market, the SOV model splits the original share in the model between the similar products, without increasing the total new product share. This approach has been available for more than 15 years, but adoption in commercial applications has been limited due to the complexity of the algorithms and the time-consuming nature of the modeling. However,

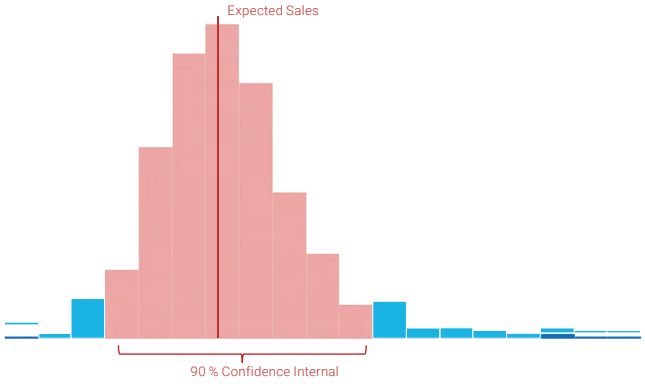
recent advances in algorithms and increases in computing power have made the approach feasible for commercial applications. The SOV approach fixes the problem with the traditional conjoint models in the crowded market context, and our research suggests that the approach provides much greater accuracy in applications like our UC example where product similarity is an issue.[11]

Forecasting in Markets With Crowded Pipelines

With SOV models in tow, it is straightforward to conduct scenario analyses for base case, upside, and downside market assumptions and simulate associated peak market shares and revenues. However, since many of these products in the pipeline are a few years away from launch, their clinical profiles are not yet fully known and, not surprisingly, it is often challenging to agree on which products will eventually launch and their specific product profiles. Monte Carlo simulation (MCS) provides a convenient solution in this situation. In a first step, we simulate randomly over possible future market configurations (i.e. the drugs that eventually launch) based on best estimates of likelihood of approval. For the products that launch in each simulation, we simulate the clinical endpoints in a second step based on an estimate of their distribution derived from historical clinical trial data, and then compute the peak market share using the conjoint model. Monte Carlo simulation of clinical trial endpoints uses recently developed machine learning estimates of clinical uncertainty to approximate the risk in clinical trial outcomes for drugs in development.[12] We can also include variations in other factors, like timing and order of entry, pricing, and market access in the analysis.

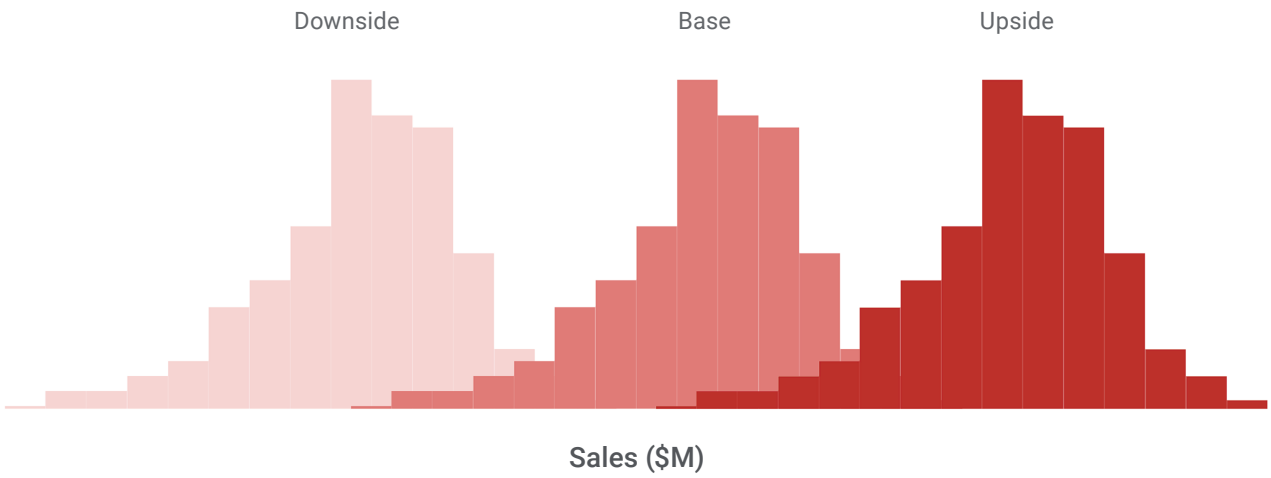
Figure 5 provides an illustration of the MCS approach for a US-only forecast focusing on one of the UC pipeline brands, assuming fixed timing and order of entry, access benchmarks from the current market, and "average" US pricing. Figure 5 depicts the frequency distribution of peak US sales for Product X in 2031 across Monte Carlo simulations. Rather than using just a point forecast for a specific market scenario, MCS generates a distribution of 2031 sales forecasts that reflect uncertainty in the products that launch and their associated clinical profiles. It is possible to identify the expected value of 2031 sales for Product X (denoted by the red line in Figure 5), and the analysis also provides an estimate of our level confidence in that estimate as indicated by the range of potential outcomes in the 90% interval.

Figure 5. 2031 US Product X Sales Forecast Distribution Over Monte Carlo Simulation



The interval forecast in Figure 5 captures the major sources of risk in the UC market - variations in competition and associated clinical profiles for the drugs that launch – and diving into the factors influencing the range of outcomes is also illuminating. MCS simulations with lower peak sales in the left-hand tail of the distribution reflect Product X profiles that are approved but not differentiated from an efficacy perspective, and there are often a large number of new competitors in these simulated markets. In simulations with much higher peak sales in right-hand tail of the distribution, Product X is significantly differentiated relative to new and existing competitors from an efficacy perspective, and the number of new competitors is less important. For the area in the middle representing the majority of scenarios, Product X is slightly/moderately differentiated from current products and new competitors, and differences in efficacy and the number of new competitors drive sales potential. It is also possible to fix base, upside, and downside scenarios for Product X, and use Monte Carlo simulation for the remaining products as shown in Figure 6. Note that this approach removes the Product X simulations with really high peak sales from consideration, but not the poor performance scenarios where other competitive products are positively differentiated.

Figure 6. 2031 US Product X Sales Forecast Base, Upside, and Downside Scenarios Distribution Over Monte Carlo Simulations



Overall, the MCS approach offers great value in these crowded markets, allowing forecasters to use sharp assumptions when appropriate information is available, while also averaging over solid estimates of risk for those factors that are consequential but unknown.

Implications

As crowded pipelines become more and more common across therapeutic areas, it will be very important to use tools for demand research and forecasting that are appropriate for these situations.While conventional fixed-profile and traditional conjoint approaches to demand research perform poorly in these situations, recently developed SOV conjoint models are a promising alternative. The SOV approach can be paired with Monte Carlo simulation (risk analysis) in the forecast to more fully articulate the risks and opportunities in these markets.

We expect manufacturers to take a fresh look at their portfolios and prioritization of assets and indications as pipelines become more crowded, and it is likely that the bar will be set higher for clinical differentiation and therapeutic benefit going forward. The importance of novelty – in MOA, method of administration, etc.…- may also increase. Manufacturers will strive to be first-in-class, and certainly best-in-class if not first. Timelines for clinical development may also be revisited and accelerated as manufacturers work to enter markers sooner. Overall, it is likely that both the frequency of crowded market forecasts and the degree of difficulty will only increase in the future.

Endnotes

[1] Citeline (2024). Pharma R&D Annual Review. In Figure 2, drugs may be classified in multiple categories.For example, the biotechnology category includes many different therapy areas and encompasses medications sourced from living organisms or their cellular components, produced through methods like genetic engineering and cell culture techniques. Common types include antibodies, recombinant proteins, autologous cell therapies, virally delivered nucleic acids, and heterologous cell therapies.

[2] IQVIA (2024). The Global Use of Medicines 2024 – Outlook to 2028, January, and previous versions of the report. Global sales increased from $964 billion in 2013 to $1.607 trillion in 2023, an increase of 62%.

[3] Deloitte Centre for Health Solutions (2022). Seize the digital momentum: measuring the return from pharmaceutical innovation.

[4] Christian F, Cannon J, The L., Smith J, Leclerc O (2023). Herding In The Drug Development Pipeline. Nature Reviews Drug Discovery. 22:617-618.

[5] Hirschler B (2018). Too many cancer drugs? Crowded market gives investors pause. Reuters. May.

[6] McIntyre G (2019). Enough with the me-too drugs. New treatments should be worthy of the people who invest their lives in clinical trials. STAT: First Opinion.

[7] Edwards F, Truelove S (1963). The course and prognosis of ulcerative colitis. Gut. 4:299–315.

[8] Based on a review of current US package inserts for Stelara, OmVoh, and Rinvoq.

[9] Traditional models include the multinomial logit and mixed multinomial logit which are used for the vast majority of product conjoint applications in commercial market research today.

[10] Dotson J, Brazell J, Howell J, Lenk P, Otter T, MacEachern S, Allenby G (2018). A Probit Model with Structured Covariance for Similarity Effects and Source of Volume Calculations. Journal of Marketing Research. ISSN: 0022-2437 (print). 55:35–47. Note: While the choice exercises in the survey remain the same, the experimental design for the new products should include a higher degree of level overlap across the profiles. See Willson D (2019). Modeling Crowded Pipelines in Pharmaceutical Markets, Sawtooth Software Conference, San Diego, September.

[11] See Willson D (2024). When you can't see the forest for the trees – demand research and forecasting in markets with crowded pipelines. Pharma Market Research Conference (PMRC) EU, Munich, April.

[12] See Willson D (2024). Incorporating risk in early-stage demand research and forecasting. Pharma Market Research Conference (PMRC) USA, Newark, February.