Global Regulatory Dissonance: A Case Study of Industry Views on the Development of Drugs for Postmenopausal Osteoporosis

Neal E. Storm, DRSc, MS, MBA, RAC1,2, and Frances J. Richmond, BNSc, MSc, PhD2

Abstract
Background: The footprint of drug distribution is multinational, but the regulatory frameworks supporting drug development, review, and approval remain largely regional. As a result, industry faces regulatory standards that may be complementary, additive, or contradictory, resulting in global regulatory dissonance (GRD). Methods: Global regulatory dissonance was explored through a case study of drug development (postmenopausal osteoporosis) using survey methodology. Results: In the feedback received, respondents generally agreed that GRD increases the complexity, timelines, and size of registration studies. Dissonant regulatory feedback on proposed labeling, applications, and benefit-risk assessments was also reported. Multiple causes of GRD were identified, including dissonant drug regulatory authority advice, guidelines, benefit-risk assessments, drug approval precedents, medical standards of care, and health technology assessments. Harmonization of guidelines, scientific advice, benefit-risk procedures, and expanded use of mutual recognition agreements were identified as mechanisms thought to reduce GRD. Conclusions: The results suggest that global access to new drugs may be enhanced through a greater understanding of GRD.

Keywords
dissonance, divergence, alignment, harmonization, convergence, strategy, guidance, guidelines, precedents

Introduction
A regulatory framework that supports new drug development must be suitable for all relevant stakeholders, including patients, the medical community, regulators, and drug developers. Drug regulatory authorities (DRAs) play a central role in this process by developing guidelines and overseeing efficient product development, with appropriate safeguards, on behalf of these stakeholders. Not surprisingly, scientific discovery sometimes outpaces the ability to translate those advances into real-world products using currently available regulatory pathways.1 Additionally, regional differences can be observed in how DRAs address novel drug development questions, as they may be influenced by differing landscapes of medical, ethical, cultural, legal, and political views.

Pharmaceutical companies occupy a unique vantage point to observe the magnitude and impact of these distinct regulatory approaches. A successful global product launch depends on an understanding of the regulatory landscape of a particular disease state in the countries in which market authorization is sought. Global regulatory strategies must seek a “common denominator” to bridge potential regional differences. This activity is informed by publicly available materials, such as (1) regulations, (2) guidelines, (3) regulatory precedents, and (4) scientific literature. Nonetheless, a substantial “reading of the tea leaves” is required to anticipate successful regulatory strategies. Differences in requirements from one jurisdiction to another have the potential to impede the access of patients to important new treatment options, but the extent to which

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global regulatory dissonance (GRD) affects drug development planning and registration activities is not clear. In this study, we have attempted to gain better insight into the ways that GRD plays out by studying it systematically in a single therapeutic area.

**Regulatory Authority Guidelines**

Two regional regulatory guidelines, from the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), have been most influential in informing the development and product labeling of postmenopausal osteoporosis (PMO) drugs globally:

- Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis (draft),
- Guideline on the Evaluation of New Medicinal Products in the Treatment of Primary Osteoporosis (CPMP/EWP/552/95 rev 2).

The concepts outlined in the FDA draft guideline are generally applicable in 2014, although this guidance was formally withdrawn in 2009. The FDA and EMA guidelines have common features but also several notable differences (Table 1).

### Table 1. Differences in the requirements for developing therapies for PMO.

<table>
<thead>
<tr>
<th>Area</th>
<th>US</th>
<th>European Union</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential indications</td>
<td>Treatment of osteoporosis in PMO</td>
<td>Treatment of osteoporosis in postmenopausal women at increased risk of fractures</td>
</tr>
<tr>
<td></td>
<td>Prevention of osteoporosis in PMO</td>
<td>Treatment of osteoporosis: 2 years; maintenance of effect after second year (3-5 years; submitted after registration)</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Treatment of osteoporosis: ≥3 years; continued postmarketing to 5 years if antifracture efficacy not proven at 3 years (nonestrogens)</td>
<td>Randomized, double-blind, placebo &gt; active controlled</td>
</tr>
<tr>
<td></td>
<td>Prevention of osteoporosis: ≥2 years; BMD endpoint appropriate once fracture efficacy is established for osteoporosis treatment indication</td>
<td>Patients with PMO at increased risk of fractures (ie, a 10-year fracture risk of 15%-20% in the spine, 5%-7.5% in the hip, and 10%-15% major nonvertebral fractures)</td>
</tr>
<tr>
<td>Control arm</td>
<td>Randomized, double-blind, placebo &gt;&gt; active controlled</td>
<td>Demonstration of antifracture efficacy (new spinal and nonspinal fractures); for nonspinal fractures, either hip or major nonvertebral fractures may be assessed</td>
</tr>
<tr>
<td>Patient population</td>
<td>Ambulatory outpatients (≥5 years postmenopausal), ≥60 years of age with symptoms and signs of PMO (ie, bone pain and height loss), with vertebral fracture and/or lumbar vertebral BMD ≥2 standard deviations below mean peak BMD</td>
<td>BMD from areas studied for fracture incidence</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Demonstration of antifracture efficacy (new vertebral fractures)</td>
<td>Efficacy at first year</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>Statistically significant improvements in BMD</td>
<td>Biochemical variables reflecting bone turnover</td>
</tr>
<tr>
<td></td>
<td>Demonstration of normal bone quality in a subset of subjects (bone biopsy)</td>
<td>Withdrawal of effect data (submitted after registration)</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; PMO, postmenopausal osteoporosis.

The concepts outlined in the FDA draft guideline are generally applicable in 2014, although this guidance was formally withdrawn in 2009. The FDA and EMA guidelines have common features but also several notable differences (Table 1). For example, they present divergent requirements for demonstrating antifracture efficacy either at the end of a 2-year (EMA) or 3-year (FDA) treatment period in a randomized controlled trial and in the recommendations related to the patient composition and efficacy variables assessed in phase 3. In addition, the EMA but not FDA requires data on fracture incidence after treatment withdrawal and on the maintenance of the effect on bone mineral density after the second year of treatment (eg, 3–5 years), although this latter dataset is not required in the original marketing authorization application. Although both the FDA and EMA recognize “treatment of osteoporosis” as a valid indication (the exact wording of these 2 indication statements generally differs), a labeled indication for the “prevention” of PMO in an osteopenic population is allowed only in the US (as evidenced by the recent approval of Duavee [conjugated estrogens/bazedoxifene, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer, Inc. (Philadelphia, PA)] for that indication) (Table 2). Under the revised 2007 EMA guideline, a separate prevention indication is no longer supported since the benefit-risk of PMO therapy is considered positive only in the treatment of patients defined as having an “increased risk of fracture.”

Additional PMO guidelines have been issued by other oversight bodies imposing other requirements. For example, fracture efficacy demonstrated in a phase 3 multiregional clinical trial must be supplemented in some countries with data from a “bridging” study that evaluates bone mineral density, a surrogate endpoint, in local populations.

Not all regulatory requirements can be recognized simply by reading the guidelines. EU regulatory and Health Technology Assessment (HTA) agencies now place greater emphasis on the need for an active- rather than a placebo-controlled pivotal study, although neither the US or EU guidelines mandate an
approach specifically. Moreover, the FDA’s thinking has evolved from allowing separate prevention and treatment indications for PMO to allowing a third indication statement (not defined in the FDA guidance) intended for patients with PMO at a high risk for fractures, defined as “a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.”7(p2) The “high risk” provision is reserved for products considered to possess known or theoretical safety risks of special concern and has been applied to some new products (teriparatide, denosumab) as a means to limit utilization to a subgroup of patients in whom the benefits are considered to outweigh the risks.

Precedents

Product approvals establish an important baseline for the assessment of subsequent products and, like case law, often serve as precedents for future regulatory decisions. Precedents can also vary from one region to another. Precedents in PMO include products belonging to 2 main classes that act as either bone catabolic agents (ie, antiresorptives such as amino-bisphosphonates, calcitonins, denosumab, estrogens, selective estrogen receptor modulators) that reduce bone resorption by inhibiting osteoblast activity or bone anabolic agents that stimulate bone growth by activating osteoblasts (ie, parathyroid hormones, strontium salts).

As judged by dissonant regulatory review outcomes for novel investigational PMO agents (Table 2), the FDA and EMA sometimes have differed in their benefit-risk decisions. Many other countries follow the decisions of these DRAs, magnifying dissonance globally. Historically, 6 novel PMO drugs were approved in the EU that were subsequently not approved in the US: bazedoxifene (Conbriza), cyclical disodium etidronate (Didronel), lasofoxifene tartrate (Fablyn), parathyroid hormone (rDNA) (Preotact), strontium ranelate (Protelos, Osseor), and tibolone (Livial). The FDA recently approved the drug combination of conjugated estrogens/bazedoxifene (Duavee) in 2013; however, the EMA has not yet authorized this product, which is currently under evaluation.

<table>
<thead>
<tr>
<th>Trade Name (Chemical or Molecular Name)</th>
<th>Description / Class of Agent</th>
<th>Year Approved (Withdrawn From Market)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livial (tibolone)</td>
<td>Selective tissue estrogenic activity regulator (STEAR) / antiresorptive agent</td>
<td>Not approved 1987b</td>
</tr>
<tr>
<td>Didronel (etidronate)</td>
<td>Bisphosphonate / antiresorptive agent</td>
<td>Not approved 1991b</td>
</tr>
<tr>
<td>Fosamax (alendronate sodium)</td>
<td>Bisphosphonate / antiresorptive agent</td>
<td>1995, 1997b 1995a,b</td>
</tr>
<tr>
<td>Evista (raloxifene HCI)</td>
<td>SERM / antiresorptive agent</td>
<td>1997, 1999a 1998a,b</td>
</tr>
<tr>
<td>Actonel (risedronate sodium)</td>
<td>Bisphosphonate / antiresorptive agent</td>
<td>2000a,b 1999a,b</td>
</tr>
<tr>
<td>Forteo (teriparatide)</td>
<td>Recombinant human PTH (1-34) analog / bone anabolic agent</td>
<td>2002a 2003a</td>
</tr>
<tr>
<td>US: Boniva; Europe: Bonviva (ibandronate sodium)</td>
<td>Bisphosphonate / antiresorptive agent</td>
<td>2003a,b 2004a,b</td>
</tr>
<tr>
<td>Protelos/Osseor (strontium ranelate)</td>
<td>Strontium salt / antiresorptive agent and putative bone anabolic agent (a.k.a., dual action bone agent, or DABA)</td>
<td>Not approved 2004a</td>
</tr>
<tr>
<td>Preotact (PTH 1-84)</td>
<td>Intact recombinant human PTH (1-84) / bone anabolic agent</td>
<td>Not approved 2006 (2014)a</td>
</tr>
<tr>
<td>US: Reclast; Europe: Aclasta (zoledronic acid)</td>
<td>Bisphosphonate / antiresorptive agent</td>
<td>2007a 2009b 2005a</td>
</tr>
<tr>
<td>Conbriza (bazedoxifene)</td>
<td>SERM / antiresorptive agent</td>
<td>Not approved 2009a</td>
</tr>
<tr>
<td>Fablyn (lasofoxifene tartrate)</td>
<td>SERM / antiresorptive agent</td>
<td>Not approved 2009 (2012)a</td>
</tr>
<tr>
<td>Prolia (denosumab)</td>
<td>Receptor activator of nuclear factor κ-B ligand (RANKL) inhibitor (human monoclonal antibody) / antiresorptive agent</td>
<td>2010a 2010a</td>
</tr>
<tr>
<td>Duavee (conjugated estrogens/bazedoxifene)</td>
<td>Combination of conjugated estrogens and bazedoxifene / antiresorptive agent</td>
<td>2013b Under EMA evaluation</td>
</tr>
</tbody>
</table>

PMO, postmenopausal osteoporosis; PTH, parathyroid hormone; SERM, selective estrogen receptor modulator.
aFor PMO treatment.
bFor PMO prevention.
Scientific Advice

Challenges in drug development may arise from dissonant advice/feedback on the same data package or study proposal. It is clear that even a thorough understanding of regulatory intelligence and guidance is rarely sufficient to inform all product-specific issues during drug development, requiring drug sponsors to seek additional input from DRAs. Scientific advice, obtained through meetings or in writing, refines the basic set of regulatory requirements set forth by regional guidelines by applying them to novel, case-specific technical issues. Companies cannot assume that the quality of scientific review, level of transparency, and timely access to medical review staff across regions will be equivalent to inform a particular issue.

Since 2009, the EMA and FDA have joined efforts in implementing a parallel scientific advice program. Although the program is discretionary and is being piloted in limited areas termed “clusters of interest” (ie, applied to limited areas such as advanced therapies, orphan drugs, new technologies, etc), the goal is promising: “to optimize product development and avoid unnecessary testing replication or unnecessary diverse testing methodologies.” However, under the pilot program, each agency continues to retain the right to issue independent guidance, in addition to the parallel advice given, thus opening the door to the possibility of 3 different sets of recommendations (eg, parallel advice plus 2 regional opinions).

Other Sources of GRD

Initiatives by various regulators and industry groups are ongoing to inform a universal benefit-risk framework as a means to facilitate aligned review outcomes. These activities derive from the premise that greater transparency in the decision framework and assumptions forming the basis for a particular benefit-risk decision will promote collaboration among DRAs on reviews, potentially resulting in a greater convergence of benefit-risk decisions.

On a more fundamental level, GRD simply reflects a natural continuum of scientific opinions, a compromise between divergent opinions of DRAs, the wider medical community, and the public at large. Ethics committee members, clinicians, and key thought leaders provide critical oversight of clinical trials in their roles as reviewers, investigators, and participants on advisory panels. Most importantly, the voice of the patient must be considered, so advocacy groups add an important dimension to directing regulatory science. Among these stakeholders, considerable controversy exists regarding the manner by which to conduct clinical trials in PMO involving (1) whether pivotal registration studies should be placebo or active controlled, (2) whether the duration of treatment should be a minimum of 3 years for a novel agent versus a shorter duration, and to a lesser extent, (3) whether fracture reduction is the most appropriate endpoint upon which to evaluate efficacy. Also, the safety of osteoporosis products weighs heavily on regional benefit-risk decisions. A key feature of PMO is that it is a chronic condition that is asymptomatic (ie, “silent disease”) until the presentation of a fragility fracture, which may be perceived by the patient to be a reversible event. Thus, a key benefit-risk issue for PMO therapies is that risk tolerance to safety concerns among patients who may otherwise be relatively healthy is understandably low. In antiresorptive agents, the first-line treatment of PMO, rare yet serious events, such as osteonecrosis of the jaw, atypical femur fractures, and esophageal cancer, have been observed in the postmarketing setting, adding an important variable to how these agents are regulated regionally.

Despite the potential importance of GRD in shaping drug development, relatively little study has been directed at the impact of GRD, particularly at the level of specific disease states and through the eyes of those most impacted by its effects: the drug developers themselves. It is not clear to what extent companies find GRD problematic and in what ways patient access to novel products is affected. This study attempts to gain insight into industry views using a novel survey instrument that has been applied specifically to the case of PMO agents.

Materials and Methods

The target population of this survey included 50 clinical/regulatory scientists from 10 companies with current/prior experience in PMO drug development, from which 42 actual responses were received. Participants were selected only if they (1) were currently employed in the pharmaceutical industry, (2) possessed drug development experience, (3) were currently or previously involved specifically in PMO drug development, and (4) were currently or previously acting in a professional capacity as an industry regulatory or clinical scientist. Participants were identified through professional networks, conferences, and referrals. No remuneration was provided to encourage participation, but the respondents were offered anonymity and a summary of the results upon completion. The survey instrument was developed with feedback from an interactive focus group including USC Regulatory Science Program (School of Pharmacy) faculty, doctoral students, and clinical scientists with expertise in PMO. The focus group evaluated the structure/flow of questions and their relevance/clarity. The final survey was administered between November 12, 2012 and March 14, 2013 (see the Appendix) using the Qualtrics (Provo, Utah) web-based survey product Research Suite. Collected data were locked and analyzed after the receipt of 42 responses, equating to an 84% response rate. Follow-up semistructured interviews were held with select study participants to discuss
findings and obtain clarification on potential areas of interest and new themes.

**Results**

**Demographics of Participants**

Respondents were well experienced and globally diverse. Most (67%) had greater than 10 years of experience in industry and were evenly distributed between those currently/previously employed as clinical scientists and regulatory scientists. Seventy-six percent of respondents were based in the US, although the roles of some of the US-based respondents centered on regulatory activities in other regions (12%). Other regions represented by survey participants (24%) were Australia/New Zealand, Canada, China, the EU, and Japan.

**Survey Responses**

Respondents recognized the challenges associated with GRD. Most (74%) agreed that GRD has increased the challenges associated with developing drugs in PMO, although 17% did not agree and 10% had no opinion. Cross-tabulation of data showed a trend that respondents with more years of experience in the development of PMO drugs concurred with this view to a greater extent.

Respondents were also asked whether a certain amount of regulatory dissonance in regional requirements may be beneficial to sponsors of investigational agents. Twenty-two of 41 respondents to this question (54%) responded “no,” and 4 responded with “no opinion.” Those responding “yes” (n = 15; 37%) were encouraged to explain their responses. In those text responses, some felt that regulatory dissonance may challenge sponsors to develop better products, despite potentially driving up development costs and limiting the number of products that a company can take forward. Others felt that different scientific or regulatory views may prompt additional clinical questions to be explored within the main registration study or uncover unforeseen issues in protocol design. Also, GRD was seen to potentially offer companies greater access to diverse scientific expertise, resulting in broader clinical programs and adding robustness to benefit-risk decision making.

**Impact and Sources of GRD and Mechanisms to Reduce Its Impact**

When asked to identify the domains of drug development most impacted by GRD, a majority of participants identified the complexity of pivotal trial conduct (83%), lengthened clinical development timelines (70%), and increased pivotal study size (61%), which a majority of participants thought reduced patient access to newer therapies (66%). Respondents were less convinced of its detrimental effects on eventual drug costs (54%) or on industry innovation (53%). Only about half of the respondents (51%) felt that GRD affected regulatory authority review times of applications or believed that their companies considered it an important factor when assessing the commercial probability of success or the net present value of a potential new PMO agent.

When asked to identify the leading causes/factors of GRD from several options, respondents identified the following, in descending order (Figure 1): (1) DRA advice (78%), (2) regional guidelines (51%), (3) benefit-risk assessments (44%), (4) drug approval precedents (37%), (5) medical standards of care (34%), and (6) health technology assessments (32%). Twenty-two percent of respondents identified other causes. Those citing “other” who provided open responses suggested the inconsistency of opinions within a DRA and changing ideas on what represents a safety issue.

The survey explored various domains in the guidelines for osteoporosis drug development that were viewed as potential

![Figure 1. General sources of global regulatory dissonance.](image-url)
sources of GRD (Figure 2); GRD was reported in all of the tested domains of the guidelines in the following descending order: (1) target population for the study (85%), (2) type of control arm (83%), (3) treatment of intrinsic factors relating to the product (mechanism of action, safety profile) (81%), (4) duration of treatment (81%), (5) duration of long-term safety follow-up (80%), (6) timing for assessing the primary efficacy endpoint (78%), and (7) recommendations for the primary (70%) and (8) secondary efficacy variables (69%).

When asked to identify a single domain resulting in the greatest degree of GRD, 4 areas of GRD emerged (Figure 3): (1) type of control group (32%), (2) recommended target population (27%), (3) timing for assessing the primary efficacy variable (15%), and (4) guidance specific to the treatment of intrinsic factors of the investigational agent (eg, safety profile, mechanism of action, novelty of investigational agent) (15%).

Dissonant outcomes from drug review and approval procedures were also considered a source of GRD. Dissonant regional indication statements resulting from labeling negotiations, dissonant and feedback received during product reviews, and divergence in the outcomes of benefit-risk assessments all were identified as sources of GRD by the large majority of respondents (94%, 90%, and 89%, respectively).

When asked to identify a single mechanism that would be most beneficial in reducing GRD, respondents identified the following in descending order (Figure 4): (1) harmonization of regulatory authority guidelines (29%), (2) joint scientific advice mechanisms (27%), (3) harmonized procedures for assessing benefit-risk (15%), and (4) mutual recognition agreements (12%).

Respondents were asked to identify from a list of organizations as the ones best positioned to take the lead in implementing...
mechanisms to reduce GRD (Figure 5). Two types of organizations, DRAs (ie, EMA, FDA, Health Canada, National Institutes of Health [NIH], Pharmaceuticals and Medical Devices Agency [PMDA], etc) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), received 90% of respondent recommendations (55% and 35%, respectively).

**Discussion**

This case study examined GRD, a concept emerging as an important driver of the current decentralized drug development process. The sample of 42 regulatory/clinical scientists was considered representative of the small, specialized base of industry experts in the PMO sector. Interestingly, only about half of these respondents (51%) believed that their firms considered GRD to be an important factor when assessing the commercial probability of success or the net present value of a potential product during business case assessments. Perhaps a similar survey should be targeted at finance/commercial staff at pharmaceutical companies, as these organizations are primarily responsible for projecting future revenue streams and thus may offer additional insights. Nevertheless, most surveyees agreed that regulatory dissonance had an unfavorable

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**Figure 4.** Potential regulatory mechanisms viewed as most beneficial in reducing global regulatory dissonance.

<table>
<thead>
<tr>
<th>Potential Regulatory Mechanisms</th>
<th>Viewed as Most Beneficial to Reducing GRD (choose one)</th>
<th>Percentage (%) of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmonized regulatory authority guidelines</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Joint scientific advice mechanisms</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Harmonized procedures for assessing benefit: risk</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mutual recognition agreements</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Voluntary harmonization type procedure</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Community referral type procedures</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Increased transparency internal meeting outcomes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other (please specify below)</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5.** Organizations best suited to lead the implementation of mechanisms to reduce global regulatory dissonance.

<table>
<thead>
<tr>
<th>Organizations Best Suited to Address GRD (choose one)</th>
<th>Percentage (%) of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory agencies (EMA, FDA, Health Canada, NIH PMDA)</td>
<td>22</td>
</tr>
<tr>
<td>International Conference on Harmonization</td>
<td>14</td>
</tr>
<tr>
<td>Pharmaceutical industry associations (EFPIA, PhRMA, etc.)</td>
<td>2</td>
</tr>
<tr>
<td>World Health Organization (WHO)</td>
<td>0</td>
</tr>
<tr>
<td>Trade organizations (DIA, RAPS, etc.)</td>
<td>0</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>2</td>
</tr>
</tbody>
</table>
impact in all of the domains evaluated with respect to clinical trial design and conduct. The link between GRD and increasing trial complexity, expanded clinical development timelines, and delayed patient access to new treatments are not new concerns and have been highlighted in a recent report by the Organisation for Economic Co-operation and Development (OECD). The report, titled “Recommendation on the Governance of Clinical Trials,” calls for “improved consistency among national regulations and their interpretations,” and on streamlined procedures for the oversight and management of clinical trials.14(p49)

The increasing complexity of trial conduct in part can be attributed to an increased reliance on multinational trials, which are “more complex to perform than national ones due in particular to the difficulties arising from the diversity of legal frameworks.”14(p16) The OECD report noted that national regulatory complexity is causing clinical studies intended to address important public health problems to be canceled or to be “so delayed that their impact is dramatically reduced.”14(p16) A finding that appears consistent with the observations from respondents in this study.

The predominance of concerns regarding the effects of regulatory dissonance on pivotal clinical study design would seem to define an area in which harmonization/alignment initiatives by DRAs might prove to be particularly valuable. The results of this study not only point to the need for an alignment of national guidelines defining general considerations of study design but also the need for aligned advice procedures. Thus, an area of further study may include whether sponsors are utilizing available parallel advice pilot programs and, if not, understanding the reasons for not pursuing these opportunities. Broadly, the results of this study point to important sources of GRD, thus suggesting a path forward whereby policy mechanisms could be directed to points in development where GRD is introduced (ie, alignment of national guidelines and scientific advice procedures, standardization of benefit-risk tools, and expanded use of mutual recognition procedures).

The qualitative insights identified by the respondents are consistent with the outcomes of marketing applications of new molecular entities (NMEs) reviewed by the FDA and EMA between 2006 and 2009.15 Although aggregate data estimate a “concordance of action for ~80% of NMEs submitted within 12 months to both agencies” with little divergence on the outcomes of marketing applications reviewed under priority review provisions, divergence was noted in the reported outcomes of NME applications designated as standard review applications. The reason cited for this difference was the “lower public health priority” given to applications designated as standard review, an insight that may in part explain some of the dissonance in PMO review outcomes. This observation may underscore the need by companies to understand the metrics of GRD at the level of the individual product class and disease state, especially for products in therapeutic areas that may not be ranked by regulatory authorities as public health priorities. The lessons learned from PMO illustrate the breadth of possible concerns related to GRD and likely generalize to other disease states where similar manifestations of GRD may occur.

Results of this study show that regulatory guidelines and treatment of benefit-risk contribute to regulatory dissonance, but respondents also viewed mechanisms to reduce dissonant regulatory advice as an important area of policy focus. Currently, policy initiatives directed at regulatory alignment often focus quite narrowly or exclusively on one or another of the areas studied here or may be limited in their current scope. A more holistic view, supported by the results, is to implement a cluster of policy solutions that target the important drivers of GRD introduced at key milestones during a product’s life cycle.

Conclusions

The multidimensional aspects of GRD require that GRD be addressed through an array of regulatory mechanisms applied to drug review and approval procedures: alignment of regulatory guidelines, scientific advice mechanisms, benefit-risk frameworks, and expanded use of mutual recognition pacts. Moreover, DRA attempts to mitigate the important effects of GRD have been measured perhaps because GRD falls outside of the immediate jurisdictional control of individual DRAs. Regulatory alignment may also be viewed as minimizing the sovereign decision-making authority of DRAs in important areas relative to local standards of care and could require a prohibitive commitment of resources and time to overcome. It is also possible that DRAs do not perceive GRD as problematic to industry, but further research is needed in this area.

Either we accept current limits to the global harmonization/alignment of regulatory standards for the clinical development of new drugs, or we must understand the entropy that is currently working against aligned regulatory pathways with the aim of developing targeted, effective methodologies to counteract its impact. Understanding these differences of opinion is of critical importance to ensuring informed and efficient drug development pathways in the 21st century.

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**References**


**Appendix**

**Survey Questions**

**I. Professional profiles of respondents**

1. How many total years of drug development experience do you have in the biopharmaceutical industry?
2. How many years of experience do you have specifically developing therapeutic products intended for the treatment/prevention of postmenopausal osteoporosis (PMO)?
3. What has been your role within your organization? Please check all that apply.
4. Please indicate the region in which you have acquired the majority of your regulatory/clinical experience. Please check all that apply.
5. What phases of drug development have you supported for therapeutic products intended for the treatment/prevention of PMO? Please check all that apply.
6. How many different therapeutic products for PMO have you supported during your regulatory/clinical career?
7. In your role, did your job responsibilities require you to interact directly with any of the following? Please check all that apply.

**II. Impact/implications of regulatory dissonance**

8. In your experience, has regulatory dissonance increased the challenges associated with developing drug therapies in PMO?
9. In your experience, has regulatory dissonance increased the clinical development timelines of PMO drugs (ie, delays to study start, lengthier clinical studies)? By how much time?
10. In your experience, has regulatory dissonance in drug registration requirements increased the regulatory authority review times of marketing authorization applications of PMO drugs? Please estimate the time added to standard application reviews.
11. In your experience, has regulatory dissonance increased the SIZE of multiregional, pivotal, phase 3 clinical studies in PMO? By how many subjects?
12. In your opinion, has regulatory dissonance increased the complexity of phase 3 trial designs or registration programs in PMO?
13. In your experience, does regulatory dissonance impact the eventual costs of PMO drugs for patients/payers?
14. In your experience, does regulatory dissonance impact patient access to important, new treatments for PMO (ie, products not approved or delayed to market)?
15. In your experience, does your company consider regulatory dissonance to be an important factor when assessing the commercial probability of success or the net present value of a potential new PMO agent?

(continued)
In your opinion, how does regulatory dissonance impact INDUSTRY INNOVATION in drug research and development (as it relates to PMO)?

Some have suggested that a certain amount of regulatory dissonance in regional guidelines/requirements for developing drug therapies may actually be beneficial to sponsors of investigational agents. Do you agree?

III. General causes/factors contributing to regulatory dissonance

In your experience, which of the following lead to the most regulatory dissonance in the setting of PMO? Please check the items that best apply.

IV. Alignment of regional indication-specific PMO guidance

In your experience, how significant is the level of regulatory dissonance in the recommendations for the type of control arm (eg, placebo or active control) in pivotal, phase 3 clinical studies in PMO?

In your experience, how significant is the level of regulatory dissonance in the recommendations for the duration of treatment in pivotal, phase 3 clinical studies in PMO?

In your experience, how significant is the level of regulatory dissonance in the recommendations for the duration of long-term safety follow-up following the assessment of the primary endpoint?

In your experience, how significant is the level of regulatory dissonance in the recommendations for the primary efficacy endpoint in pivotal, phase 3 clinical studies in PMO?

In your experience, how significant is the level of regulatory dissonance in the recommendations for the secondary endpoints in pivotal, phase 3 clinical studies in PMO?

In your experience, how significant is the level of regulatory dissonance in the recommendations for the timing of the primary endpoint assessment (eg, 24 vs 36 months) in pivotal, phase 3 clinical studies in PMO?

In your experience, how significant is the level of regulatory dissonance in the recommended target population to be studied in the pivotal, phase 3 clinical studies of investigational agents for PMO?

In your view, do intrinsic factors relating to the investigational agent under study (eg, safety profile, mechanism of action, novelty of product) impact the level of regulatory dissonance?

Among the areas identified above, which in your view results in the greatest degree of regulatory dissonance when designing pivotal, phase 3 studies in PMO?

Please assess the level of regulatory dissonance that you have observed between drug regulatory authorities in their assessments of BENEFIT-RISK for the same PMO agent.

V. Dissonance relating to drug review and approval procedures

Please assess the level of regulatory dissonance resulting from divergent drug regulatory authority feedback received during product reviews, meetings, or negotiations.

Please assess the level of regulatory dissonance between drug regulatory authorities in terms of allowable indication statements for product labeling.

In your view, are there other sources of regulatory dissonance that arise during the development of PMO agents that should be considered by this study? If you do not believe that there are other sources of regulatory dissonance, please indicate “none.”

VI. Potential policy solutions to reduce regulatory dissonance

In your view, which of the following potential mechanisms would be most beneficial in reducing regulatory dissonance? Please check one item.

In your view, which of the organizations listed below should take the lead in implementing mechanisms to reduce regulatory dissonance? Please check one item.

Given your drug development experience, do you think that the mechanism you selected above to reduce regulatory dissonance in PMO would be helpful if applied in other disease areas?

This is the end of the survey. Thank you for your responses and time. Please feel free to elaborate on any of your responses in this survey. Please also indicate whether you would be open to discussing your feedback for the purpose of informing this study.