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Considerations and good practices with respect to inside information disclosures by listed biotech companies

Addressees

This document is addressed to listed biotech companies undertaking clinical trials, especially those with a limited pipeline of product candidates and no or a limited number of commercial products.

Objective

The aim is to assist those companies, especially newly listed ones (with potentially limited experience), in respecting inside information disclosure requirements and preventing market abuse infringements. Given the specific nature of their activities (scientific developments with multidimensional clinical trial results; gradual, stepwise processes; judgements to be made from a scientific and clinical perspective), compliance with those requirements may be particularly challenging for biotech companies, specifically with regard to when and what to disclose.

This document has been circulated for consultation with a selected group of experts.

Scope

The document focuses on:

- the disclosure of inside information during the conduct of the clinical trials. Disclosures regarding post-authorisation issues (such as inspections and reimbursement) are not covered;
- certain specific topics. This document does not replace or extensively repeat the market abuse legislation and disclosure rules or ESMA guidance.

Structure, content and nature

The document summarizes the general legal requirements and contains considerations and good practices (numbered respectively as [C-x] and [GP-x]).

Certain considerations (such as opinions of the FSMA about what information can be considered inside information and at what probability) and good practices (such as opinions of the FSMA about relevant disclosures to include in press releases) may create the impression that the FSMA wishes to prescribe when and what biotech companies should disclose. However, the FSMA certainly has no intention to push towards premature or unnecessarily detailed disclosures.

Without prejudice to the requirement of providing timely and accurate information to investors in accordance with the applicable legislation, the FSMA acknowledges:

- that the assessment of when and what to disclose will significantly depend on the specific facts and circumstances of each case, with judgements to be made from a scientific and clinical perspective;
- that there should be sufficient flexibility to strike an appropriate balance (not too fast but also not too slow, not too much but also not too little), taking into account other legitimate interests.

Instead, the principal aim of the FSMA is to invite biotech companies to take an analytical and sufficiently reasoned approach, at all times, to assessing when and what to disclose.

Although this document cannot capture the specificities of each case, the FSMA believes that including specific considerations and good practices (derived from observations on how different biotech companies are already communicating) provides useful insights that can help (other) biotech companies analyse and decide on the appropriate timing and content of disclosure in their particular case, and prevent them from overlooking elements that might be important.

Materiality

All views expressed by the FSMA in this document are based on the assumption that the materiality test was positive. Whether information is material is a matter of judgment that depends on the specific facts and circumstances of each case. For conceptual purposes, we consider in this document that the information at the disposal of the issuer relates to a product candidate that has a significant revenue potential, taking into account the expected likelihood for and the timing of a potential marketing authorisation. However, it should be remembered that this document cannot capture the specificities of each case, and information may also be considered material in other situations not covered here, or because of other considerations not mentioned in this document.

Responsibility of the issuer

The issuer bears sole responsibility for identifying what information is material and when inside information comes into existence (see Part I), deciding whether to disclose immediately or to delay disclosure if immediate disclosure would prejudice the issuer's legitimate interests (see Part II), and determining what disclosures are required to properly inform the investors (see Part III).

Complementary material

Legislation and circulars

The legislation and circulars regarding market abuse and disclosure obligations for listed companies can be consulted on the website of the FSMA.

Industry-based guidance

The UK BioIndustry Association has published the guide "Best practice for communicating R&D progress to investors and the public", which is available via <http://bia.me/RDcommsguide>.

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Introduction

In accordance with the Market Abuse Regulation (MAR)¹, issuers have to inform the public as soon as possible of inside information. Inside information is information of a precise nature, which has not been made public, and which would be likely to have a significant effect on the share price.

The clinical development of a product candidate by a biotech company is a gradual process in several phases, with an increase in patient enrolment and in efficacy and safety data over time and a dialogue with medical product regulatory authorities. Consistent with the MAR provisions indicating that intermediate steps of a protracted process can be inside information, inside information can come into existence at different moments of the clinical development before the full pivotal and confirmatory phase III results are known and a decision about marketing authorisation is made.

Identifying when inside information comes into existence (see Part I) can be challenging, since the value of a product candidate generally depends on the expected revenue potential (assuming market acceptance), taking into account the expected likelihood and timing of a potential marketing authorisation, which in turn depend on the clinical trial results. In addition, clinical trials concern scientific developments with multidimensional test results and statistical inference, which may be difficult for investors with less knowledge and experience in scientific and clinical matters to understand and interpret correctly. This means that determining the content of press releases (see part III) may also be challenging. Therefore:

[C-01]

The FSMA considers it of the utmost importance that biotech companies take an analytical and sufficiently reasoned approach, at all times, to assessing when and what to disclose.

The FSMA also understands that sector-specific interests may impact the timing and the content of disclosures. Biotech companies typically attach great importance to:

- their relationship with medical product regulatory authorities;
- their relationship with other biotech or big pharma companies in partnerships;
- the ability to present detailed clinical trial results at peer-reviewed scientific conferences and publish them in peer-reviewed scientific journals (as a validation of study results, to reference for commercial purposes and to affect decision-making by the medical community).

Although the FSMA acknowledges that biotech companies should have sufficient flexibility to strike an appropriate balance with regard to when and what to disclose:

[C-02]

The protection of other interests by biotech companies should never prejudice providing timely and accurate information to investors in accordance with the applicable legislation.

Nevertheless, a delay of disclosure may be possible under certain circumstances (see Part II) and the disclosures need not be too detailed: the information should just enable investors to assess the effect on the issuer's position, business and results (see Part III).

¹ Regulation (EU) No 596/2014 of the European Parliament and of the Council of 16 April 2014 on market abuse (market abuse regulation) and repealing Directive 2003/6/EC of the European Parliament and of the Council and Commission Directives 2003/124/EC, 2003/125/EC and 2004/72/EC

Part I - Determination of inside information

Legal requirements

According to Article 7 of MAR:

Inside information comprises information of a precise nature, which has not been made public, and which would be likely to have a significant effect on the share price (paragraph 1, (a)).

- Information shall be deemed to be of a precise nature if it indicates a set of circumstances which exists or which may reasonably be expected to come into existence, or an event which has occurred or which may reasonably be expected to occur, where it is specific enough to enable a conclusion to be drawn as to its possible effect on the share price (paragraph 2).²
- Information which would be likely to have a significant effect on the share price shall mean information a reasonable investor would be likely to use as part of the basis of his or her investment decisions (paragraph 4).

The intermediate steps of a protracted process can also be deemed to be of a precise nature and can therefore also be inside information (paragraph 2 and 3).

A. Considerations

Biotech companies may generate an extensive news flow during the clinical development of their different product candidates. Too frequently issuing press releases, without taking materiality into account, could, however, lead to an information overload that makes it difficult for investors to distinguish between what is less and more important. Therefore:

[C-03]

Biotech companies should assess the materiality of the product candidate and of the information regarding that product candidate, and when such information is considered inside information, they should disclose it through a separate press release.

The value (and hence the materiality) of a product candidate generally depends on the expected revenue potential (assuming market acceptance), taking into account the expected likelihood and timing of a potential marketing authorisation. This in turn depends on the risk-benefit assessment, taking into account the clinical trial results and clinical relevance.

In this document, it is assumed that the information relates to a material product candidate which is, in accordance with the conceptual definition above, a product candidate that has a significant revenue potential for the issuer.^{3 4}

² It need not be possible to predict how the share price will change. The only information excluded is information that is vague or general, from which it is impossible to draw a conclusion as regards its possible effect on the share price (European Court of Justice, 11 March 2015).

³ A product candidate can be tested for different indications. In this document it is also assumed that the information relates to its development for an important indication (with significant revenue potential).

⁴ It should nevertheless also be taken into account that product candidates that are initially not material can become material during their clinical development following, for example, their clinical trial results or the halt of the development of other product candidates in the pipeline of the company.

This will usually be the case for most or all of the product candidates of biotech companies with a limited pipeline of product candidates and no or a limited number of commercial products.

[C-04]

For a material product candidate, the FSMA is of the opinion that:

intermediate events or conclusions along the clinical development process that significantly alter (1) the assessment of the revenue potential, (2) the likelihood and the timing of a potential marketing authorisation and/or (3) the company's go/no-go decision to move to the next phase of the clinical development program, will in most cases qualify as inside information.

For biotech companies, inside information typically arises from (non-exhaustive):

- the efficacy and safety results;
- the recruitment progress;
- the decision to halt a clinical trial;
- the marketing authorisation decisions;
- the entering into or ending of a partnership.

This document cannot capture the specificities of each case. It does not discuss all situations that may constitute inside information⁵, nor does it provide for all aspects that should be taken into account.⁶ The issuer bears sole responsibility for identifying when inside information comes into existence.

1. Efficacy and safety results

To determine when efficacy and safety results may constitute inside information, different aspects and factors have to be taken into account regarding:

- the phase of the clinical development;
- the interim results;
- the trial organisation and data governance.

a) Phase of the clinical development

Efficacy

Inside information regarding efficacy results may arise as soon as patients with the disease of interest are treated, so from a proof-of-concept (typically phase IIA) trial onwards and even before results might become statistically compelling. Obtaining statistical significance is typically not yet the (ultimate) purpose before a phase III trial. Only a confirmatory phase III trial is usually sufficiently powered to detect a clinically relevant benefit with a scientifically acceptable degree of certainty.

⁵ Inside information also typically arises in the context of, for example, mergers and acquisitions (including takeover bids) and cash-impacting events (such as financing rounds).

⁶ Issuers should, for example, also take into account their previous disclosures (such as whether new events or conclusions cast doubt on prior disclosures), prior market reactions (such as how the share price has reacted to prior disclosures and the relative importance of the product candidate in the analysts' valuations) and market expectations (such as about when analysts expect the end of the trial or a potential marketing authorisation decision and commercial launch).

Although the probability that efficacy results qualify as inside information increases in the course of the clinical development process, the FSMA is of the opinion that (exploratory, non-controlled) proof-of-concept (phase IIA) efficacy results may already constitute inside information under certain circumstances (even if the primary objective and endpoint concern safety).

Inside information may arise earlier if, amongst other things:

- there are no (effective) treatments for the disease of interest;
- the efficacy endpoints can be objectively measured (not based on a subjective assessment by the patients), thereby reducing the probability that the results might be merely a placebo effect and lowering the importance of a control group (with blinding of study participants) to consider the first (non-controlled) efficacy results as inside information
- the results are related to a product candidate of a biotech company with a limited pipeline and no or a limited number of commercial products.

These elements increase the value relevance of early efficacy results.

Taking into account the primary addressees of this document (see the front page)⁷:

[C-05]

For a material product candidate, the FSMA is of the opinion that:

it is not only (confirmatory) pivotal phase III results that qualify in most cases as inside information, but usually also (controlled) intermediary phase IIB results, as well as (exploratory, non-controlled) proof-of-concept phase IIA results.

Safety

Information on safety is obtained from the first human (phase I) trial onwards. Therefore, inside information regarding safety results may arise in every phase of the clinical development.

[C-06]

For a material product candidate, the FSMA is of the opinion that:

- **unexpected (numbers of) (serious) adverse events (taking the Reference Safety Information as the basis for the expectedness assessment and depending on, for example, the patient population or the mechanism of action) qualify in most cases as inside information irrespective of the clinical trial phase;**
- **to the extent that its safety profile has already been well-established and the product candidate has been shown to be safe, negative safety information is more likely to qualify as inside information than positive safety information.**

The FSMA acknowledges that negative safety findings do not necessarily imply that no marketing authorisation can be obtained nor that these findings would always be completely negative for commercial success. However, in the assessment of whether safety results constitute inside information, it should be taken into account that negative safety findings may significantly reduce not only the likelihood of marketing authorisation, but also the revenue potential. Product candidates may, for example, receive a marketing authorisation, but nevertheless contain a (black box) warning indicating serious side effects and patient groups that should not use the product.

⁷ For those companies, a product candidate will usually already be material from the beginning.

b) Interim results

Accumulating data may be monitored on an ongoing basis and be analysed at pre-defined moments (for example, after the follow-up of a certain number of patients). Therefore:

[C-07]

**For a material product candidate, the FSMA is of the opinion that:
interim results can qualify as inside information.**

Inside information may arise during a trial before all the data from the full intended sample of patients have been collected and analysed, and so before all results are known. Although absolute (statistical) certainty about the results may be reached only at or near the end of a trial, a significant change in the probability of success might already have been observed during the trial. In addition, small numbers of meaningfully large effects (or the absence of meaningful effects) can, for example, be materially relevant independently of the level of statistical significance.

The probability that interim results might be inside information increases, amongst other things:

- with the number of patients for which the results are already known;
- when a clear trend can be observed;
- with the strength of the results (taking into account both clinical and, when relevant, statistical significance, although the latter is unlikely to be determinative in itself⁸).

On the other hand, it might, for example, take longer for results to become inside information for dose-finding studies when doses have to be escalated.

[C-08]

For a material product candidate, the FSMA is of the opinion that:

- **although small numbers of meaningfully large effects can be materially relevant, in general, negative (trends in) results will qualify as inside information sooner than positive results⁹;**
- **a decision to halt a trial for efficacy, futility or safety reasons will in most cases qualify as inside information (see also below – 3. Decision to halt a clinical trial).**

c) Trial organisation and data governance

The moment when clinical trial observations may become inside information also depends on how the trial is organised, including how the data are managed and for whom they are blinded.

[C-09]

For a material product candidate, the FSMA is of the opinion that:

when the data are not blinded for the issuer, results may constitute inside information at any moment if and to the extent that the issuer can assess the results on an ongoing basis.

However, issuers often outsource data collection, management and analysis to Contract Research Organisations (CRO) and monitoring activities to Data Monitoring Committees (DMC), and the data

⁸ In other words, biotech companies cannot rely only on statistical significance when deciding what they need to disclose to investors regarding clinical trial results.

⁹ Negative trends do not often reverse themselves to become beneficial and statistically significant (see for example “Futility approaches to interim monitoring by data monitoring committees” (DeMets D. L., 2006, *Clinical Trials*, 3: 522-529 - <https://www.ncbi.nlm.nih.gov/pubmed/17170036>)).

(including treatment allocation codes in the case of randomised trials) are typically blinded for as many individuals as – and to the largest extent – practicable. Nevertheless:

[C-10]

For a material product candidate, the FSMA is of the opinion that:

even when the data are blinded for the issuer, results may also constitute inside information without or before a data transfer to the issuer and even when the amount of information communicated to the issuer is limited.¹⁰

Inside information may, for example, arise when the DMC has analysed the (interim) data and has shared its conclusions and recommendations with the issuer without (for the moment) sharing specific (interim) data and/or results (in order to maintain confidentiality).

In this context, for example, a DMC's conclusion and recommendation not to stop, but to continue the trial may in itself affect the investors' judgment regarding the value of the product candidate by revealing that the results lie within a particular range, namely that the product candidate is neither extremely effective nor hopeless nor obviously unsafe (especially if investors, for example, expect that a stopping boundary would be crossed).¹¹

2. Recruitment progress

The value of a product candidate also depends on the timing of a potential marketing authorisation. This timing depends, amongst other things, on the number of patients to be recruited during the different subsequent trials and the recruitment rate. However, recruitment is often slower than expected, with many trials (especially multicentre, randomised, controlled trials) failing to reach their planned sample size within the envisaged timing.

[C-11]

For a material product candidate, the FSMA is of the opinion that:

- **issuers should assess on an ongoing basis, irrespective of the phase of the clinical development, whether the recruitment and treatment of patients is on track;**
- **a significant deviation between the actual and expected level of patient recruitment and treatment will in most cases qualify as inside information, as it may significantly affect the end of the trial and the timing of a potential marketing authorisation. A recruitment delay will in most cases be inside information irrespective of the actions that are considered or will be taken to resolve the problem;**
- **the fact that the first patient(s) having been treated or that a certain proportion of the target sample has been reached will usually not qualify as inside information if there is no significant deviation from the expected level of patient recruitment and treatment and the envisaged timing.**

¹⁰ When outsourcing activities, issuers should take into account that persons from a CRO or DMC, for example, may also possess inside information and have to comply with the market abuse rules. In accordance with Article 18, paragraph 2 of MAR, the issuer should take all reasonable steps to ensure that such persons that are on the insider list acknowledge in writing the legal and regulatory duties entailed and are aware of the sanctions applicable to insider dealing and unlawful disclosure of inside information.

¹¹ See also "Predicting clinical trial results based on announcements of interim analyses" (Broglio K. R. et al., 2014, *Trials*, 15:73 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3973959/>).

3. Decision to halt a clinical trial

[C-12]

For a material product candidate, the FSMA is of the opinion that:

the decision to halt a trial or to withdraw a marketing authorisation application constitutes inside information in most cases, irrespective of the reason why and of any further plans.

The decision to *temporarily* halt a trial may also qualify as inside information to the extent that there would be a significant delay or for another, more fundamental reason (such as safety concerns) that caused the halt, in which case it is also important to take into account the potential relationship with and impact on other trials with the same product candidate.

4. Marketing authorisation decisions

A clinical development involves a dialogue with medical product regulatory authorities and a marketing authorisation application procedure consists of different steps.

[C-13]

For a material product candidate, the FSMA is of the opinion that:

marketing authorisation decisions by important¹² medical product regulatory authorities qualify as inside information in most cases.

In the case of an authorisation procedure via the European Medicines Agency (EMA), this will typically already be the case when one of its scientific committees (such as the Committee for Medicinal Products for Human Use (CHMP) or for Orphan Medicinal Products (COMP)) has given its scientific opinion (based on the final formal vote), even though the European Commission still has to take the recommendation into consideration and convert it into a legally binding decision.

[C-14]

For a material product candidate, the FSMA is of the opinion that:

inside information may also arise from the dialogue with medical product regulatory authorities before a marketing authorisation decision has been made.

Inside information may arise from contacts with medical product regulatory authorities during the trials and during the marketing authorisation procedure based on elements, such as comments, objections or additional requests, which may have a significant impact on the probability and timing of a potential marketing authorisation and on the revenue potential (for example, restrictions in use).

In the case of an authorisation procedure via EMA, an issuer may, for example, be informed about the trend (outcome of a trend vote) amongst members of a scientific committee regarding whether they are in favour of recommending the granting of a marketing authorisation. It might already be possible for an issuer at that time (ahead of the final vote and recommendation) to reasonably conclude whether a positive or negative decision is highly likely to be given and therefore the outcome of such a vote constitutes inside information.

¹² An important medical product regulatory authority is typically (1) the first authority that makes a decision or (2) an authority that provides access to an important market in terms of revenue potential.

In the case of an authorisation procedure via the US Food and Drug Administration (FDA), a scientific advisory committee of outside experts convened by the FDA may, for example, have voted on the acceptability of the risk-benefit profile for approval. Although such votes are not binding on the FDA, they might significantly impact the probability of a positive or negative decision and therefore the outcome of such a vote constitutes inside information.

Although the examples above cover (centralised) authorisation procedures via EMA and FDA, similar reasoning may apply to (decentralised) authorisation procedures via national authorities.

5. Entering into or ending a partnership

Pre-revenue biotech companies often out-license their product candidates by entering into R&D or commercialisation partnerships with other biotech or big pharma companies.

[C-15]

For a material product candidate, the FSMA is of the opinion that:

when assessing whether entering into a partnership is inside information, the issuer should take into account not only the quantitative aspects (such as the deal structure-payment terms), but also the qualitative aspects of the deal (such as the scope of the rights and the partner's R&D experience or commercialisation network).

Inside information may arise not only when rights are out-licensed, but also, for example, when rights are in-licensed or in the case of other types of collaboration agreements.

[C-16]

For a material product candidate, the FSMA is of the opinion that:

inside information may arise before the finalisation and signing of the partnership agreement.

Depending on the circumstances, this may, for example, already be the case when a binding letter-of-intent is signed or later, before all conditions to which the agreement is subject, are fulfilled.

B. Good practices

The determination of inside information can be more challenging than, for example, in the context of financial results or M&A, where historical financial information can be used as a basis of comparison.

1. Internal procedures

[GP-01]

The FSMA considers it important that biotech companies have appropriate internal procedures for assessing the nature of information (inside information or not), including sufficiently detailed documentation of the judgments made and the underlying reasoning.

This may help to demonstrate, when required, that a reasoned and consistent approach has been followed. A disclosure committee comprising, for example, members of the senior management (including the chief medical officer and chief regulatory officer) for purposes of the assessment, and an escalation procedure to determine when and how other persons should inform the disclosure committee of issues that might be inside information, may form an important part of those internal procedures.

2. Gradual processes

It may be challenging for biotech companies to determine when observations with respect to the (absence of sufficient) recruitment or when accumulating results (from trials for which the data are not blinded for the issuer) constitute inside information. Therefore:

The FSMA considers it good practice for material product candidates, without prejudice to the inside information disclosure obligation, to:

- **[GP-02]**
discuss the status of the trials in their periodic reporting, including the level of recruitment and treatment progress;
- **[GP-03]**
disclose results at a pre-determined frequency (for example, after the follow-up of certain proportions of the target sample), with the frequency to be determined as a function of the organisation of the trial and the expected trial duration;
- **[GP-04]**
disclose a calendar with the expected timing¹³ of clinical (progress and results) milestones in their periodic reporting¹⁴, including a discussion of any changes made to this calendar.
A significant change with respect to the calendar that constitutes inside information should, however, also be disclosed through a separate press release.

Complying with these good practices may help to reduce potential criticism regarding arbitrary timing of disclosure and to create a more predictable disclosure environment compared to when a biotech company discloses only at the moment that inside information arises.

¹³ An expected timing does not have to be an exact date; an indicative period that is neither too wide nor too narrow may be sufficient (see also [GP-21], [GP-28], [GP-31] and [GP-34]).

¹⁴ It is also recommended that this calendar is published on the website (next to the calendar of periodic publications).

Part II - Timing of disclosure of inside information

Legal requirements

Article 17 (1) of MAR requires that inside information is disclosed *as soon as possible* by the issuer.

As an exception to this rule, **Article 17 (4) of MAR** provides that an issuer may, on its own responsibility, delay the disclosure provided that all of the following conditions are met:

- immediate disclosure is likely to prejudice the legitimate interests of the issuer;
- delay of disclosure is not likely to mislead the public;
- the issuer is able to ensure the confidentiality of that information.

Where an issuer has delayed the disclosure of inside information, it has the legal obligation to inform the FSMA of the delay immediately after the information is disclosed to the public, and provide a written explanation of how the conditions were met.¹⁵

This document cannot capture the specificities of each case. The issuer bears sole responsibility for deciding whether to disclose immediately or to delay disclosure (if legitimate).

A. Considerations

1. Immediate disclosure

Inside information should be disclosed *as soon as possible*. If inside information arises during trading hours, issuers are reminded that, to respect the '*as soon as possible*' disclosure requirement and to prevent investors executing transactions without being fully informed, they should not await the close of trading but disclose *immediately* during trading hours after having requested that the FSMA (market surveillance: +32 (2) 220.59.00) temporarily suspend the trading of its shares.

2. Delay of disclosure

The MAR Guidelines by ESMA (ESMA/2016/1478) provide a non-exhaustive, indicative list of legitimate interests for which a delay is possible. Those examples are, however, not biotech-specific.

Specifically for biotech companies, the FSMA is of the opinion that the delay of disclosure of inside information is possible, for example:

- [C-17]
for the disclosure of clinical trial results, if additional analyses and discussions are required in order to inform the market correctly on the main results and conclusions based on the data in their possession at that moment.

An issuer may, for example, want to delay the disclosure of overall efficacy results for:

- safety data analyses (for which the importance depends on the extent to which the safety profile of the product candidate has already been well-established, taking into

¹⁵ See also Article 4 of Commission Implementing Regulation (EU) 2016/1055 of 29 June 2016 laying down implementing technical standards with regard to the technical means for appropriate public disclosure of inside information and for delaying the public disclosure of inside information.

account, amongst other things, prior experience with the (type of) product candidate and indication of interest);

- subgroup analyses to control the consistency across subgroups of clinical importance or to check credible subgroups regarding particular treatment effects (which is of particular importance for heterogeneous populations and for pivotal trial results that will be the basis for the regulatory labelling).

In this context, however, please see also below [C-20].

– [C-18]

where there is a dialogue with medical product regulatory authorities (such as during a marketing authorisation application procedure), when immediate disclosure is not permitted under the applicable laws or regulations or the directions of that authority.¹⁶

It may, for example, be possible that an issuer has to delay the disclosure of a marketing authorisation (intermediary) opinion, such as the outcome of a trend vote, or a (final) decision of which it has been informed, while having to await an official publication by the medical product regulatory authority.

– [C-19]

when conducting negotiations for concluding a partnership, where the outcome of such negotiations would likely be jeopardised by immediate disclosure.

3. Restrictions on the delay of disclosure

a) General

Issuers that decide to delay the disclosure of inside information should take into account that:

- they bear sole responsibility for this decision and for determining how long the disclosure can be legitimately delayed;
- after this decision has been made, they still have to use their best efforts, to the extent possible, to disclose the inside information as soon as possible;
- where the confidentiality of that inside information is no longer ensured, they have to disclose it to the public as soon as possible;
- this is not possible in situations where this is likely to mislead the public;¹⁷
- equity financing transactions are not allowed when holding unpublished inside information.

¹⁶ If an issuer has delayed disclosure because it was not permitted under the directions of a medical product regulatory authority, the FSMA requests that appropriate evidence also be included in its notification to the FSMA (for example, procedural rules or guidelines, evidence of having informed that authority in writing of its obligations under MAR, the authority's feedback and the contact details of the relevant staff member or representative of the authority).

¹⁷ The MAR Guidelines ESMA/2016/1478 provide a non-exhaustive, indicative list of such situations. This would, for example, be the case where the inside information is materially different from a previous public announcement or the inside information is in contrast with the market's expectations, based on signals that the issuer has previously sent to the market.

b) Efficacy and safety results

It is common for biotech companies to delay the disclosure of inside information regarding clinical trial results during the data analysis, because all data have to be analysed in depth and discussed with internal and external experts in order to draw scientifically correct conclusions.

Although the FSMA acknowledges that different steps have to be undertaken for a correct risk-benefit assessment and a proper disclosure of inside information, biotech companies should:

- take into account that,
 - a complete and extensive analysis of all aspects and details beyond the top-line results is not required for the disclosure of inside information;
 - additional analyses and discussions for which it is self-evident that they will not change the main results and conclusions cannot justify a delay of disclosure;
 - a stepwise communication might be necessary in certain cases (with additional insights from further analyses and discussions - that do not change the main results and conclusions - being communicated later on);
- find the appropriate balance between timeliness of disclosure and depth of analysis and discussion that is required to draw the top-line results and conclusions and disclose them in a correct and not misleading way;
- be able to justify, if they have delayed the disclosure of inside information for additional analyses and discussions, that disclosure was not possible or appropriate (yet) without those additional analyses and discussions.

In this context:

[C-20]

The FSMA is of the opinion that:

- **when the safety profile of the product candidate is already well-established, delaying the disclosure of efficacy results is usually not possible in order to wait for the outcome of further safety analyses that are unlikely to provide important new information;**
- **when it is clear that a trial has failed, delaying the disclosure of this main conclusion, which is inside information, is usually not possible in order to wait for the outcome of additional analyses and discussions, such as, in confirmatory trials, for subgroup analyses to identify positive results based on subgroups that do not meet the credibility criteria.**

In general, it may be clear that a clinical trial has failed when the results are such that it is unlikely that a positive risk-benefit profile could still be concluded from further analyses.

Specifically, a confirmatory trial has formally failed when there is no statistically persuasive evidence regarding the primary efficacy objective. From a statistical point of view, even where a significant subgroup effect or other success in the secondary endpoints may be observed, no confirmatory conclusions are typically possible. In that case, the results will typically be inadequate to support a marketing authorisation, and one or more additional trials will usually have to be conducted.¹⁸

¹⁸ See, for example, Section 5.4 of the EMA guideline on the investigation of subgroups in confirmatory clinical trials (January 2019): https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf

B. Good practices

1. Internal procedures

[GP-05]

The FSMA considers it important that biotech companies, when assessing the nature of information and having determined that certain information qualifies as inside information, also appropriately document the reasoning with respect to the timing of disclosure.

This may help to demonstrate, when required, that a reasoned and consistent approach has been followed. In any event, where an issuer has delayed the disclosure of inside information, it has the obligation to inform the FSMA and provide a written explanation of how the conditions were met.

[GP-06]

The FSMA considers it important that biotech companies have effective procedures and measures in place (such as a pre-drafted press release) to ensure that the time between when inside information arises (or when confidentiality is breached in the case of a delay in the disclosure of inside information) and its publication is as short as possible.

In any event, in the case of a delay in the disclosure of inside information, issuers are legally required to be able to provide evidence on the arrangements put in place to disclose the relevant inside information as soon as possible where confidentiality is no longer ensured.

2. Disclosure by other parties

Sometimes information on the same matter is also disclosed by other parties (such as by a medical product regulatory authority or, in the case of a partnership, by another biotech company).

[GP-07]

The FSMA recommends that, without prejudice to the legal requirements, the issuer aligns its timing of disclosure as much as possible with the timing of disclosure by the other party.

Issuers are requested to inform the FSMA about the other party's intention (to the extent known) in order to evaluate whether a trade suspension may be necessary (for example, in order to prevent investors executing transactions without being fully informed and if the other party were to publish during the trading hours of the stock exchange where the issuer's shares are listed).

3. Additional market abuse preventing measures

[GP-08]

In addition to the legal requirements, the FSMA recommends that biotech companies take additional measures to prevent market abuse when and where they deem appropriate.

Issuers can, for example, establish additional closed periods during which insiders shall not conduct any transactions, and contact the FSMA at any time to request a temporary trading suspension.

This may, for example, be appropriate in the case of disclosure of clinical trial results when:

- there is uncertainty about when exactly inside information arises and whether or not the delay in the disclosure of inside information would be justified;
- the issuer needs additional time for further analyses and discussions and to prepare an appropriate communication.

Part III - Content of disclosure of inside information

Legal requirements

A press release with inside information should make it possible to assess the effect of the information on the issuer's position, business and results, and should ensure that investors are not misled.

- Although **MAR** does not contain specific rules with regard to the content of the inside information to be disclosed, it states, in **Article 12 (1) (c)**, that the dissemination of information that gives or is likely to give false or misleading signals is considered market manipulation.
- According to **Article 5 of the Royal Decree on the obligations of issuers**¹⁹, issuers have to make the necessary information available to the public in order to ensure the transparency, integrity and proper operation of the market. The information provided has to be true, accurate and genuine, and shall enable securities holders and the public to assess the effect of the information on the issuer's position, business and results. These requirements also apply to inside information.

A number of good practices are set out below in order to help biotech companies meet these requirements. The first section below provides general good practices irrespective of the type of information. In the second section, specific good practices can be found organized according to the type of information (in the following order: efficacy and safety results, recruitment progress, decision to halt a clinical trial, marketing authorisation decisions, entering into or ending a partnership).^{20 21}

Issuers should take into account that the importance of the specific good practices for meeting the legal requirements depends on the specific facts and circumstances. This document cannot, however, capture the specificities of each case. The issuer bears sole responsibility for determining which disclosures (including those on the non-exhaustive list of specific good practices mentioned below) are required for investors to make an informed investment decision.

A. General good practices

1. Non-technical and technical information

Investors in biotech companies have varying levels of knowledge and experience in scientific and clinical matters (in addition to financial matters). Clinical trials, however, concern scientific developments with multidimensional test results and statistical inference, which may be difficult for investors with less specialised knowledge to understand and interpret correctly. This means that a biotech company should not provide solely (technical) disclosures that can be understood only by more knowledgeable investors. However, not providing essential (technical) disclosures (such as statistical information or other details when relevant), on the assumption that less knowledgeable investors cannot understand them or interpret them correctly, is unsatisfactory as well.

¹⁹ Royal Decree of 14 November 2007 on the obligations of issuers of financial instruments admitted to trading on a regulated market

²⁰ It is also reminded that, when a press release contains inside information, this should be stated on the press release in accordance with Article 2 of the MAR Commission Implementing Regulation (EU) 2016/1055.

²¹ The FSMA is of the opinion that, if an issuer would decide to issue a separate press release for events that are not considered to have a significant impact on the share price (non-inside information), it is important that it is clear from (the content of) the press release that the issuer believes the impact is not significant.

Therefore, the FSMA considers it good practice to:

- [GP-09]
include a balanced mix of non-technical and (supporting) technical information, thus allowing investors with different levels of knowledge and experience in scientific and clinical matters to make an informed investment decision;
- [GP-10]
ensure that the technical information does not obscure the main, non-technical, messages and that those main messages are always easy to find and understand.

2. Hard and soft information

The FSMA asks issuers to:

[GP-11]

disclose information as factually and objectively as possible.

However, clinical development involves interpretation and judgment, and soft information (such as an issuer's view and forward-looking information) may also be considered useful for investors.

Therefore, the FSMA recommends to:

- [GP-12]
only disclose soft information based on reasonable grounds;
- [GP-13]
include, where necessary, meaningful cautionary statements and explanations.

In particular, biotech companies sometimes disclose quantitative information that is (partially) based on forecasts of sales volume (such as partnership deal values when royalties are included).

The majority of such forecasts have, however, been observed to be highly inaccurate (mostly a significant overestimation), and the greatest forecast errors typically occur at the earliest stages of the clinical development.²² A more reliable forecast is usually possible only after the product launch, when more credible information about the forecast parameters is available. Nevertheless, the level of forecast error has been observed to stay high until several years after the commercial launch.

Therefore, the FSMA advises to:

[GP-14]

only disclose information based on expected revenues only if a reasonable forecast can be made, and if such information would be included, to disclose the key underlying assumptions.

3. Symmetry of information

Sometimes information on the same matter is also disclosed by other parties (such as by a medical product regulatory authority or, in the case of a partnership, by another biotech company).

²² See, for example, "Pharmaceutical forecasting: throwing darts?" (Cha M. et al., 2013, *Nature Review Drug Discovery*, 12: 737-738 - <https://www.nature.com/articles/nrd4127>).

To ensure that certain investors are not deprived of essential information compared to other investors, the FSMA asks the issuers to:

- [GP-15]
closely cooperate, to the extent possible, with the other party;
- [GP-16]
disclose information that is the same, at least in all material respects, taking into account that different (lower) disclosure obligations for the other party do not discharge the issuer of the obligation to provide the required information in accordance with the applicable legal requirements.

The FSMA urges issuers to inform potential collaboration partners in good time about its disclosure obligations, as law takes precedence over contractual confidentiality clauses.

4. Internal review before public release

It may be challenging for biotech companies to publish a balanced mix of technical and non-technical information that is scientifically correct and, at the same time, easy to understand.

Therefore, the FSMA considers it good practice to:

[GP-17]

ensure, without prejudice to the requirement to disclose as soon as possible, that persons with different types of expertise have reviewed the information before its public release and that appropriate internal procedures are established for this purpose.

Although senior executives and investor relations officers usually have at least a general understanding of regulatory, scientific and clinical matters, it is good practice to ensure that the information is also reviewed by experts. A multidisciplinary review should help ensure that the communication is correct, objective and balanced, with meaningful cautionary statements and explanations being added where necessary. Moreover, a review by a public relations practitioner might also be useful to check for comprehensibility and readability. However, issuers should bear in mind that press releases for the investment community should not be marketing tools.

B. Specific good practices

1. Efficacy and safety results

When disclosing information on efficacy and safety results, the FSMA considers it good practice to:

a) General

[GP-18]

provide a clear heading and summary that accurately reflects the content of the press release.

A good practice would be to provide a summary in the form of a list of the main conclusions.

[GP-19]

explain the main features of the clinical trial:

- Key features concern the clinical phase, objective and design (such as the research question, blinding, control group, randomisation, target population, sample size and endpoints);
- A good practice would be to have a section with the main features of the trial after the body of the press release, entitled “About the [name of the trial]”, and to refer to (other documents on) the issuer’s own website or clinical trial register websites for more information.

[GP-20]

provide a clear and well-structured discussion of the main results and conclusions, giving a balanced view of favourable and less favourable findings.

The discussion depends on and has to be adapted in accordance with, for example, the trial objective and design, whether it concerns top-line or full results, the extent to which the safety profile has already been established and the novelty of the results (whether or not this is the first time that results of a particular trial are disclosed).

- Although it can be accompanied by another document with more information (for example, an analyst call presentation), the press release itself should contain all important findings;
- A good practice would be to also provide relevant contextual information (see below – (d)).

[GP-21]

mention the next material step and, to the extent possible, the expected timing.

b) Objectives and endpoints

[GP-22]

include an explicit and unambiguous statement (in the summary) on whether or not the primary objectives and endpoints (for the primary analysis sample) have been met.

This is without prejudice to the fact that the interpretation of clinical trial results depends on the totality of the evidence, and therefore a binary conclusion on a single endpoint would be overly simplistic.

- If there are also key secondary objectives and endpoints with important findings:

[GP-23]

include a discussion of the results in relation to (1) the primary objectives and endpoints and (2) the key secondary ones, while making a clear distinction between both;

- If the clinical trial includes a control group with a placebo or active comparator:

[GP-24]

include a discussion of the results after treatment (1) versus the baseline situation (before treatment) and (2) versus the control group, while making a clear distinction between both.

c) Specific results

[GP-25]

provide an objective and unambiguous discussion of the results with:

- **sufficient quantitative information to support the main conclusions, giving insight into the clinical and, when relevant, statistical strength (typically indicated via p values).**
 - This information is important for investors to be able to determine the likelihood of future success and, therefore, to enable them to assess the effect on the issuer's position;
 - A good practice would be, where possible and useful, to use tables that give a quantitative overview of the main results and can be easily read together with the accompanying explanatory text;
 - Qualitative statements might, nevertheless, be sufficient in certain cases, such as, for example, with regard to the safety data, when the primary endpoint concerns efficacy, the safety profile is already well-established and there are no unexpected (numbers of) (serious) adverse events.

- **at least those explanations and details that are necessary to ensure investors are not misled, such as disclosures on how the issuer reached and presented its results.**

Therefore, the FSMA recommends that issuers consider providing relevant explanations and details regarding, for example:²³

- the analysis sample and subgroup analyses;
- not pre-specified (post-hoc) analyses (adjustments);
- the p values and associated analysis method.

Although the FSMA is aware that certain information is sometimes saved for scientific conferences and journal publications, taking into account their embargo and prior publication policies, it reminds issuers that they should provide all information that enables investors to assess the effect of the information on the issuer's position, business and results.

[GP-26]

not overstate the significance and novelty of the results, but:

- **distinguish, where relevant, between statistical and clinical significance.**
 - Statistically significant results are not necessarily clinically significant, and the demonstration of an effect of at least a minimum size is sometimes even considered essential for a marketing authorisation;
 - Such a distinction might not only be relevant when the trial is powered to obtain statistical significance. Even if this were not the case, the distinction can also be important when statements about “significance” are included in the press release;
 - When stating, for example, that the results are “significant”, it is important that it is clear to the reader what this means (for example, are the results statistically and/or clinically significant, and, if there is a control group, does this relate to the results versus the baseline situation or versus that group?).

²³ See also “Press releases for Phase 2 clinical trial topline results: Have the objective pre-specified efficacy results been disclosed?” (Su Z. & Livoti C., 2016, *Contemporary Clinical Trial Communications*, 4:A1-A2 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5935892/>)

- **mention important caveats such as study limitations.**

It is important that cautionary statements and explanations are added, where necessary, in order to help investors with different levels of knowledge and experience to interpret the results correctly.

- **ensure that the novelty of the results is clear.**

If it is not the first time that results of a particular trial are disclosed (for example, interim results were already published), it is good practice to include a reference to the previous communication and a comparison with the previously disclosed results.

d) Contextual information

[GP-27]

provide or refer to relevant contextual information about, for example:

- **the indication of interest and target market (size and trends);**
- **the competitive landscape with existing treatments and their risk-benefit profile;**
- **the product candidate (and active comparator if used as control group) and how the issuer believes it can fill a gap, improving the risk-benefit profile versus other treatments.**

A good practice would be:

- to have sections with concise contextual information after the body of the press release, entitled “About the [indication of interest/product candidate/active comparator]”;
- to refer to other documents of the issuer (such as the annual report or a prospectus) or third-party reports for more details or as a reference indicating the source of the information.

2. Recruitment progress

When disclosing a deviation between the actual and expected level of patient recruitment, the FSMA considers it good practice to:

- **[GP-28]**
provide, to the extent possible, a revised indication of the timing for the disclosure of new results/the end of the ongoing trial/the start of the next material step;
- **[GP-29]**
mention, in the case of a recruitment delay, the actions that will be taken or at least are considered to resolve the problem.

3. Decision to halt a clinical trial

When disclosing that a clinical trial has been halted, the FSMA considers it good practice to:

- **[GP-30]**
mention the fundamental underlying reason and considerations;
- **[GP-31]**
provide, to the extent possible, information on the probability and (earliest) timing for a potential resumption of the trial or the potential start of a new (modified) trial;

- [GP-32]
mention, if relevant, the potential impact on other trials with the same product candidate or the absence thereof.

4. Marketing authorisation decisions

When disclosing a marketing authorisation decision, the FSMA considers it good practice to:

- [GP-33]
explain the scope and any limitations or restrictions;
- [GP-34]
mention the next material step and, to the extent possible, the expected timing.

5. Entering into or ending a partnership

When disclosing a new partnership, the FSMA considers it important to:

[GP-35]

provide sufficient qualitative as well as quantitative information.

- Qualitative information is, for example, a description of the partner, of the partnership's objective and advantages, of the transferred rights, their scope and the degree of exclusivity, and of material clauses with important rights and obligations.
- Quantitative information concerns the deal structure-payment terms.

Of particular relevance is:

- whether or not there is a direct cash impact via an up-front payment and the amount;
- a distinction between the other main components, such as milestone fees and royalty payments, with, for the latter, at least an indication of their magnitude;
- if a "total partnership deal value" is mentioned, clarity about the components which can be achieved by including a definition of how this figure is obtained (with respect to the inclusion of royalties: see above – General good practices: 2. Hard and soft information);
- whether or not – and the extent to which – the issuer will (continue to) bear (part of) any significant (R&D or other) costs.

When disclosing the end of a partnership, the FSMA considers it good practice to:

- [GP-36]
mention, to the extent known, the fundamental underlying reasons and considerations;
- [GP-37]
disclose not only the direct financial impact (for example: termination payments), but also to provide longer-term considerations (for example: new partner search or alternatives).

Addendum

Interviews, presentations and scientific publications

No revelation of inside information to a limited audience

[C-21]

The FSMA reminds issuers that no inside information can be revealed to a limited audience.

No inside information can, for example, be disclosed in interviews to the press, in presentations to investors, analysts or scientists, or in scientific publications (such as papers and posters), without the issuer having disclosed this as inside information to the public and all securities holders by means of a press release in accordance with the legal requirements.

[GP-38]

The FSMA considers it good practice for issuers to:

- **publish, to the extent possible, their presentations and publications on their own website or at least provide a link to the third-party website (whether open or closed access);**
- **organise conference calls during which analysts can ask questions and investors can “listen only”, and make a recorded replay available on their website.**

Statements during interviews and presentations

[C-22]

The FSMA is of the opinion that one should stay as close as possible to the official communication and be as factual and objective as possible during interviews and presentations, abstaining from any overstatement of the significance of clinical trial results and of revenue potential and from any value judgment with regard to the present or future value of the company’s shares.

It should be taken into account that the dissemination of false or misleading information, including rumours and news that give, or are likely to give, false or misleading signals as to the price of a financial instrument, is considered as an infringement of MAR (see Recital 47 and Article 12 (1) (c) of MAR).

Announcement of a presentation or publication

The announcement *itself* of a presentation or publication does not constitute inside information.

The FSMA considers it important that:

- **[C-23]**
such an announcement does not create the impression that the acceptance for presentation (at a conference) or publication (in a scientific journal) is driven by the (clinical and statistical) significance of the results;
- **[C-24]**
if such an announcement repeats clinical trial results that have already been disclosed, it is clear that these are not new results (a good practice in that context would be also to include a reference to the press release about those results).