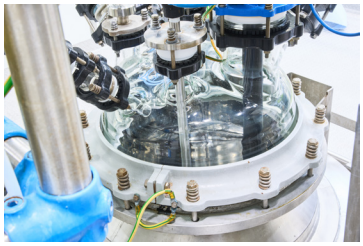
Streamlining Early Drug Development:

Efficient Synthesis of Highly Potent Compounds

Rob Abbenhuis, *Division Manager CHEM*



Drug discovery of newly identified clinical targets is an exciting and dynamic field for scientists working in academia, start-ups and small to large pharmaceutical companies. During design and screening lead compounds are selected based on their optimum receptor interaction demonstrated in further in-vitro preclinical trials as well as in-vivo animal trials. The continuous advance in medicinal chemistry enables the development of highly potent compounds with the required drug-like properties [1,2]. The increasing focus of drug research on the unmet clinical needs in oncology, inflammatory disease and antiviral compounds lead to more compounds with complex pharmacological activity, toxicity, and benefit-risk profiles [3–5]. Several of these compounds are highly potent active pharmaceutical ingredients (HPAPI) with foreseen pharmacological and toxicological activity at low doses. Compounds with novel pharmacological actions also carry a high risk of unknown toxicology or off-target effects due to the limited safety data and lack of class reference compounds. Such drug candidates are considered as HPAPI by default until their toxicology profile is fully established [6]. To progress quickly into the clinical program a phase appropriate synthesis of sufficient drug substance according to the project needs and stage is required. Due to the limited and unknown safety profiles of such compounds, synthesis is performed in specialized facilities and by a dedicated organization.

Drug synthesis challenges in early development

Timely entry into the clinical trial program depends on the synthesis of sufficient drug substance and is known to be a critical milestone. The challenges arise from the fact that drug synthesis has yet to be developed, while at the same time ensuring the protection of workers and the environment [7]. In addition, there are still no standardized definitions for various toxicological terms and no clear guidelines on the classification of new chemical entities into categories and specific handling requirements [8,9]. Consequently, the available data must be evaluated individually for each compound to derive the necessary safety and precautionary measures during manufacture [10]. A rational risk mitigation approach is applied by Ardena to specifically support fast track, priority, accelerated and break-through designation programs in drug synthesis and drug product manufacturing.

Rational risk-based and phase-appropriate approach in drug synthesis

Establishing a comprehensive toxicological profile of a new compound remains difficult in the early stages of drug development and can significantly impact the development program as data generation is a lengthy and expensive process [11,12]. The lack of data, particularly concerning the novel pharmacological actions of compounds potentially designated as Highly Potent Active Pharmaceutical Ingredients (HPAPI), and the transformation of process intermediates to conform with acceptable occupational exposure levels, poses a significant obstacle. To overcome this issue in early drug discovery, a risk-based approach is considered [13,14]. This approach consists of a combination of a comprehensive review of the available safety, preclinical and physicochemical compound properties, a risk assessment including available data bases and literature (e.g., ISPE Risk MaPP [15]; US NIOSH Hazardous drug alert [16], etc.,), layout and design of the synthesis process including facility, equipment, flow and a risk mitigation strategy, conducted before running the first synthesis campaign (Figure 1).

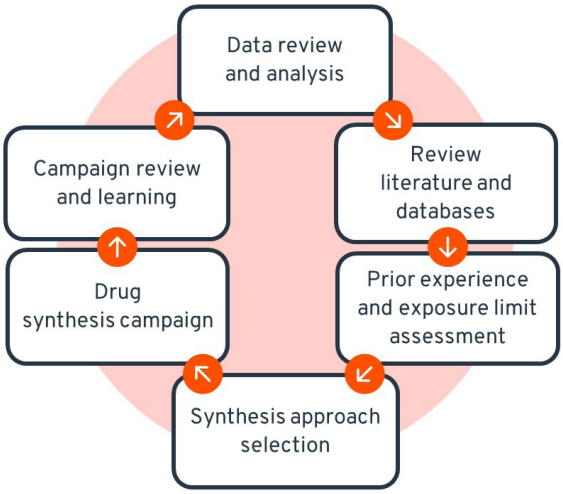


Figure 1: Rational risk mitigation approach and continuous improvement process applied by Ardena.

The risk-based approach will be continuously up-dated as more clinical and safety relevant data become available during the course of the project. The objective continues to be identification of and adaptation to the most efficient and cost-effective API synthesis compliant with the Environment, Health and Safety (EHS) standards and regulatory requirements during the drug development program.

The goal of the initial and follow-up risk assessments is to determine and update the relevant safety values throughout the manufacturing of the drug substance. The Acceptable Daily Exposure (ADE) and Permitted Daily Exposure (PDE), used in Europe and USA respectively, describe the acceptable limits (mg/kg body weight) of cross-contamination of intermediates or drug products due to dust, vapors, aerosols, equipment, or operators clothing etc. during the manufacturing process [17,18]. The Occupational Exposure Limits (OEL) describe the acceptable limits of specific airborne particles (µg/m3) to which workers may be exposed, as well as the type of exposure risks such as inhalation or dermal [19]. While the ADE/PDE and OEL levels are established upon completion of the full safety data package, Occupational Exposure Bands (OEB) are used during the early development (Figure 2). The OEB classification is based on the initial risk assessment considering an exposure range to the compound at negligible risk for the workers and ensures that efficient precautionary measures are in place during synthesis [20].

The determination of the limits is compound specific and considers if the compound is toxic at any value (e.g., cytotoxic, genotoxic) or has a threshold value of toxicity (e.g., No-Observed-Adverse-Effect Level (NOAEL)) [21]

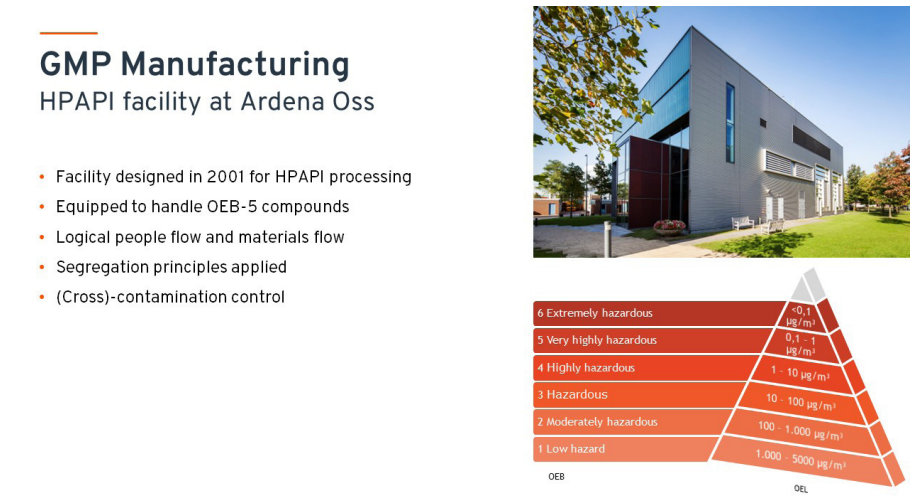


Figure 2: OEB banding strategy used by Ardena assuring safety and efficiency in drug synthesis at all development stages.

Drug synthesis: Process development and design

After determining the operative OEB for the compound and its intermediates during synthesis, the potential synthetic routes are evaluated and the most suitable synthesis approaches are defined. The selection of the synthesis processes to be evaluated will be guided by the principles of efficiency, low exposure risk, scalability, and analytical monitoring for example by qualified process analytical technologies.
Based on experience and knowledge a parallel synthesis approach is applied to accelerate the development according to Quality by Design (QbD) principles [22]. Potentially Critical Quality Attributes (CQA) are identified early in the process to establish the design space and determine the safest and most efficient synthesis. Building a solid understanding of the operational parameter ranges supports process optimization, scaling up, robustness, consistent quality, and safety of the synthesis. Other factors considered include facility lay out, equipment design, personnel, process flow, cleaning, and desired physical API properties most suitable for the finished product development and manufacturing.
Alongside the synthetic process, sensitive qualitative and quantitative analytical methods for the intermediates, artefacts, impurities, and the compound are developed and qualified. The analytics are essential for the safety and cleaning monitoring as well as the process monitoring even within a contained chemical manufacturing process.

Manufacturing of HPAPI and compounds with limited toxicity data

In order to deal with unknowns and uncertainties due to limited toxicology data in compound synthesis each manufacturing campaign is performed under the relevant safety conditions and precautions as well as according to the ICH Q11 guideline [23]. Based on experience of chemists, toxicologists, and high-profile operators familiar and trained on HPAPI manufacturing, a good balance between effective safety, development timelines and investments are established. Hazard analysis and hygiene risk assessments determine if the synthesis or certain steps of the synthesis require a segregation concept, pressure cascading or containment technology.

In addition, automated systems can be considered which allow continuous recording of the process parameters to support design space development of CQA through data acquisition, evaluation and analysis.
The qualification of multipurpose process equipment includes a cleanability assessment using swab or rinse analysis and fluorescent dye testing to study as well as establish and qualify the cleaning procedure. Post manufacturing the cleaning process is validated by various verification tests to confirm the absence of any cross-contamination.
The adoption of a risk-based approach to expedite drug synthesis and facilitate the supply of pre-clinical and clinical materials, even in the absence of comprehensive toxicology and safety data, can be optimized through the default adoption of segregation and containment technologies. Gathering important information and experience with the synthesis by the above approach allows rapid optimization, simplification, and classification into the appropriate OEB band as further safety data arise and the full safety data package will become available before the commercialization of the product.

Conclusion

The exponential advances in biomedical sciences have shifted drug discovery towards unmet medical needs and substantially shorter drug development timelines [24]. Such programs face the challenge of the need for drug substance synthesis with only limited toxicological and pharmacological data or predicted HPAPI classification. Ardena has extensive expertise in finding the right balance between EHS, regulatory requirements, early entry into clinical trials and rapid patient access. Dedicated manufacturing and analytical facilities, experienced and trained workers, and established rational risk-based approaches provide an integrated platform for synthesis and drug product manufacturing at the critical interface from the pre-clinical through to the clinical stage. The approach follows a long-term perspective by accruing product and process knowledge and controls based on QbD principles to ensure scalability and transferability as well as manufacturing optimization and simplification as more safety data become available.

References

1. A.G. Schwaid, I. Cornella-Taracido, Causes and Significance of Increased Compound Potency in Cellular or Physiological Contexts, J Med Chem. 61 (2018) 1767–1773. https://doi.org/10.1021/acs.jmedchem.7b00762.
2. D.R. Owen, C.M. N Allerton, A.S. Anderson, L. Aschenbrenner, M. Avery, S. Berritt, B. Boras, R.D. Cardin, A. Carlo, K.J. Coffman, A. Dantonio, L. Di, H. Eng, R. Ferre, K.S. Gajiwala, S.A. Gibson, S.E. Greasley, B.L. Hurst, E.P. Kadar, A.S. Kalgutkar, J.C. Lee, J. Lee, W. Liu, S.W. Mason, S. Noell, J.J. Novak, R. Scott Obach, K. Ogilvie, N.C. Patel, M. Pettersson, D.K. Rai, M.R. Reese, M.F. Sammons, J.G. Sathish, R.P. Shankar Singh, C.M. Steppan, A.E. Stewart, J.B. Tuttle, L. Updyke, P.R. Verhoest, L. Wei, Q. Yang, Y. Zhu, An oral SARS-CoV-2 M pro inhibitor clinical candidate for the treatment of COVID-19, n.d. https://www.science.org.
3. C.A. Pinto, Z. Balantac, S. Mt-Isa, X. Liu, O.L. Bracco, H. Clarke, T. Tervonen, Regulatory benefit–risk assessment of oncology drugs: A systematic review of FDA and EMA approvals, Drug Discov Today. 28 (2023). https://doi.org/10.1016/j.drudis.2023.103719.
4. C. Moreau Bachelard, E. Coquan, P. du Rusquec, X. Paoletti, C. Le Tourneau, Risks and benefits of anticancer drugs in advanced cancer patients: A systematic review and meta-analysis, EClinicalMedicine. 40 (2021). https://doi.org/10.1016/j.eclinm.2021.101130.
5. M. Senior, Fresh from the biotech pipeline: fewer approvals, but biologics gain share, Nat Biotechnol. 41 (2023) 174–182. https://doi.org/10.1038/s41587-022-01630-6.
6. R.G. Sussman, A.R. Schatz, T.A. Kimmel, A. Ader, B.D. Naumann, P.A. Weideman, Identifying and assessing highly hazardous drugs within quality risk management programs, Regulatory Toxicology and Pharmacology. 79 (2016) S11–S18. https://doi.org/10.1016/j.yrtph.2016.05.025.
7. D.C. Blakemore, L. Castro, I. Churcher, D.C. Rees, A.W. Thomas, D.M. Wilson, A. Wood, Organic synthesis provides opportunities to transform drug discovery, Nat Chem. 10 (2018) 383–394. https://doi.org/10.1038/s41557-018-0021-z.
8. R.G. Sussman, B.D. Naumann, T. Pfister, C. Sehner, C. Seaman, P.A. Weideman, A harmonization effort for acceptable daily exposure derivation – Considerations for application of adjustment factors, Regulatory Toxicology and Pharmacology. 79 (2016) S57–S66. https://doi.org/10.1016/j.yrtph.2016.05.023.
9. P.A. Weideman, A.M. Pecquet, M.A. Maier, Harmonization efforts for deriving health-based exposure limits in the pharmaceutical industry – Advancing the current science and practice, Regulatory Toxicology and Pharmacology. 79 (2016) S1–S2. https://doi.org/10.1016/j.yrtph.2016.07.016.
10. J. Gould, C.M. Callis, D.G. Dolan, B. Stanard, P.A. Weideman, Special endpoint and product specific considerations in pharmaceutical acceptable daily exposure derivation, Regulatory Toxicology and Pharmacology. 79 (2016) S79–S93. https://doi.org/10.1016/j.yrtph.2016.05.022.
11. E.C. Faria, J.P. Bercu, D.G. Dolan, E.J. Morinello, A.M. Pecquet, C. Seaman, C. Sehner, P.A. Weideman, Using default methodologies to derive an acceptable daily exposure (ADE), Regulatory Toxicology and Pharmacology. 79 (2016) S28–S38. https://doi.org/10.1016/j.yrtph.2016.05.026.
12. T. Janela, J. Bajorath, Large-Scale Predictions of Compound Potency with Original and Modified Activity Classes Reveal General Prediction Characteristics and Intrinsic Limitations of Conventional Benchmarking Calculations, Pharmaceuticals. 16 (2023). https://doi.org/10.3390/ph16040530.
13. F. Pognan, M. Beilmann, H.C.M. Boonen, A. Czich, G. Dear, P. Hewitt, T. Mow, T. Oinonen, A. Roth, T. Steger-Hartmann, J.P. Valentin, F. Van Goethem, R.J. Weaver, P. Newham, The evolving role of investigative toxicology in the pharmaceutical industry, Nat Rev Drug Discov. 22 (2023) 317–335. https://doi.org/10.1038/s41573-022-00633-x.
14. E.A.G. Blomme, Y. Will, Toxicology Strategies for Drug Discovery: Present and Future, Chem Res Toxicol. 29 (2016) 473–504. https://doi.org/10.1021/acs.chemrestox.5b00407.
15. ISPE, ISPE Risk MaPP, (2017).
16. FDA, NIOSH Hazardous Drug Alert, (2023).

17. EMA, Committee for Medicinal Products for Human Use (CHMP) Committee for Medicinal Products for Veterinary Use (CVMP) Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, 2014. www.ema.europa.eu/contact.
18. E. V. Sargent, E. Faria, T. Pfister, R.G. Sussman, Guidance on the establishment of acceptable daily exposure limits (ADE) to support Risk-Based Manufacture of Pharmaceutical Products, Regulatory Toxicology and Pharmacology. 65 (2013) 242–250. https://doi.org/10.1016/j.yrtph.2012.12.007.
19. C. Jandard, H. Hemming, M. Prause, C. Sehner, M. Schwind, M. Abromovitz, E. Lovsin Barle, Applicability of surface sampling and calculation of surface limits for pharmaceutical drug substances for occupational health purposes, Regulatory Toxicology and Pharmacology. 95 (2018) 434–441. https://doi.org/10.1016/j.yrtph.2017.12.020.
20. J.C. Graham, J. Hillegass, G. Schulze, Considerations for setting occupational exposure limits for novel pharmaceutical modalities, Regulatory Toxicology and Pharmacology. 118 (2020). https://doi.org/10.1016/j.yrtph.2020.104813.
21. D.G. Dolan, B.D. Naumann, E. V. Sargent, A. Maier, M. Dourson, Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations, Regulatory Toxicology and Pharmacology. 43 (2005) 1–9. https://doi.org/10.1016/j.yrtph.2005.06.010.
22. ICH Q8R2, Committee for Human Medicinal Products ICH guideline Q8 (R2) on pharmaceutical development, 2017. www.ema.europa.eu/contact.
23. ICH Q11, ICH guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological/ biological entities), 2012. www.ema.europa.eu.
24. FDA, 2022 Annual Report, 2023.

Navigating you through drug development