

DEVIL'S ADVOCATE TOOL GUIDE

Background

The analysis of the competitive environment for a product in development (*Product X* belonging to *Class X*) typically involves compiling a list of potentially relevant competitors. This list would typically include approved products (the current options) and new products in development (the pipeline). After selecting those products that are specifically relevant for the target patient segment and the geography *Product X* is being developed for, a set of competitors is obtained that can be visualized in form of a 'filtered brickwall'.

While giving an overview on the overall competitive situation, the brickwall by itself does not offer guidance on (i) how many and which pipeline products are likely to 'make it' to compete with *Product X*, and (ii) what this would mean for the peak share potential for *Product X*. Numerous approaches involving different methodologies and leading to different levels of analytical depth, duration, and costs of the analysis can be used to address these questions and may include accessing internal expertise in form of CI colleagues or external expertise. In most cases, input by internal or external therapy area experts is involved to address key uncertainties such as the future treatment landscape and the likely place of therapy of *Product X* therein. This requires expertise, time, and budget, which are not always available at the time of need and in particular in the early stages of product development. Also, in our experience, therapy area expert-driven analyses tend to overestimate the share of *Product X* vs. other pipeline candidates for various reasons.

We therefore wanted to develop a tool that would allow for a relatively quick analysis of the pipeline and a high-level estimate of the peak share potential of new products without need for input by therapy area experts. The intended use was to deliver a quick view, which then could be complemented by other approaches, and/or could also be used to challenge potentially overoptimistic product forecast based on therapy area expert input (which is why we also call it the 'devil's advocate tool'). On a qualitative level it allows to ask good questions with the objective to critically review key forecast assumptions.

Overall Model Framework

The tool combines a pipeline analysis with a market model. After entering key data for your *Product X* and its current or potential future competitors from of a 'filtered brickwall' type analysis, a *probability-adjusted pipeline analysis* delivers a view on the *probable* future treatment landscape your *Product X* will compete in, while competitors could include other products belonging to the same class (*Class X*), or other classes/MOAs.

The results of this analysis, together with the assumptions for *Product X* and the current treatment options, are then fed into a *simple market model*. The latter assigns patient shares for classes and products based on *order of entry* and the *profile* at a class level and product level, and thereby delivers peak share potentials at three levels: Share of *Product X* in *Class X*, share of *Class X* in the target patients, and share of *Product X* in target patients.

The allocation of patient share via *order of entry* is based on actual/expected launch dates from the pipeline analysis. The allocation of patient share via the *overall profile* is based on a simple one-dimensional rating vs. the current standard of care. Of note, while in the present online tool we aimed to keep it as simple as possible, we are also developing a more complex tool that has additional functionalities that allow for a more flexible and versatile use of the pipeline analysis module and also considers a wider and more granular set of aspects in the market model (details available upon request).

Probability-Adjusted Pipeline Analysis

The tool assumes that your product (*Product X* belonging to *Class X*) launches at the expected time with the expected profile, and that the current treatment options will still be available in future. The *probability adjusted pipeline analysis* aims to deliver an ‘objective’ view about which additional options would probably enter from the pipeline, based on historical data. As a first step, the tool calculates the likeliness of approval and the expected date of approval for each individual pipeline competitor on basis of (i) indication area, (ii) product type, (iii) latest phase of development, and (iv) start of latest phase of development as entered for each pipeline competitor by the user. These calculations are based on a data set we derived from published historical data on the duration and success probability of clinical drug development phases in the US over the last decade. The sources for these publications included the Biomedtracker database, FDA review documents, and others. Our data set covers the entire clinical development from Phase 1 to submission, as well as 16 indication area categories and 14 product types (**Table 1**, key references see below, details available upon request).

As a next step, the calculated launch probabilities of individual products in development are used to calculate the actual expected number of newly approved classes and the number of newly approved products within *Class X*. In order to establish an *order of entry*, the expected treatment options in the future treatment landscape (either classes or products) are allocated into five ‘baskets’: (i) *Class X/Product X*, (ii) current options launched before *Class X / Product X*, (iii) current options launched after *Class X / Product X*, (iv) new options from pipeline launched before *Class X / Product X*, and (v) new options from pipeline launched after *Class X / Product X*. Each of the ‘baskets’ could be empty or contain one or more products/classes and is assigned an average time lag vs. expected launch of *Product X / Class X* and an average *profile*. Of note, the present tool has a capacity of up to 10 classes as expected future treatment options for the target patients and for up to 10 products in *Class X*.

Indication Area Category				Product Type Category			
1	ALL indication areas	9	Metabolic	1	ALL Product Types	8	Peptide
2	Allergy	10	Neurology	2	ALL Biologics	9	Protein
3	Autoimmune	11	Oncology	3	ADCs	10	siRNA/RNAi
4	Cardiovascular	12	Ophthalmology	4	Antisense	11	Small molecule
5	Endocrine	13	Psychiatry	5	CAR-T	12	Vaccine
6	Gastroenterology	14	Respiratory	6	Gene therapy	13	OFF-PATENT*- Biologic
7	Hematology	15	Urology	7	Monoclonal antibody	14	OFF-PATENT*- Small molecule
8	Infectious disease	16	OTHER indication area				

Table 1. Indication areas (total 16) and product types (total 14) covered by the tool. OFF PATENT means products containing off-patent APIs that are however developed via a stand-alone full approval pathway (Ph1-Ph3). The tool is not suited to consider products developed via abbreviated Generics or Biosimilar approval pathways.

Simple Market Model

The *simple market model* assigns a peak share potential for *Class X* and *Product X* based on their *order of entry* and *profile* versus other options in the expected future treatment landscape. The tool follows a similar algorithm to separately calculate the expected peak shares of *Class X* in the target patients and the expected peak shares of *Product X* in *Class X*. In both cases, it considers current options as well as expected additional future options as derived from the *probability-adjusted pipeline analysis* and allocated to the five ‘baskets’ (see above). For the allocation of shares to the ‘baskets’ based on *order of entry*, three approaches can be chosen from: Modified Zipf’s Law, PIMS, and Proportional (details available on request). For the allocation of shares based on *profile*, the model uses certain factors, which are a measure of the responsiveness of one variable (patient shares) in response to a change in another

variable (the profile). The tool assumes that the impact of *profile* differences on the patient shares will increase with specialization of the health care professional typically treating the target patients. The model has three types of care that can be chosen from, with increasing impact of profile differences: Primary care, Mixed/undefined, and Specialty Care (details available upon request). The specific factors used in the tool have been tested and refined in several of our market models, and, based on our experience, are seen to deliver reasonable market share estimates based on clinical benefit profile differences. The model then combines the shares based on *order of entry* and *profile* to a final total share for each of the 'baskets' for *Class X* and *Product X*. As a last step, the share of *Class X* in target patients and the share of *Product X* in *Class X* is combined to result in the expected peak share potential of *Product X* in the target patients.

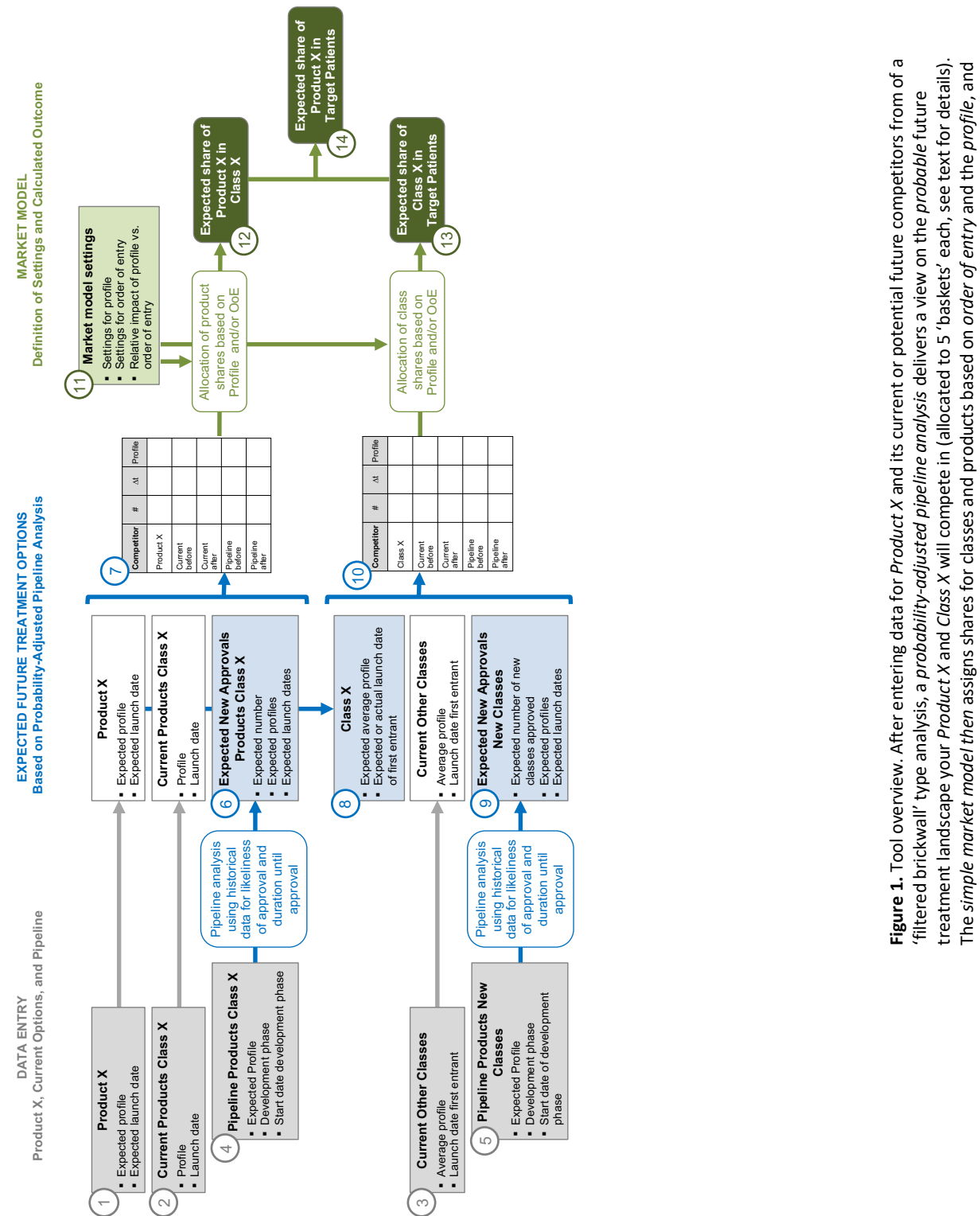


Figure 1. Tool overview. After entering data for *Product X* and its current or potential future competitors from of a 'filtered brickwall' type analysis, a *probability-adjusted pipeline analysis* delivers a view on the *probable* future treatment landscape your *Product X* and *Class X* will compete in (allocated to 5 'baskets' each, see text for details). The *simple market model* then assigns shares for classes and products based on *order of entry* and the *profile*, and

DATA ENTRY ON DASHBOARD

When opening the tool, you can either start a new analysis or continue an analysis that you had previously worked on and saved to your computer. In the latter case, you can continue wherever you stopped and saved the previous session. When starting a new analysis, you need to enter the data/expectations around your product for a specific target indication. Please define the target indication as precisely as possible, and later do only enter other products/classes specifically approved for or in development for this specific target indication. Of note, there are different views you can choose from for the dashboard: On the upper right section of the dashboard, there are two dropdown menus to choose (i) standard vs. compact view and (ii) display of products Class X only vs. classes only vs. both.

- **ADD PRODUCT X AND DEFINE INDICATION** (Step 1 in Figure 1). Enter the details for your product: name (free text), manufacturer (optional), name of Class X (free text), the specific target indication (free text), the broader indication area (dropdown), the product type (dropdown), the current phase of development (dropdown), the expected launch date (calendar), and the expected profile vs. current standard of care (dropdown). The model will automatically position a box for your product in the top half of the dashboard, depending on its development phase.

As next step, enter the current treatment options for the target patient's segment. This could be other product(s) belonging to *Class X*, that have been launched already (if any), and/or other classes. The latter are not looked at on an individual product level, but only at the higher class level.

- **ADD CURRENT PRODUCTS CLASS X** (upper left part of DASHBOARD, Step 2 in Figure 1). Enter the details for any other product of *Class X* that has already been approved in the target indication (if none have, you can skip this step). You can add new products clicking on the plus button in the respective area in the upper left part of the dashboard. A window will open that asks for the name of the product (free text), the manufacturer (optional), the product type (drop-down, should be same as Product X), the date of approval (calendar) and the overall profile vs. current SoC. The class name is pre-set based on what was entered for *Product X* and the development phase is pre-set to 'approved'.
- **ADD OTHER CURRENT CLASSES** (lower left part of DASHBOARD, Step 3 in Figure 1). If you have entered one or more current products for *Class X* in Step 2, a respective box for *Class X* will automatically be generated in this section that will display the average profile and the launch date of the first entrant in *Class X* based on your prior entries. To add other classes currently approved in the target patients, click on the plus button. A window will open that asks for the name of the class (free text), the product type (dropdown), the name of the first approved product (free text), the first product approval date (calendar), and the class average overall profile vs. current SoC (dropdown).

As next step, the pipeline for new products in development for the target patient segment needs to be entered. This could include other products belonging to *Class X* and/or products in development that represent to new classes. *Importantly, new products in development that are follow-up products belonging to other classes that are launched already by definition are considered 'current option' and not included in the analysis.*

- **ADD PIPELINE PRODUCTS CLASS X** (upper right part of DASHBOARD, Step 4 in Figure 1). By clicking on the plus buttons at the respective development phase, a window will open to enter details of additional products belonging to *Class X* that are currently in development for the

target patient segment. While the class and the development phase will be pre-set, you will be asked to enter the product name (free text), the manufacturer (optional), the product type (drop-down, should be same as Product X), the start date of the development phase (dropdown) and the expected overall profile vs. current SoC. In you have no data/information on the expected profile, we recommend to assume '3 – average').

- **ADD PIPELINE PRODUCTS NEW CLASSES** (lower right part of DASHBOARD, Step 5 in Figure 1). By clicking on the plus buttons at the respective development phase, a window will open to enter details of products being developed for the target patient segment, *which neither belong to Class X nor belong to any of the classes already listed under classes in market*. For each of these products, enter the product name (free text), the manufacturer (optional), the class (free text), the product type (dropdown), the current development phase (dropdown) the start date of that development phase (calendar), and the expected overall profile vs. current SoC (dropdown - again, if you have no data/information on the expected profile, we recommend to assume '3 – average'). A new box will appear for each of the products you enter, with a colour code for the class, and a positioning depending on development phase.

MARKET MODEL SETTINGS AND OUTPUT

The tool will generate a view on the future treatment landscape in form of 5 'baskets' on class and product level, based on the data you entered for Product X, the current options and the calculated outcome of the probability-adjusted pipeline using the data you entered for the pipeline products (Steps 6-10 in Figure 1). The tool will furthermore allocate market shares among these 'baskets' on class and product level (steps 12-14 in Figure 1) based on the Market Model Settings, which are preset but can be adapted (step 11 in Figure 1). The calculations are active in the back as soon as a Product X is entered, and the impact of any new entry can instantly be seen by changing view to OUTPUT.

The main view of the OUTPUT are the calculated shares in form of 3 pie charts: (i) share of *Product X* in *Class X* (left, Step 12 in Figure 1), (ii) share of *Class X* in target patients (middle, Step 13 in Figure 1), and (iii) share of *Product X* in target patients (right, step 14 in Figure 1). While the latter pie chart only combines values from the middle and the left chart, more details around the allocation of shares on class level (middle) and product level (right) can be seen in tabulated format when clicking on the respective DETAILS buttons. Both tables have the same format and summarize (i) the calculated view on the future treatment landscape in terms of the 5 'baskets', derived from the consideration of the current options plus the results of the probability-adjusted pipeline analysis, and (ii) more details around the allocated shares (based on *order of entry* only, based on *profile* only, and based on both aspects with a relative weighting as defined in the Market Model Settings. The tables also illustrate how the values for the 5 'baskets' are condensed into the 3 values that are displayed in the respective graphs.

- **CHANGING THE MARKET MODEL SETTINGS** (button in top line of DASHBOARD and OUTPUT, Step 11 in Figure 1). To see and/or change the settings for the market model, you can click on the respective button on the top line that is common to the DASHBORAD and the OUTPUT view. A window will open, that allows you to change the settings and see the impact in real time. You can change how the tool allocates shares based on order of entry – Modified Zipf's Law is pre-set, but you can also choose PIMS Table or Proportional. You can also choose the type of care that has an impact on how profile differences translate into share differences - mixed/unknown is pre-set, but you can switch to primary care or specialty care, which will decrease or increase the relative impact of profile differences. In addition, there are sliders to change the relative contribution of *order of entry* vs. *profile* when allocating shares. The upper slider is for the allocation of shares of products, e.g., *Product X* in *Class X*, and is pre-set to

50% each. The lower slider is for the allocation of shares to classes, e.g., Class X in target patient, and is pre-set to 25% *order of entry* vs. 75% *profile*.

SAVING DATA AND EXPORTING DASHBOARD AND OUTPUT

By clicking SAVE, the current status of the data and tool settings will be saved locally to your computer in form of a json file. This is also the file to open locally, if you want to continue an analysis that you had previously worked on. By clicking on the respective icons, you can export and locally save to your computer the DASHBOARD view or any element of the OUTPUT. If you want to start a new analysis, you can click START OVER (be aware, that all prior data entries will be cleared by this step).

Caveats and Limitations

The testing of this tool with internal consulting projects indicates that this simple tool is useful to generate a quick view on how the future competing treatment options will *probably* look like, and to get to a quick estimate on peak share potential of a new product based on the expected launch time and profile. However, the tool works with several simplifications.

The *probability-adjusted pipeline analysis* uses historical data on success probability and development timelines, which may not be fully relevant for new classes/MOAs. Furthermore, this historical data is from the US, which is why the tool should only be used to look at the US market. In addition, we used rather broad definitions of indication areas and product types for this analysis to avoid small sample size biases, which however cannot reflect potentially relevant particularities for the specific target patient segment and/or product type.

The overview on the probable future treatment landscape then puts products/classes into ‘baskets’ with average profiles and average launch dates, which tends to level out potentially relevant particularities of individual development candidates. Finally, the *simple market model* assigns patient shares based on order of entry and profile, which on one hand reflects common practice in the field, but which on the other hand has not yet been fully proven and calibrated with scientific rigor for specific indications except for selected case studies.

It is also important to note that an ‘overall profile’ used in this tool for simplicity cannot fully reflect the actual complex interplay of efficacy, safety, admin, market access, etc. of individual products to drive their respective market performance. We therefore recommend not to use the results of this tool on a stand-alone basis, but rather to see them as a first ballpark orientation before going into a more detailed analysis or to provide a sense check for peak market share predictions based on other approaches (‘devil’s advocate’).

KEY REFERENCES

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