

An intro to the world of Biotech/Life Science indices

Long the sole purview of the investor community, corporate issuers are coming to the realization that market indices are also important to them. There are millions of indices out there, but only a handful that dominate the market, namely: the S&P 500, Russell 1000, MSCI ACWI and CRSP US Total Market. For a variety of reasons some Biotech and Life Sciences companies may not qualify for inclusion in one or more of the big four indices. Not to worry – there are other well-recognized indices out there that these companies may be eligible for, including several specifically covering the Biotech and Life Sciences arena.

Key take aways

- **Most equity fund money is concentrated in a few prominent indices**
Together the S&P 500, Russell 1000, CRSP US Total Market and MSCI ACWI indices account for about half of equity fund assets globally, about half of which is indexed. Other indices covering mid and small cap issuers also have strong followings.
- **Several indices uniquely target the Biotech/Life Sciences arena**
ICE has three Biotech indices tracked by \$10.5bn in index fund assets, or 19% of the Biotech fund market. A total of \$9.6bn, mostly in actively managed funds, is using the Nasdaq Biotech index, and the S&P Biotech Index follows with \$9.4bn in index fund assets.
- **Not all Biotech indices are alike**
They cover the same market segment, but each index has its own methodologies and rules, leading to significant differences between the ICE (ICEBIO), Nasdaq (NBI) and S&P (SPBIO) Biotech index holdings. An issuer can be in one or more of these alternatives.
- **Large compositional differences can lead to significantly different results**
Since they have different holdings, the main Biotech indices can have significantly different performance results, depending on what part of the economic cycle we are in. Over the long haul, it is ICEBIO that ranks on top for the last 3-, 5- and 10-year periods.
- **Biotech has done well versus the major broad indices**
Though it has underperformed in certain years, an equal blend of ICEBIO, SPBIO and NBI indices generated a 12.18% 10-year annualized return. Over the same period, a blend of the S&P 500 and Russell 1000 gained 11.39%, and a blend of the S&P 600 and Russell 2000 gained 9.93%.

Why indices matter.

Indices strongly influence portfolio stock selection decisions and therefore are critically important to issuers trying to get on investors' radar screens.

Indices are the backbone for the investment processes used by most funds and asset managers. Based on a review of over \$34 trillion in equity investment portfolios globally, over 98% make use of a benchmark index. This investment universe includes both indexed and actively managed portfolios.

Indexed funds and portfolios try to match the performance of the selected index by holding the same securities and in the same relative weights, so index inclusion is clearly important if you want to attract those funds as buyers. At the same time, inclusion in the indices used by actively managed funds – i.e., funds that are trying to beat their index – is also very important to issuer companies as index constituents are the starting point against which these funds position their over and underweight bets. Passive indexed funds have been the fastest-growing segment of the market, but active funds remain the larger of the two by a wide margin.

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Together, the S&P 500, MSCI ACWI, Russell 1000 and CRSP US Total Market indices are used by almost 50% of assets in global equity investment portfolios. Notably, three of the four only include U.S. companies and three of the four are skewed toward large and mid-cap sized companies. The good news is that issuers who do not meet one or both of those criteria still have opportunities for inclusion in other important indices that may target small or micro-cap issuers and/or specific sectors or investment themes such as Healthcare, Biotech and Life Sciences.

Exhibit 1: Global equity investment portfolio AUM (USD in millions)

Index ¹	Country criterion	Size segment	Active	Indexed	Total	% of Total	% Active	% Indexed
S&P 500	US	Large	4,427,172	3,199,834	7,627,006	22%	58%	42%
MSCI ACWI	Global Dev & EM	Large, Mid	3,325,679	308,826	3,634,505	11%	92%	8%
Russell 1000	US	Large, Mid	3,094,579	333,055	3,427,635	10%	90%	10%
CRSP US Total Market	US	Mega, Large, Mid, Small, Micro	4,266	1,888,174	1,892,440	6%	0%	100%
All other			10,480,578	7,131,800	17,612,377	52%	60%	40%
Total			21,332,274	12,861,688	34,193,962	100%	62%	38%
Top four share of AUM			51%	45%	48%			

¹ Includes variants and sub-indices.

Source: Morningstar as of December 2022

What is the key index for the Biotech/Life Science market?

For a long while, the Nasdaq Biotechnology Index (NBI) and the S&P Biotechnology Select Industry Index (SPBIO) were the dominant indices measuring Biotech companies. Then, in June 2021 the iShares Biotechnology ETF – the largest Biotech fund with \$8.7bn in assets as of December 2022 – switched its underlying benchmark to the ICE Biotechnology Index (ICEBIO) from NBI, and ICEBIO quickly rose to prominence. Now ICEBIO, together with two other ICE indices (the NYSE Arca Biotechnology and Dynamic Biotech & Genome Intellidex Index) place ICE on top with \$10.5 billion in AUM tied to its Biotech indices, followed by NBI (\$9.6bn) and SPBIO (\$9.4bn).

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Exhibit 2: Biotech ETFs and Open-End Funds AUM Dec 2022 (USD MM)

Index	Active	Indexed	Total	% Total
ICE Biotechnology		8,747	8,747	16%
NYSE Arca Biotechnology		1,492	1,492	3%
Dynamic Biotech & Genome Intellidex		251	251	0%
ICE total		10,489	10,489	19%
Nasdaq Biotechnology	8,304	1,329	9,633	18%
S&P Biotechnology Select Industry		9,449	9,449	17%
All other (40 indices)	22,347	2,950	25,297	46%
Total	30,650	24,217	54,868	100%

Source: Morningstar, December 2022

All Biotech indices are not alike.

There are significant compositional differences between the main Biotech indices. Most notably, ICEBIO and SPBIO are pure Biotech indices while NBI includes Pharma.

ICEBIO, NBI and SPBIO all carry the same “Biotechnology Index” name but that belies the fact that underneath the covers they are very different indices. That is not to say one is better than the other. It simply points to the fact that they measure different baskets of stocks, and fund managers and institutional investors will gravitate to one or the other for different reasons.

One of the most obvious differences is that the ICEBIO and SPBIO indices are designed as “pure” biotech benchmarks, while NBI includes Pharma as well as Biotech companies. There are also differences in the way the different providers define the Biotech sector. For example, the ICE Biotech definition includes companies involved in Biotech Tools & Diagnostics, whereas S&P maintains a separate Life Sciences Tools & Services category and companies in this category are only included in SPBIO index if there are fewer than 35 qualifying stocks in the index, which is currently not the case.

Other differences affecting the compositions of the three indices include the fact that SPBIO is limited to US companies while ICEBIO and NBI are not. Conversely, NBI is limited to stocks listed on Nasdaq whereas ICEBIO and SPBIO include stocks listed on all the major US exchanges. Additionally, SPBIO constituents are equally weighted, while ICEBIO and NBI constituents are capitalization weighted. That gives SPBIO a higher exposure to small cap names than the other two indices. A more detailed comparison of the inclusion criteria across the three indices is provided in Appendix 2.

These rule differences leave SPBIO with significantly fewer constituents than its two peers – it currently holds 152 constituents versus 270 for ICEBIO and 273 for NBI – with the exclusion of non-US companies and higher minimum market cap size filters being the greatest contributors to the smaller SPBIO constituency. Meanwhile, even though they have comparable constituent

counts, the ICEBIO and NBI also have many differences in their respective holdings, mostly due to the inclusion of multiple exchange listings in ICEBIO versus the inclusion of Pharma companies in NBI.

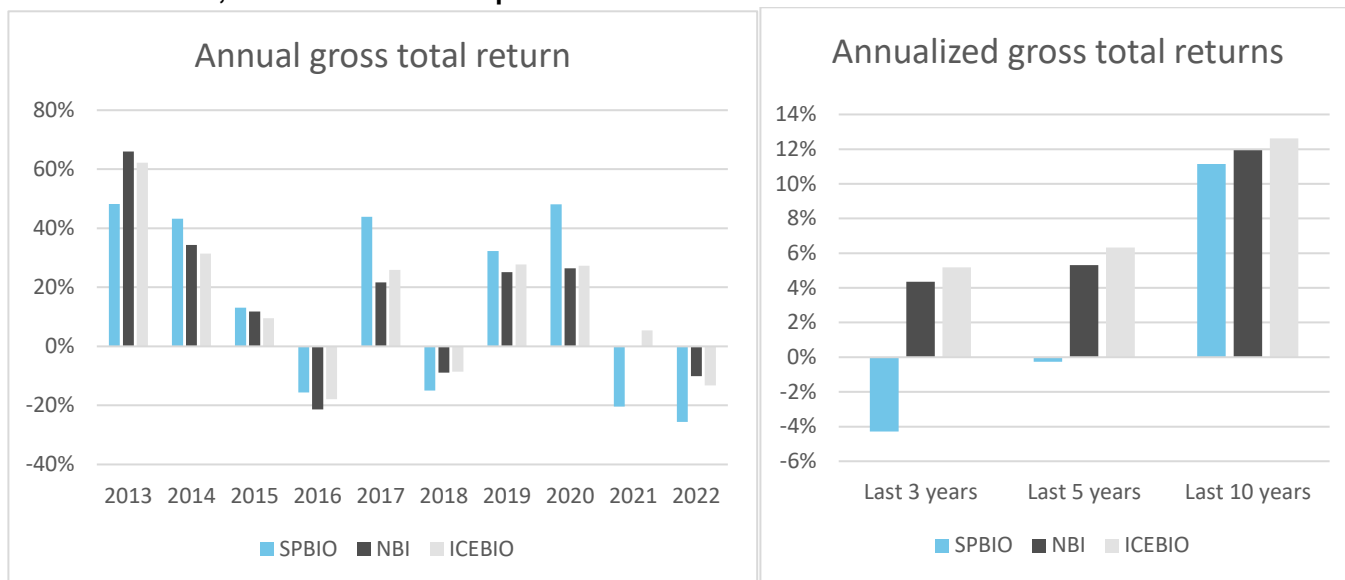
How have compositional differences affected results?

As mentioned earlier, the fact that the three flagship Biotech indices have significant compositional differences does not necessarily make one better than the others. But these are factors that investors do consider when selecting a benchmark index, particularly as it relates to potential performance. Past performance is not a predictor of future performance, but we think one can gain insights into the risk/return trade-offs of different indices based on past results. And, since there are meaningful differences in the compositions of the three indices, we believe it is important to look over an extended period of time to avoid narrowly focusing on performance in a short period that may be biased toward one over another due the point in the economic cycle covered by that particular period.

SPBIO has often been found at the top or bottom of the historical performance rankings. Meanwhile, ICEBIO often ranked in the middle but had the best long-term return.

A comparison of annual returns over the last 10 years shows that SPBIO has tended to gravitate toward either end of the performance spectrum – ranking on top six times and on bottom four times, but never in the middle. On the other hand, NBI has topped the rankings twice, landed on bottom four times and placed in the middle of the three indices four times. ICEBIO has been more balanced than the other two, ranking in the middle six times, while placing at the top and bottom of the rankings twice each. SPBIO has performed best in up markets, leading the other two in 5 of the 6 years with positive returns, but underperforming in 3 of the 4 down years. Notably, over extended periods of time, it is ICEBIO that ranks on top for the last 3-, 5- and 10-year periods.

Exhibit 3: SPBIO, NBI and ICEBIO comparative returns



Source: FactSet

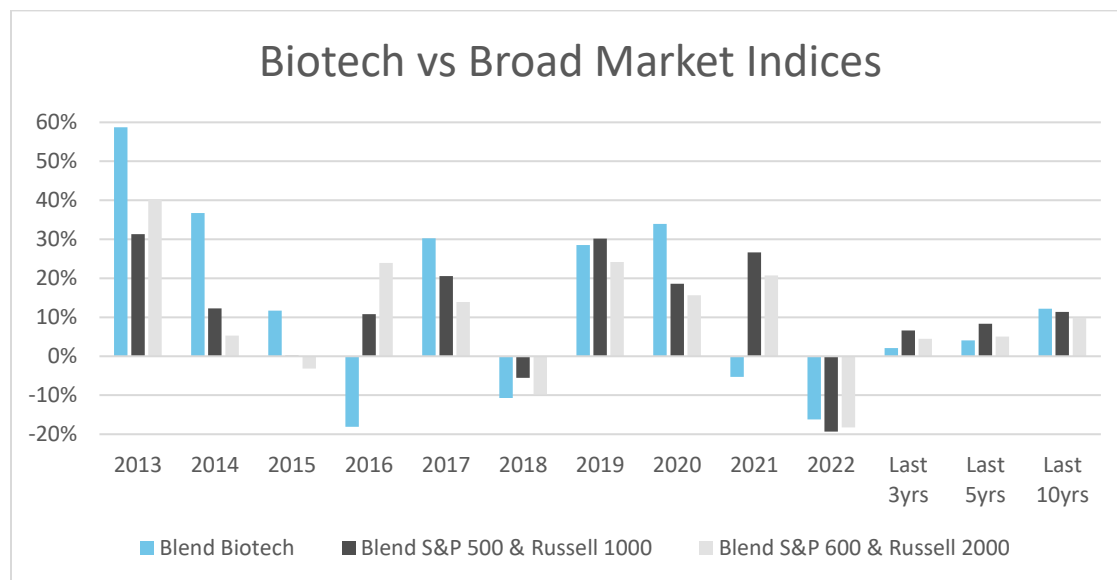
How do Biotech indices compare to the broad market?

Though they have had years of underperformance, an equal blend of ICEBIO, NBI and SPBIO has had better long term returns than blends of prominent indices.

While it is useful to understand how the biotech indices have performed relative to each other, we believe it is also important to look their collective performance relative to the broader market. Based on the last 10 years, the answer to that question is that they have done very well. During that period, an equal blend of the ICEBIO, SPBIO and NBI indices generated a 12.18% annualized return. Over the same period, a blend of the two most prominent large/mid-cap indices (S&P 500 and Russell 1000) generated an 11.39% annualized return, and a blend of the two most prominent small-cap indices (S&P 600 and Russell 2000) generated a 9.93% return.

Of course, it has not always been smooth sailing for the biotech indices. Collectively, they lagged both the large/mid and small-cap index blends by sizable margins over the last 3 and 5 years with a large downturn in 2021 accounting for the bulk of the shortfalls. Nonetheless, the biotech index blend came out ahead of the other two blends in 6 of the last 10 years and ranked second once, while landing at the bottom of the heap just three times, including 2016 and 2018 as well as 2021.

Exhibit 4: Biotech versus Broad Market Index returns



Source: FactSet

Looking beyond Biotech.

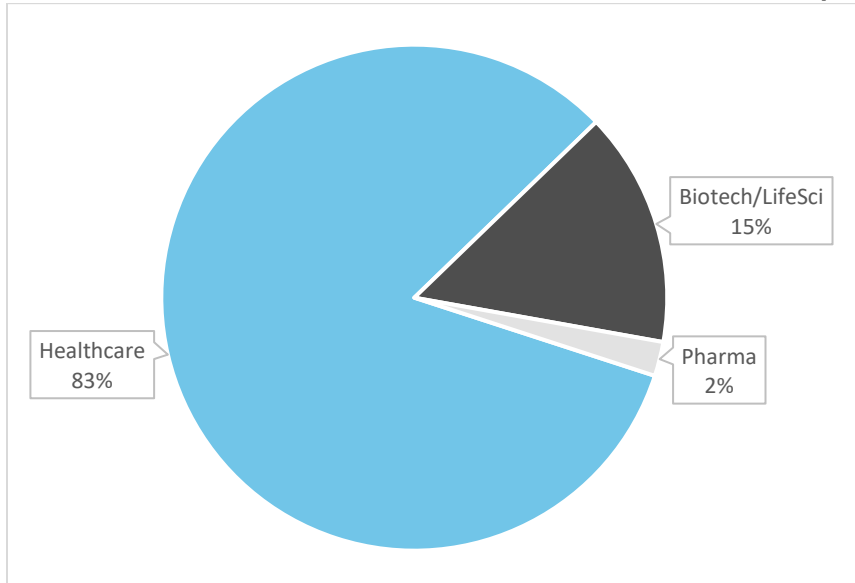
In addition to the main Biotech indices, there are number of other indices catering to the Life Sciences space, including Healthcare and Pharma indices.

We highlighted the fact that the Nasdaq Biotechnology Index is a hybrid that includes Pharma as well as Biotech companies. There are also several pure Pharma indices out there – most notably the FTSE World Health & Pharmaceuticals index – but the fund segment following those indices is relatively small (\$8bn in fund assets versus \$53bn in Biotech funds). Notably, Biotech and Pharma companies can also qualify for inclusion in the broader Healthcare sector indices (\$290bn in fund assets), not to mention major large, mid, and small-cap indices. In fact, of the 326 companies included in one or more of the three main Biotech indices, two-thirds are also in one or both of the two indices tracked by the largest healthcare ETFs: the S&P Health Care Select Sector and MSCI US IMI Health Care 25/50 indices.

At the end of the day, inclusion in any of these indices should help put a company’s stock on the radar screens of the funds that use them as benchmarks. And while the more indices in which a company finds itself the better, the relative importance of each is likely a function of the total assets invested in the funds that are benchmarked to those indices. Most indices are “rules-based”, meaning that constituent selection is based on a published set of rules and

methodologies. Therefore, it is important for issuers to understand the key criteria on which their index eligibility is determined.

Exhibit 5: Assets in Healthcare, Biotech and Pharma ETFs and open-end funds



Source: Morningstar, December 2022

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Appendix 1: Indices used by Biotech & Life Sciences ETFs and Open-end funds

Biotech & Life Sciences ETFs and Open-End Funds AUM Dec 2022

Index	Active	Indexed	Total AUM	% Active	% Indexed
1 Nasdaq Biotechnology	8,303,644,528	1,329,034,019	9,632,678,546	86.2%	13.8%
2 S&P Biotechnology Select Industry		9,448,729,188	9,448,729,188	0.0%	100.0%
3 S&P 500	9,441,984,560		9,441,984,560	100.0%	0.0%
4 ICE Biotechnology		8,746,730,655	8,746,730,655	0.0%	100.0%
5 MSCI World Health Care	4,754,423,343		4,754,423,343	100.0%	0.0%
6 Not benchmarked	3,433,407,043		3,433,407,043	100.0%	0.0%
7 MSCI ACWI	1,648,710,887		1,648,710,887	100.0%	0.0%
8 NYSE Arca Biotechnology		1,491,655,354	1,491,655,354	0.0%	100.0%
9 Lipper Health/Biotech Fund Average	1,429,281,470		1,429,281,470	100.0%	0.0%
10 CSI Biotechnology Thematic		1,293,961,678	1,293,961,678	0.0%	100.0%
11 MSCI USA IMI Biotechnology 10/40	559,806,920		559,806,920	100.0%	0.0%
12 MVIS US Listed Biotech 25		495,226,043	495,226,043	0.0%	100.0%
13 MSCI World Pharma, Biotech and LifeSci	349,576,275		349,576,275	100.0%	0.0%
14 Dynamic Biotech & Genome Intellidex		251,031,782	251,031,782	0.0%	100.0%
15 MSCI World/Pharma Bio & Life	224,039,139		224,039,139	100.0%	0.0%
16 Solactive Genomics		210,905,607	210,905,607	0.0%	100.0%
17 Solactive China Biotech		154,444,146	154,444,146	0.0%	100.0%
18 95% CSI Biotech + 5% RMB Deposit Rate		147,495,947	147,495,947	0.0%	100.0%
19 Hang Seng HK Listed Biotech		127,570,915	127,570,915	0.0%	100.0%
20 Dow Jones Biotechnology		122,853,596	122,853,596	0.0%	100.0%
21 50% Nasdaq Biotech + 50% S&P 500 Pharma Select Industry	118,136,023		118,136,023	100.0%	0.0%
22 50% MSCI ACWI Info Tech + 50% Nasdaq Biotech	104,138,646		104,138,646	100.0%	0.0%
23 Hang Seng Hong Kong-Listed Biotech		94,204,319	94,204,319	0.0%	100.0%
24 AMEX Biotech Holders		89,926,734	89,926,734	0.0%	100.0%

Biotech & Life Sciences ETFs and Open-End Funds AUM Dec 2022

Index	Active	Indexed	Total AUM	% Active	% Indexed
25 North American Marijuana 50% JPM Med Tech + 25% MSCI World Health Care + 25% S&P	88,369,607		88,369,607	100.0%	0.0%
26 Biotech Select Industry	56,023,010		56,023,010	100.0%	0.0%
27 50% MSCI World Health Care + 50% Nasdaq Biotechnology	48,679,853		48,679,853	100.0%	0.0%
28 MSCI ACWI Health Care	46,708,782		46,708,782	100.0%	0.0%
29 95% S&P Biotech Select Industry + 5% RMB Deposit Rate 95% CSI 800 Pharmaceuticals & Biotech + 5% Inter-Financial Institution		46,631,587	46,631,587	0.0%	100.0%
30 Dep		42,254,609	42,254,609	0.0%	100.0%
31 CNI Vaccine and Biotechnology		28,191,106	28,191,106	0.0%	100.0%
32 95% Nasdaq Biotechnology + 5% RMB Current Deposit Rate 55% S&P 500 Info Tech + 25% S&P 500 Comm Svcs + 20% S&P/TSX		25,863,940	25,863,940	0.0%	100.0%
33 Capped Info Tech	20,046,318		20,046,318	100.0%	0.0%
34 LifeSci Biotechnology Clinical Trial		17,471,814	17,471,814	0.0%	100.0%
35 LifeSci Biotechnology Products		17,277,345	17,277,345	0.0%	100.0%
36 CNI Vaccine and Biotechnology + PBC Demand Deposit Rate		15,358,200	15,358,200	0.0%	100.0%
37 94% Nasdaq Biotechnology + 6% call pr krw	14,851,377		14,851,377	100.0%	0.0%
38 KODEX KOSDAQ 150 Healthcare		6,337,581	6,337,581	0.0%	100.0%
39 Solactive Genomics v2		6,241,535	6,241,535	0.0%	100.0%
40 BM&FBOVESPA IBovespa	3,886,819		3,886,819	100.0%	0.0%
41 LifeSci Biothreat Strategy		3,529,798	3,529,798	0.0%	100.0%
42 Solactive China Biotech Innovation		2,585,926	2,585,926	0.0%	100.0%
43 Solactive China Biotech v2		1,597,101	1,597,101	0.0%	100.0%
44 Euronext NEXT Biotech	345,788		345,788	100.0%	0.0%
45 Other	4,439,432		4,439,432	100.0%	0.0%
Total	30,650,499,820	24,217,110,526	54,867,610,346	55.9%	44.1%

Source: Morningstar

Appendix 2: Comparison of Biotechnology Index Rules

	NBI	ICEBIO	SPBIO
Parent	na	na	Must be a member of the S&P Total Market Index.
Exchange	Nasdaq Global Select Market or the Nasdaq Global Market.	New York Stock Exchange (NYSE), NYSE American, Cboe BZX, NASDAQ Global Select Market, NASDAQ Global Market.	NYSE, Nasdaq Capital Market, NYSE Arca, Cboe BZX, NYSE American, Cboe BYX, Nasdaq Global Select Market, Cboe EDGA, Nasdaq Select Market, Cboe EDGX.
Sector	The security must be classified under the Biotechnology Subsector or Pharmaceuticals Subsector according to the Industry Classification Benchmark (ICB), a product of FTSE International Limited.	Must be classified in the Biotechnology Sub-Industry Group of the ICE classification schema.	Must be classified under the Biotechnology Sub-Industry of the GICS classification schema. Supplementary: if there are fewer than 35 qualifying Biotechnology Sub-industry stocks, then additional stocks can be selected from the Life Sciences Tools & Services Sub-indices to bring the total to 35 constituents.
Country	No restrictions	No restrictions	Must be classified as a U.S. company, which requires the following: - file 10-K - U.S. is a plurality of fixed assets and revenues - primary listing in U.S.
Float	No criterion	A minimum 5% security-level free float.	No criterion
Security types	Eligible security types generally include American Depositary Receipts (ADRs), common stocks, ordinary shares, shares of beneficial interest and limited partnership interests.	Common stocks, ordinary shares, ADRs, shares of beneficial interest and limited partnership interests.	Only common stock is included. ADRs are excluded.
Liquidity	Minimum 100,000 share average daily trading volume from the start of the year up to the Reconstitution reference date.	Minimum 100,000 share minimum average daily volume over the ten months preceding the reference date.	A float-adjusted liquidity ratio (FALR), defined as the annual dollar value traded divided by the float-adjusted market capitalization (FMC), is used to measure liquidity.

	NBI	ICEBIO	SPBIO
Weighting	<p>Full market capitalization-weighted with certain constituent caps imposed. ADR weights are based on the actual depository shares outstanding as reported by the depository banks.</p> <p>Note: Nasdaq also publishes an equal weight version of the index.</p>	<p>Float-adjusted market capitalization-weighted subject to certain constituent caps imposed. ADR weights are based on the full underlying ordinary outstanding subject to a cumulative 10% cap on all ADRs in the index.</p>	<p>Equal weighted</p> <p>Note: S&P also publishes the S&P Biotechnology Select Industry FMC Index (USD), which is float-adjusted market capitalization weighted.</p>
Size	<p>Each security must have a minimum market capitalization of \$200 million (not float adjusted).</p>	<p>Each security must have a minimum market capitalization of \$200 million (not float adjusted).</p>	<p>Meet one of the following float-adjusted market capitalization (FMC) and float-adjusted liquidity ratio (FALR) requirements:</p> <p>a. Be a current constituent, have an FMC greater than or equal to US\$ 300 million, and have an FALR greater than or equal to 50%.</p> <p>b. Have an FMC greater than or equal to US\$ 500 million and an FALR greater than or equal to 90%.</p> <p>c. Have an FMC greater than or equal to US\$ 400 million and an FALR greater than or equal to 150%.</p>

Source: Nasdaq, S&P and ICE index methodology documents

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