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Early chemical development at Legacy Wyeth Research☆

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This article describes an approach to early process development in the context of the productivity model in legacy Wyeth (i.e. to deliver two New Drug Applications per year for New Molecular Entities). As a result of the model, the cycle time from lead selection to phase I decreased and the number of compounds in early development increased. In response, Wyeth Chemical Development devised a resource-neutral approach to early process development, which is described here. This model harvested synergies from integrating advanced technologies and aggressive sourcing with a matrix research organization and efficient ways of working. It provided a model that met the business needs of our former organization while ensuring the timely delivery of high-quality active pharmaceutical ingredients and safe, scalable processes.

Introduction

Over the years, drug development costs in the pharmaceutical industry have risen considerably while profits have remained flat or have declined [1–5]. The latter is a consequence of various factors, including increased generic penetration within the marketplace, managed health care, re-importation and fewer regulatory approvals for new molecular entities [4,6]. Large pharmaceutical companies have responded to these financial pressures by increasing overall development productivity and reducing overall development costs [7–16].

From 2001 onward, Wyeth pursued a productivity model that had as its objective the submission of two New Drug Applications for New Molecular Entities every year [17]. To support this goal, an average of 13 small-molecule compounds advanced to the development track [18], and 8–12 Investigational New Drug applications (INDs) were filed annually [19]. To support the productivity model, the Discovery organization's output increased by a factor of approximately six, requiring changes to their ways of working [20]. In addition, in 2005 changes in the preclinical development paradigm resulted in a contraction of the lead selection to the IND submission cycle time from 18 months to 12 months.

The larger early development portfolio and shorter cycle times translated to a considerable increase in workload for the early-stage development chemists and engineers. Furthermore, the productivity enhancement soon resulted in an expanded late-stage portfolio, so that from 2003 to 2008 resources gradually shifted away from early development to support the expanded late development activities. In fact, because Chemical Development as a whole remained resource-neutral over this period of time, the average Process Chemistry FTEs working on early development projects decreased by over 25% (Fig. 1).

In response, a more efficient approach to early process research and development was designed, implemented [21] and subsequently refined. Three underlying principles were the foundation for this model: organizational efficiency (i.e. a well-trained, technologically advanced and change-agile process chemistry organization fashioned to enable rapid and flexible deployment of resources); the judicious utilization of embedded centers of expertise to complement the knowledge and skills of the process chemists and engineers; and the integration of material sourcing with early-stage scale-up to outsource non-core activities and focus internal resources on synthesis steps that had a greater impact on active pharmaceutical ingredient (API) quality.

☆ Wyeth was acquired by Pfizer on 15 October 2009.

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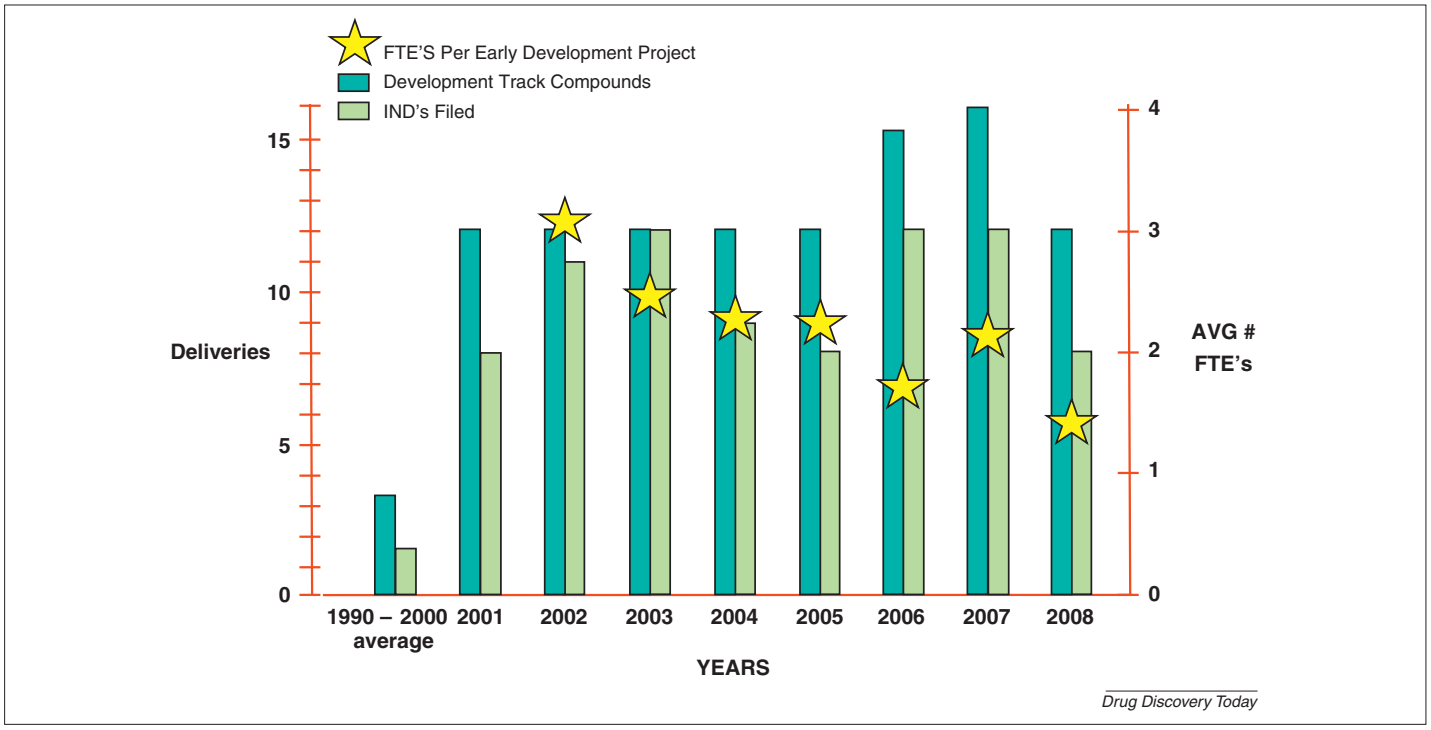


FIGURE 1

FTEs per early development project (2000–2008).

Early development workflow

Chemical Development organization

Chemical Development was responsible for devising and developing safe, efficient and scalable processes to support preclinical and clinical studies and for the transfer of the manufacturing process to an external supplier during phase II for small-molecule API. Located on multiple sites, the department was organizationally composed of Synthesis Research & Development (SRD), Scale-up Operations, Material Operations, Process Safety and Radiosynthesis [22].

SRD encompassed Process Chemistry (PC) and the Technology Functions. PC was responsible for process research (e.g. route selection), early process development, initial scale-up and any ensuing development. The Technology Functions that supported the process chemists comprised Process Chemistry Technologies (PCT), Chemical Engineering Technologies (CET), the Catalytic Hydrogenation Team (CHT) and the Continuous Flow Team. The last two were cross-functional teams with no direct organizational reporting lines.

The Scale-up Operations group maintained two Kg laboratories and a pilot plant and was responsible for producing clinical Good Manufacturing Practice (cGMP) batches of API. Material Operations was responsible for sourcing and delivery of starting materials and any advanced intermediates for development projects, as well as performing GMP inventory management. They, together with SRD and Scale-up Operations, supported our colleagues in the API Technical Operations group [23] during the process co-development and scale-up by outside suppliers who typically provided API for phase III and beyond.

Deliverables

The time interval between lead selection and the initiation of phase I stretched across several development phases: preselection, predevelopment and preclinical (Fig. 2). During the preselection phase, Discovery prepared multiple compounds [24] for single/ascending-dose pharmacokinetic studies, preliminary solid-form assessment and pre-formulation work [25]. The technology transfer from Discovery to Chemical Development occurred just after the selection of a single lead and was facilitated by the initial discovery meeting. Within two to four months of lead selection, an approximately 500 g batch of API was prepared by SRD for early-stage drug safety studies and formulation development [26]. Shortly thereafter a batch (typically 5 kg) was produced in a cGMP environment by Scale-up Operations to support both IND-enabling studies and phase I clinical trials [27]. As the compound advanced through clinical trials, additional API was prepared in our Pilot Plant, then outsourced to an external manufacturer to supply API for phase III and beyond. Once outsourced, process development continued to be supported by Chemical Development, API Technical Operations and the external supplier as necessary.

Underlying principles

Organizational efficiency

As the number of early development projects increased and the delivery cycle times decreased, a matrix system was implemented that separated the project and group leadership roles. Individual Project Leaders, whose role was to oversee multiple projects, were no longer necessarily Group Leaders. This paradigm switch facilitated resource allocation and broadened access to in-house experts. Projects were assigned to SRD Project Leaders who, to meet project demands, could access resources from any of the PC groups and Technology Functions. To ensure fairness and alignment, the resource allocation decisions were made collectively by the SRD Project Leaders weekly.

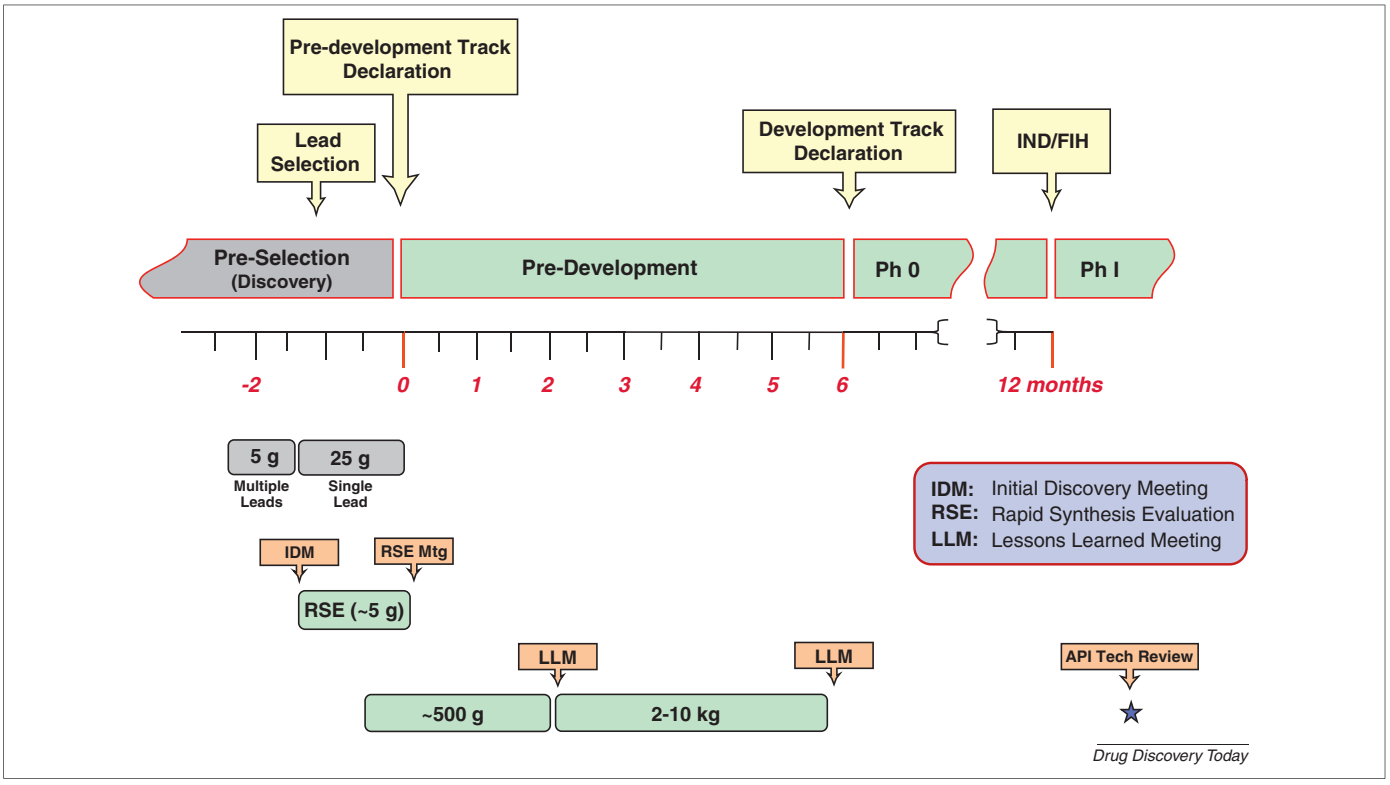


FIGURE 2

Early development API deliveries.

To further support the organization's capabilities, programs were established to help scientists broaden their skill sets. For example, a mandatory six week Kg laboratory internship advanced the SRD chemists' understanding of scale-up operations and helped harmonize our practices in this area. Web-based e-learning seminars covering a variety of technical topics (e.g. industrial mixing, filtration/drying and crystallization) were created with the aid of an external vendor and were made available to anyone in Chemical Development.

Specialized Centers of Expertise in SRD

Several specialized functions and teams were established (PCT, CET, CHT and the Continuous Flow Team) to centralize technologies and expertise that we felt were crucial to our operations, yet not so easily accessed and/or mastered by the bench chemists. The Technology Functions established knowledge centers with expertise in several areas (e.g. Design of Experiments, process modeling and state-of-the-art process technologies). Two points should be made: related expertise was housed under a single 'roof' to avoid redundancy, ensure critical mass and maintain lower operating expenses; however, each function's workflow was integrated with Process Chemistry operations. Decision-making with regard to priorities, project objectives and resource allocation was a shared responsibility.

The PCT group performed reaction screening and optimization studies using multi-reactor synthesizers in response to in-house service requests. This enabled linear PC workflows to become parallel PCT/PC workflows and shorten development time. In addition, they performed studies that addressed process understanding, experimental design and process modeling [28].

The CET group had primary responsibility for identifying a suitable solid form of the API and developing a robust and scalable crystallization process to deliver it. Once again, parallel reactor workflows and automated laboratory reactors were used to map the API final form space [29], ensuring the product we delivered was suitable for formulation development [30].

The remaining technology function teams (CHT and the Continuous Flow Team) comprised members from the PC and PCT groups. The mission of the CHT was to apply high-throughput technologies and internal catalysis expertise to screen and develop stereoselective catalytic hydrogenations for prochiral substrates. The Continuous Flow Team was assembled to explore applications of continuous processing chemistry in the production of API and evaluate whether particular steps were better suited to the advantages offered by flow chemistry [31]. Special attention was given to batch processes that were run at high temperature or involved the preparation of energetic intermediates [32] and processes with molecular stability concerns owing to either the reaction, work-up conditions, or extended cycle times that would be observed on scale.

Integration of sourcing and process development

Synthesis planning and material sourcing were complementary activities that brought about the reduction of development timelines and the conservation of internal resources. Material Operations facilitated the sourcing and purchasing of starting or raw materials. Sourcing, initiated during the preselection phase, was based on the Discovery route, incorporating feedback from SRD's early route assessments. Intermediates that were disclosed in the public domain and occurred in the synthesis before the proposed

regulatory starting material were primary candidates for early sourcing. The successful sourcing of downstream intermediates reduced the need to expend internal laboratory and scale-up resources on the early, higher volume steps of a process. In addition, the close dialogue between PC and Material Operations helped ensure that synthesis strategy changes and the longer term sourcing approach were not mutually exclusive.

Working paradigm

Harmonized ways of working and templates for key activities were introduced to communicate expectations at each gate in the API process (Fig. 3). Each box represents a different aspect of the early development workflow, including milestones and governance decisions (yellow), activities such as API batch preparation (blue), and key meetings that also served as gates (green). SIPOCs (suppliers, inputs, process activities, outputs and customers) were created for each of the activities, decision points and gates. They defined the activities that needed to occur, the requisite documentation, the suppliers of the documentation, expected outputs, stakeholders and recipients of the information [33].

At the time of lead selection, a Project Leader from SRD was assigned to oversee the technical transfer from Discovery to Chemical Development and to coordinate the process research and development activities of PC, PCT and CET. Laboratory work could start quickly because Material Operations typically procured starting materials and/or advanced intermediates at-risk before the selection of a lead based on Discovery input.

After the initial discovery meeting, a 2–4 week laboratory assessment of the Discovery chemistry was undertaken (the rapid synthesis evaluation, or RSE). The main goal of the RSE was to thoroughly assess the viability of the Discovery process. An additional outcome was the early generation of API that enabled the CET group to initiate studies on API form selection. In cases in which it had been determined *a priori* that the Discovery process or aspects thereof was impracticable, a laboratory assessment of alternative chemistries was carried out instead. After the RSE exercise, representatives from PC, PCT, CET, Material Operations, the Kg laboratories, Process Safety and Analytical Chemistry participated in an RSE meeting to decide on the choice of synthetic route, strategies for the development of a process capable of supplying 5 kg of API, and which starting materials should be ordered at-risk to be available for the upcoming Kg laboratory campaign.

Once the synthetic route was chosen, development work to better understand the chemistry, develop isolations and improve

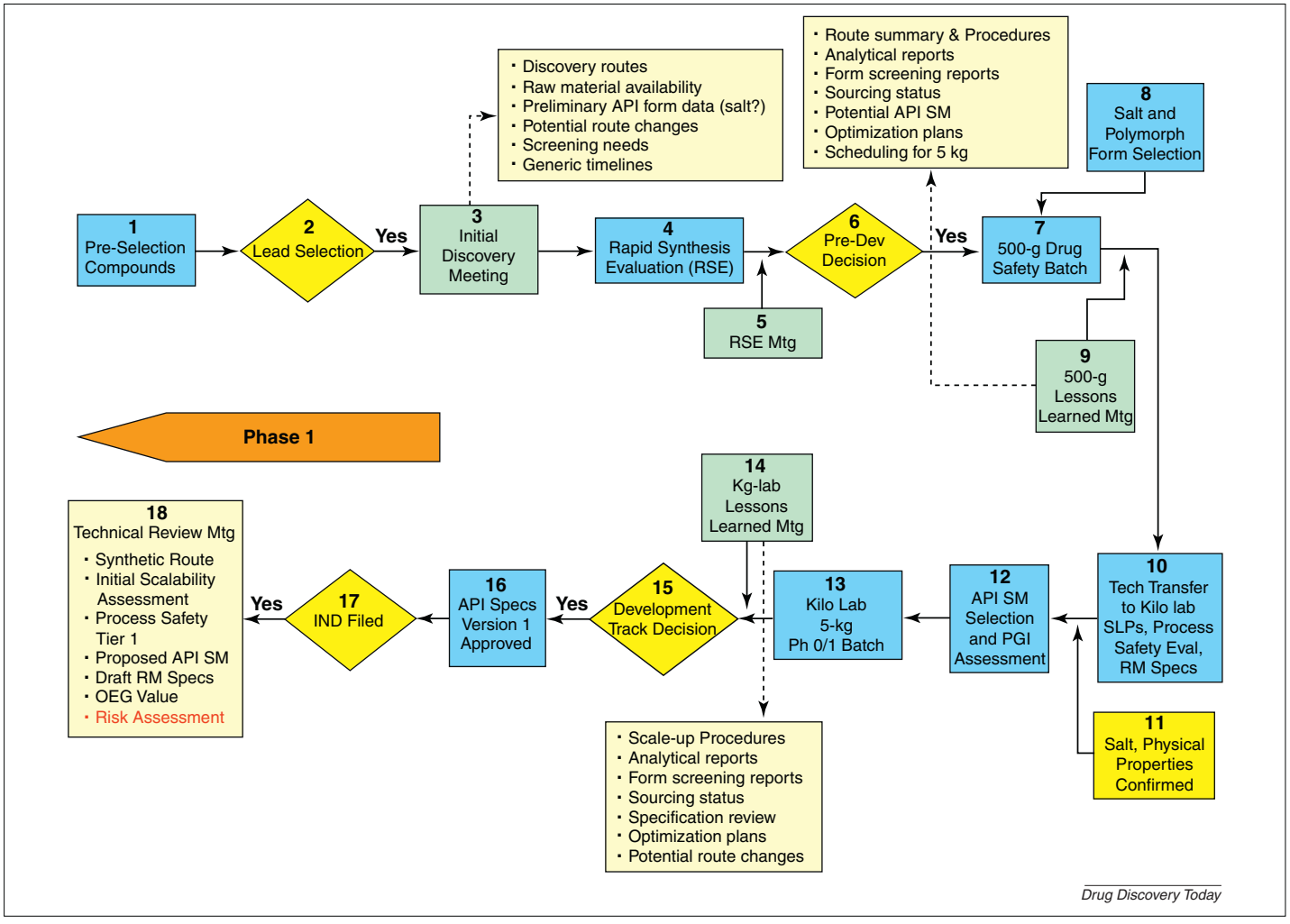


FIGURE 3

Early development process map.

robustness, reliability and scalability occurred in parallel with the 500 g production campaign. During the production campaign, reactions were scaled up in the laboratory in 2–30-L jacketed cylindrical glass reactors. A lessons learned meeting followed the successful delivery and release of the 500 g batch. This meeting was the formal beginning of the technical transfer to the scale-up operations unit and a vehicle to ensure strategic alignment relative to development activities moving forward. Each step of the developed synthetic process was documented using a standard laboratory procedure (SLP) template, and the procedure was demonstrated by the author of the SLP in jacketed cylindrical reactors for the personnel from the scale-up operations unit. The executed SLP and observations made during the demonstration run served as the basis for drafting the batch record used for the production of the GMP lot of API. In cases in which the receiving team members were not able to travel to the demonstration site, video streaming was used to maintain the opportunity of a live demonstration run [34]. Standardizing a live demonstration of the chemistry into our workflow resulted in a high 'first time right' success rate and was integral to achieving compressed delivery timelines.

After the completion of the 500 g batch of API and before completing the 5 kg batch, an evaluation of known or potential genotoxic impurities was conducted [35–39]. All reagents, starting materials and intermediates were referenced against the Material Safety Data Sheets and the Carcinogenic Potency Database (http://potency.berkeley.edu/) and were evaluated by *in silico* predictive software (e.g. Derek) [40]. Any alerts that arose were addressed by purging argument justifications, Ames testing, or appropriate specifications based upon the established staged Threshold of Toxicological Concern guidelines [41].

Although a single lot of API was usually supplied to support both IND-enabling studies and the beginning of phase I, a separate batch was sometimes prepared to meet compound demands for projects whose IND-enabling safety studies had been accelerated. In either case, once Scale-up Operations' first batch of API was released, a lessons learned meeting ensued. Pilot Plant representatives participated if they had not been involved during the first campaign to set the stage for further scale-up. Shortly after the IND filing, an API Technical Review meeting was held to discuss synthetic routes, cost of goods, opportunities for process improvements, our future quality by design strategy and potential process analytical technology applications.

Illustrative case study

The case study that follows is meant to exemplify the previously described operational model. The example shows the value provided by Material Operations and illustrates our ability to achieve accelerated deliveries by early engagement of Scale-up Operations. It also highlights the benefits of the interface between SRD and Discovery, the value of the Technology Functions and the additional benefits of early involvement of Scale-Up Operations.

Sulfonamide **10** (Scheme 1) was identified as a preselection candidate by Discovery. The medicinal chemistry route to **10** relied on a non-selective synthesis that generated a 2:1 mixture of racemic diastereomers followed by preparative chiral High Pressure Liquid Chromatography (HPLC). The most potent isomer was selected for development—one of the minor isomers later identified as **10**. As the compound advanced, larger quantities of API were required, so an enantioselective synthesis was developed by Discovery [42,43].

Although **10** had not yet been declared a lead candidate, SRD worked with Discovery to broker the early integration of CHT to evaluate the enantioselective hydrogenation of unsaturated acid **3**. Sufficient quantities of **3** were prepared from acetophenone **2** by Discovery and transferred to CHT. High-throughput screening identified a preferred catalyst (Solvias Walphos ligand W008-1), which provided the saturated acid **4** in quantitative yield and 99% ee [44]. Discovery scaled up the reaction and developed a process that delivered multi-gram quantities of **4**. The remaining stereocenter was set using Evan's auxiliary methodology [45] and provided the 5 g and 25 g batches of sulfonamide **10** to support exploratory pharmacokinetic studies.

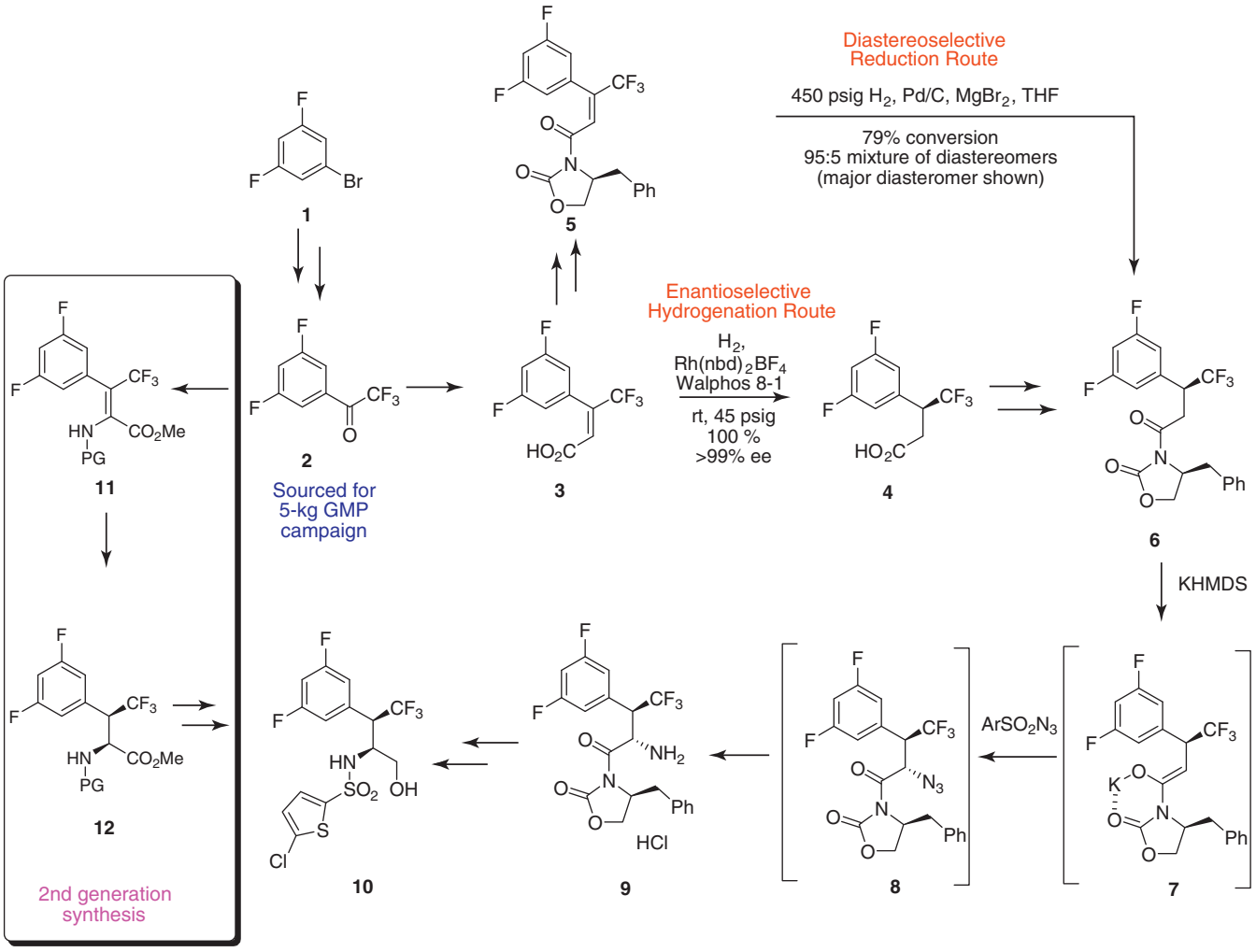
When the project transitioned into Chemical Development, the absolute stereochemistry of **10** had been assigned and development activities to support the delivery of the 500 g batch were accelerated. Discovery had reported preliminary results on an alternative route to **6** that proceeded through the diastereoselective reduction of **5**. This route used the chiral auxiliary to establish both stereocenters in a stepwise manner and obviated the need for a potentially expensive enantioselective hydrogenation. Although expediency drove the Discovery decision to forgo the underdeveloped diastereoselective reduction of olefin **5** in favor of the enantioselective hydrogenation of **3**, the former had now become more attractive on the basis of cost.

Material Operations' sources of pentafluoroacetophenone **2** had lead times too long to be used in the 500 g campaign. Pentafluoroacetophenone **2** was ordered at risk for the 5 kg campaign but made in-house for the 500 g batch starting from compound **1**.

Olefin **5** was prepared by SRD and provided to Scale-up Operations for the diastereoselective reduction to **6**, capitalizing on the larger hydrogenation reactor capacity available in the Kg laboratory. Although the laboratory yield was 80%, the yield of **6** obtained during the first scale-up run was a disappointing 33%. The increased cycle time at the larger scale caused considerable decomposition of **6** during workup and isolation. A modified workup stabilized the process and afforded a respectable 76% yield in the second batch. Involving Scale-up Operations during the 500 g batch campaign reduced the cycle time for the conversion of **5** to **6**, accelerated the API delivery by two weeks, enabled the PC scientists to focus development efforts on the downstream steps and highlighted a processing liability for the reduction of **5** to **6** in time to be improved for the 5 kg campaign (*vide infra*).

In-house testing by the Process Safety Group verified the published thermal data on triisopropylbenzenesulfonyl azide (trisyl azide) [46] and endorsed the protocols for the handling of intermediate **8**. In addition, Material Operations secured a source of trisyl azide as a stock solution in toluene rather than as a solid as had been used for earlier batches.

Having addressed the safety issues, attention shifted to ensure that the process to generate compound **10** was robust at scale. High-throughput screening was used to identify conditions for the diastereoselective reduction of **5** to **6** while *in situ* Fourier Transform Infra Red (FTIR) spectroscopy was used to define conditions for the conversion of **6** to **8** at a reaction temperature supported by the available scale-up vessels without loss of facial selectivity.



SCHEME 1

Synthetic routes to **10**.

Shortly after the low yield was observed in the Kg laboratory, PCT explored the reaction space (solvent, temperature and time) for the diasteroselective reduction of **5** to **6**, using a range of chelating agents. $MgCl_2$ was found to give an acceptable compromise between selectivity and stability during work-up and product isolation. During the 5 kg batch preparation, nine reductions of **5** were run in the Kg laboratory using $MgCl_2$. The minor diastereomer was efficiently purged during isolation and afforded **6** in >99% (w/w) purity with an average yield of 83% [47].

Although the conversion of **6** to **8** was carried out at −65 °C in the laboratory during the 500 g batch preparation, that reaction temperature could not be supported in the available vessels during the 5 kg batch preparation. To meet the delivery, the conversion of **6** to **8** would either need to run successfully at −40 °C as a semi-batch process or be run in a custom-made flow reactor that was capable of reaching jacket temperatures of −90 °C. PCT and PC began to evaluate both a continuous flow process in a variety of flow-technology equipment [48] and the feasibility of increasing the operating temperature for a semi-batch process. Although some success was achieved with both approaches, the semi-batch process was easier to implement within the time constraints imposed upon the batch delivery. In semi-batch mode, a >95% assay yield of **8** was achieved when enolate **7** was held at −40 °C for 45 min before the trisyl azide charge. *In situ* FTIR demonstrated that the deprotonation of **6** was essentially instantaneous upon the addition of potassium hexamethyldisilazane at all temperatures evaluated. The half-life of enolate **7** at −45 °C was approximately 12 h, whereas at −10 °C, the half-life was approximately 3 h. The *in situ* FTIR study also provided valuable safety data by demonstrating that trisyl azide reacted with **7** as it was added so that no accumulation of the reagent occurred [49]. Upon scale-up, the conversion of **6** to **8** proceeded without complication, providing on average a 63% yield of **8** for the two steps [50].

The remaining steps of the process were developed using a sequence of screen (PCT), evaluate (PCT/PC), demonstrate (PC) and execute on scale (Scale-up Operations) that resulted in the successful delivery of a 5 kg batch of **10** within the requested timeframe. Demonstration runs for Scale-up Operations began approximately four weeks after the 500 g batch delivery, and the 5 kg batch was delivered four months later. With support from CHT, proof of concept for a shorter second-generation route was also achieved in the event that future scale-up batches were required. This approach avoided the low temperature requirements for conversion of **6** to **8**, use of trisyl azide and established

both chiral centers in a single step via enantioselective hydrogenation of **11** to generate **12**. Subsequent functional group manipulations converted **12** to **10**. The overall yield of **10** from **2** using this second generation route was 43%.

Case study summary

A collaborative effort between Discovery and SRD led to the parallel development of two effective strategies for the enantioselective synthesis of **10**. An ensuing coordinated effort within Chemical Development enabled delivery of a 500 g and a 5 kg batch of **10** within seven months of the asset transfer to Chemical Development. After delivery of the 5 kg batch, proof of concept was achieved at a gram scale for a second-generation route that established both chiral centers in a single step.

Concluding remarks

The pharmaceutical industry is currently under tremendous pressure to reduce costs and improve productivity. Recent reports have highlighted the state of the industry, and details of how process R&D organizations have responded have appeared [6,10,11,13,15,51–54]. Profound changes in the legacy Wyeth business model to deliver two New Drug Applications per year motivated Chemical Development to develop the above-described productivity paradigm, which enabled us to face the combination of a sixfold increase in Discovery output with a 25% decrease in cycle time in a resource-neutral environment. Organizational efficiency, judicious utilization of technical skills and knowledge, an approach to outsourcing that ensured internal resources focused on the synthesis steps that had the greatest impact on API quality, and efficient internal – as well as interdepartmental – communication systems led to synergies, which made this challenge manageable. Additional stressors, such as a larger late-stage pipeline, a further increase in early-stage candidates or additional in-licensed assets, would have eventually pushed this model to its limits and led us to implement additional changes, such as increasing headcount and/or further externalization of non-core activities. However, during the time this model operated, it was quite effective for us. Above and beyond the specifics of the legacy Wyeth context, we hope that this article will also provide some food for thought for other organizations with similar challenges.

Acknowledgements

We thank the project leaders, chemists, engineers and operators within Chemical Development who have demonstrated the benefits of this model through the many successful API deliveries our department has made in support of the Legacy Wyeth Research organization. We are also grateful to our many collaborators in Discovery, Analytical and Quality Sciences, Pharmaceutical Development, Drug Safety and Metabolism, and Project Management.

Appendix A. Supplementary data

Please see S1 in the Supplementary data online at the online version, at doi:10.1016/j.drudis.2010.11.008.

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18 In Wyeth terminology, DT marked the beginning of pre-clinical development studies during which time IND-enabling safety and tolerability studies were conducted
19 To frame the productivity model, Wyeth filed an average of fewer than two INDs per year in the 1990s
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22 A chart of the organization is included in the supporting information
23 New Products & Process Development was created in late 2007 as part of the Wyeth Commercial organization to increase our post-POC API and drug product process development capabilities. The API Technical Operations group was a part of New Products & Process Development and as such worked together with Chemical Development to co-develop potential commercial API processes
24 Each of the leads being prepared at this point followed lead optimization work done previously by the medicinal chemistry group. Typically, the 'best' compounds from the lead optimization work were prepared in larger quantity, screened further, and a single lead was nominated to advance
25 For more information on the system used within Wyeth's Discovery Organization to support these functions, see Ref. [17]
26 This 500 g batch was the first batch of API to be fully characterized and released by our Analytical and Quality Science group
27 Delivery of the cGMP batch of API initiated the IND-enabling pre-clinical studies and occurred approximately six months after the start of predevelopment. Because the initiation of phase I typically began six months later, this operating model of targeting six months for the predevelopment stage followed by six months for preclinical development was referred to internally as the '6 + 6' paradigm

28 This was accomplished through the use of automated lab reactors and *in-situ* FTIR equipment

29 Final form encompasses the anhydrous/solvate/hydrate possibilities of neutral/co-crystal/salt forms as well as the polymorph space for the selected form

30 For a discussion of our salt and polymorph selection strategy, see Ku, S. (2010) Salt and polymorph selection strategy based on the biopharmaceutical classification system for early pharmaceutical development. *Am. Pharm. Rev.* 13, 22–30

31 For a recent overview of this rapidly developing field, see the special issue of *Organic Process Research and Development* devoted to Continuous Processes: (2008) *Org. Process Res. Dev.* 12, 904

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33 The process map shown in Fig. 3 was first implemented in 2004 and modified to varying degrees over the next several years to meet the changing needs of the organization. Although Chemical Development was the 'owner' of the process, the design and subsequent modifications were the result of a collaborative effort between us and our key stakeholders (Discovery, Commercial, Pharmaceutical Development, Analytical & Quality Sciences and Project Management)

34 Another benefit of this technology was the reduced need for costly and time-consuming travel between sites

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40 In addition, by-products, mechanism-based intermediates, and potential reaction with impurities carried over from prior steps are evaluated on a case-by-case basis

41 TTC Threshold of Toxicological Concern – established by the EMEA guidance, see European Medicines Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP). Guideline on the limits of genotoxic impurities. CPMP/SWP/5199/02; London, UK, June 28, 2006 (http://www.ema.europa.eu/pdfs/human/swp/519902en.pdf). Accessed January 21, 2010

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43 The absolute stereochemistry of **10** had not yet been determined, thus developing a synthesis capable of preparing any of the four isomers was desirable

44 Screening was performed using an Endeavor Catalyst Screening System from Biotage/Argonaut. Approximately 40 experiments were carried out over seven days

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48 The flow chemistry was evaluated in both an AFRICA system from Syrris and in a system that was manufactured in house. Details of our AFRICA system have been published recently; see Ref. [26]

49 The azido functional group has a strong stretch (2090–2150 cm^{-1}) that is easily seen in the FTIR experiments. This stretch was assigned as the asymmetric stretch due to the N3 group on the basis of vapor phase date published recently by the Novartis group. See Wiss, J. *et al.* (2010) Safety improvement of chemical processes involving azides by online monitoring of the hydrazoic acid concentration. *Org. Process Res. Dev.* 10, 349–353

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