27 September 2022
EMA/782210/2022
Committee for Medicinal Products for Human Use

ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials

Step5

Transmission to CHMP	28 March 2019
Adoption by CHMP	28 March 2019
Release for public consultation	29 March 2019
End of consultation (deadline for comments)	29 September 2019
Final adoption by CHMP	16 September 2022
Date of coming into effect	16 March 2023

E19 Document History

Code	History	Date
E19	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation (document dated 28 February 2019).	3 April 2019
E19	Endorsement by the Regulatory Members of the ICH Assembly under *Step 4,* including a title change from "Optimisation of Safety Data Collection" to "A Selective Approach to Safety Data Collection in Specific Late-Stage Pre-approval or Post-Approval Clinical Trials".	27 September 2022

ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials

Table of contents

1. Introduction

1.1. Objective of the guideline

This Guideline is intended to provide internationally harmonised guidance on the use of selective safety data collection that may be applied in specific late-stage clinical trials that may be pre-approval or post-approval. Selective safety data collection refers to the reduced collection of certain types of data in a clinical trial after thorough consideration of factors that would justify such an approach. By tailoring the method of safety data collection, it may be possible to carry out clinical trials with greater efficiency by streamlining the approach to data collection. This may facilitate the conduct of large-scale efficacy and safety clinical trials with large numbers of participants and long-term follow-up.

In all circumstances in which the use of selective safety data collection is considered, the welfare of every trial participant should be safe-guarded.

1.2. Background

A robust safety database is the basis upon which the safety profile of a drug[1] is characterised.

Knowledge about a medicinal product's safety profile continually evolves as safety data accumulates over time. Throughout the course of medicinal product development sponsors collect extensive safety-related data that may include vital signs and other physical examination data, laboratory data, and all adverse events. In specific phase 3 or post-approval clinical trials, if the safety profile of a drug is well-understood and documented, collection of comprehensive safety data may provide only limited additional knowledge of clinical importance. In such circumstances, a more selective approach to safety data collection may be adequate.

Regulators, sponsors, and investigators have a shared interest in facilitating the conduct of clinical trials that could yield important new medical knowledge and advance public health. With the growing complexity and size of clinical trials, it is recognised that a uniform approach no longer applies to all clinical trials. In some instances, a selective, i.e., risk proportionate, approach to safety data collection may be acceptable.

This document describes circumstances in which it may be appropriate to reduce the collection of safety data in late-stage pre-approval and post-approval clinical trials, e.g., long-term outcome trials, when appropriate and with agreement from regulatory authorities (see Section 2.7).

Sponsors and investigators will need to ensure that routine patient care is not compromised by use of a selective safety data collection approach (see Section 2.1).

1.3. Scope of the guideline

This Guideline is intended to apply mainly to collection of safety data from interventional clinical trials primarily in the post-approval setting. In some circumstances, it may be considered for use in the pre-approval setting.

Pre-approval Setting

In the pre-approval setting, comprehensive safety data collection is generally expected in order to elucidate the frequency, severity, seriousness, and dose-response of adverse events, including potential differences across subsets, e.g., demographic; medical history; and/or concomitant therapy.

[1] For the purpose of this Guideline, the term "investigational product" should be considered synonymous with "drug" and "medicinal product," and includes both human drugs and biological products.

In rare cases, when sufficient safety data are available from completed clinical trials, selective safety data collection may be justifiable in phase 3 trials.

Post-approval Setting

Once a drug has been approved, comprehensive collection of all safety data may provide only limited additional knowledge of clinical importance. In such circumstances, a more selective approach to safety data collection may be adequate as long as the trial objectives and the welfare of trial participants are not compromised.

This guidance is not applicable to gene therapy or rare/orphan disease clinical trials. With limited numbers of prospective participants for such trials, the collection of comprehensive safety data, from every participant, is warranted.

Selective collection of safety data following the principles of this Guideline does not alter local/regional safety reporting requirements.

2. General principles

2.1. Ensuring safety of trial participants

Safety monitoring in a clinical trial serves two purposes: 1) to protect the safety and wellbeing of individual trial participants; and 2) to obtain safety information to be used in the assessment of the risk profile of the investigational medicinal product.

The selective safety data collection approach described in this Guideline refers to the recording of certain data (see Section 2.5) by investigators in case report forms, as well as to their reporting to sponsors for subsequent evaluation and submission to regulatory authorities. Importantly, this approach does not affect the responsibilities of investigators, as health care professionals, to monitor trial participants and ensure they are treated according to prevailing standards of care. Specifically, selective safety data collection does not affect the monitoring and clinical care of individual trial participants or documentation of their adverse events in medical records. Moreover, selective safety data collection does not obviate other reporting obligations of health care professionals, such as safety reporting in accordance with local/regional requirements.

For example, consider a drug where the safety data are well characterised, where hypoglycaemia is a known adverse drug reaction and routine blood glucose monitoring is recommended in labelling. In a clinical trial utilising selective safety data collection, blood glucose should be monitored in the same way it would be monitored in clinical practice; however, the data do not need to be recorded in the case report form (CRF) or reported to the sponsor as long as they are not stipulated in the protocol and not associated with a serious adverse event. Blood glucose levels and hypoglycaemia would be recorded in the CRF, however, if they are stipulated in the protocol, e.g., as an adverse event of special interest (AESI), deemed to be clinically relevant, or associated with serious adverse events.

2.2. Factors that contribute to a conclusion that the safety profile of a drug is sufficiently characterised to justify selective safety data collection

The factors listed below can contribute to the conclusion that the safety profile of a drug is sufficiently characterised to justify selective safety data collection in a proposed clinical trial. The presence or absence of any of these factors alone is not determinative; however, the greater the number of applicable factors, the stronger the support for selective safety data collection.

Regulatory status

1. The regulatory status of the product, i.e., whether the drug has received marketing authorisation from a regulatory authority.

Mechanistic factors

2. Understanding of the drug's mechanism of action; characterisation of off-target effects (untoward effects mediated through targets other than the target of interest, e.g., mineralocorticoids and gynecomastia; minoxidil and hirsutism).

3. Knowledge of the safety profile of drugs in the same pharmacologic class, e.g., support for selective safety data collection would be stronger for a member of a well-established pharmacologic class of drugs than for a drug that is the only member of its class.

Clinical safety database

4. The number of drug-exposed trial participants who contributed to the characterisation of the drug's safety. In general, the larger the number, the greater the confidence in the prior characterisation of safety.[2]

5. The consistency of the safety profile across clinical trials where comprehensive safety data collection was utilised.

6. The intensity of safety monitoring in the previous clinical trials used to characterise the drug's safety. For example, the number and type of safety parameters monitored (e.g., laboratory measures, vital signs), thoroughness of assessment, and frequency and duration of monitoring can be important.

Similarity of the planned clinical trial to previous trials

7. The planned dose and dosing frequency in the proposed clinical trial. In general, the planned dose or dosing frequency of the drug should not exceed what was studied in previous clinical trials used to characterise the drug's safety.

8. The duration of exposure. The duration of exposure in previous clinical trials should be adequate to support the duration in the proposed trial.

9. Comparability of the drug product (e.g., pharmaceutical form, drug substance, excipients) and route of administration. The drug product and route of administration for the proposed clinical trial should be comparable to those used in previous trials to characterise safety.

10. Similarity of the population in previous clinical trials to the population in the planned trial with respect to important demographic characteristics, concurrent and previous illnesses, concomitant therapies, and other factors, e.g., cytochrome P450 (CYP) phenotype. Selective safety data collection would not be feasible if the population to be studied is more susceptible to adverse drug effects than the population included in the clinical trials used to characterise safety, e.g., older or younger trial participants, or trial participants who have renal or hepatic impairment or factors associated with greater cardiovascular risk.

Clinical pharmacology

11. Drug-drug interactions have been well characterised.

12. Drug metabolism and excretion are well described and understood.

[2] In principle, the number of patients exposed to investigational product should sufficiently exceed those outlined in ICH E1.

Non-clinical data

13. Nonclinical toxicology data have been well characterised.

Post-authorisation data

14. Quantity and quality of post-approval safety data. Sufficiency of data is related to several factors, e.g., duration of marketing, number of participants exposed, method of data collection.

2.3. Baseline data

Use of a selective safety data collection approach does not change considerations for baseline data collection determined by the clinical trial objectives. Baseline data are essential to ensure that prospective trial participants are eligible for trial enrolment. Furthermore, baseline data are needed for assessment of efficacy and safety in subgroups based on, for example, demographics, baseline disease characteristics, concurrent and previous illnesses, and concomitant therapies.

2.4. Data that should generally be collected

In accordance with ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and ICH E6: Good Clinical Practice, an adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following list includes the data elements that should generally be collected, but is not meant to be comprehensive:

1. Serious adverse events (see ICH E2A; ICH E6)
2. Important medical events (see ICH E2A)
3. Medication error/overdose (intentional or unintentional)
4. Adverse event that led to study drug discontinuation
5. Pregnancy and lactation exposure and outcomes
6. Adverse events of special interest, including laboratory abnormalities, identified in the protocol as critical to safety evaluations (see ICH E6; ICH E2F: Development Safety Update Report; CIOMS VI).

When allowed/permitted by regional or local regulations and supported by adequate justification in the protocol, a selective collection of some of the data listed above could be considered in these regions.

Serious adverse events considered efficacy or safety endpoints, which would not be subject to unblinding and expedited reporting (see ICH E2A), should be prospectively agreed upon with the regulatory authority(ies) and described in the clinical trial protocol. They should be collected and monitored on a regular basis through an independent data monitoring committee (IDMC) established by the sponsor (see ICH E6).

2.5. Data that may be appropriate for selective collection

When selective safety data collection is justified, it may be acceptable to limit collection of certain data (while ensuring the safety of trial participants in line with Section 2.1):

1. Non-serious adverse events may not need to be collected, or collection may be reduced in frequency.
2. Various types of laboratory monitoring (e.g., serum chemistries, haematology) electrocardiograms, and imaging trials may not be necessary, or monitoring may be performed at a reduced frequency.
3. Physical examinations and vital sign data may not need to be collected or may be collected at reduced frequency.
4. Once concomitant medication use is documented at baseline, changes in concomitant therapies (e.g., changes in dose, added therapies, discontinuation of therapies) may not need to be collected.

However, should any of the events listed in Section 2.4 be required for collection as per the study protocol, sponsors may also need to collect relevant information (e.g., medical records, laboratory data) to characterise such event(s) should they occur, including any follow-up information.

2.6. Benefit-risk considerations for selective safety data collection

It should be recognised that the contribution of non-serious adverse events to the benefit-risk profile of a drug may differ depending on the indication of use and patient characteristics (e.g., age, cardiovascular risk factors). These factors should be considered when accepting the comparability of patient populations and the applicability of selective safety data collection. Specifically, when the safety of a drug is sufficiently characterised in a patient population with severe disease (e.g., late-stage cancer, heart failure), comprehensive safety data collection may still be warranted in a patient population with less severe disease (e.g., migraine, hypertension) to ensure that the benefits outweigh the risks in the latter patient population.

2.7. Early Consultation with Regulatory Authorities

Clinical trials must be conducted in accordance with local and regional laws and regulatory requirements. Sponsors considering selective safety data collection should gain prospective agreement with regulatory authorities. Considerations include: 1) whether the safety profile of a drug is sufficiently characterised to justify selective safety data collection; and 2) the specifics of the planned methods of implementation (see Section 3).

It is possible to conduct a multi-regional clinical trial using a single protocol with selective safety data collection if the safety profile of the product is considered to be sufficiently characterised, and all regulatory authorities agree with the proposed approach. A well-designed multi-regional clinical trial that takes this Guideline into account will help the sponsor reach agreement with regulatory authorities in multiple regions (see ICH E17: General Principles for Planning and Design of Multi-Regional Clinical Trials).

If a sponsor or applicant plans to use clinical trial results for regulatory purposes in multiple regions, obtaining scientific advice in those regions prior to trial initiation is strongly recommended.

2.8. Situations where selective safety data collection may be considered

After careful consideration of the factors listed in Section 2.2 and a determination that the safety profile of a drug is sufficiently characterised, selective safety data collection may be appropriate for the situations listed below. The list is not meant to be comprehensive; selective safety data collection may be appropriate in other circumstances as well. Additional examples and situations for applying selective safety data collection may be found in Section 3.

1. Clinical trials to support a new indication of an approved drug where the two populations are similar (e.g., with respect to demographic characteristics, comorbidities, concomitant therapies), or when the patient population in the new indication was well represented in the trials that supported the approved indication. For example:

    1.1. A clinical trial of an anti-thrombotic drug previously approved for reduction of cardiovascular events in patients with coronary artery disease, to support a new indication to reduce cardiovascular events in patients with peripheral artery disease;

    1.2. A clinical trial of a drug previously approved for the treatment of diabetes, to support a new indication for the treatment of heart failure, where many of the patients in the diabetes trials had co-existing heart failure.

2. Clinical trials intended to expand the label information of an approved drug with additional endpoints in the same patient population. For example:

    2.1. A drug is developed for heart failure with a large (e.g., thousands of patients) outcome trial. If the safety profile is well characterised, selective safety data collection may be appropriate for a trial in a similar heart failure population to demonstrate a symptomatic benefit, e.g., improvement in physical function based on a 6-minute walk test; improvement in a patient-reported outcome;

    2.2. A drug was previously approved to improve symptoms or a validated surrogate endpoint, e.g., blood pressure, haemoglobin A1c, creatinine clearance. If the safety profile has been well characterised, selective safety data collection may be appropriate for a clinical trial designed to demonstrate improvement in an outcome, e.g., need for hospitalisation, need for dialysis in the same patient population.

3. Safety trials designed to further investigate potential safety concerns focussing on specific parameters, e.g., visual impairment, pulmonary toxicity, cognitive dysfunction, major adverse cardiovascular events (MACE). Selective safety data collection may be appropriate if the safety profile has been well characterised.

4. Clinical trials designed to provide additional evidence of efficacy, where the safety profile of the drug has been well characterised. For example, consider a situation where a drug is submitted to a regulatory authority for authorisation. After comprehensive review, the regulatory authority(ies) determines that the safety profile of the drug has been well characterised; however, an additional clinical trial is required prior to authorisation to provide additional evidence of efficacy. Selective safety data collection may be appropriate for this clinical trial.

3. Implementation of selective safety data collection

Having considered the general principles outlined in Section 2 with respect to when it may be appropriate to reduce collection of certain types of safety data, a number of approaches for selective safety data collection may be considered. These implementation methods are meant to be flexible with respect to the particular types of data for which collection can be reduced, as well as the monitoring intervals for these data. Regardless of the method chosen, it is essential to ensure patient safety and adherence to local and regional laws and regulations.

The selective safety data collection approach should be carefully planned and clearly described within the relevant clinical trial documents (e.g., protocol; monitoring plan; statistical analysis plan), with reference to this Guideline (see Section 4). Given that investigators may not be familiar with selective

safety data collection, CRFs should be well-designed, and investigators should receive appropriate training.

When safety findings are presented, the approaches should be described in the appropriate document(s), e.g., ICH E2F; ICH E3: Structure and Content of Clinical Study Reports; and ICH M4: Common Technical Document.

The following examples of methods of implementation are not meant to be all-inclusive.

3.1. Selective safety data collection for all patients in a clinical trial

For all participants in a clinical trial, the parameters listed in Section 2.4 would be collected throughout the trial; however, collection of some or all of the data types listed in Section 2.5 would be limited. For example:

1. Consider an approved drug with a well characterised safety profile. The drug is known to increase transaminases through its mechanism of action. A clinical trial is conducted where one of the key objectives is to determine the optimal monitoring paradigm for serum transaminases to avoid liver toxicity. The parameters listed in Section 2.4 would be collected throughout the clinical trial, and serum transaminases would be evaluated at regular intervals; however, the data described in Section 2.5 would not be collected;
2. Consider a cardiovascular outcomes clinical trial for an approved drug with a well characterised safety profile with a primary composite endpoint that includes deaths, non-fatal myocardial infarctions, and non-fatal strokes. These are serious adverse events that would always be collected as described in Section 2.4, and they could be adjudicated; however, the data described in Section 2.5 would not be collected.

3.2. Comprehensive safety data collection for a specific subset(s) of the population, with selective safety data collection for other patients

Comprehensive safety data would be collected for specific subset(s) of the patient population where additional information is deemed important; however, safety data collection would be reduced for other patients. For example:

1. If the patient population in previous clinical trials included few patients over the age of 65, it could be of value to collect additional safety data on this population in a new trial in the same or a related indication. Thus, comprehensive safety data would be collected for patients aged 65 and over, whereas data collection would be reduced for patients under age 65;
2. Specific patient subsets could undergo comprehensive safety monitoring based on other factors (e.g., race, ethnicity, sex, baseline disease status, renal/hepatic impairment, CYP metabolizer status, genetics, geographic location), with selective safety data collection for other patients.

3.3. Comprehensive safety data collection for the initial period of the clinical trial, with selective data collection thereafter

In certain settings, comprehensive safety data could be collected from the beginning of the clinical trial through some pre-determined period, with selective safety data collection thereafter.

In longer clinical trials, safety monitoring is typically performed quite frequently at the beginning of the trial, but the frequency is decreased as the trial proceeds. The planned reduction in monitoring frequency is a variation of selective safety data collection, based on the premise that data collected

during the early part of the clinical trial will adequately characterise non-serious adverse events, as well as important changes in vital signs and laboratory abnormalities. This concept may be expanded—specifically, collection of some types of safety data could be reduced or discontinued for patients once a specific duration of follow-up is achieved, e.g., interval physical examinations and laboratory investigations could be discontinued once patients have been followed through 12 months. For example:

1. Consider a clinical trial of a preventive vaccine in which solicited signs and symptoms are recorded daily for a pre-specified period post-vaccination (e.g., 7 days), all unsolicited adverse events are collected for approximately 4 weeks post-vaccination, and serious adverse events and pre-specified AESIs are collected for at least 6 months post-vaccination (1);
2. Consider a cardiovascular outcomes trial that is initiated pre-marketing and ongoing at the time of drug approval. At the time of approval, the safety of the drug will have been sufficiently characterised in the indicated patient population. From that point forward, adoption of a selective safety data approach could be appropriate for the ongoing trial;
3. Consider a clinical trial of the efficacy of a drug designed to prevent or delay an important outcome such as dementia or end-stage kidney disease. Assuming it would take many years to collect sufficient endpoint events to achieve adequate statistical power, it may be appropriate to utilise selective safety data collection once comprehensive safety data have been collected for all patients for a reasonable duration, e.g., one year.

3.4. Comprehensive safety data collection in a representative subset of the population, with selective safety data collection for other subsets

Some efficacy clinical trials and specific safety clinical trials require enrolment of many thousands of participants to achieve adequate statistical power. In these settings, such as a large clinical outcomes trials, the number of participants planned for enrolment may greatly exceed the number needed to assess non-serious adverse events, changes in vital signs, and laboratory abnormalities. In this setting, comprehensive safety data could be collected for only a representative subset of participants, with selective safety data collection in other participants (see Section 2.5). For example:

1. Comprehensive data could be collected at randomly selected sites, perhaps half of the sites in every country or geographic area, with reduced safety data collection at other sites;
2. Comprehensive data could be collected for randomly selected patients across all sites, with reduced safety data collection for other patients.

When using these methods, it is important that patients who receive comprehensive safety monitoring are representative of the entire population. Thus, selection bias should be avoided, adequate diversity of the patient population with comprehensive data collection needs to be ensured, and the method for randomly selecting sites or patients should be described in the protocol and other relevant trial documents.

4. Practical considerations for selective safety data collection

A sponsor considering selective safety data collection should consider impacts to patients, trial conduct, data analysis, and interpretation. The feasibility of such approaches and plans for implementation should be discussed with regulatory authorities in advance, and agreement should be

reached. Although these approaches can improve efficiency, there are disadvantages. Some questions that may arise retrospectively cannot be explored if the data were never collected, e.g., issues with respect to concomitant medications, laboratory parameters, blood pressure.

Concerns may emerge during the conduct of clinical trials utilising selective safety data collection that will require intensification of safety monitoring or reversion to comprehensive safety data collection. Such changes may create logistical challenges with respect to trial sites, protocols, and data collection forms.

The use of selective safety data collection may present complexities for data analysis, presentation, and summarisation. If selective safety data collection is used uniformly in a clinical trial (i.e., for all patients in a trial; throughout the trial), analyses are straightforward; however, frequency summaries would need to describe the specifics of the approach for safety data collection to enable interpretation of the results. In contrast, if the methods of safety data collection are not consistent for all patients in a clinical trial or are not consistent throughout the duration of a trial, data obtained under a comprehensive safety data approach and data collected under a selective safety data approach cannot be pooled. Methods for aggregating the data should be delineated within the protocol and associated analysis plans. Analysis and summarisation should be appropriate for the collection approach(es) and results should clearly identify data summaries where interpretation is impacted by the collection approach.

5. Relationship with other guidelines/regulations

5.1. Other ICH guidelines relevant to the conduct of clinical trials and clinical safety data management

This Guideline should be considered in conjunction with other ICH Guidelines relevant to the conduct of clinical trials and clinical safety data management, e.g., ICH E2A; ICH E2F; ICH E1: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; ICH E3; ICH E6; ICH E8: General Considerations for Clinical Studies; and/or ICH E17. Evaluation of the information generated through post-approval pharmacovigilance activities is also important for all products to ensure their safe use, e.g., ICH E2E: Pharmacovigilance Planning; ICH E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH E2C: Periodic Benefit-Risk Evaluation Report.

5.2. Other non-ICH scientific guidance documents of interest

Given the need for scientific justification of selective safety data collection, pre-existing guidelines on the same topic and regulatory requirements for safety data collection, the following regional and national scientific guidance documents are referenced in addition to the list of ICH Guidelines that supports the selective data collection approach (non-exhaustive list):

1. FDA, United States. Guidance for Clinical Trial Sponsors-Establishment and Operation of Clinical Trial Data Monitoring Committees. March 2006;
2. EC, Europe. Guideline on Data Monitoring Committees. 2005. EMEA/CHMP/EWP/5872/03;
3. FDA, United States. Guidance for Industry on "Determining the Extent of Safety Data Collection Needed in Late-stage Premarket and Post-approval Clinical Investigations". February 2016. And further relevant guidelines from the various ICH contributor countries/regions;

4. EC, Europe. Risk Proportionate Approaches in Clinical Trials; Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation. 25 April 2017. (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use.

6. Glossary

Adverse event:
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see ICH E2A and ICH E6).

Adverse event of special interest:
An event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted (based on CIOMS VI; see ICH E2F).

Important medical event:
Medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent serious outcomes; these events require medical and scientific judgement and fall under the expedited reporting rules (see ICH E2A).

Serious adverse event:
Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect
  (see ICH E2A and ICH E6)

7. References

1. WHO Expert Committee on Biological Standardization. Sixty-seventh report. Geneva. World Health Organization; 2017 (WHO technical report series; no.1004); annex 9 - Guidelines on clinical evaluation of vaccines: regulatory expectations; p. 503-73